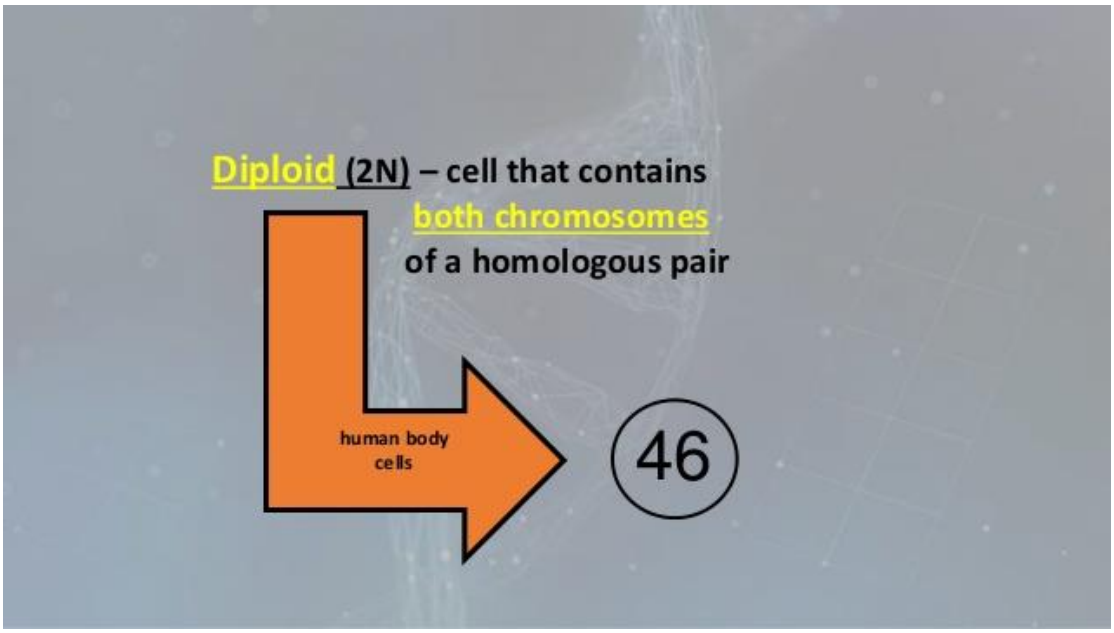
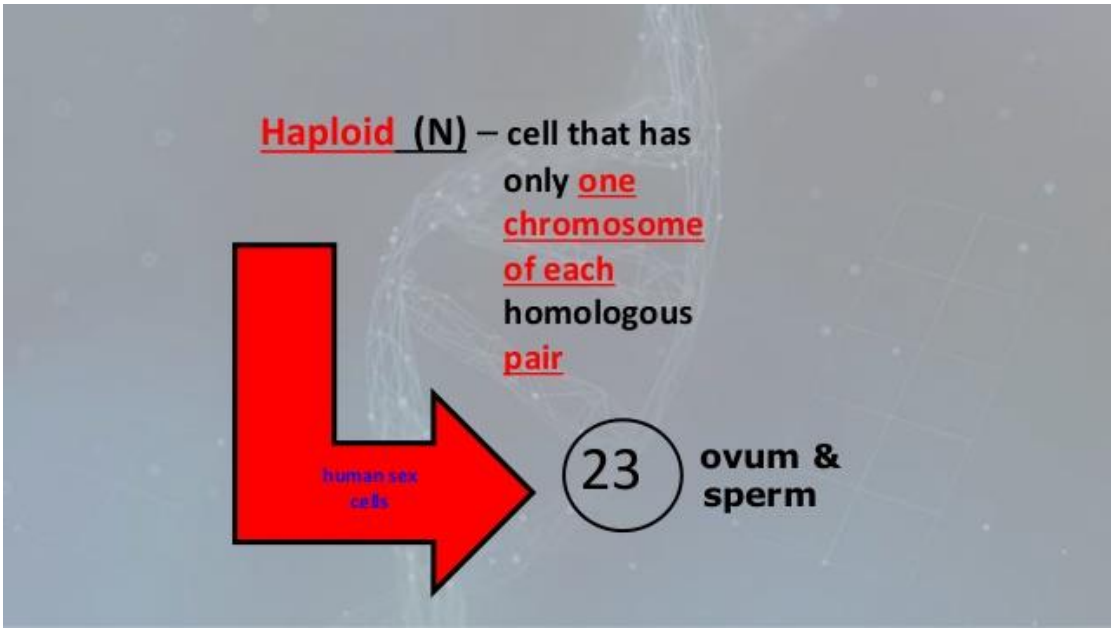
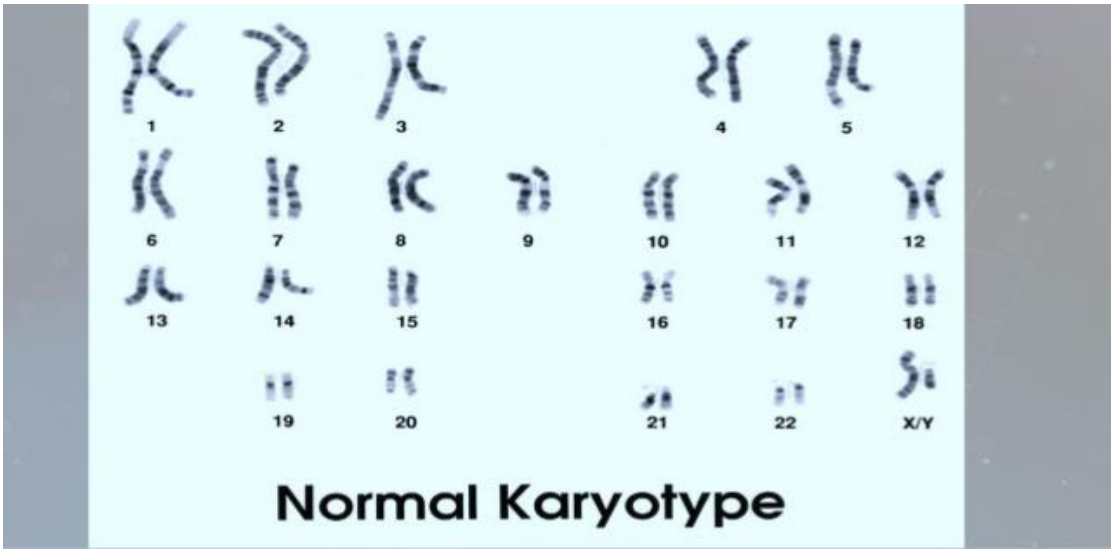
HUMAN GENETICS

