PATHOLOGY

MD

PATHOLOGY

GENETIC DISORDERS

GENETIC DISORDERS

GENETIC DISORDERS

Learning Objectives

- Answer questions about disorders involving an extra autosome and chromosomal deletions
- Demonstrate understanding of Mendelian disorders, autosomal recessive/dominant, and x-linked recessive/dominant conditions
- Solve problems concerning triplet repeat mutations
- Explain information related to mitochondrial DNA disorders and multifactorial inheritance

GENETIC DISORDERS

Disorder involving extra chromosome

Down syndrome

Edward syndrome

Patau Syndrome

Disorder involving chromosomal deletion

Cri du Chat syndrome

Disorders involving Sex Chromosome

Klinefelter syndrome

Turner Syndrome

GENETIC DISORDERS

Mendelian disorder

- Point Mutation
- Frameshift Mutation

Autosomal recessive disorder

- Cystic fibrosis
- Phenylketonuria
- Alkaptonuria
- Albinism
- Glycogen storage disorder
- Tay SACHS DISEASE
- Neiman Pick disease
- Gaucher's Disease
- Mucopolysaccharides

GENETIC DISORDERS

AUTOSOMAL DOMINANT DISORDERS

- Familial hypercholesterolemia
- Marfan syndrome
- Ehlers-Danlos syndrome
- Neurofibromatosis
- von Hippel-Lindau disease

GENETIC DISORDERS

X-LINKED RECESSIVE CONDITIONS

- Lesch-Nyhan syndrome
- Testicular feminization
- Bruton agammaglobulinemia
- Menkes disease

GENETIC DISORDERS

X-LINKED DOMINANT CONDITIONS

Hypertrichosis

Vit D dependent rickets

GENETIC DISORDERS

TRIPLET REPEAT MUTATIONS

- Fragile X syndrome
- Huntington disease

GENETIC DISORDERS

GENOMIC IMPRINTING

- Prader-Willi syndrome
- Angelman syndrome

MITOCHONDRIAL DNA DISORDERS

- Leber hereditary optic neuropathy
- Myoclonic epilepsy with ragged red fibres (MERRF)

GENETIC DISORDERS

MULTIFACTORIAL INHERITANCE

Multifactorial inheritance

GENETIC DISORDERS

Down syndrome (trisomy 21).

The most common **karyotype** is 47, XX, +21. Down syndrome is the **most common of the chromosomal disorders**.

The risk increases with maternal age to an incidence of 1 in 25 live births in women age ≥45.

Pathogenesis involves

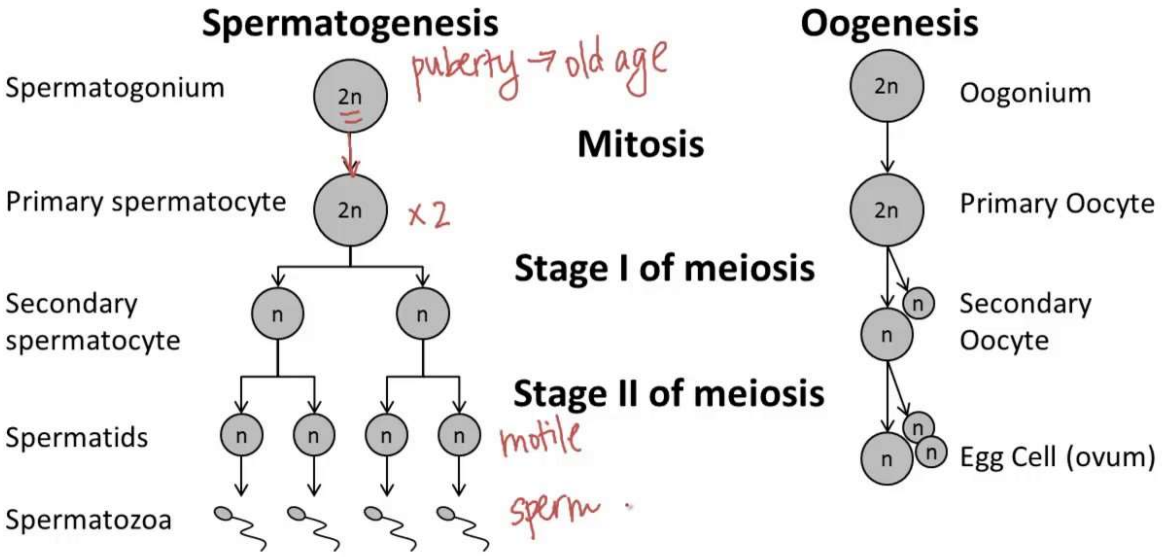
- Meiotic nondisjunction (95%),
- Robertsonian translocation (4%),
- Mosaicism due to mitotic nondisjunction during embryogenesis (1%).: Mosaic Down syndrome, or mosaicism, is a rare form of Down syndrome. Down syndrome is a genetic disorder that results in an extra copy of chromosome 21. People with mosaic Down syndrome have a mixture of cells. Some have two copies of chromosome 21, and some have three

Clinical findings can include intellectual disability; mongoloid facial features (flat face, low-bridged nose, and epicanthal folds); Burchfield spots (speckled appearance of the iris); muscular hypotonia; broad short neck; palmar (simian) crease; and congenital heart defects. Endocardial cushion defect, if present, leads to the formation of an atrioventricular canal (a common connection between all 4 chambers of the heart). Additional clinical problems that can develop include duodenal atresia (“double-bubble” sign); Hirschsprung disease; increased risk (15–20 fold) of acute lymphoblastic leukaemia (ALL); and Alzheimer disease (by age 40 virtually all will develop Alzheimer disease).

GENETIC DISORDER

Down Syndrome

How are sperm and eggs produced?



Stunted growth	90%[25]	Slanted eyes	60%[12]
Umbilical hernia	90%[26]	Shortened hands	60%[24]
Increased skin on back of neck	80%[20]	Short neck	60%[24]
Low muscle tone	80%[27]	Obstructive sleep apnea	60%[20]
Narrow roof of mouth	76%[24]	Bent fifth finger tip	57%[12]
Flat head	75%[12]	Brushfield spots in the iris	56%[12]
Flexible ligaments	75%[12]	Single transverse palmar crease	53%[12]
Proportionally large tongue[28]	75%[27]	Protruding tongue	47%[24]
Abnormal outer ears	70%[20]	Congenital heart disease	40%[24]

GENETIC DISORDERS | Clinical Symptoms

GENETIC DISORDERS

Down Syndrome

GENETIC DISORDERS

Prenatal tests include maternal serum tests, ultrasonography, amniocentesis, and chorionic villus sampling.

Median life expectancy is 47 years.

GENETIC DISORDERS

Edwards syndrome

(trisomy 18) is caused by nondisjunction. The risk increases with maternal age.

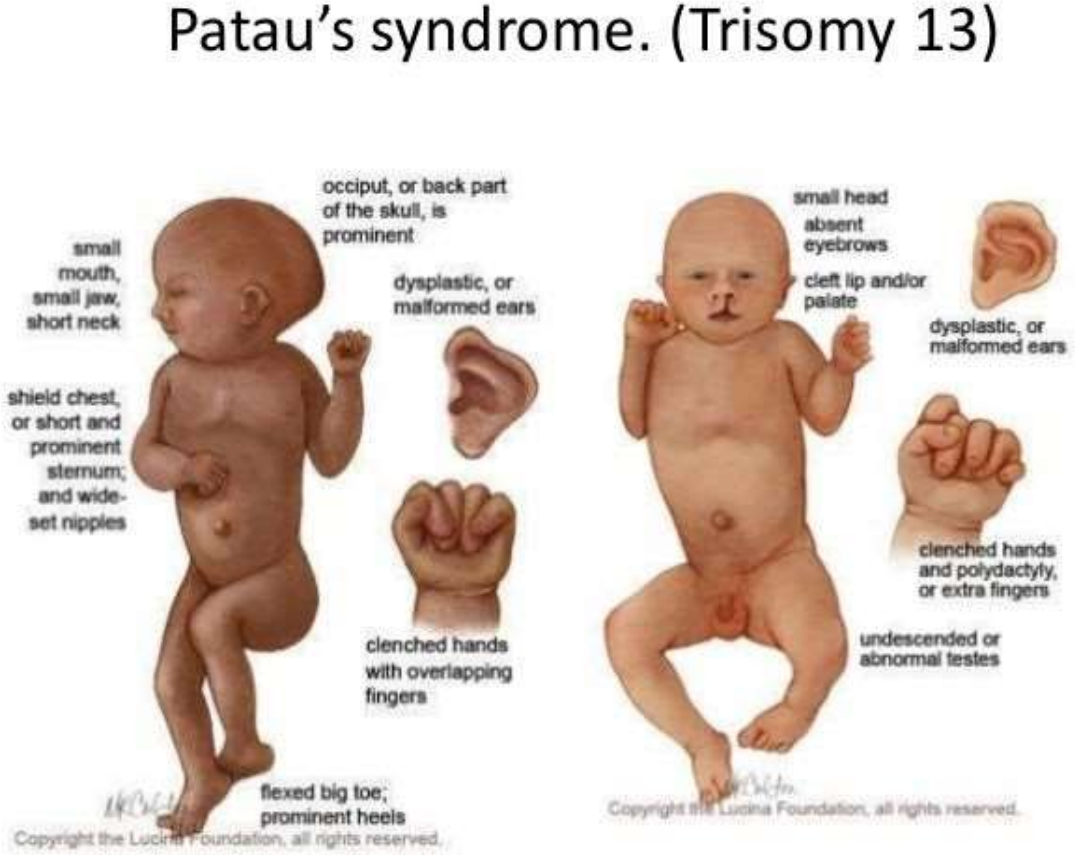
Clinical findings can include

- Intellectual disability;
- low-set ears and
- Micrognathia;
- Congenital heart defects;
- Overlapping flexed fingers; and
- Rocker-bottom feet.

There is a very poor prognosis due to severe congenital malformations.

GENETIC DISORDERS

Edward Syndrome



GENETIC DISORDERS

Patau syndrome

(trisomy 13) is caused by nondisjunction. The risk increases with maternal age.

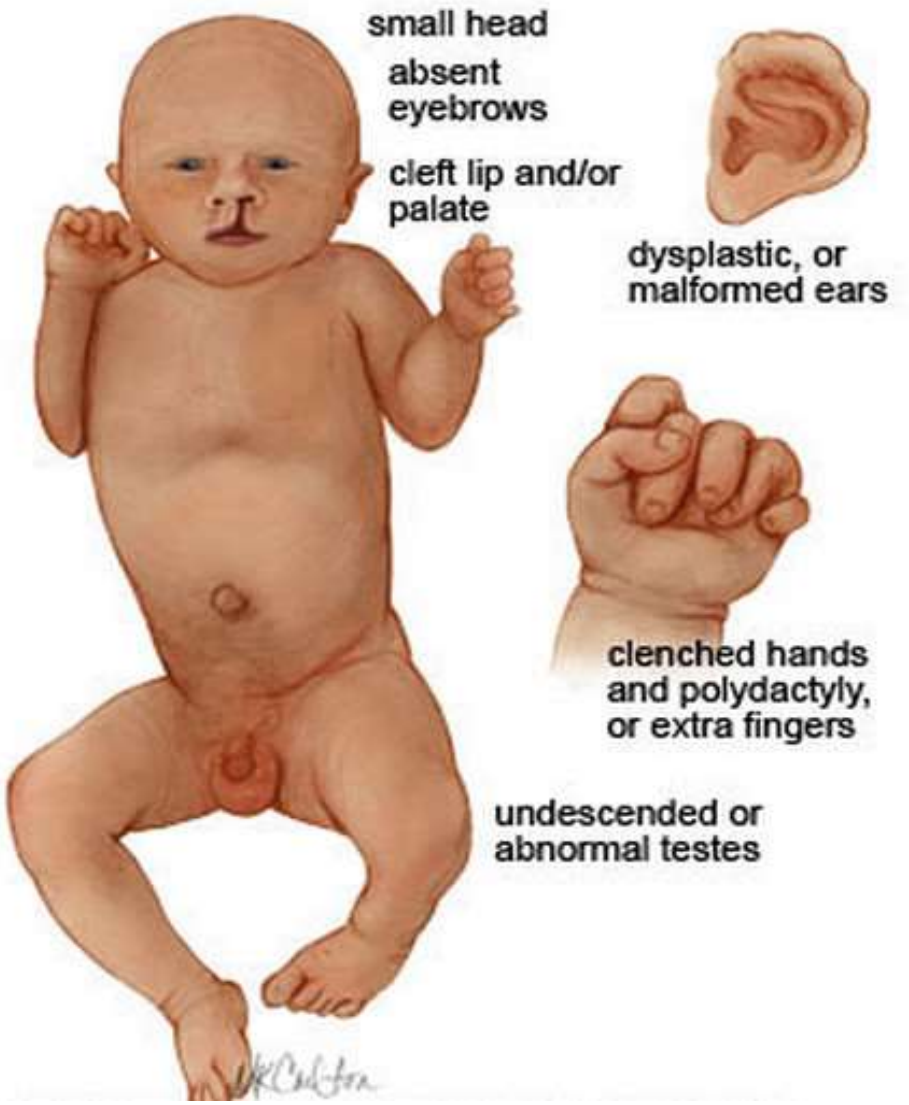
Clinical findings can include

- Intellectual disability;
- cleft lip and/or palate;
- Cardiac defects;
- renal abnormalities;
- microcephaly;
- holoprosencephaly; and
- polydactyly.

