INDIVIDUAL GENETIC DISEASES

This pdf was prepared by
Stephan Grundy for
ReviewPathology.com

Note on References

See box to the right for reference notations.

PubMed references usually link to abstracts, which provide useful information. But most abstracts link to a free, full-text article for in-depth reading.

Image references usually link to a whole page of images. The images themselves may be useful, but care must be taken to ensure that they relate to the topic of the text. Images are most valuable as a gateway to publications related to the topic. Clicking on the image will take you to the publication. However, to get the full publication it sometimes may be necessary to copy the url and transfer it to your browser.

- **Reference notations: when references are listed, the following suffixes indicate:**
- **pm = PubMed**
- **w = Wikipedia**
- **i = Images (usually Google images)**
- **rg = ResearchGate**
- **yt = YouTube**
- **sd = Science direct**
- **ow = Other website**
- **Selected text = PubMed, Wikipedia, or images**

Categories of Inherited Diseases

- Autosomal dominant
- Autosomal recessive
- X-linked (dominant and recessive)
- Y-linked
- Multifactorial (polygenic)
- Mitochondrial

Autosomal Dominant Diseases

Examples of autosomal dominant diseases

- Familial hypercholesterolemia
- Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- Hereditary spherocytosis
- Marfan syndrome
- Huntington disease

What is familial hypercholesterolemia (FH)?

- Familial hypercholesterolemia (1w, 2i) is a monogenic elevation of low density lipoprotein (LDL) cholesterol
- Incidence: 1/500
- Inheritance: autosomal dominant (1i, 2i, 3i) (heterozygous FH vs homozygous FH [1i, 2i, 3i, 4i)
- Genetic defect: LDL receptor (1i, 2i, 3i, 4i) gene mutations (1i, 2i, 3i, 4i, 5i)
- Clinical manifestations: severe hypercholesterolemia (elevated LDL), tendon xanthomas (1i, 2i, 3i), xanthalasma, premature coronary heart disease (1i, 2i, 3i), videos 1, 2, 3

What is autosomal dominant polycystic kidney disease (ADPKD)?

- ADPKD (1w, 2i) is an inherited form of polycystic kidneys
- Incidence: 1/1000 (1i, 2i, 3i)
- Inheritance pattern: autosomal dominant (1i, 2i)
- Genetic defect: Polycystin-1 (PKD-1) (1i, 2i, 3i, 4i) mutations (1i, 2i, 3i, 4i) and polycystin-2(PKD-2) mutations (1i, 2i)
- Pathology: Epithelial cell proliferation → tubular cysts (1i, 2i, 3i) → polycystic kidneys (1i, 2i, 3i) → chronic renal failure
- Clinical manifestations: acute loin pain, hematuria, ballotable kidneys, hypertension, chronic renal failure, anemia, liver cysts, berry aneurysm rupture (subarachnoid hemorrhage) videos 1, 2, 3

What is hereditary spherocytosis?

- Hereditary spherocytosis (*1w*) is an anaemia characterized by sphere-shaped erythrocytes .
- Incidence: 1/5000 (Northern Europe)
- Inheritance pattern: autosomal dominant but incomplete penetrance (1i, 2i, 3i, 4i)
- Genetic defects: Defects in spectrin (alpha and beta) (1i, 2i, 3i, 4i), Ankyrin (1i, 2i, 3i, 4i), band 3 protein (1i, 2i, 3i), protein 4.2, and other membrane proteins
- Clinical manifestations: hemolytic crisis (1i, 2i), aplastic crisis, pigmented gallstones (1i, 2i, 3i, 4i), leg ulcers, videos 1, 2, 3

What is Marfan syndrome?

- Marfan syndrome (1w, 2i) is a condition characterized by disordered connective tissue.
- Incidence: 1/5000
- Inheritance: Autosomal dominant
- Genetic defect: fibrillin-1 gene (1i, 2i, 3i, 4i) (FBN1 gene) with mutations (1i, 2i, 3i, 4i, 5i)
- Clinical manifestations: variable skeletal, ocular, and cardiovascular abnormalities, videos 1, 2, 3, 4

What is Huntington disease?

- Huntington disease (1w, 2i) is characterized by progressive death of brain cells
- Incidence: 1/10,000
- Inheritance: autosomal dominant
- Pathology: degeneration and atrophy of striatum, and later, cerebral cortex
- Genetics: Excessive CAG repeats; video
- Clinical: videos 1, 2, 3, 4, 5

What are some other autosomal dominant diseases?

- Tuberous sclerosis
- Neurofibromatosis type I
- Neurofibromatosis type 2
- Retinoblastoma
- Myotonic dystrophy
- Familial adenomatous polyposis
- Achondroplasia
- Ehlor's Danlos (vascular)
- Acute intermittent porphyria
- Hypertrophic obstructive cardiomyopathy
- Von Willebrand disease
- Polydactyly
- Osteogenesis Imperfecta (Except Type VII)
- Hereditary hemorrhagic telengiactasia (Osler-Weber-Rendu syndrome)
- Adult osteopetrosis type II
- Hypokalemic periodic paralysis

What are some well-known autosomal recessive diseases?

- Sickle cell anemia
- Cystic fibrosis
- Tay-Sachs disease
- Phenylketonuria
- Mucopolysaccharidoses
- Glycogen storage diseases
- Galactosemia

What is sickle cell anaemia?