Overview

Each somatic cell has 46 chromosomes: 22 pairs of autosomes, and 1 pair of sex chromosomes (XY in a male, XX in a female). Germ cells (ova or sperm) contain 22 autosomes and 1 sex chromosome, for a total of 23. At fertilization, the full diploid chromosome complement of 46 is again realized in the embryo.



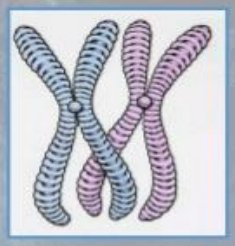


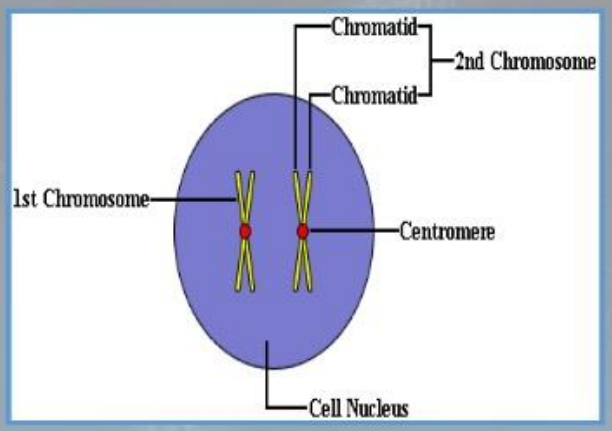


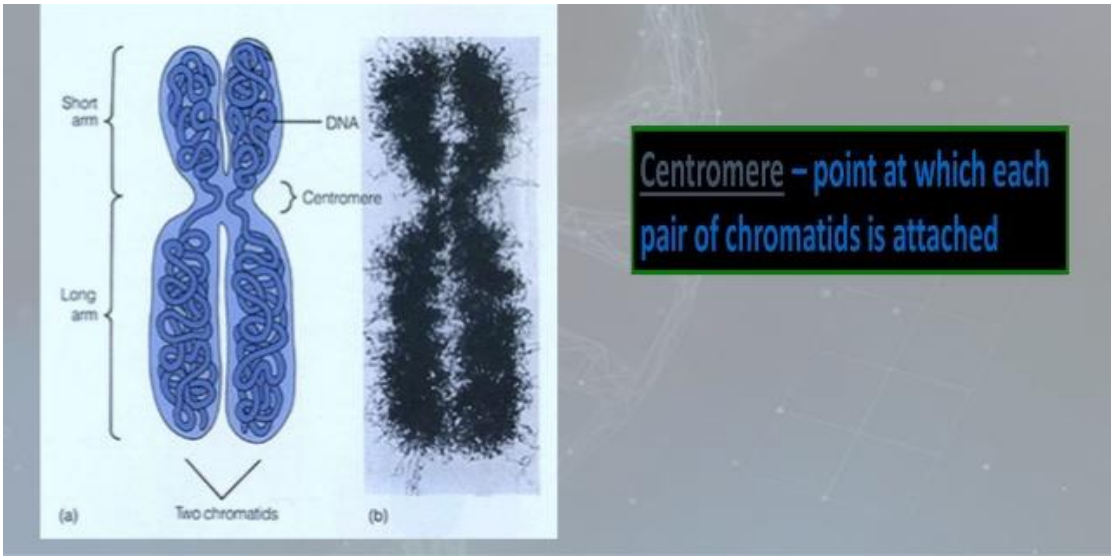
Homologous Chromosomes

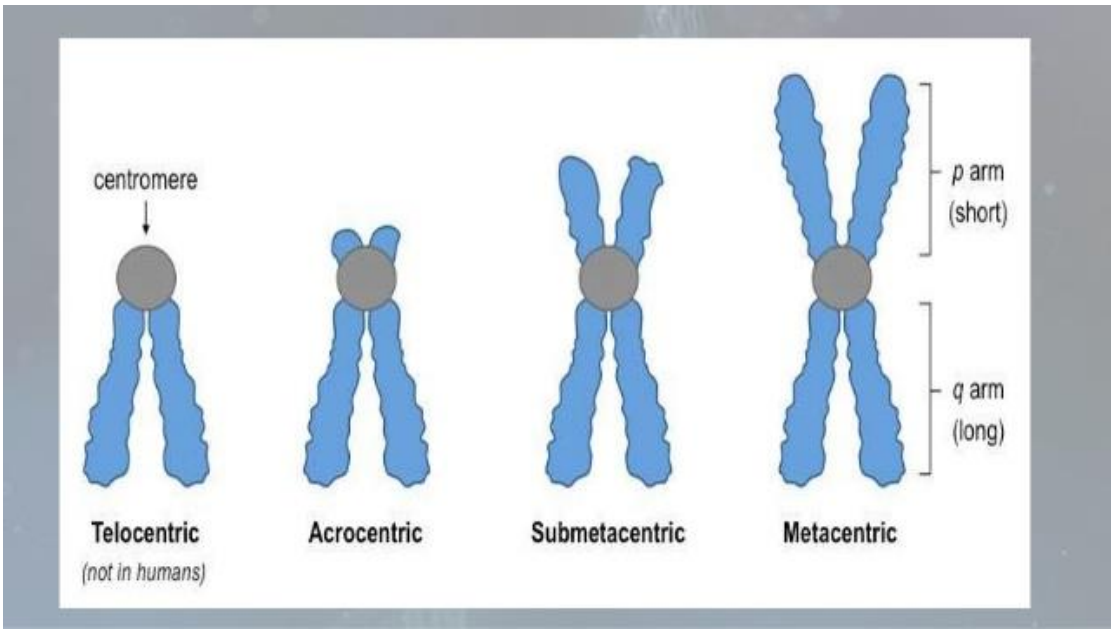
pair of chromosomes that have same size and shape

- **human body cells have 23 homologous pairs**

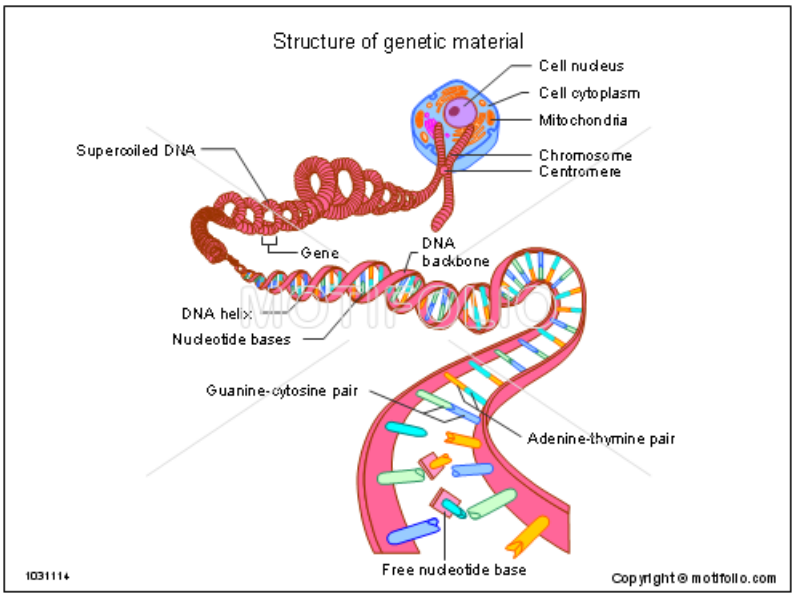


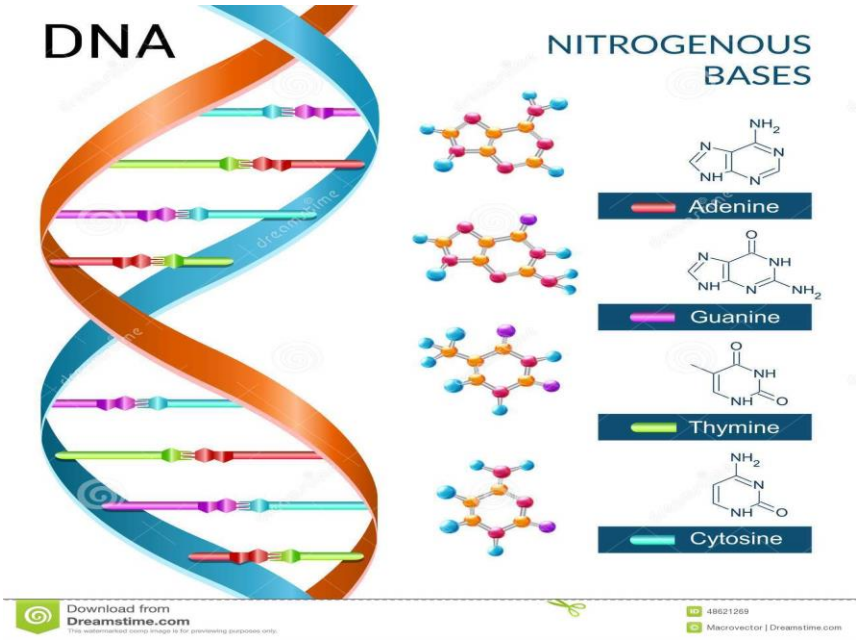






DNA is made out of two long, twisted strands that contain complementary genetic information (like a picture and its negative). A gene is a segment of DNA that is passed down from parents to children and confers a trait to the offspring.





Most of the genetic material is contained in the cell's nucleus. The mitochondria (the cell's energy-producing organelles) contain their own unique genome. The **mitochondrial chromosome** consists of a double-stranded circular piece of DNA. The proteins that occupy the mitochondria are produced either in the mitochondria, using information contained in the mitochondrial genome, or are produced outside of the mitochondria, using information contained in the nuclear genome and transported into the organelle. Sperm do not usually contribute mitochondria to the developing embryo, so all mitochondria are maternally derived and a child's mitochondrial genetic makeup derives exclusively from the child's biological mother.