The very poor prognosis is due to severe congenital malformations.

GENETIC DISORDERS

Patau Syndrome



GENETIC DISORDERS

DISORDERS INVOLVING CHROMOSOMAL DELETIONS

Cri du chat syndrome is due to deletion of the short arm of chromosome 5.

Clinical findings include a characteristic

- High-pitched cat like cry;
- Intellectual disability;
- Congenital heart disease;
- Microcephaly.

Microdeletions include 13q14 (retinoblastoma gene) and 11p13 (WAGR complex [Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability [previously known as mental retardation]). Microdeletions are too small to be detected by karyotyping and require molecular techniques for detection.

GENETIC DISORDERS

Cri Du Chat

To listen the audio Click on the Icon

GENETIC DISORDERS

DISORDERS INVOLVING SEX CHROMOSOMES

Klinefelter syndrome

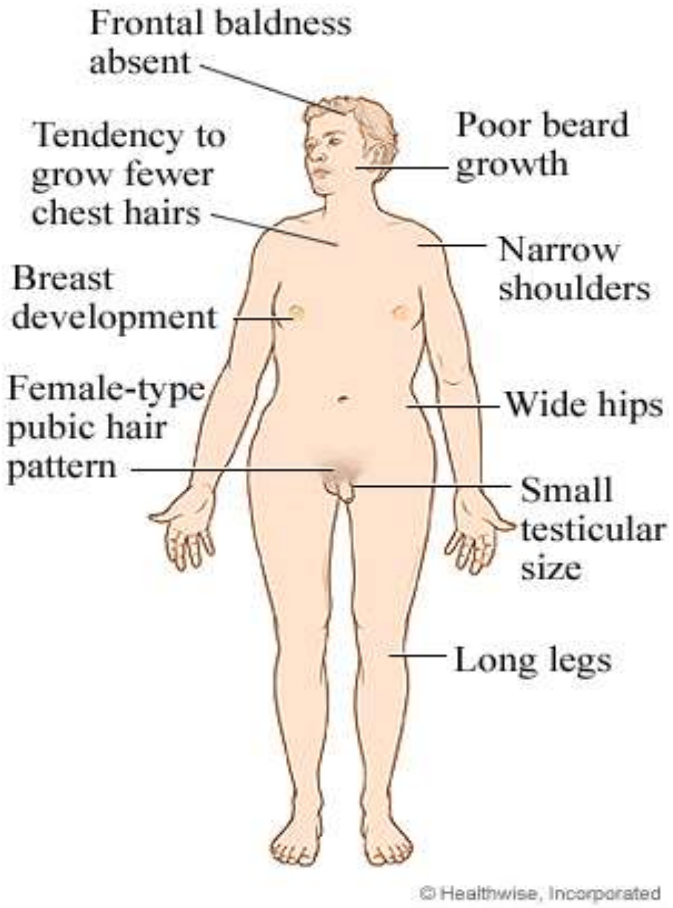
is caused by meiotic nondisjunction and is a common cause of male hypogonadism. The most common karyotype is 47,XXY. Lab studies show elevated FSH and LH with low levels of testosterone.

Clinical findings include

- Testicular atrophy,
- Infertility due to azoospermia,
- Eunuchoid body habitus,
- High-pitched voice;
- Female distribution of hair; and
- Gynecomastia.

GENETIC DISORDERS

Klinefelter's Syndrome



GENETIC DISORDERS

Turner syndrome is a common cause of female hypogonadism. The most common karyotype is 45,X. The second X chromosome is necessary for oogenesis and normal development of the ovary.

Clinically, patients

- fail to develop secondary sex characteristics and have
- short stature with
- widely spaced nipples.

Other features

- gonadal dysgenesis with atrophic streak ovaries; primary amenorrhea;
- infertility.

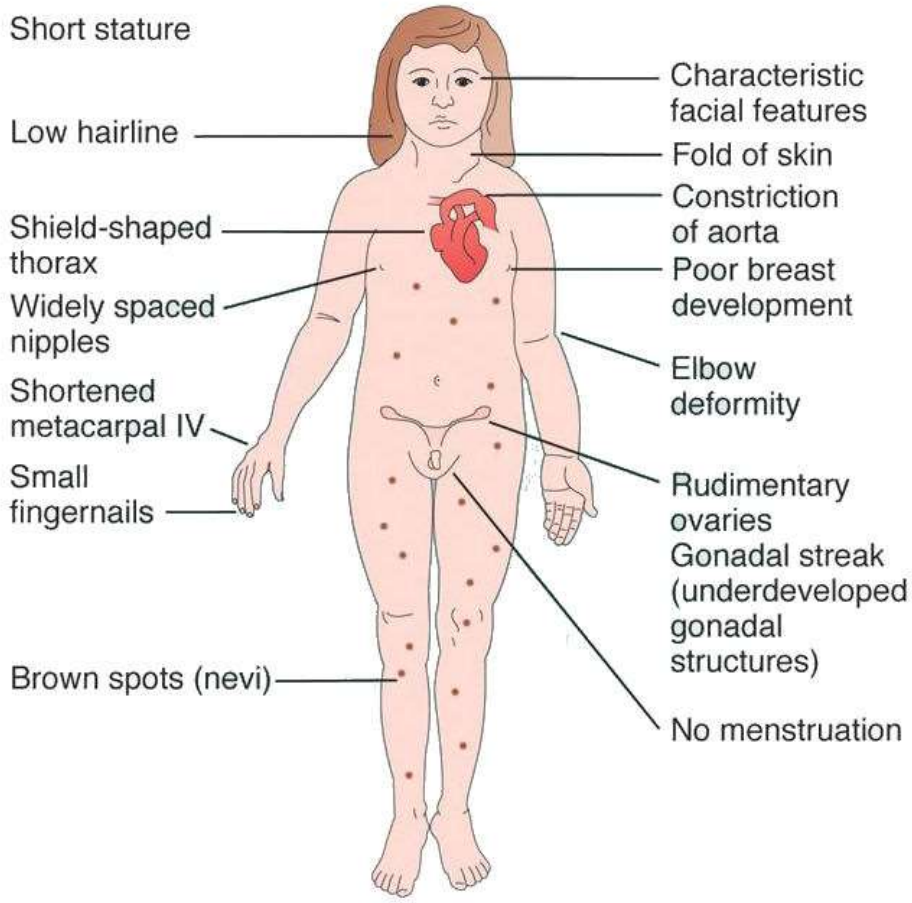
Clinical features involving other organ systems include

- cystic hygroma and webbing of the neck;
- hypothyroidism;
- congenital heart disease (preductal coarctation of the aorta and bicuspid aortic valve); and
- hydrops fetalis.

Females with 45,X/46,XY mosaicism are at risk for gonad blastoma, microdeletions.

GENETIC DISORDERS

Turner syndrome



GENETIC DISORDERS

Determination of sex can be established by a variety of methods that do not necessarily completely agree.

- **Karyotypic** (genetic) sex refers to which sex chromosomes an individual has; the presence of a Y chromosome results in testicular development.
- **Gonadal** sex refers to the presence of ovarian or testicular tissue.
- **Ductal sex** refers to the presence of Müllerian (female: Fallopian tube, uterus, cervix, and upper portion of vagina) or Wolffian (male: epididymis, vas deferens, seminal vesicles, and ejaculatory ducts) duct adult derivatives.

Phenotypic (genital) sex refers to the external appearance of the genitalia. Individuals with **ovotesticular disorder** have both ovarian and testicular tissue, which is an extremely rare condition. The most common karyotype of ovotesticular disorder is 46,XX. The gonadal sex can be either an ovary on one side and testis on the other, or ovotestes, in which there is a gonad with both testicular and ovarian tissue. The ductal sex is often mixed, and the phenotypic sex shows ambiguous genitalia.

The **46,XX DSD category** includes individuals (formerly characterized as female pseudohermaphrodites) with disorders of ovarian development, androgen excess, vaginal atresia, and cloacal exstrophy. The **46,XY category** includes individuals (formerly characterized as male pseudohermaphrodites) with disorders of testicular development, disorders of androgen synthesis, severe hypospadias and cloacal exstrophy.

GENETIC DISORDERS

Mendelian disorders are characterized by single gene mutations. Common types of mutations include point mutations and frameshift mutations.

- **Point mutations** occur with a single nucleotide base substitution, which may produce a variety of effects. The form of point mutation called synonymous mutation (silent mutation) occurs when a base substitution results in a codon that codes for the same amino acid. The form of point mutation called missense mutation occurs when a base substitution results in a new codon and a change in amino acids. The form of point mutation called a nonsense mutation occurs when a base substitution produces a stop codon and therefore produces a truncated protein.
- **Frameshift mutations** occur when insertion or deletion of bases leads to a shift in the reading frame of the gene.

GENETIC DISORDERS

The location of a mutation will alter its potential effects. Mutations involving coding regions of DNA may result in abnormal amino acid sequences; decreased production of the protein; truncated or abnormally folded protein; or altered or lost function of the protein. Mutations of promoter or enhancer regions may interfere with transcription factors, resulting in decreased transcription of the gene.

Patterns of inheritance for genetic diseases show wide variation, and the genetic pattern of a disease may be classified as autosomal dominant; autosomal recessive;

- X-linked recessive; X-linked dominant; triplet repeat mutations; genomic imprinting; mitochondrial; or multifactorial.