- Definition: genetic disease causing sickling of RBCs (1w, 2i)
- Incidence: 1/500 (US African Americans)
- Hematology: video 1, 2,
- Inheritance: autosomal recessive
- Genetics: Genotype: SS
- Clinical manifestations: hemolytic anemia, episodes of pain (sickle cell crisis), frequent infections, growth retardation, eye involvement, pigment gallstones. Videos 1, 2, 3, 4, 5

What is cystic fibrosis?

- Cystic fibrosis (1w, 2i) is characterized by mucous blockage in pancreas and lungs
- Incidence: 1/3200 (USA)
- Inheritance: autosomal recessive
- Pathology: pancreatic insufficiency and obstructive pulmonary disease
- Genetic basis: CFTR protein (1w) and its gene mutations
- Videos: 1, 2, 3, 4, 5

What is Tay-Sachs disease?

- Tay-Sachs disease (1w, 2i) is genetic disorder of brain and spinal cord
- Incidence: 1/3500
- Pathology: Nerve cell accumulation of ganglioside (GM2)
  Genetic basis: HEXA gene mutation
- Symptoms: progressive involvement of brain and spinal cord.
- Videos: 1, 2, 3, 4, 5, 6, 7 very good, 8, 9 good, 10

What is phenylketonuria?

- Phenylketonuria is caused by decreased metabolism of phenylalanine
- Inheritence & incidence: autosomal recessive & 1/10,000
- Metabolic defect: phenylalanine ↛ tyrosine (1, 2, 3, 4, 5,); excess phenylalanine → phenylketones in urine
- Genetic defect: deficiency in phenylalanine hydroxylase (1, 2, 3, 4)
- Clinical: Delayed physical and social development, loss of pigmentation, eczema, seizures, movement disorders
- Videos: 1, 2, 3, 4, 5, 6

What are mucopolysaccharidoses?

- Mucopolysaccharidoses (i1, i2, i3, i4, i5)are several metabolic disorders resulting from absence or malfunctioning of lysosomal enzymes required for catabolism of mucopolysaccharides (glycosaminoglycans) (i1, i2, 3, i4, i5, i6) Videos 1, 2, 3.
- Glycosaminoglycans are long chains of various disaccharides that occur in the cells of bone, cartilage, tendons, corneas, skin and connective tissue.
- There are 7 different forms of mucopolysaccharidosis

(i1, i2, i3, i4)

What is MPS I Hurler(IH)/Scheie (IS)?

- MPS IH Hurler syndrome is a lysosomal storage disease leading to accumulation of two glycoaminoglycans (dermatan sulfate and heparan sulfate) in lysosomes.
- Inheritance/incidence: autosomal recessive; 1/100,000
- Defect: deficiency of two defective copies of the IDUA gene (4p16.3), which encodes for α-alpha-L-iduronidase (i1, i2, i3, i4 , i5, i6)
- Clinical: gargoylism, spinal abnormalities, growth retardation, deafness, progressive intellectual disability Videos: (1, 2, 3, 4, 5)
- MPS IS Scheie is a less severe form of α-alpha-L-iduronidase deficiency (i1, i2, i3)

What is MPS-III Sanfilippo Syndrome?

There are 4 forms of MPS-III Sanfilipo syndrome (A-D). The 4 forms are clinically indistinguishable but are due to different gene defects. It is a lysosomal storage disease resulting in accumulation of glycoaminoglycans. Symptoms include enlarged liver and spleen and diverse CNS manifestations. Involved gene deficiencies are summarized in Wikipedia as shown below. Discussions are provided by the internet: 1, 2, 3, 4, 5, 6 Videos 1, 2, 2a, 3, 4, 5

Genetics of MPS-III

MPS-III type	gene	enzyme	chromosomal region
MPS-III A	SGSH	heparan N-sulfatase	17q25.3
MPS-III B	NAGLU	N-acetyl-alpha-D-glucosaminidase	17q21.2
MPS-III C	HGSNAT	acetyl-CoA:alpha-glucosaminide N-acetyltransferase	8p11.21
MPS-III D	GNS	N-acetylglucosamine-6-sulfatase	12q14.3

What is MPS IV Morquio syndrome?

- Morqui syndrome is a lysosomal storage disease with accumulation of keratan sulfate
- Incidence: about 1/200,000
- Inheritance: autosomal recessive.
- Genetics: From A: galactosamine-6 sulfatase deficiency
  Form B: beta-galactosidase deficiency
- Clinical manifestations: cardiovascular abnormalities,, growth retardation, and skeletal deformities(hypermobile joints, long fingers, flared ribs).
- Videos: (1, 2, 3)

What is MPS VI Maroteaux–Lamy syndrome?

- Maroteaux–Lamy syndrome (1GARD) is a lysosomal storage diseaseknown as polydystrophic dwarfism
- Incidence: 1/>50,000
- Inheritance: autosomal recessive
- Genetics: deficiency of arylsulfatase B (N-acetylgalactosamine 4-sulfatase) (i1, i1a, i2)
- Clinical: shortened trunk, crouched stance, and restricted joint movement, heart valve dysfunction (Videos 1, 2, 3)

What is MPS VII Sly syndrome?

- Sly syndrome (1GERD, 2pm) (Wm. S.Sly) is a lysosomal storage disease similar to Hurler syndrome
- Inheritance/incidence: autosomal recessive; 1/250,000
- Genetics: deficiency in β-glucuronidase
- Clinical: Hurler-like facies, macrocephaly, sacrospinal deformity, hepatosplenomegaly, and mental retardation
- Videos: 1, 2, 3, 4

What are the glycogen storage diseases (GSD)?