The gene is the fundamental unit of inheritance and the ultimate determinant of all phenotypes. The DNA of a normal human cell contains an estimated 30,000 to 120,000 genes, but only a fraction of these are used (or *expressed*) in any particular cell at any given time. For example, genes specific for erythroid cells, such as the hemoglobin genes, are not expressed in brain cells. A gene exerts its effects by having its DNA *transcribed* into an mRNA, which is, in turn, *translated* into a protein, the final effector of the gene's action.

Gene is a specific sequence of DNA containing genetic information required to make a specific protein, so each gene is a segment of DNA.

GENETIC DISORDERS

1- Chromosomal disorders

1- Numerical abnormalities: extra (e.g. Trisomy 13, 18, 21, Klinefleter) or missing (e.g. Turner).

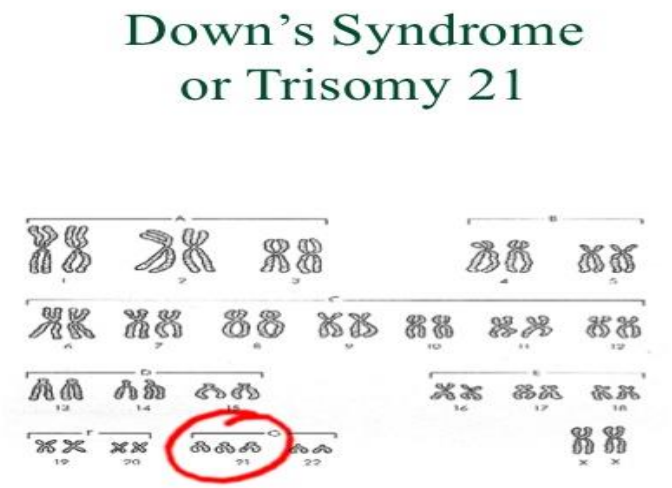
2- Structural abnormalities: e. g. deletion, translocation, or duplication of parts of chromosome.

Down's Syndrome

DS is the most common abnormality of chromosomal number. It occurs in 1 of every 1000 births.

Etiology

1- Most cases (92.5%) are due to non-disjunction; As a result of non-disjunction, there are three copies of chromosome 21 (Trisomy 21); it is designated 47,XY,+21.



2- In 4.5% of cases, the extra chromosome is part of a **robertsonian translocation**, which occurs when the long arms (q) of two acrocentric chromosomes (numbers 13, 14, 15, 21, or 22) fuse at the centromeres, and the short arms (p) are lost.

3- In approximately 1% to 2% of children with DS, mosaicism occurs. These individuals have two populations of cells: one with trisomy 21 and one with a normal chromosome complement.

Phenotype

1- The characteristic facial appearance, with brachycephaly, flattened occiput, hypoplastic midface, flattened nasal bridge, upslanting palpebral fissures, epicanthal folds, and large protruding tongue, is apparent at birth. Infants also have short broad hands, often with a single transverse palmar crease, and a wide gap between the first and second toes.
2- The severe hypotonia may cause feeding problems and decreased activity.
3- Approximately 50% of children with DS have **congenital heart disease**, including atrioventricular canal.
4- Approximately 10% of newborns with DS have **gastrointestinal tract anomalies**.
5- Four percent to 18% of infants with DS are found to have congenital hypothyroidism, which is identified as part of the newborn screening program. Acquired hypothyroidism is a more common problem. Thyroid function testing must be monitored periodically during the child's life.
6- children with DS also have an increased risk of **leukemia**, with a 10- to 20-fold increase in risk compared with individuals without DS.
7- Children with DS are more susceptible to infection, more likely to develop cataracts, and approximately 10% have atlantoaxial instability with risk of spinal cord injury. Many individuals older than 35 years of age develop Alzheimer-like features.

Trisomy 18

Trisomy 18 (47,XX,+18 or 47,XY,+18) is the second most common autosomal trisomy, occurring in approximately 1 in 7500 live births. More than 95% of conceptuses with trisomy 18 are spontaneously aborted in the first trimester. Trisomy 18 is usually lethal; fewer than 10% of affected infants survive until their first birthday. Most infants with trisomy 18 are small for gestational age. Clinical features include prominent occiput, micrognathia, low-set and malformed ears, short sternum, rocker-bottom feet, hypoplastic nails, and characteristic clenching of fists—the second and fifth digits overlap the third and fourth digits.

Trisomy 13

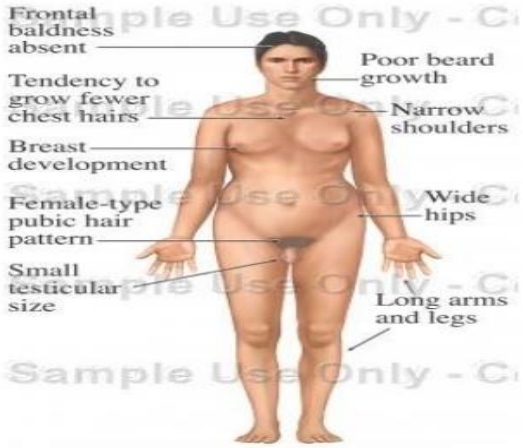
The third of the common trisomies, trisomy 13 (47,XX,+13 or 47,XY,+13) occurs in 1 in 12,000 live births. It is usually fatal in the first year of life.
These infants are IUGR and microcephalic. Midline facial defects such as cyclopia (single orbit), cebocephaly (single nostril), and cleft lip and palate are common, as are midline central nervous system anomalies, such as holoprosencephaly. The forehead is generally sloping, ears are often small and malformed, and microphthalmia or anophthalmia may occur. Polydactyly of the hands is common. Most infants with Trisomy 13 also have congenital heart disease. Many infants with this condition have a punched-out scalp lesion over the occiput called **aplasia cutis congenita;** when seen

in conjunction with polydactyly and some or all of the facial findings, this finding is essentially pathognomonic for the diagnosis of trisomy 13.