GENETIC DISORDERS

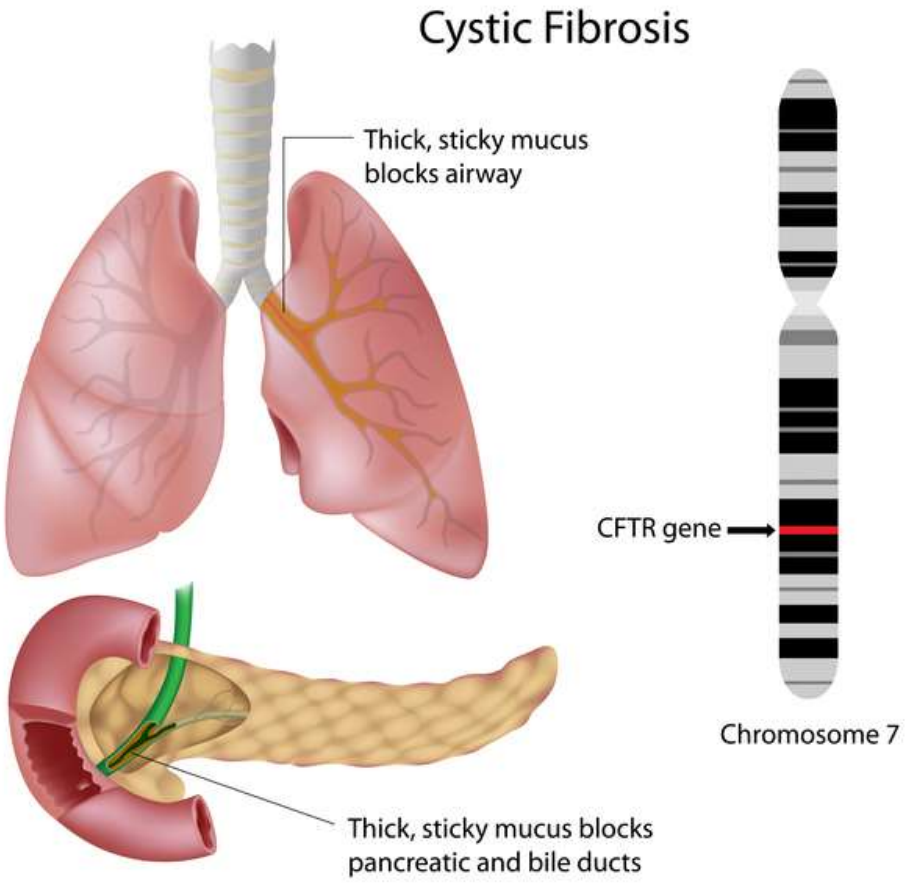
Cystic fibrosis (CF)

Is the most common lethal genetic disorder in Caucasians. It is due to mutation of the chloride channel protein, cystic fibrosis transmembrane conductance regulator (CFTR), whose *CFTR* gene is located on chromosome 7 and most commonly has been damaged by a deletion of the amino acid phenylalanine at position 508 (ΔF508). The defective chloride channel protein leads to abnormally thick viscous mucus, which obstructs the ducts of exocrine organs.

- Diagnosis can be established with a sweat test (elevated NaCl) or DNA probes.
- Due to improved therapies, some patients live into their forties, but with this increase in longevity there has been an increase in liver disease. Patients succumb to pulmonary disease.
- The 3 most common pulmonary infections are *S aureus, H. influenzae*, and *P. aeruginosa*. Lung transplantation is a treatment option. Patients infected with *Burkholderia Cepacia* complex and who undergo transplant have a worse prognosis.

GENETIC DISORDERS

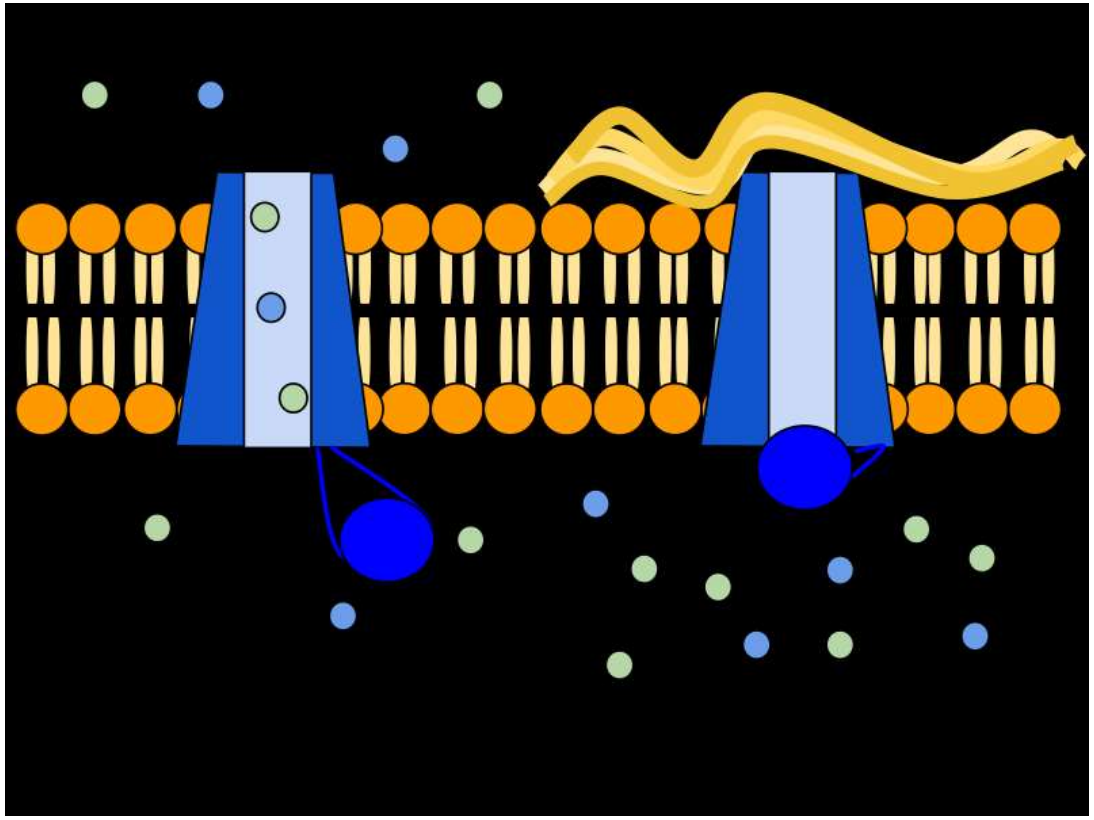
Cystic Fibrosis



GENETIC DISORDERS

Cystic Fibrosis

Chloride Channel malfunction



GENETIC DISORDERS

Phenylketonuria (PKU)

Is due to deficiency of phenylalanine hydroxylase, resulting in toxic levels of phenylalanine and a lack of tyrosine.

Clinically, affected children are normal at birth but, if undiagnosed and untreated, develop intellectual development disorder by age 6 months. The lack of tyrosine causes light-coloured skin and hair, since melanin is a tyrosine derivative.

- Affected children may have a mousy or musty odor to the sweat and urine (secondary to metabolite [phenylacetate] accumulation).
- Screening for PKU is done at birth. Treatment is dietary restriction of phenylalanine, including avoidance of the artificial sweetener aspartame.

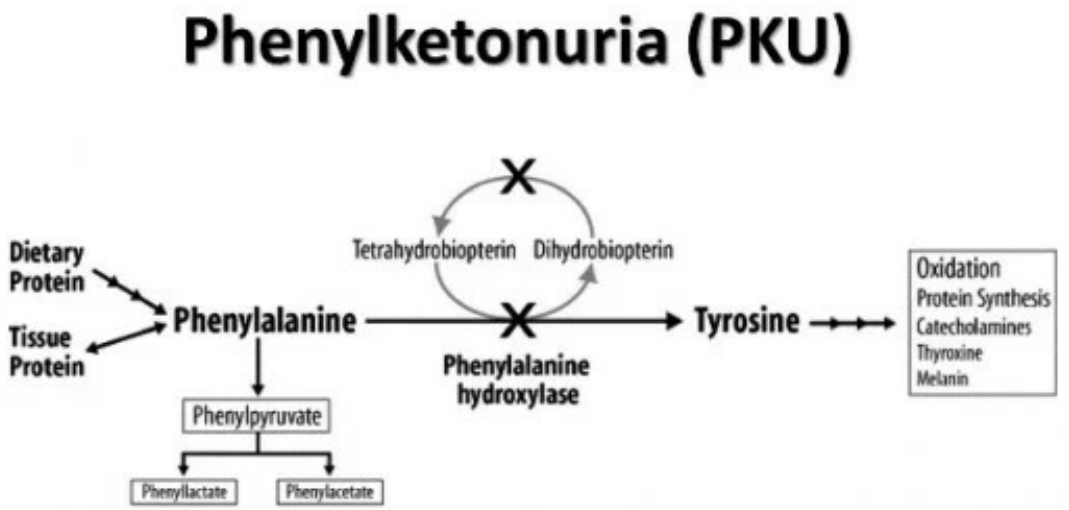
A genetic variant, **benign hyperphenylalaninemia**, has partial enzyme deficiency with mildly increased levels of phenylalanine which are insufficient to cause intellectual disability.

In a minority of cases, an abnormality of the cofactor tetrahydrobiopterin causes a variant that does not respond to dietary restriction.

Transplacental accumulation of phenylalanine can cause problems with fetal development in cases of maternal PKU. Prevention requires maternal dietary restriction.

GENETIC DISORDERS

Phenylketonuria



GENETIC DISORDERS

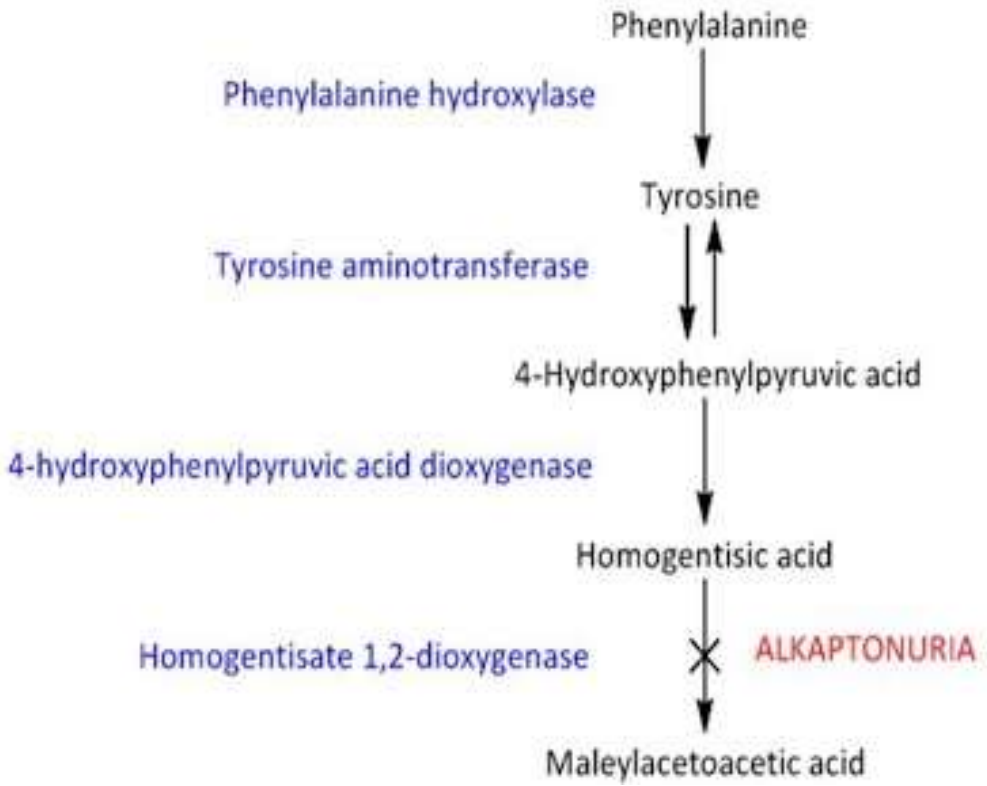
Alkaptonuria (ochronosis) occurs when deficiency of homogentisic acid oxidase results in the accumulation of homogentisic acid. The homogentisic acid has an affinity for connective tissues (especially cartilage), resulting in a black discoloration (because of oxidation of homogentisic acid).