- Glycogen storage diseases are caused by defects in glycogen synthesis or breakdown or glycolysis.
- Incidence: 1/20-25,000 (USA)
- Inheritance: Autosomal recessive
- Genetics: Several types (1, 2, 3) GSD 0 (1GARD, 1i,2i, 3i) GSD I (1NORD, 1i,2i, 3i, 4i) GSD II (1NORD,1i, 2i) GSD III (1GARD, 1i, 2i, 3i) GSD IV (1NORD, 1, 2, 3) GSD V (1GARD, 1i,2i, 3i, 4i) GSD VI (1GARD)
- Clinical: hepatomegaly, hypoglycemia, weak muscles

What are other autosomal recessive disorders?

- Abetalipoproteinemia (1, 2, 3, 4, 5)
- Bernard-Soulier syndrome.
- Bloom syndrome.
- Carpenter syndrome.
- Chediak-Higashi syndrome.
- Chondrodystrophy.
- Congenital adrenal hyperplasia
- Cystinosis, Cystinuria.
- Dubin-Johnson syndrome.
- Familial Mediterranean Fever.
- Fanconi Anemia.
- Friedrech's Ataxia.
- Gaucher's disease.
- Hartnup Disease.
- Krabbe Disease.
- Niemann Pick Disease.
- Shwachman-Diamond syndrome.
- Thalassemia.
- Werner syndrome.
- Wilson's Disease.
- Xeroderma pigmentosa

Genetic X,Y Chromosomal Diseases

X-linked Recessive Disorders

What are the causes of X-linked recessive diseases?

- Occur most often in males.
- Since males have only one X chromosome, a single recessive gene on that X chromosome causes the disease.
- Diseases like hemophilia and Duchenne muscular dystrophy occur because of a recessive gene on the X chromosome.

If a mother is disease carrier on one X chromosome and the father is not a carrier, what is the expected outcome?

- **25% chance of a healthy boy**
- **25% chance of a boy with disease**
- **25% chance of a healthy girl**
- **25% chance of a carrier girl without disease**

If the father has an X-linked recessive disease and the mother is not a carrier, what are the expected outcomes?

- 100% chance of a healthy boy
- 100% chance of a carrier girl without disease

For x-linked recessive disorders, if the mother is a carrier and the father has the disease, what are the expected outcomes?

- **25% chance of a healthy boy**
- **25% chance of a boy with the disease**
- **25% chance of a carrier girl**
- **25% chance of a girl with the disease**

Why are males more likely to have an X-chromosome disorder than are females?

- Males have only one X-chromosome. Since females have two X-chromosomes, a defect in one chromosome can be off set by normality in the X-chromosome partner.

What are most common forms of X-linked recessive disorders?

- Red-green color blindness
- Hemophilia A: clotting Factor VIII deficiency
- Hemophilia B (Christmas Disease): deficiency of clotting Factor IX.
- Duchenne muscular dystrophy: mutations in the dystrophin gene.
- Becker's muscular dystrophy: milder form of Duchenne
- X-linked ichthyosis: deficiency of the steroid sulfatase
- X-linked agammaglobulinemia
- Glucose-6-phosphate dehydrogenase deficiency: Favism

X-linked Dominant Disorders

What is an X-linked dominant inheritance disorder?

- X-linked dominant inheritance indicates that a gene responsible for a genetic disorder is located on the X chromosome, and only one copy of the allele is sufficient to cause the disorder when inherited from a parent who has the disorder (Wikipedia)

What are examples of X-linked dominant diseases?

- Vitamin D resistant rickets: X-linked hypophosphatemia
- Rett syndrome: Developmental defects; scoliosis
- Most cases of Alport syndrome: Glomerulonephritis (type 4 collagen defect)
- Incontinentia pigmenti: Disorder of skin, hair, teeth, nails and CNS
- Giuffrè–Tsukahara syndrome: radial ulnar synostosis and microcephaly
- Goltz syndrome: Focal dermal hypoplasia
- X-linked dominant porphyria: defect in porphyrin metabolism
- Fragile X syndrome

Y-linked Disorders

What is the Y chromosome?

- The male has two sex chromosomes--X and Y
- Sex is determined by the SRY gene on the Y chromosome
- SRY is responsible for the development of a male.
- Other Y chromosome genes contribute to male fertility.
- The Y-chromosome has about 59 million base pairs, which encodes for over 200 genes.

What is a Y-linked disorder?

- **Since only males have a Y chromosome, in Y-linked inheritance, a mutation can only be passed from father to son**

What conditions have been associated with Y-chromosomal polymorphisms?

- Y-chromosomal polymorphisms have implicated in male-specific (spermatogenic failure, testis and prostate cancer) and prevalently male-associated (hypertension, autism) diseases (Krausz et al.Ann Med. 2004;36(8):573-83).

Sex Chromosomal Aneuploidy

What is Turner syndrome?

- Turner syndrome (1w, 2i) is known as 45,X or 45,X0, in which a female is partly or completely missing an X chromosome.
- Signs and symptoms include:

- short and webbed neck
- low-set ears
- short stature
- amenorrhea (without treatment)
- no breasts (without treatment)
- congenital heart dedects
- hypothyroidism
-predispostion to diabetes
- visual and hearing defects

What is Klinefelter syndrome?