Klinefleter syndrome

Occurring in 1 in 500 male births, KS is the most common genetic cause of hypogonadism and infertility in men. It is caused by the presence of an extra X chromosome (47,XXY).
Before puberty, boys with KS are phenotypically indistinguishable from the rest of the population. Adolescents and young adults with KS tend to be tall, with long limbs, gynecomastia occurs. Because of failure of growth and maturation of the testes, males with KS have testosterone deficiency and failure to produce viable sperm with failure to develop secondary sexual characteristics, such as facial hair, deepening of the voice, and libido. In adulthood, osteopenia and osteoporosis develop. Because of these findings, testosterone supplementation is indicated.

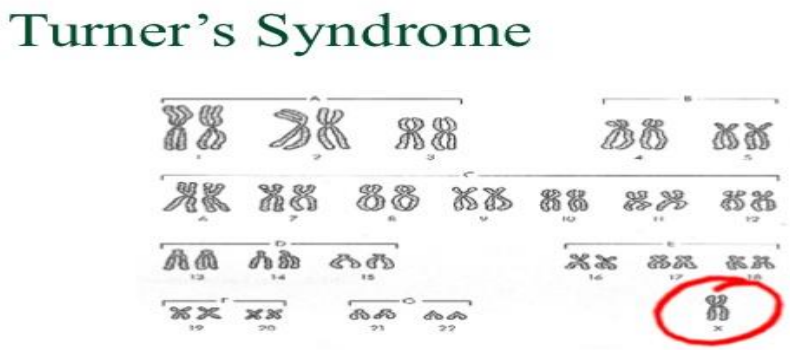
Klinefleter's



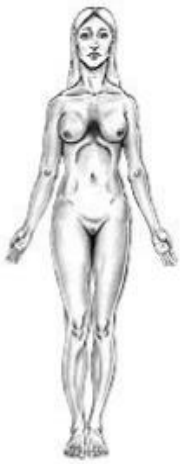
Turner syndrome

TS is the only condition in which a monosomic conceptus survives to term; however, 99% of embryos with 45,X are spontaneously aborted. 45,X is occurring in 1 in 3200 liveborn females. Affected women tend to have normal intelligence and life expectancy. There is webbing of the neck, with or without cystic hygroma, a shield-like chest with widened internipple distance, and puffiness of the hands and feet. Internal malformations may include congenital heart defect (in 45%, coarctation of the aorta is the most common anomaly). Renal anomalies, including horseshoe kidney, are seen in more than 50% of patients. Short stature is a cardinal feature of this condition, and acquired hypothyroidism is estimated to occur five times more than in the general
population. The presence of streak gonads (gonadal dysgenesis) instead of well-developed ovaries leads to estrogen deficiency, which prevents these women from developing secondary sexual characteristics and results in amenorrhea.

Many girls with TS escape detection during the newborn period because phenotypic features are subtle.



Turner's



- Turner syndrome is associated with underdeveloped ovaries, short stature, webbed, and is only in women.
- Bull neck, and broad chest. Individuals are sterile, and lack expected secondary sexual characteristics.
- Mental retardation typically not evident.
- Chromosomal or monogenic?

Cri du Chat Syndrome

A deletion in the short arm of chromosome 5 is responsible for cri du chat syndrome, with its characteristic catlike cry during early infancy, the result of tracheal hypoplasia. Other clinical features include low birth weight and postnatal failure to thrive, hypotonia, developmental disability, microcephaly, and craniofacial dysmorphism. Clefts of the lip and palate, congenital heart disease, and other malformations may be seen.

2- Gene abnormalities

Small changes (mutations) may occur in a specific gene. These changes do not affect the structure of the chromosomes.

Mutations

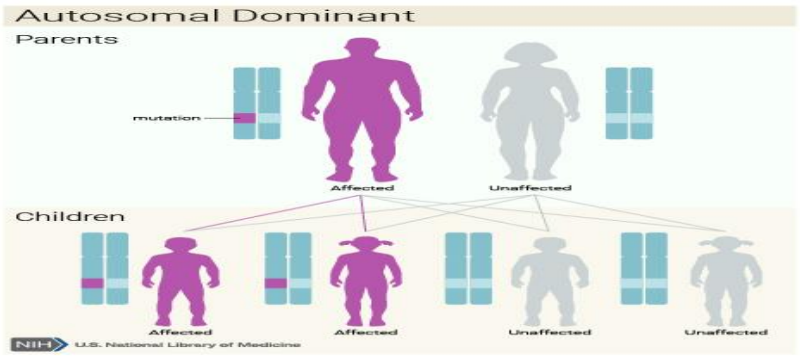
- Gene mutations can be either inherited from a parent or acquired. A hereditary mutation is a mistake that is present in the DNA of virtually all body cells. Hereditary mutations are also called *germ line* mutations because the gene change exists in the reproductive cells and can be passed from generation to generation, from parent to newborn. Moreover, the mutation is copied every time body cells divide

- Mutations occur all the time in every cell in the body. Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants. But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age. Over time, mistakes can accumulate.