Clinical features include

- urine that is initially pale yellow but turns black upon standing,
- black-stained cartilage, which causes discoloration of the nose and ears.
- Alkaptonuria also predisposes for early onset of degenerative arthritis

GENETIC DISORDERS

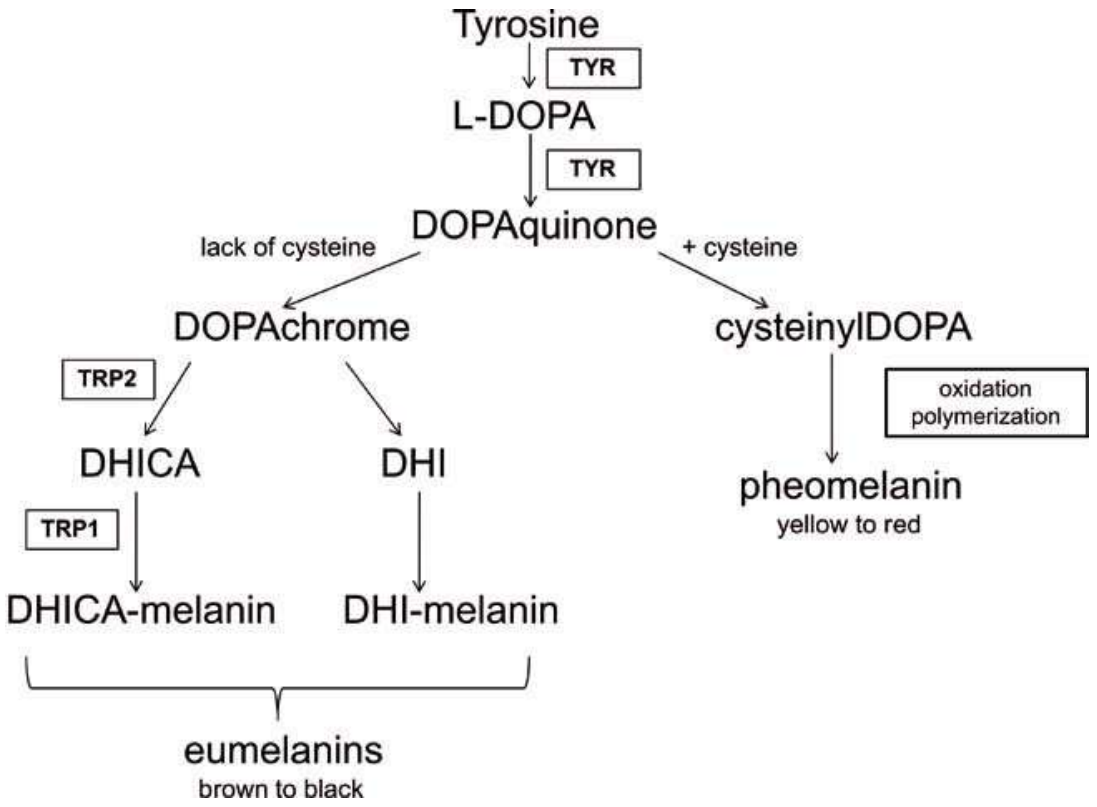
Alkaptonuria



GENETIC DISORDERS

Albinism is caused by a lack of the enzyme tyrosinase needed for melanin production.

Affected individuals show deficiency of melanin pigmentation in the skin, hair follicles, and eyes (oculocutaneous albinism), with resulting increased risk of basal cell and squamous cell carcinomas.



GENETIC DISORDERS

Albinism

GENETIC DISORDERS

The **glycogen storage diseases** are a group of rare diseases that have in common a deficiency of one of the enzymes necessary for the metabolism of glycogen, which results in the accumulation of glycogen in the liver, heart, and skeletal muscle.

- **Type I (von Gierke disease)** is due to a deficiency of *glucose-6-phosphatase*, and is characterized clinically by hepatomegaly and hypoglycaemia.
- **Type II (Pompe disease)** is due to a deficiency of *lysosomal* α*-1,4-glucosidase (acid maltase)*, and is characterized clinically by hepatomegaly, skeletal muscle hypotonia, cardiomegaly, and death from cardiac failure by age 2 years.
- **Type V (McArdle syndrome)** is due to a deficiency of *muscle glycogen phosphorylase and* is characterized clinically by exercise-induced muscle cramps.

GENETIC DISORDERS

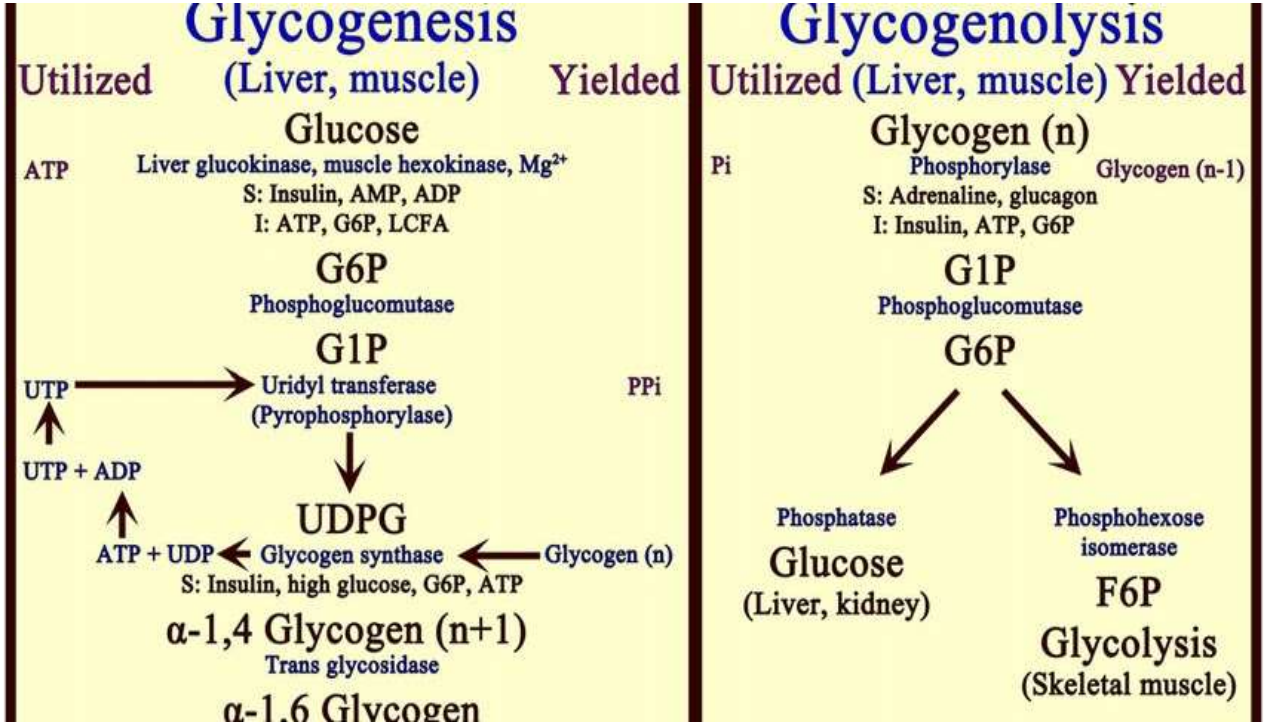
Glycogen storage Disorder

Type	Affected tissue	Enzyme defect	Clinical features	Tissue needed for diagnosis*	Outcome
1 (Von Gierke's disease)	Liver, intestine, kidney	Glucose-6-phosphatase	Hepatomegaly, hypoglycaemia, stunted growth, obesity, hypotonia	Liver	If patients survive initial hypoglycaemia, prognosis is good; hyperuricaemia is a late complication
2 (Pompe's disease)	Liver, muscle, heart	Lysosomal α-glucosidase	Heart failure, cardiomyopathy	Leukocytes, liver, muscle	Death in first 6 months; juvenile and adult variants seen
3 (Forbes' disease)	Liver, muscle (abnormal glycogen structure)	Amylo-1, 6-glucosidase	Like Type I	Leukocytes, liver, muscle	Good prognosis
4 (Andersen disease)	Liver (abnormal glycogen structure)	1,4-α-glucan branching enzyme	Failure to thrive, hepatomegaly, cirrhosis and its complications	Leukocytosis, liver, muscle	Death in first 3 years
5 (McArdle disease)	Muscle only	Phosphorylase	Muscle cramps and myoglobinuria after exercise (in adults)	Muscle	Normal lifespan; exercise must be avoided

*tissue obtained is used for the biochemical assay of the enzyme.

GENETIC DISORDERS

Glycogen storage Disorder



GENETIC DISORDERS

Tay-Sachs disease

is due to a deficiency of Hexosaminidase A (due to mutation of *HEXA* gene on chromosome 15), which leads to the accumulation of GM2 ganglioside in the lysosomes of the CNS and retina. Tay-Sachs is common in

Ashkenazi Jews (1 in 30 carrier rate).

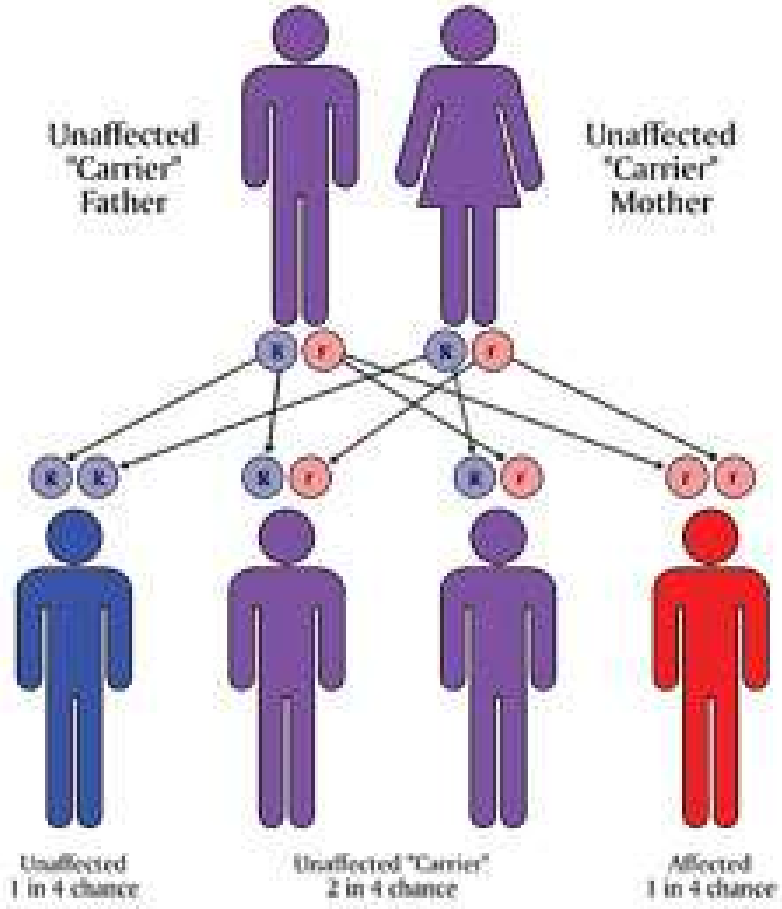
The distribution of disease involves the retina (cherry-red spot due to accentuation of the macula) and central nervous system (dilated neurons with cytoplasmic vacuoles). Affected children are normal at birth, but by 6 months show onset of symptoms (progressive mental deterioration and motor incoordination) that progress to death by age 2–3 years.

Electron microscopy shows distended lysosomes with whorled membranes; the diagnosis can also be established with enzyme assays and DNA probes.

GENETIC DISORDERS

Tay Sachs Disease

Tay–Sachs disease is caused by insufficient activity of the enzyme hexosaminidase A. Hexosaminidase A is a vital hydrolytic enzyme, found in the lysosomes, that breaks down sphingolipids. When hexosaminidase A is no longer functioning properly, the lipids accumulate in the brain and interfere with normal biological processes. Hexosaminidase A specifically breaks down fatty acid derivatives called gangliosides; these are made and biodegraded rapidly in early life as the brain develops. Patients with and carriers of Tay–Sachs can be identified by a simple blood test that measures hexosaminidase A activity.



GENETIC DISORDERS

Niemann-Pick disease

Is caused by a deficiency of sphingomyelinase, which leads to the accumulation of sphingomyelin within the lysosomes of the CNS and reticuloendothelial system (monocytes and macrophages located in reticular connective tissue). Niemann-Pick is common in Ashkenazi Jews (note similarity to Tay-Sachs disease).

The distribution of disease depends on the form of disease, but can involve the retina (cherry-red spot, note similarity to Tay-Sachs disease); central nervous system (distended neurons with a foamy cytoplasmic vacuolization, note similarity to Tay-Sachs disease); and reticuloendothelial system (hepatosplenomegaly, lymphadenopathy, and bone marrow involvement; note difference from Tay- Sachs disease).