- Klinefelter syndrome (1pm, 2i) occurs in males with genetic 47, XXY
- Major features are:
  - infertility
  - small testes
- Less prominent features are:
  - weaker muscles
  - greater height
  - poor coordination
  - less body hair
  - breast growth
  - reduced libido

What is Triple-X syndrome?

- Triple X syndrome (1w, 2i), also known as trisomy X or 47, XXX, occurs in females and is characterized by

  > an extra X chromosome, and sometimes by

  - learning difficulties
  - decreased muscle tone
  - seizures
  - renal disorders

What are XYY and XXYY syndromes?

- Males with XYY syndrome (1w) have an extra Y chromosome
  - There are 47 chromosomes, instead of the usual 46, giving a 47,XYY karyotype.
  - Symptoms *may* include being taller than average, acne, and learning problems.
  - Aggressive behavior is been ruled out.
- Males with XXYY syndrome have 48 chromosomes instead of the typical 46.
  - Hypogonadism and various behavioral symptoms have been reported.

Mitochondrial DNA Diseases

What are characteristics of mitochrondial DNA inheritance?

Essentials of mitochondrial DNA inheritance (1w)

- **Mitochondria have 37 genes**
- **Mitochrondial DNA is transmitted from mother to all offspring (rarely there is paternal transmission)**
- **Usually, there is no DNA recombination (with exceptions)**
- **DNA defects are inherited equally by males and females**

What are examples of mitochondrial DNA diseases?

- Mitochondrial myopathies (1w)
- Diabetes mellitus and deafness (DAD) (1w)
- Leber's hereditary optic neuropathy (LHON) (1w)
- Leigh syndrome, subacute sclerosing encephalopathy (1w)
- Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP) (1w)
- Myoneurogenic gastrointestinal encephalopathy (MNGIE) (1w)
- Myoclonic epilepsy with ragged red fibers (MERRF) (1w)
- Progressive myoclonic epilepsy (1w)
- Mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS) (1w)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (1w)

What organs are most commonly affects by mitochondrial DNA disease?

- **Brain**
- **Muscles**
- **Heart**
- **Liver**
- **Nerves**
- **Eyes**
- **Ears**
- **Kidneys**

NIH Genetic and Rare Disease Informatin Center

What are the most common signs and symptoms of inherited mitochondrial DNA diseases?

- Poor growth
- Loss of muscle coordination
- Muscle weakness
- Seizures
- Autism
- Problems with vision and/or hearing
- Developmental delay
- Learning disabilities
- Heart, liver, and/or kidney disease
- Gastrointestinal disorders
- Diabetes
- Increased risk of infection
- Thyroid and/or adrenal abnormalities
- Autonomic dysfunction
- Dementia

NIH Genetic and Rare Disease Information Center

Multifactorial (Polygenic) Diseases

What is a multifactorial (polygenic) disease?

- A multifactorial disease is one in which there is genetic susceptibility but environmental factors must be present for the disease to become manifest.
- Multifactorial diseases are sometimes called polygenic diseases because of multiple genes affect susceptibility.

What are typical forms of multifactorial disease?

- Coronary heart disease
- Stroke
- High blood pressure,
- Adult onset diabetes
- Many forms of cancer
- Obesity.

Diseases of Chromosome Structure

What are common forms of autosomal trisomy?

- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)
- Trisomy 9
- Trisomy 8 (Warkany syndrome 2)

What are clinical features of Down syndrome (trisomy 21)?

- Flat face with an upward slant to the eyes
- Short neck
- Abnormally shaped ears
- Protruding tongue
- Small head
- Deep crease in the palm of the hand with relatively short fingers
- White spots in the iris of the eye
- Poor muscle tone, loose ligaments, excessive flexibility
- Small hands and feet
- Spine disorders such as scoliosis, kyphosis or lordosis
- Cataracts
- Congenital heart disease
- Gastrointestinal abnormalities
- Musculoskeletal and movement problems
- Epilepsy
- Hearing loss
- Speech apraxia
- Sleep disorders
- Feeding disorders
- Developmental disabilities
- Eye problems, such as cataracts
- Thyroid dysfunctions
- Dementia

What are clinical features of Edwards syndrome (trisomy 18)?

- Slow growth before birth
- Low birth weight.
- Congenital heart disease
- Small, abnormally shaped head
- Small jaw and mouth
- Overlapping fingersDeath in first year (5-10%)
- Severe intellectual disability

What are the forms of trisomy of the X chromosomes?

- **XXX (Triple X syndrome)**

  - Affected XXX females tend to be taller than average and may have learning disabilities reduce muscular tone, and rarely seizures and kidney dysfunction.