Types of inheritance of gene mutation

1- Autosomal chromosomal inheritance

Autosomal Dominant Inheritance



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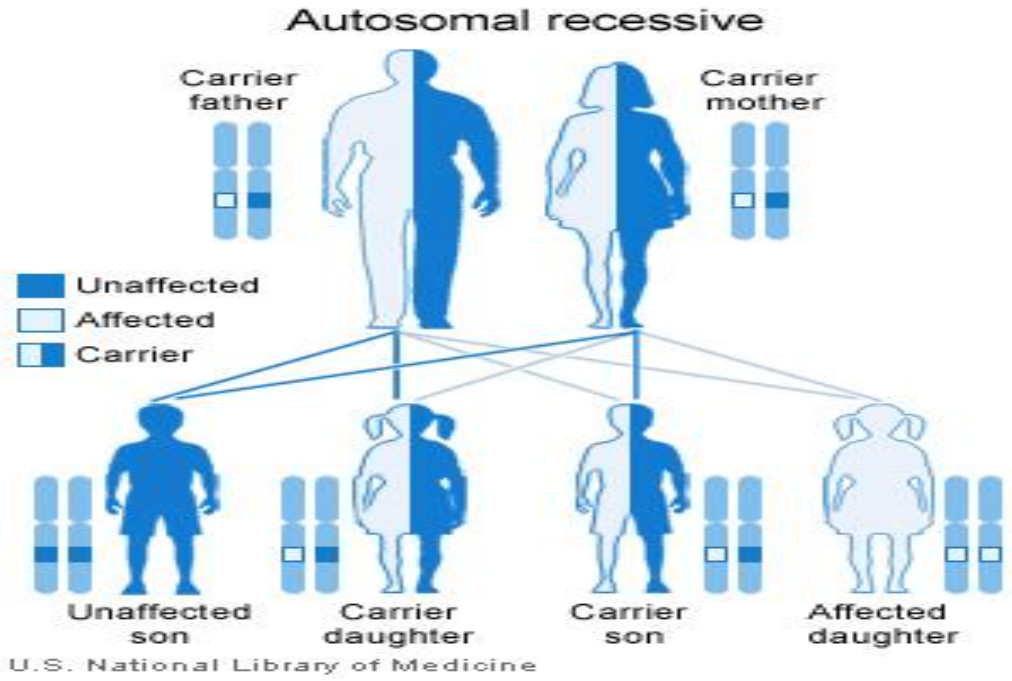
Department of Human Genetics

Characteristics of Autosomal Dominant Disorders

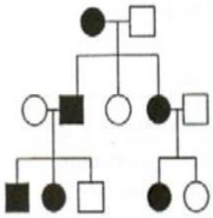
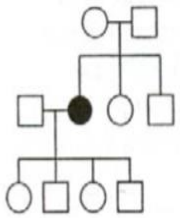
- appears in every generation
- each affected person has an affected parent (exceptions!)
- each child of an affected parent has 50% risk to inherit trait.
- unaffected family members don't transmit phenotype to children (exceptions again).
- males and females equally likely to transmit the trait, to children of either sex.
- male-to-male transmission
- new mutations relatively common