In Niemann-Pick **types A and B**, there is a mutation affecting an enzyme that metabolizes lipids; organomegaly occurs, and with type A, there is severe neurologic damage. In **type C**—the most common form—a defect in cholesterol transport causes ataxia, dysarthria, and learning difficulties. All forms are lethal, usually before adulthood.

*Reticular Connective Tissue. Reticular tissue, a type of loose connective tissue in which reticular fibers are the most prominent fibrous component, forms the supporting framework of the lymphoid organs (lymph nodes, spleen, tonsils), bone marrow and liver.

GENETIC DISORDERS

Gaucher disease

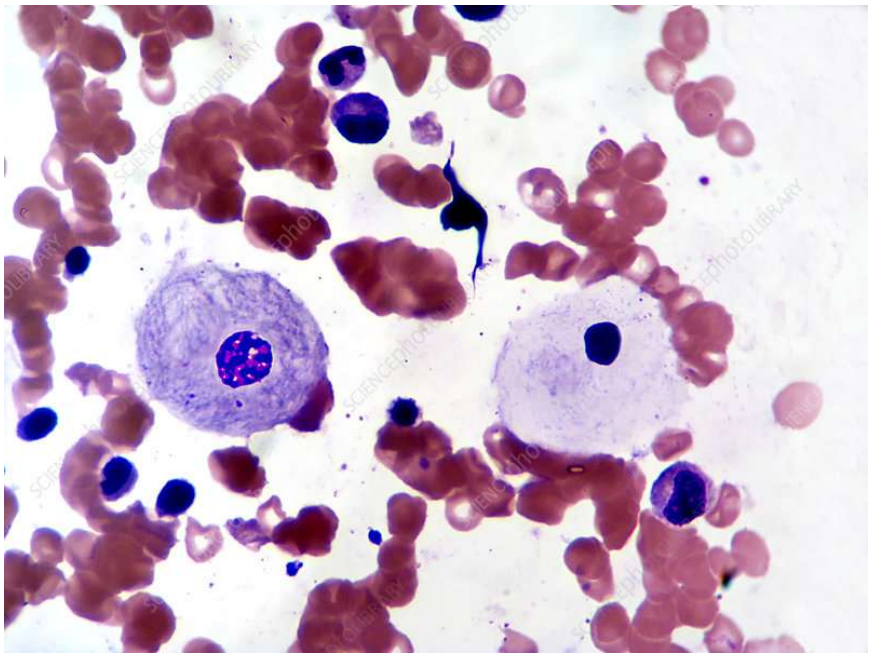
Is the most common lysosomal storage disorder. Deficiency of Glucocerebrosidase leads to the accumulation of glucocerebroside, predominately in the lysosomes of the reticuloendothelial system (monocytes and macrophages located in reticular connective tissue).

Type I represents 99% of cases and presents in adulthood with hepatosplenomegaly; thrombocytopenia/pancytopenia secondary to hypersplenism; lymphadenopathy; and bone marrow involvement that may lead to bone pain, deformities, and fractures. Central nervous system manifestations occur in **types II and III**.

The characteristic **Gaucher cells** are enlarged macrophages with a fibrillary (tissue paper–like) cytoplasm. Diagnosis can be established with biochemical enzyme assay of glucocerebrosidase activity.

Acute Neuronopathic Gaucher Disease (Type 2)

- Strabismus
- Retroflexion of the neck
- Cortical thumbs
- Visceromegaly
- Failure to thrive
- Cachexia



GENETIC DISORDERS

Gaucher's disease

GENETIC DISORDERS

Mucopolysaccharidosis (MPS)

Is a group of lysosomal storage disorders characterized by deficiencies in the lysosomal enzymes required for the degradation of mucopolysaccharides (glycosaminoglycans).

Clinical features:

Intellectual disability;

cloudy cornea;

hepatosplenomegaly;

skeletal deformities and

coarse facial features;

joint abnormalities;

and cardiac lesions.

MPS I (Hurler syndrome) is the severe form and is due to deficiency of α-L-iduronidase.

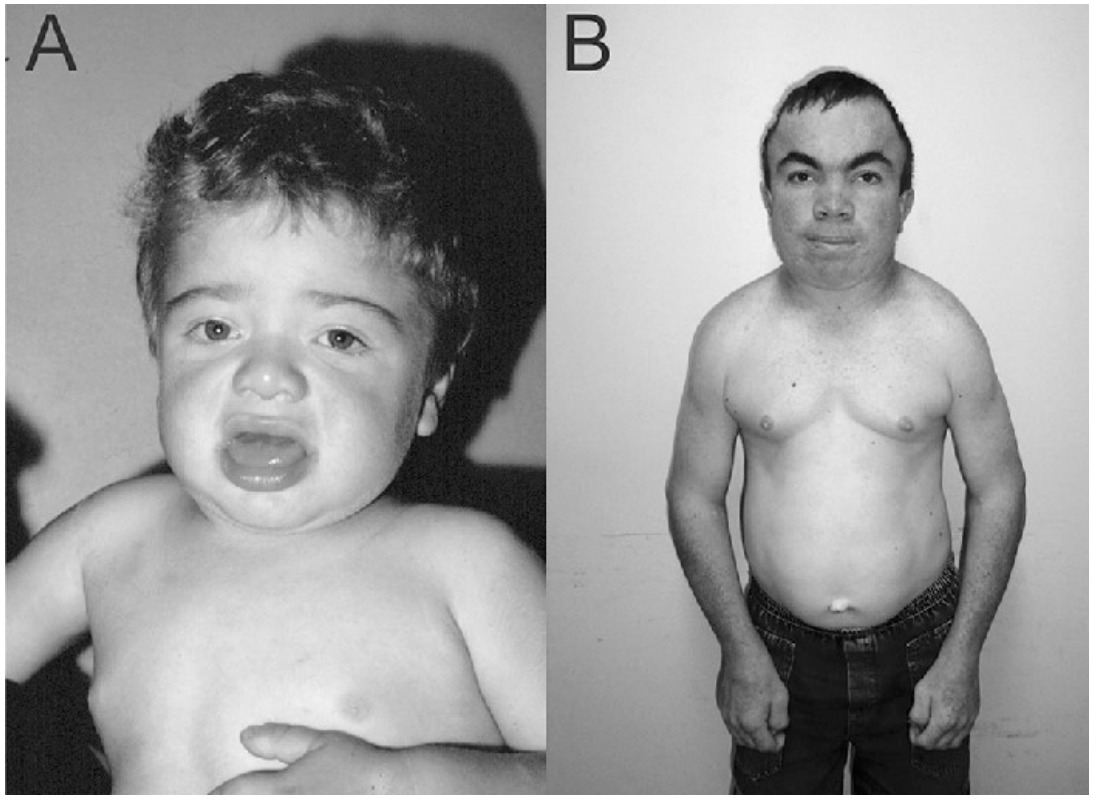
MPS II (Hunter syndrome) is a milder form; it shows X-linked recessive inheritance and is due to a deficiency of L-iduronate sulfatase.

GENETIC DISORDERS

Hurler Syndrome

GENETIC DISORDERS

Hurler Syndrome



GENETIC DISORDERS

Familial hypercholesterolemia is the most common inherited disorder (incidence

1 in 500) and is due to a mutation in the low-density lipoprotein (LDL) receptor gene

(LDLR) on chromosome 19. The mutations in the LDL receptor cause increased levels of circulating cholesterol, loss of feedback inhibition of HMG-coenzyme A (HMG-CoA) reductase, and increased phagocytosis of LDL by macrophages.

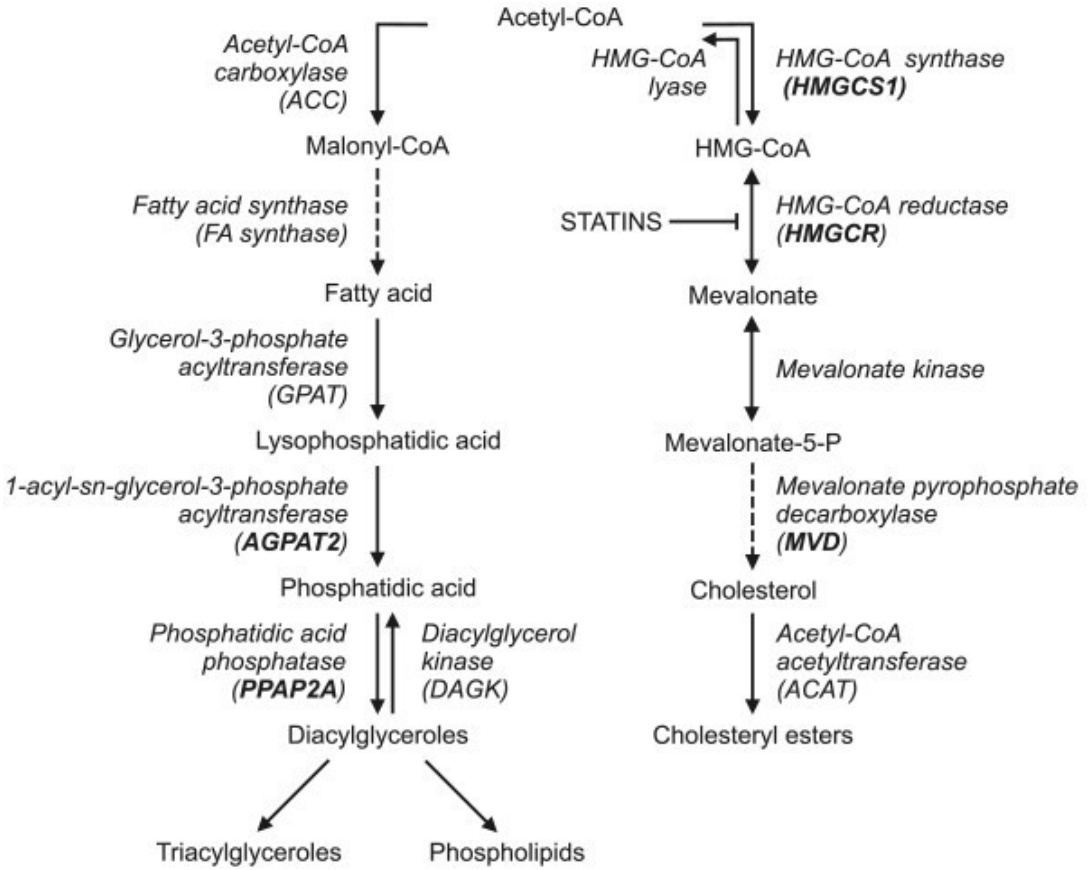
There are 5 major **classes of mutation**.

- **Class I:** no LDL receptor synthesis
- **Class II:** defect in transport out of the endoplasmic reticulum
- **Class III:** defect in LDL receptor binding
- **Class IV:** defect in ability to internalize bound LDL
- **Class V:** defect in the recycling of the LDL receptor

Clinical features include elevated serum cholesterol (heterozygotes have elevations of 2–3 times the normal level and homozygotes have elevations of 5–6 times the normal level), skin xanthomas (collections of lipid-laden macrophages), xanthelasma around the eyes, and premature atherosclerosis (homozygotes often develop myocardial infarctions in late teens and twenties).

GENETIC IDORDERS

Familial Hypercholesteremia



GENETIC DISORDERS

Marfan syndrome is due to a mutation of the **Fibrillin** gene (*FBN1*) on chromosome 15q21. Fibrillin is a glycoprotein that functions as a scaffold for the alignment of elastic fibers.