- **XXY (Klinefelter syndrome)**

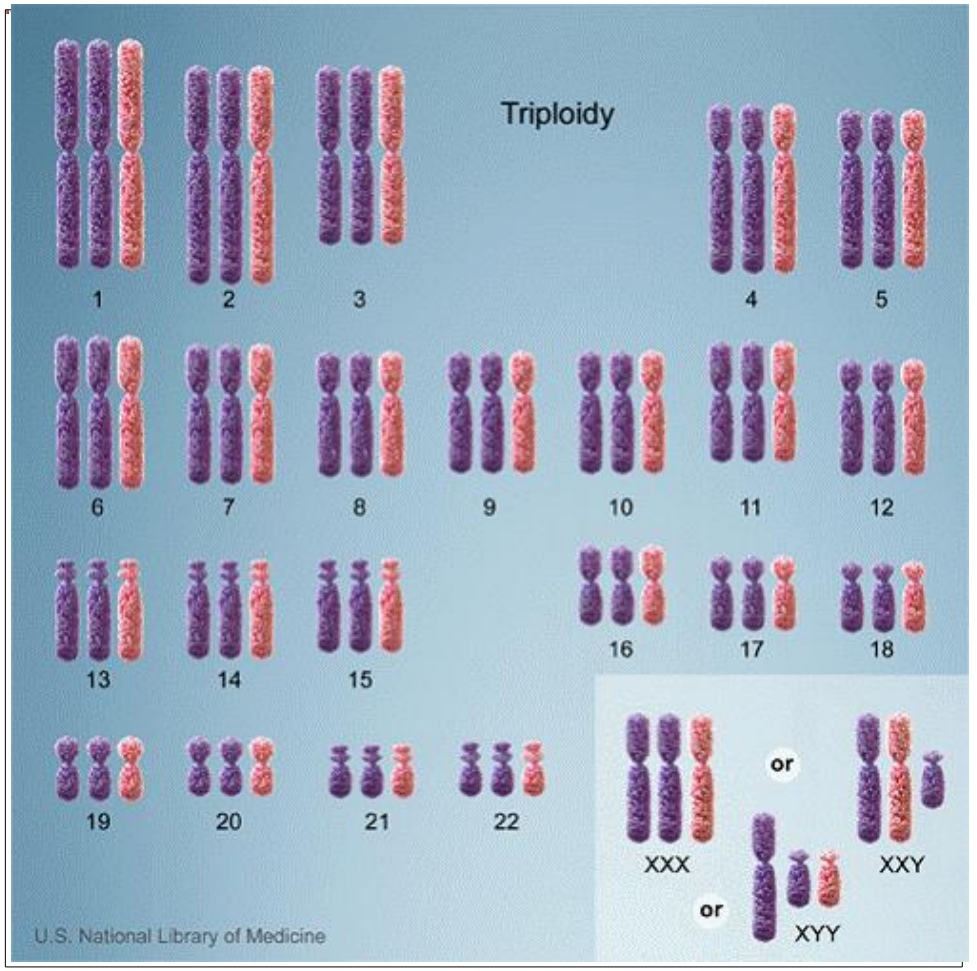
  - Affected XXY males primarily have infertility and small testicles, but sometimes are tall, poorly coordinated, have reduced body hair, and gynecomastia.

What are examples of aneuploidy on the Y chromosome?

- XYY syndrome: This condition and associated with relatively few symptoms
- XXYY syndrome: this condition is characterized by developmental delay, speech impairment, behavior outburst and mood swings, learning disabilities, intellectual impairment, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorders, tall stature, scoliosis, low muscle tone, sterility, delayed sexual development, and undescended testicles

What are clinical features of triplody?

- Holoprosencephaly,
- Hydrocephalus
- Ventriculomegaly
- Arnold–Chiari malformation
- Agenesis of the corpus callosum
- Neural tube defects.
- Cleft lip/palate
- Hypertelorism
- Club foot
- Syndactyly
- Congenital heart defects
- Hydronephrosis
- Omphalocele
- Meningocele (spina bifida).



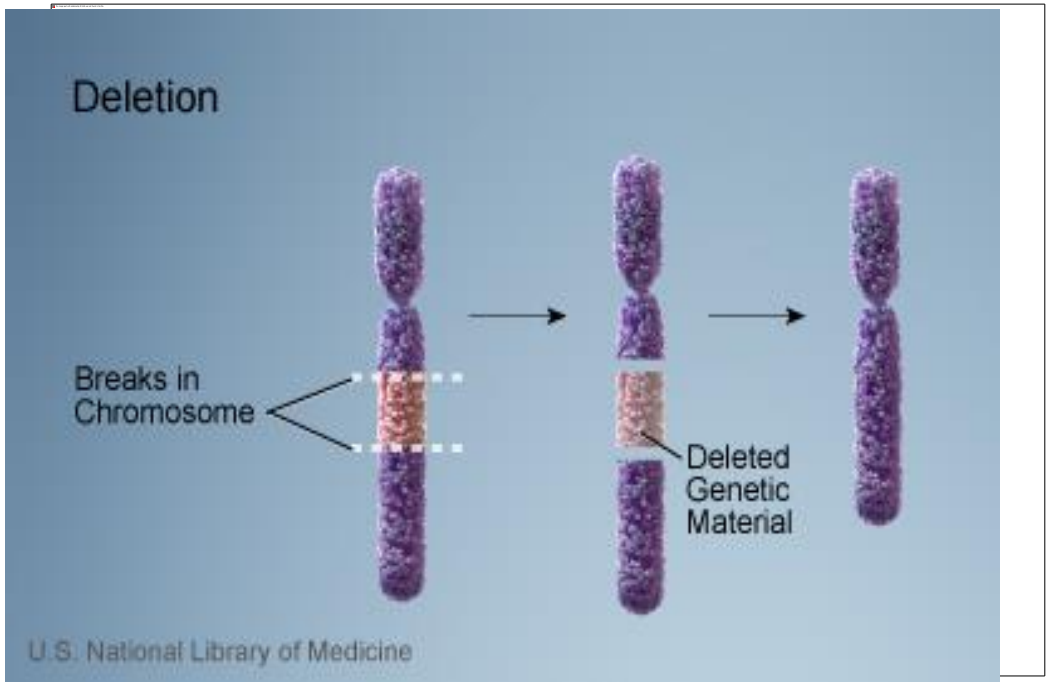
What are examples of chromosomal deletions?