Autosomal Recessive Inheritance

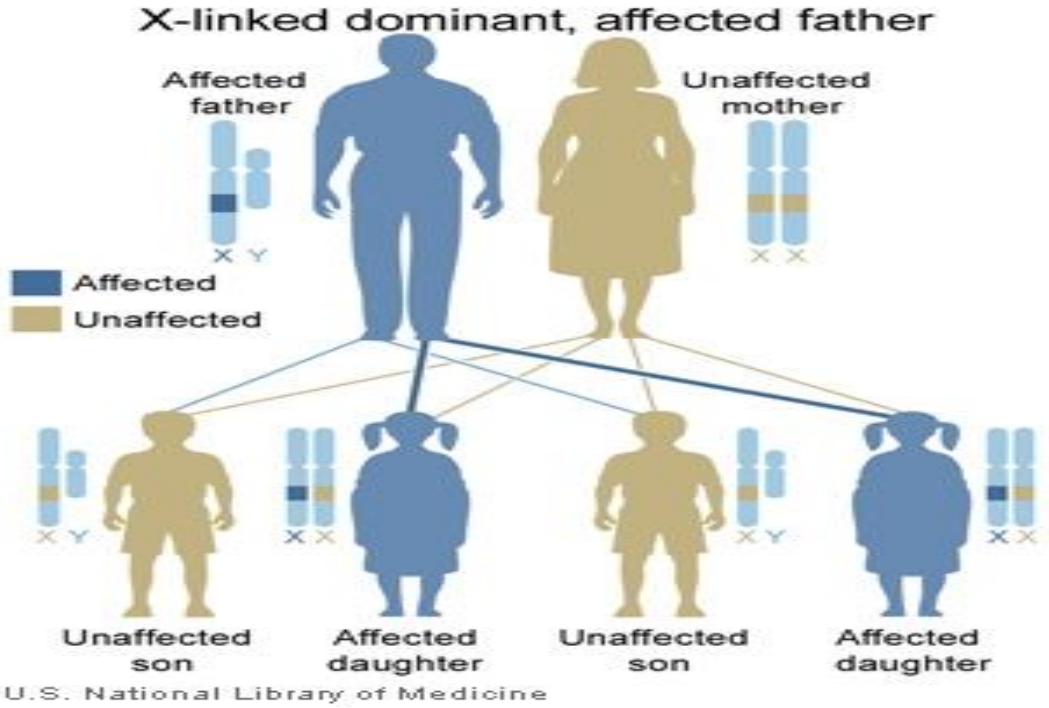


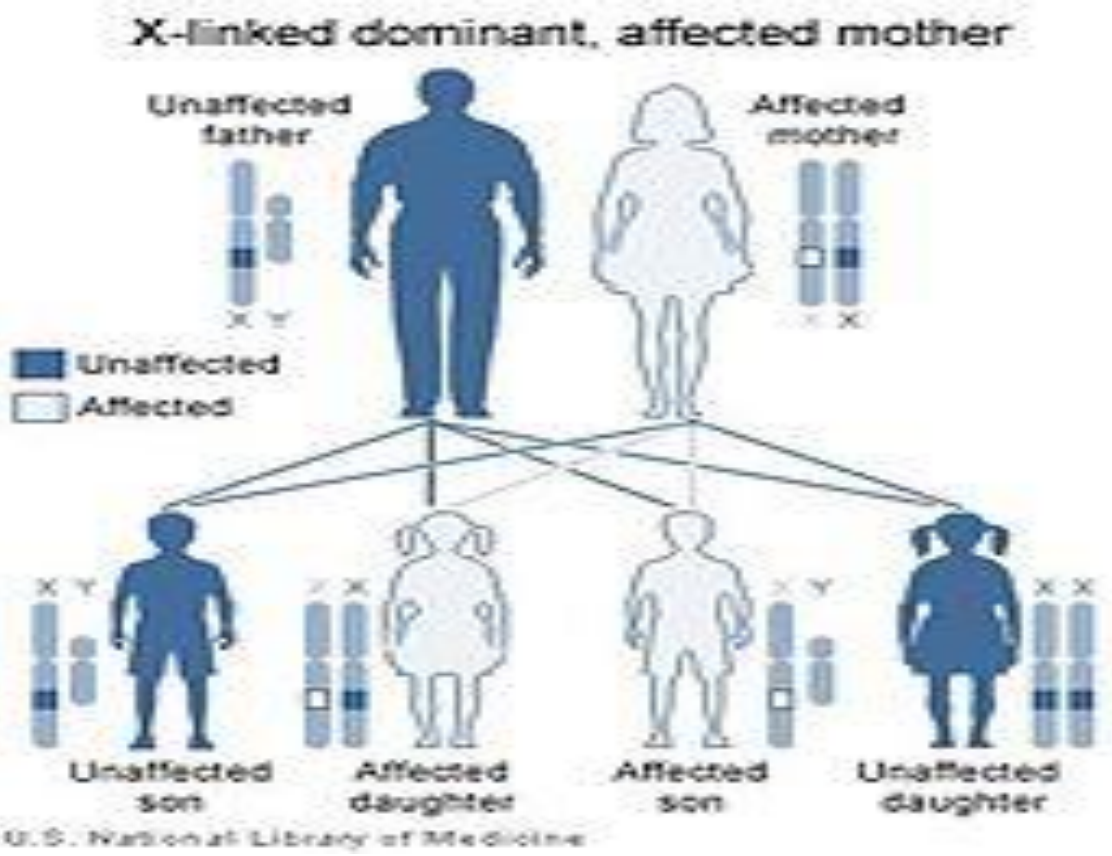
Characteristics of Autosomal Recessive Inheritance

1. An autosomal recessive phenotype, if it appears in more than one member of a kindred, typically is seen only in the sibship of the proband, not in parents, offspring, or other relatives.
2. For most autosomal recessive diseases, males and females are equally likely to be affected.
3. Parents of an affected child are asymptomatic carriers of mutant alleles.
4. The parents of the affected person may in some cases be consanguineous. This is especially likely if the gene responsible for the condition is rare in the population.
5. The recurrence risk for each sib of the proband is 1 in 4.

TYPE OF INHERITANCE	CHARACTERISTICS	EXAMPLES
Autosomal dominant 	▪ Both sexes equally affected ▪ Vertical transmission ▪ Father-to-son transmission ▪ Affected individuals transmit trait to ~50% offspring	▪ Huntington disease ▪ Achondroplasia ▪ NF type 1 ▪ Marfan syndrome ▪ Familial hypercholesterolemia
Autosomal recessive 	▪ Both sexes equally affected ▪ Usually no prior family history ▪ Consanguinity ▪ Mating between two carriers transmits trait to ~25% offspring	▪ Hurler syndrome ▪ Hereditary hemochromatosis ▪ Cystic fibrosis ▪ Sickle-cell anemia ▪ Phenylketonuria (PKU) ▪ β-thalassemia ▪ Tay-Sachs