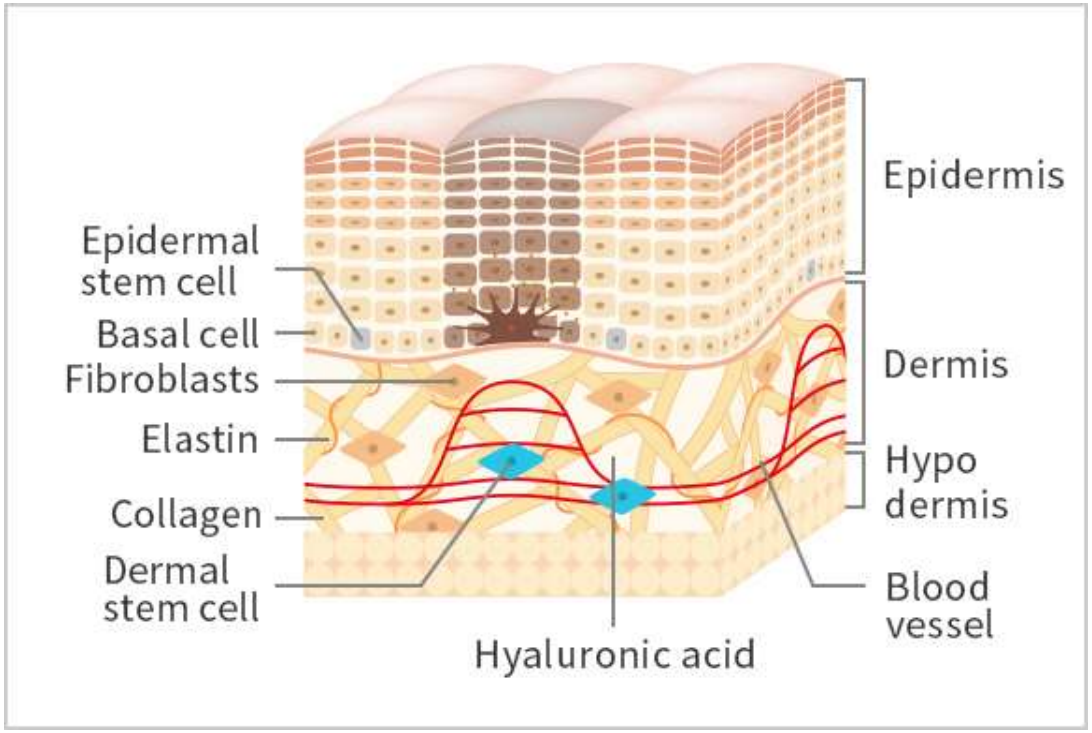
Clinical features include

- skeletal changes (tall, thin build with long extremities,
- hyperextensible joints,
- pectus excavatum [inwardly depressed sternum],
- and pectus carinatum [pigeon breast])
- and abnormal eyes (ectopia lentis, characterize by bilateral subluxation of the lens).
- The cardiovascular system is also particularly vulnerable; it may show cystic medial degeneration of the media of elastic arteries with a loss of elastic fibers and smooth muscle cells with increased risk of dissecting aortic aneurysm (a major cause of death), dilatation of the aortic ring potentially leading to aortic valve insufficiency, and/or mitral valve prolapse.

Genetic Disorder

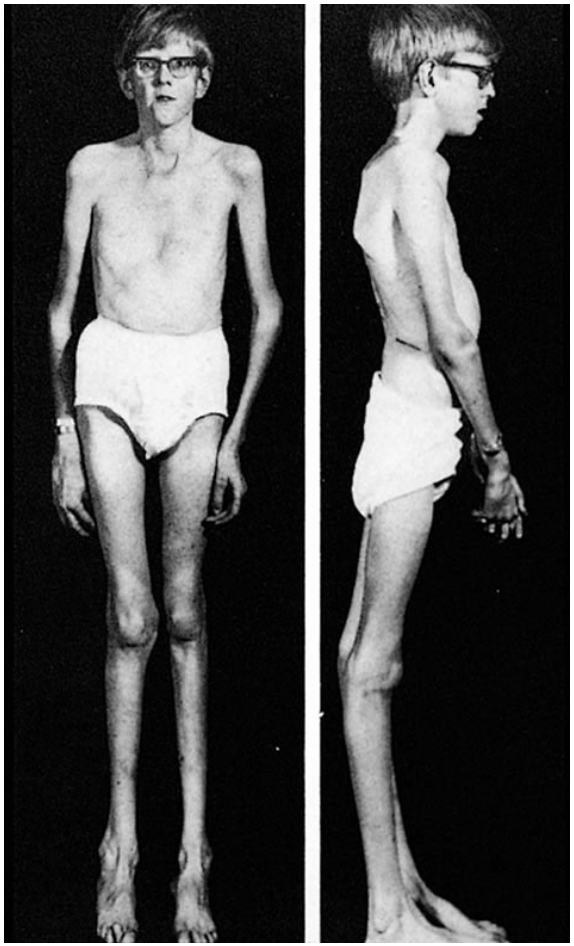
Marfan Syndrome

Elastin



GENETIC DISORDER

Marfan Syndrome



GENETIC DISORDERS

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue diseases that have in common a defect in collagen structure or synthesis.

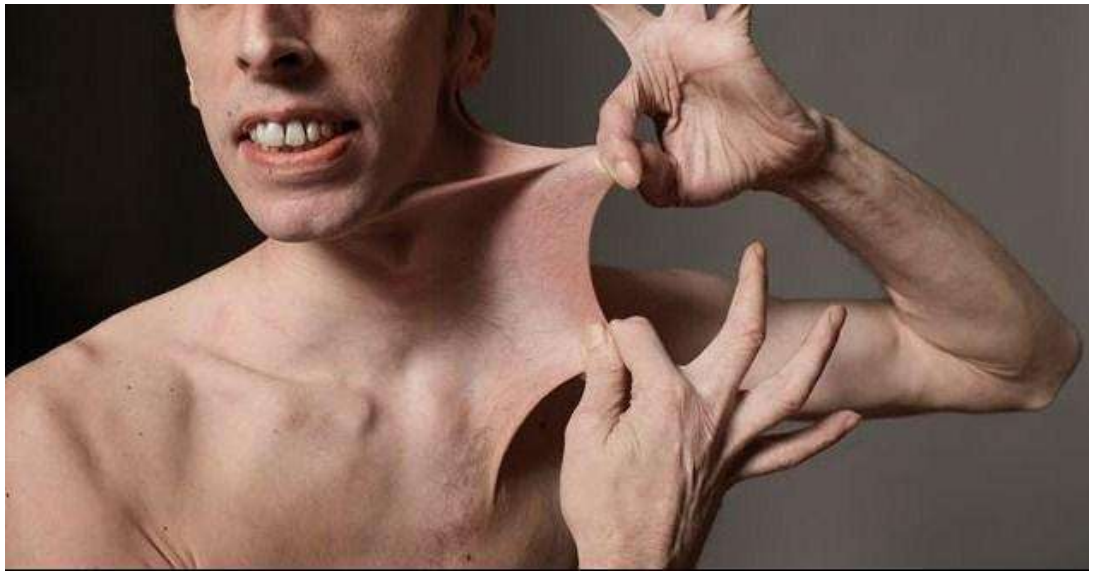
Clinically, the disease causes hyperextensible skin that is easily traumatized and hyperextensible joints secondary to effects on the joints and adjacent ligaments.

There are several variants with different modes of inheritance.

- **Kyphoscoliosis EDS**: Autosomal recessive form
- **Vascular variant EDS**: Autosomal dominant form that causes rupture of vessels and bowel wall
- **Classical EDS**: Autosomal dominant form that causes a type V collagen defect; patients have a normal lifespan

GENETIC DISORDER

Ehlers Danlos Syndrome



GENETIC DISORDERS

Ehlers Danlos Syndrome

Villefranche classification	Berlin classification	Protein abnormality	Gene abnormality
Classical	EDS type I/II	Type V collagen	COL5A1, COL5A2
Hypermobility	EDS type III	Unknown	Unknown
Vascular	EDS type IV	Type III collagen	COL3A1
Kyphoscoliosis	EDS type VI	Lysyl hydroxylase deficiency	PLOD1
Arthrochalasia	EDS type VIIA/B	Type I collagen	COL1A1, COL2A2
Dermatosparaxis	EDS type VIIC	N-proteinase	ADAMST2

EDS: Ehlers-Danlos syndrome

GENETIC DISORDERS

Neurofibromatosis

Type 1 (**von Recklinghausen disease**) neurofibromatosis (90% of cases) has an incidence of 1 in 3,000. The condition is due to a mutation of the tumor suppressor gene *NF1* located on chromosome 17 (17q11.2). The normal gene product (neurofibromin) inhibits p21 ras oncoprotein.

• Affected individuals characteristically have multiple neurofibromas and benign tumors of peripheral nerves that are often numerous and may be disfiguring. The plexiform variant of the neurofibromas is diagnostic.

• Rarely (3%), malignant transformation of a neurofibroma may occur.

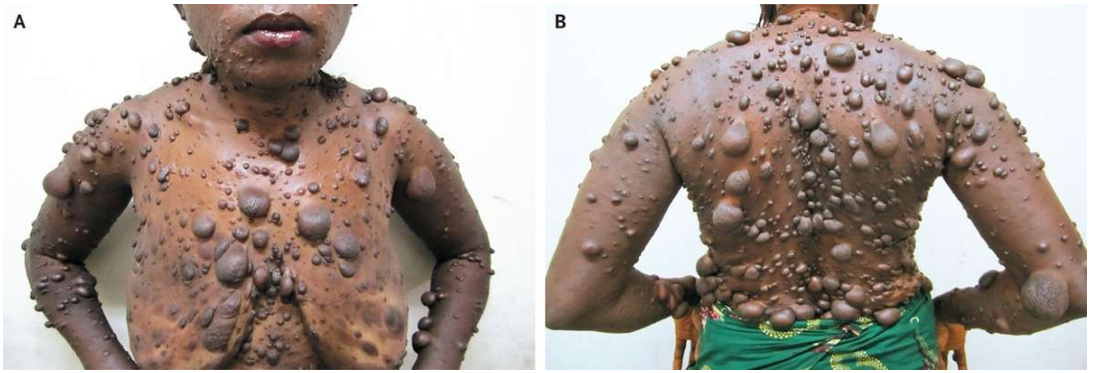
• Other clinical features include pigmented skin lesions (6 or more “cafeau- lait spots” that are light brown macules (Macules: Small circumscribed changes in the color of skin that are neither raised (elevated) nor depressed.)usually located over nerves);

Pigmented iris hamartomas (Lisch nodules);

And increased risk of meningiomas and pheochromocytoma, an adrenal tumor that also occurs with von Hippel-Lindau disease and MEN 2.