- 4p deletion
- 5p deletion
- Prader-Willi (1i, 2i)

  - 15q11-q13 region deletion

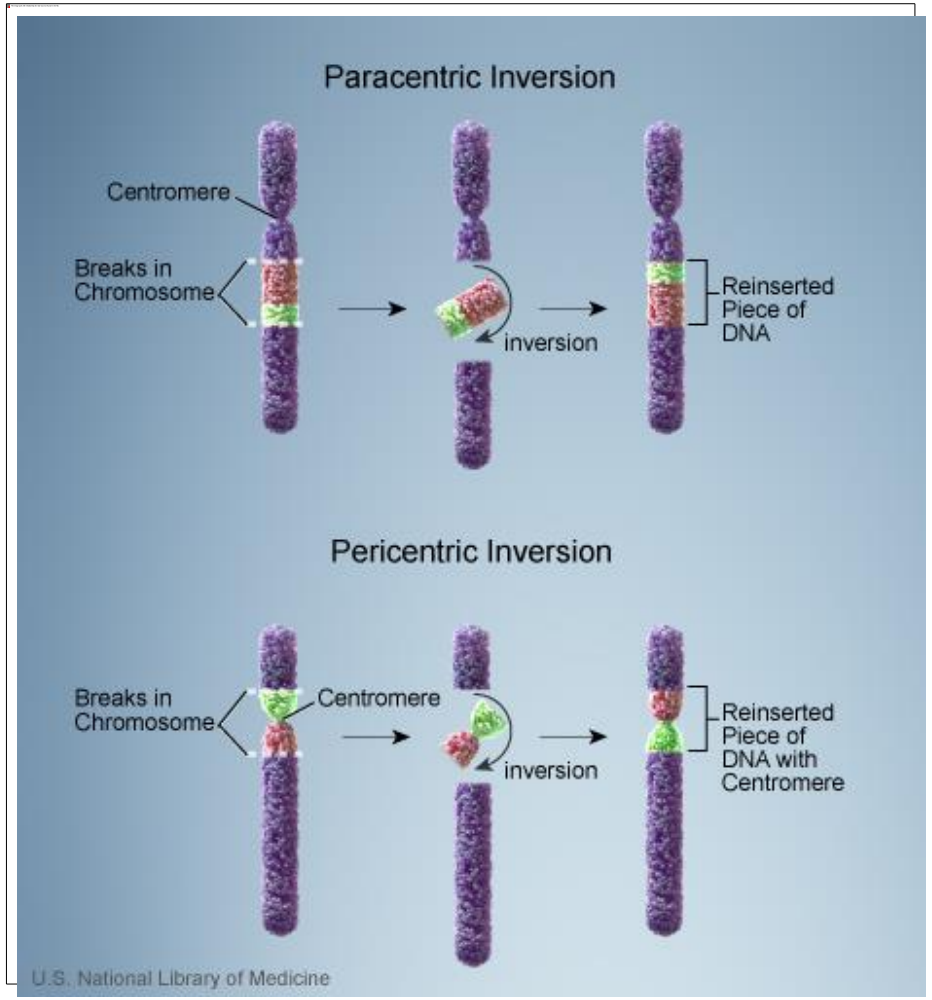
- Angelman syndrome

  - 15q11-q13 region deletion



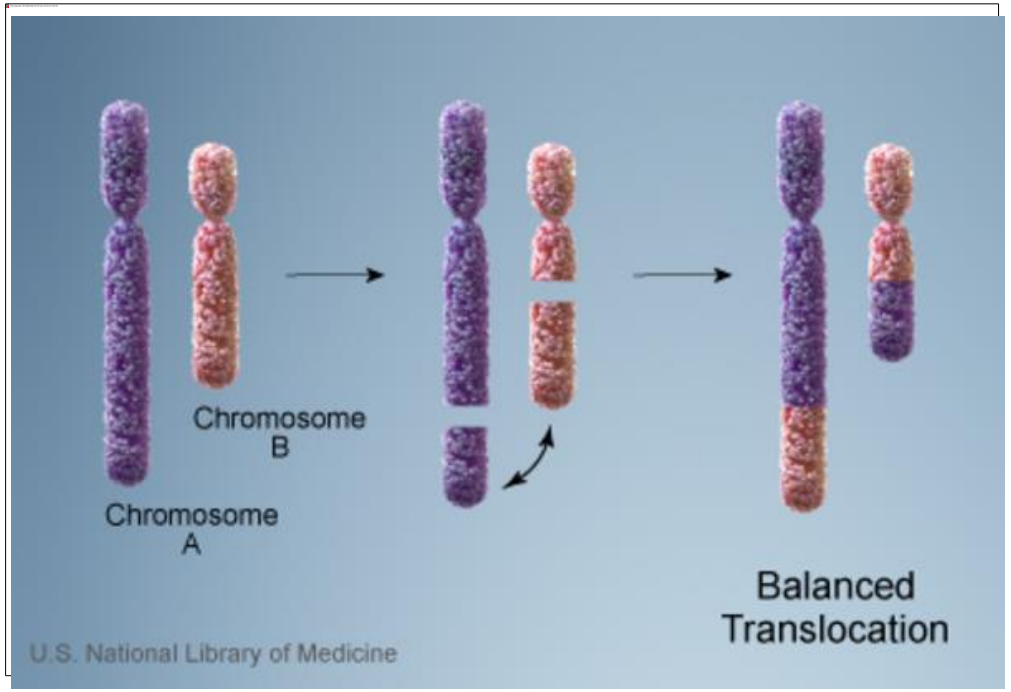
What are the clinical manifestations of a chromosomal inversion?