2- Sex Chromosome Inheritance

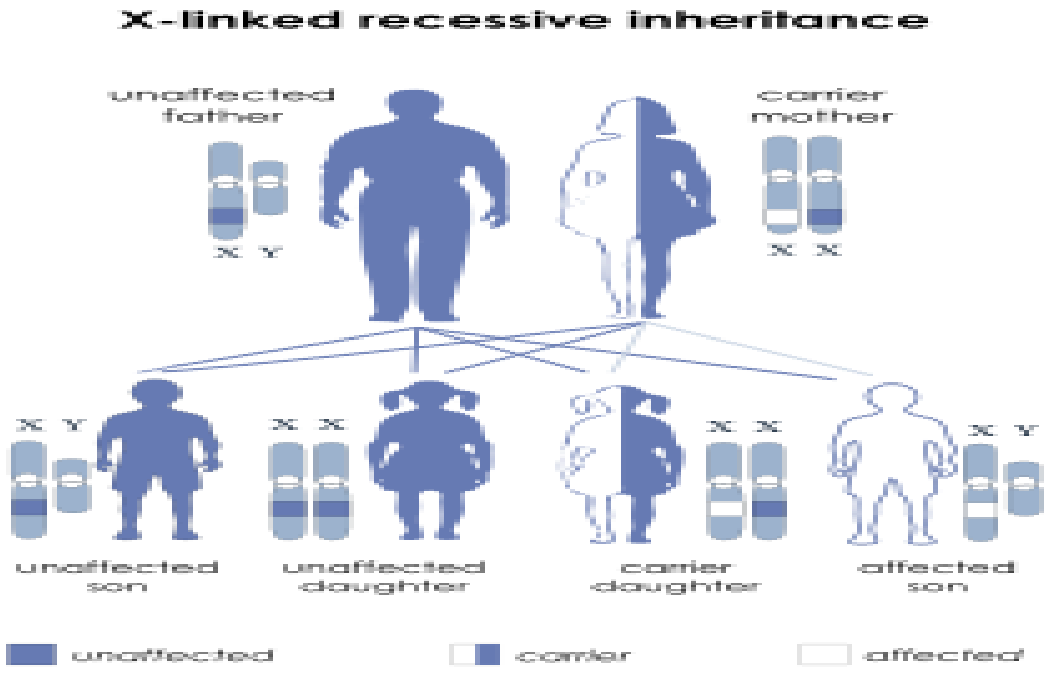




Characteristics of X-linked dominant diseases include:

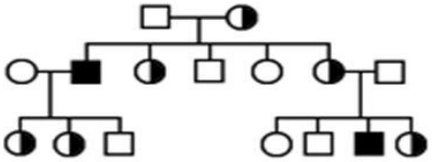
- Never passed from father to son.
- Affected males produce only affected females. An affected male only has one X chromosome to pass on to his daughters
- Affected females produce **50%** normal and **50%** affected offspring.. >>>> heterozygous
- Males are usually more severely affected than females. Some X-linked dominant traits may even be lethal to males.
- Females are more likely to be affected. Since females have **2** X chromosomes, they have **2** "chances" to inherit the mutated allele.

X- linked Recessive Inheritance



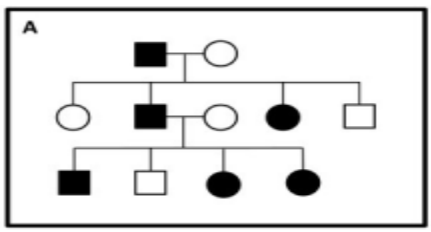
X-linked Recessive

- X-linked recessive traits are not clinically manifest when there is a normal copy of the gene.
- All X-linked recessive traits are fully evident in males because they only have one copy of the X chromosome, thus do not have a normal copy of the gene to compensate for the mutant copy.
- For that same reason, women are rarely affected by X-linked recessive diseases, however they are affected when they have two copies of the mutant allele.
- Because the gene is on the X chromosome there is no father to son transmission, but there is father to daughter and mother to daughter and son transmission.
- If a man is affected with an X-linked recessive condition, all his daughter will inherit one copy of the mutant allele from him.

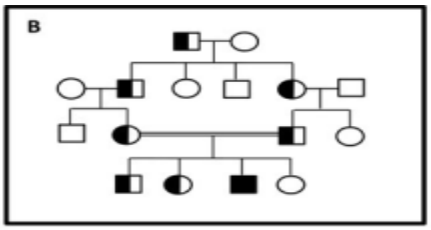


- **Duchenne muscular dystrophy (DMD)**
- **Hemophilia A**
- **X-linked severe combined immune disorder (SCID)**
- **Some forms of congenital deafness**

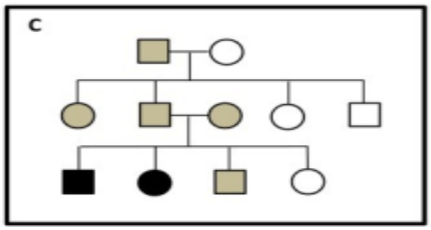
Family Pedigree



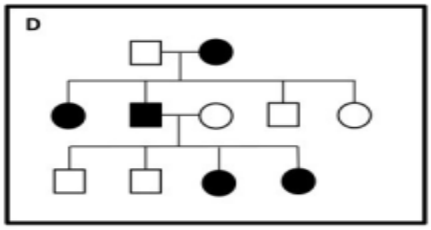
Autosomal dominant inheritance



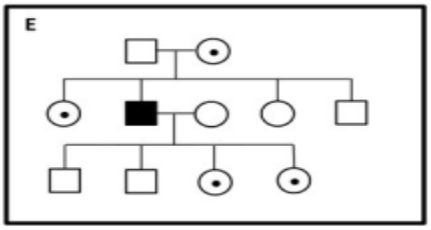
Autosomal recessive inheritance



Autosomal co-dominant inheritance



X-linked dominant inheritance



X-linked recessive inheritance