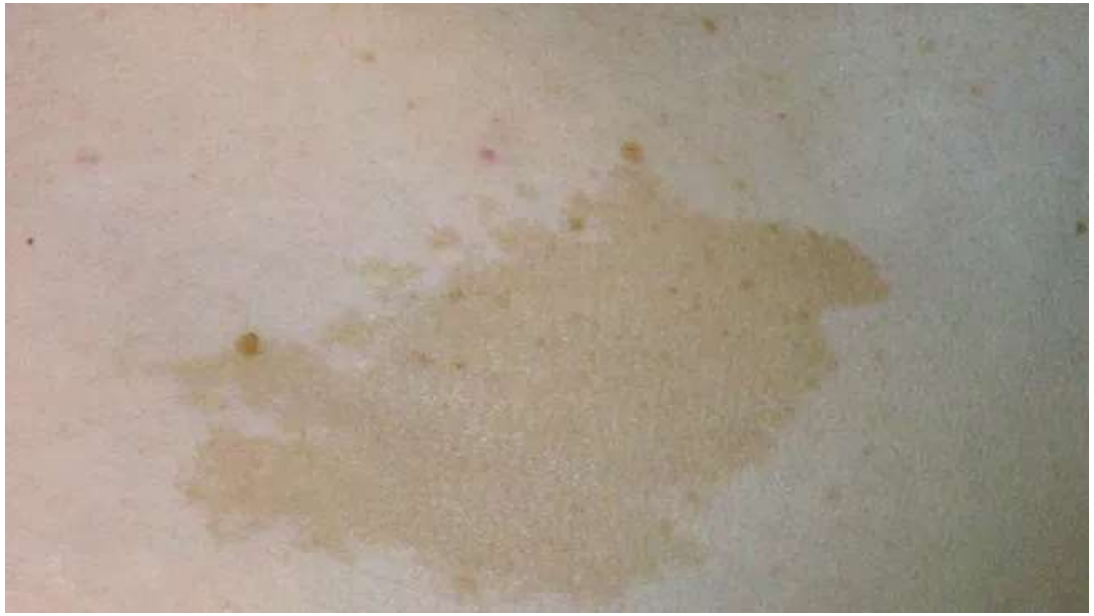
GENETIC DISORDER

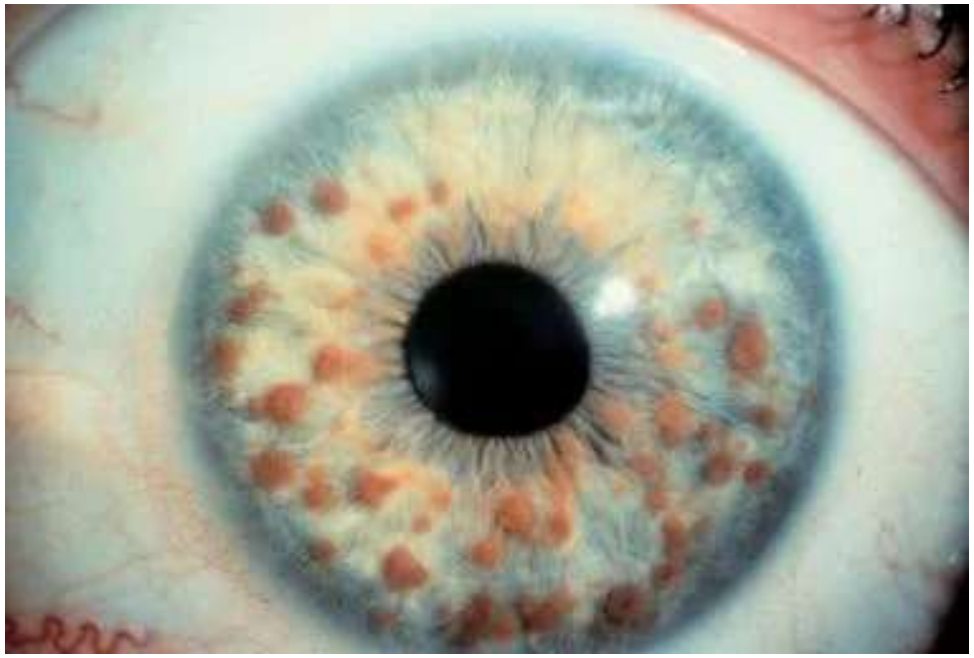
Neurofibromatosis

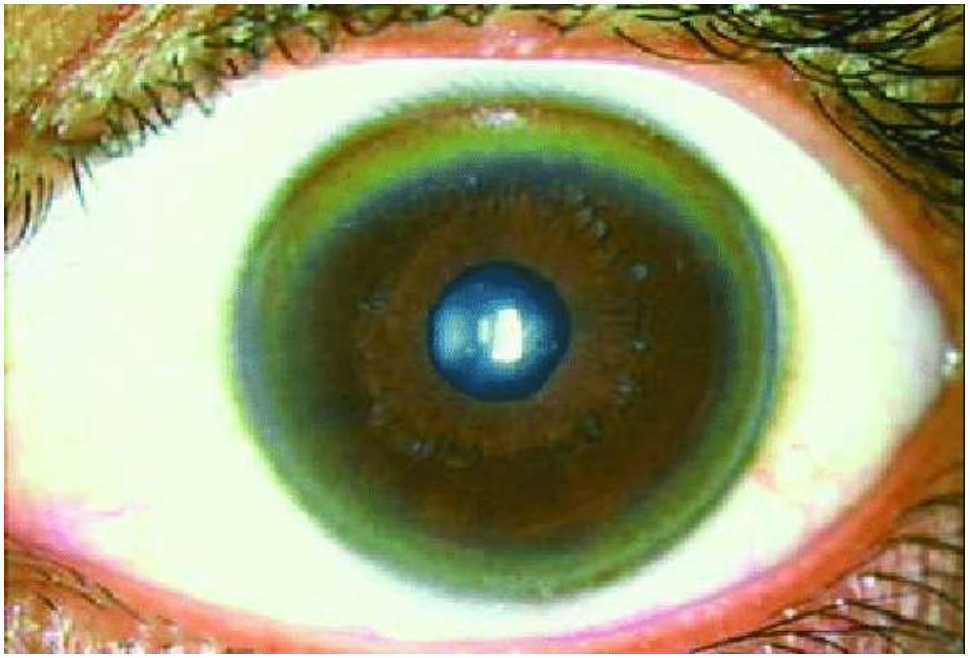


GENETIC DISORDERS

Café E Lieu spot







GENETIC DISORDER

Lisch nodule

GENETIC DISORDERS

Arcus senilis

GENETIC DISORDERS

Type 2 (**bilateral acoustic**) neurofibromatosis (10% of cases) has an incidence of 1 in 45,000.

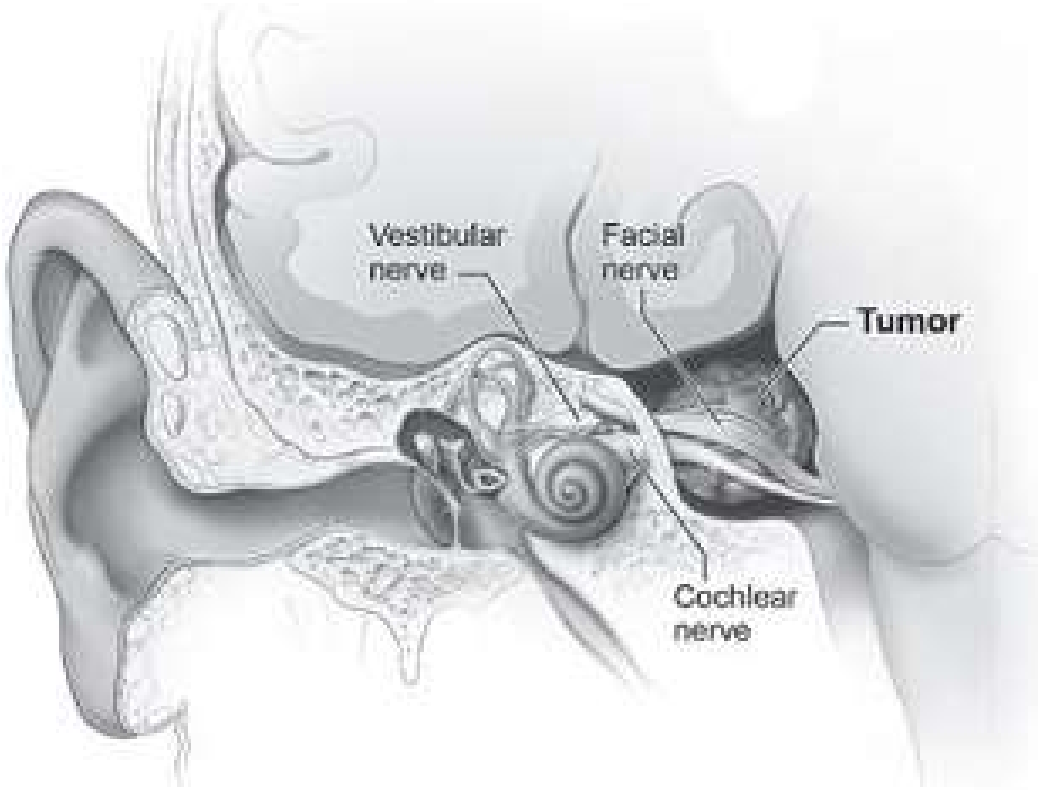
- There is a mutated Tumor suppressor gene *NF-2* (22q12.2) on chromosome 22.
- The normal gene product (merlin) is a critical regulator of contact-dependent inhibition of proliferation.

Clinical features include

- vestibular schwannomas (acoustic neuromas), and
- increased risk of meningioma and ependymomas.

GENETIC DISORDER

Vestibular Schwannoma



GENETIC DISORDERS

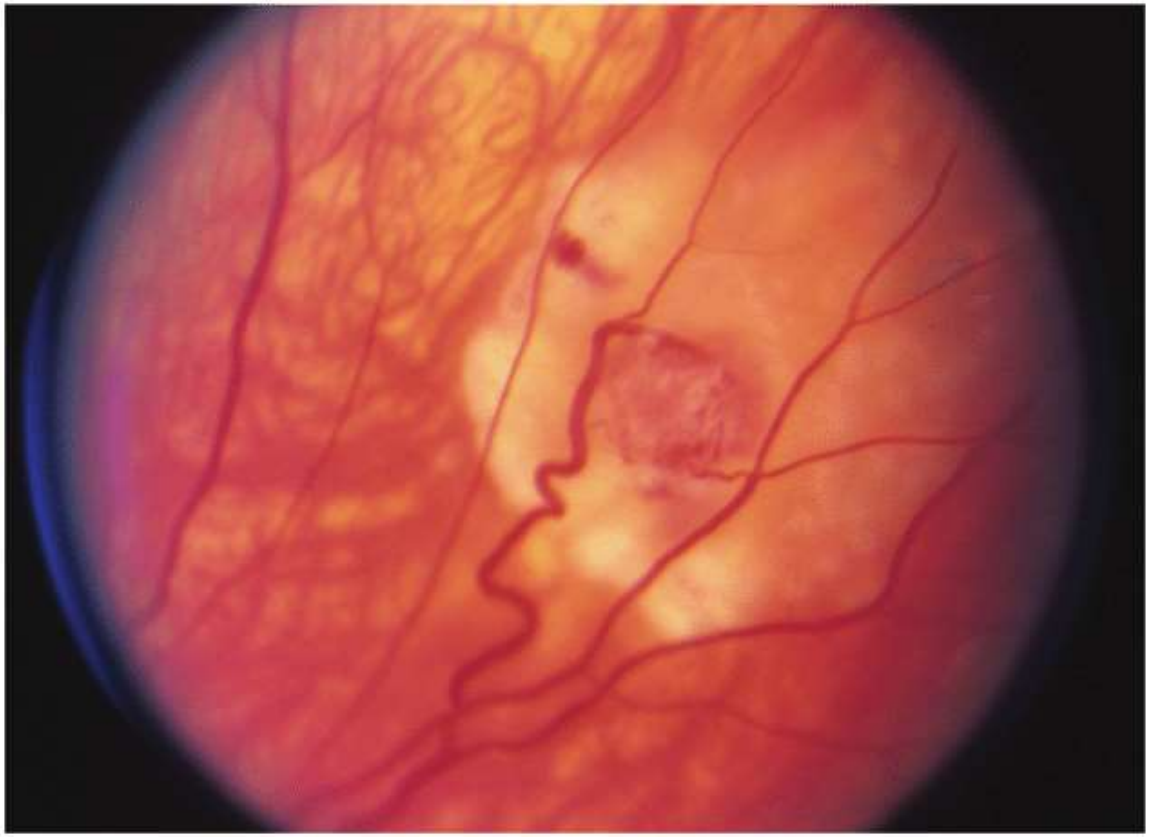
Von Hippel-Lindau disease is due to a mutation of the Tumor suppressor gene *VHL* on chromosome 3p (3p26-p25). The normal gene product's main action is to tag proteins (e.g., hypoxia inducible factor 1a [a transcription factor that induces the expression of angiogenesis factors]) with ubiquitin for degradation.

Clinical manifestations can include retinal hemangioblastoma (von Hippel Tumor); hemangioblastomas of the cerebellum, brain stem, and spinal cord (Lindau Tumor); cysts of the liver, pancreas, and kidneys; and multiple bilateral renal cell carcinomas.