- An inversion is a chromosome rearrangement in which a segment of a chromosome is reversed end to end.
- Since genetic material is not lost, clinical signs and symptoms generally are absent or minimal.



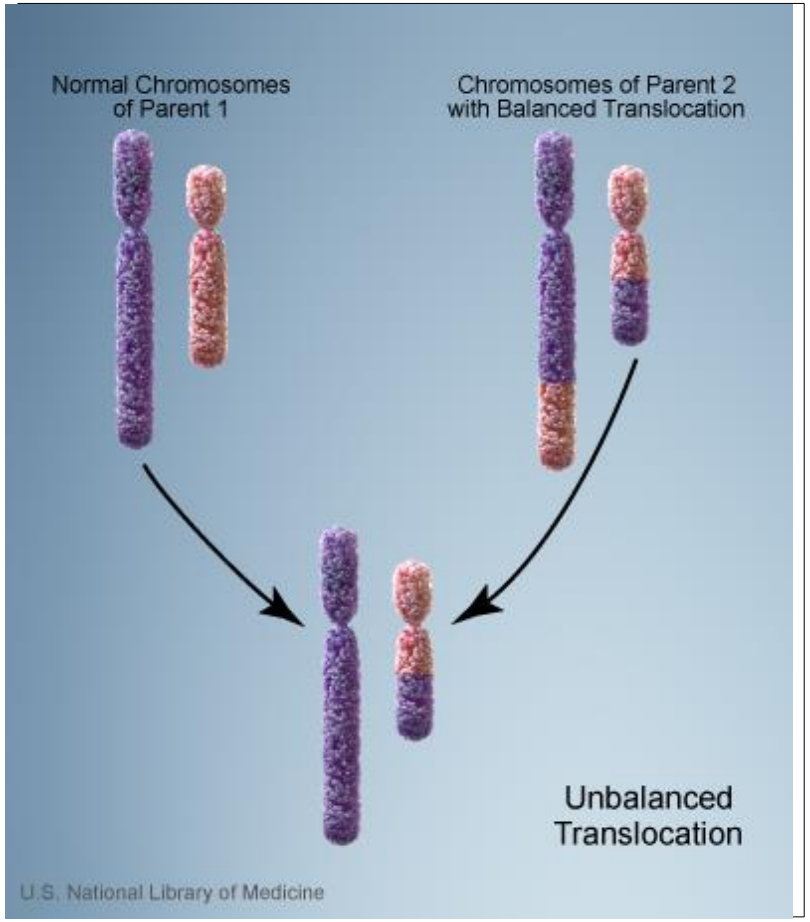
What are the clinical consequences of a balanced translocation?

- **Translocations can be balanced (in an even exchange of material with no genetic information extra or missing, in contrast to unbalanced (causing extra or missing genes (1i) .**
- **Since genetic material is not lost, symptoms often are minimal.**



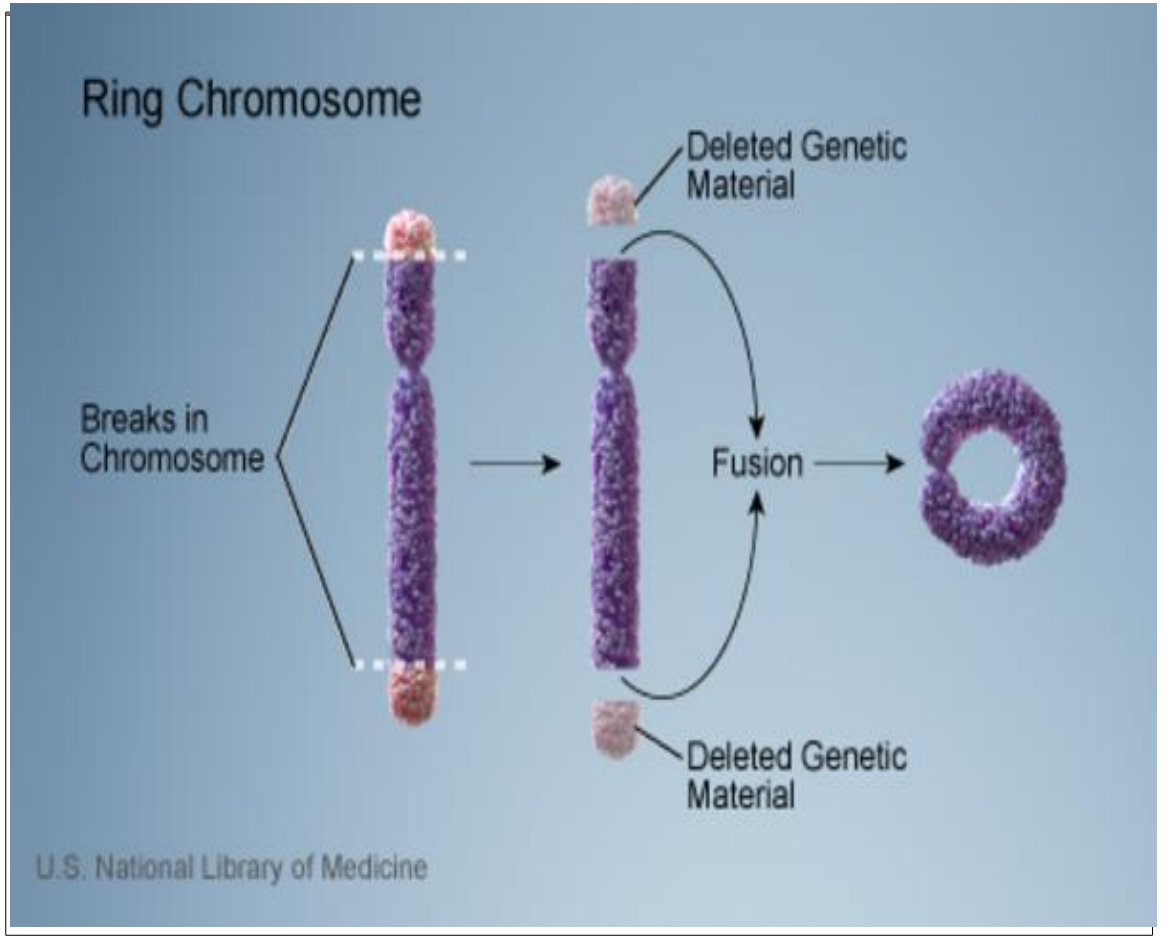
What are the clinical consequences of unbalanced translocations?

- In unbalanced translocations, the exchange of chromosome material is unequal resulting in extra or missing genes.
- Unbalanced translocations can lead to monosomy and trisomy, which can result in developmental delay and intellectual disability.



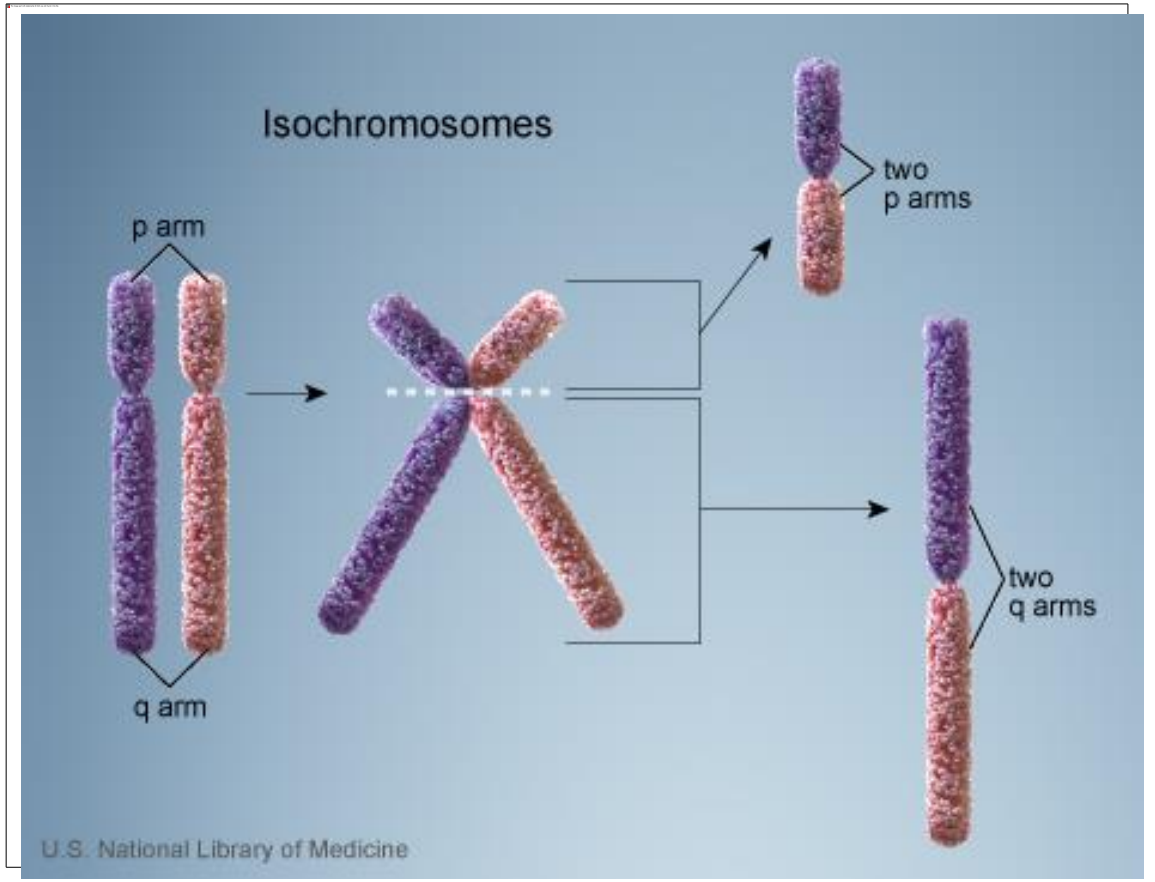
What are the clinical consequences of a ring chromosome?

- Growth retardation
- Small stature
- Facial abnormalities
- Hand abnormalities
- Low muscle tone
- Reproductive abnormalities
- Autism



What clinical consequences of isochromosomes?

- Isochromosomes carry increased risk for various neoplasms



What are the clinical consequences of a dicentric chromosome?

- **A dicentric chromosome are associated with various intellectual, neurological and physical disabilities.**