GNETIC DISORDER

Von hippel Lindau Disease

Retinal Hemangioblastoma



GENETIC DISORDERS

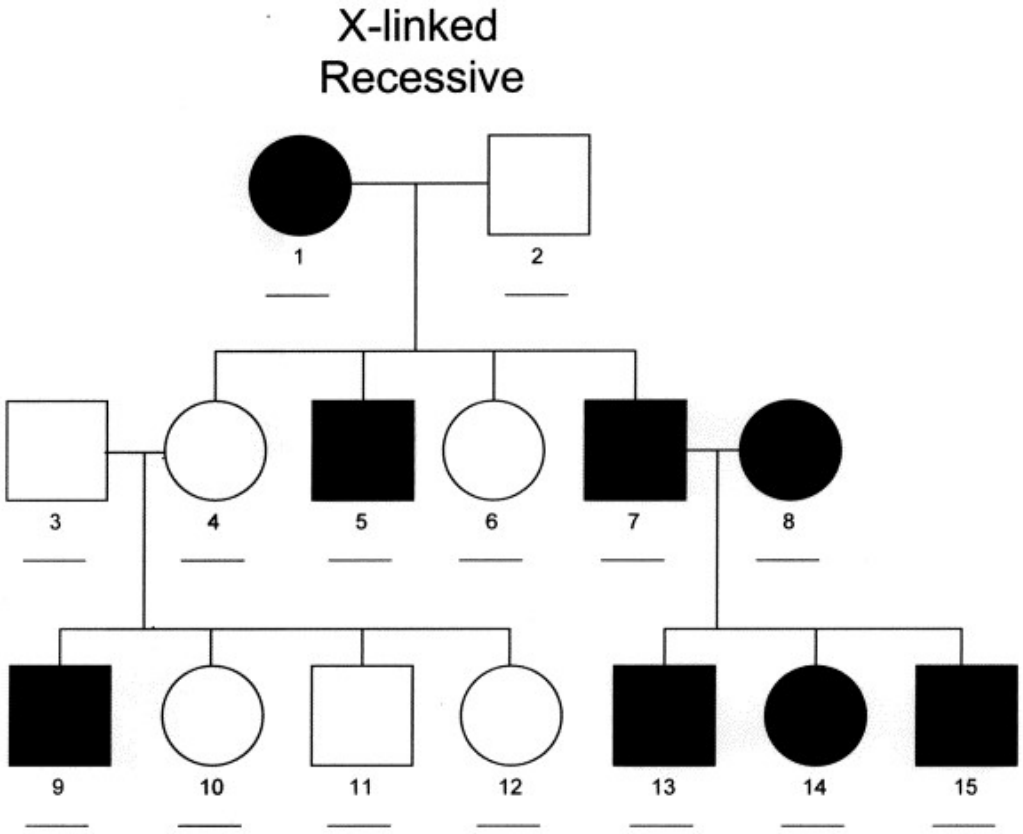
X-LINKED RECESSIVE CONDITIONS

In **X-linked recessive conditions**, males with a mutant recessive gene on the X chromosome have the condition, while daughters of affected males are obligate carriers, who in many situations are asymptomatic.

- Sons of affected males do not carry the mutation.
- Daughters of carrier females may be either normal or carriers.
- Sons of carrier females may be affected or normal (because males are hemizygous for the X chromosome).

GENETIC DISORDER

X linked Recessive

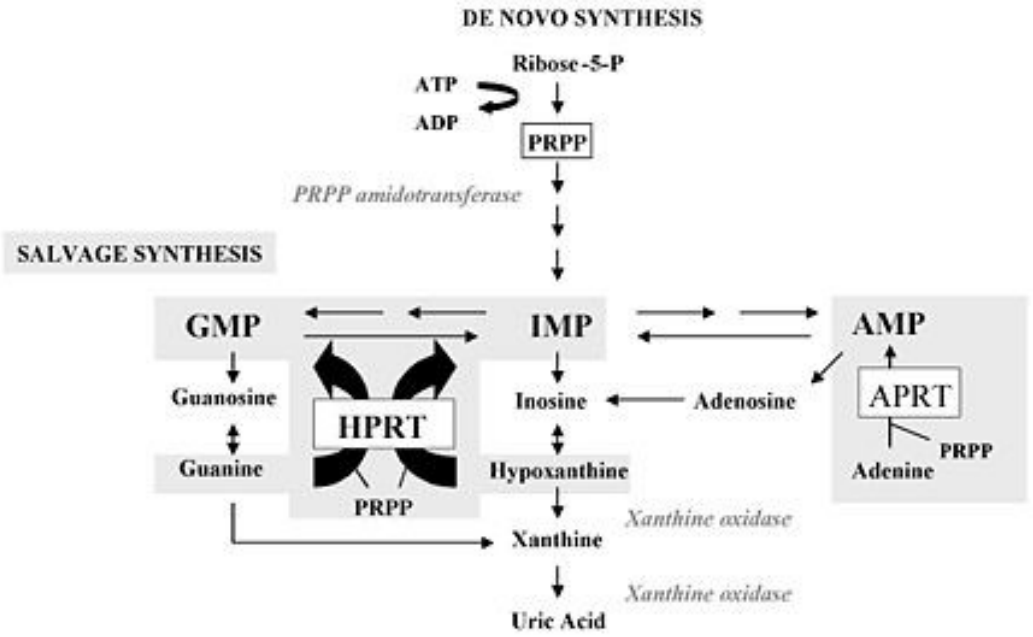


GENETIC DISORDERS

Lesch-Nyhan syndrome results from deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT), which impairs salvaging of the purines hypoxanthine and guanine. Clinical features include intellectual disability, hyperuricemia, and self-mutilation.

GENETIC DISORDER

Lesch neyhan syndrome



GENETIC DISORDERS

Testicular feminization is an androgen insensitivity that causes failure of normal masculinization of external genitalia of XY males.

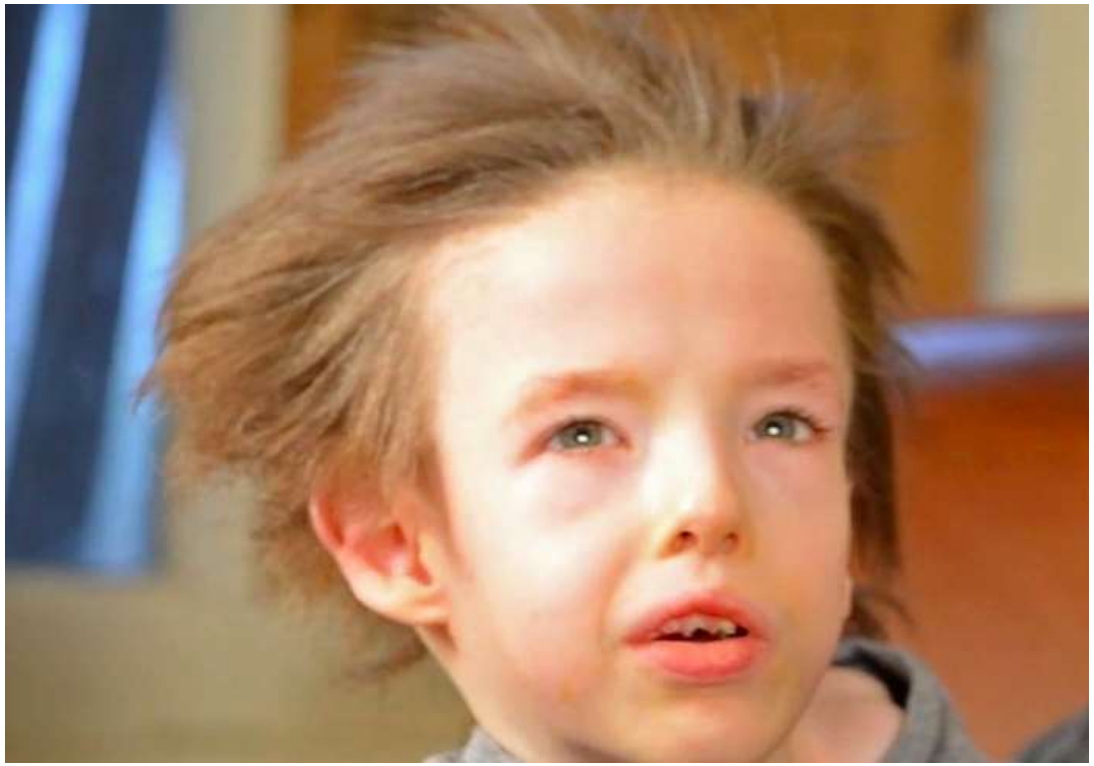
Androgen insensitivity (testicular feminization) syndrome is a rare inherited form of male pseudo hermaphroditism that occurs in phenotypically normal women with adequate breast development, normal external genitalia, a vagina of variable depth, absent uterus, and sparse or absent pubic hair and axillary hair. These patients have male karyotype (XY) and negative sex chromatin. The gonad (undescended testis) may be intraabdominal, inguinal, or labia.

GENETIC DISORDERS

In **Bruton agammaglobulinemia**, defective Bruton tyrosine kinase (*Btk*) at band Xq21.3 causes complete failure of immunoglobulin production characterized clinically by complete absence of antibodies in serum and recurrent bacterial infections.

GENETIC DISORDERS

In **Menkes disease**, a mutation of the *ATP7A* gene impairs copper distribution. Infants show failure to thrive, and death occurs in the first decade.



GENETIC DISORDERS

X-LINKED DOMINANT CONDITIONS

X-linked dominant conditions are like X-linked recessive, but both males and females show disease. An example is

1. Alport syndrome, which is a hereditary glomerulonephritis with nerve deafness. Alport syndrome can also be inherited in other patterns.
2. Vitamin Dependent rickets

GENETIC DISORDERS

TRIPLET REPEAT MUTATIONS

Fragile X syndrome is due to triplet nucleotide repeat mutations, so that the nucleotide sequence CGG repeats typically hundreds to thousands of times. The mutation occurs in the *FMR-1* gene (fragile X mental retardation-1) on the X chromosome (Xq27.3).

Disease behaves as an X-linked dominant disease that causes intellectual disability in all affected males and 50% of female carriers.

The characteristic phenotype includes

1. Elongated face with a large jaw,
2. large everted ears, and
3. Macroorchidism.

The condition can be diagnosed with DNA probe analysis.

GENETIC DISORDERS

Fragile X Syndrome

SYMPTOMS

- Behavioral aspects
- Physical features
  - Large, protruding ears
  - Long face
  - High-arched palate
  - Hyperextensible finger joints
  - Double-jointed thumbs
  - Flat feet
  - Soft skin
  - Postpubescent macroorchidism
  - Hypotonia
- Neurological

GENETIC DISORDERS

Huntington disease is due to a triplet repeat mutation (CAG) of the *HTT* gene that produces an abnormal protein (huntingtin), which is neurotoxic and causes atrophy of the caudate nucleus. Huntington disease has an early onset (age range: 20–50 years) of progressive dementia with choreiform movements.

GENETIC DISORDERS

GENOMIC IMPRINTING

Genomic imprinting refers to differential expression of genes based on chromosomal inheritance from maternal versus paternal origin.

In **Prader-Willi syndrome**, microdeletion on paternal chromosome 15 {del(15)(q11;q13)} causes intellectual disability, obesity, hypogonadism, and hypotonia.

Angelman syndrome, microdeletion on maternal chromosome 15 {del(15) (q11;q13)} causes intellectual disability, seizures, ataxia, and inappropriate laughter.

The inheritance of a deletion on chromosome 15 from a male produces Prader-Willi syndrome, whereas inheritance of the same deletion from a female produces Angelman syndrome

GENETIC DISORDERS

MITOCHONDRIAL DNA DISORDERS

Mitochondrial DNA codes for mitochondrial oxidative phosphorylation enzymes; inheritance is only from mother to child, because only the ovum contributes mitochondria to the zygote. Examples include:

GENETIC DISORDERS

Leber's hereditary optic neuropathy causes loss of retinal cells, which leads to central vision loss.

GENETIC DISORDERS

Myoclonic epilepsy with ragged red fibers (MERRF) is a mitochondrial disorder characterized by epilepsy, ataxia, peripheral neuropathy and deterioration in cognitive ability. Sensorineural hearing loss and ocular dysfunction can also develop. Patients have short stature and cardiomyopathy. On muscle biopsy, ragged red fibers are seen on Gomori trichrome staining due to the accumulation of mitochondria.

GENETIC DISORDERS

MULTIFACTORIAL INHERITANCE

Multifactorial inheritance refers to disease caused by a combination of multiple minor gene mutations and environmental factors. Examples include open neural tube defects and type 2 diabetes mellitus.