Inheritance patterns

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Disorders

- Chromosomal disorders
- Monogenic disorders
- Polygeneic/multifactorial/Complex disorders
- Mitochondrial disorders
- Cancer/somatic mutations

Human Molecular Genetics by Strachan T and Read AP, 5th edition, CRC Press

Monogenic Disorders

These are the disorders caused by the inheritance of the single mutated gene from parent to offspring known as "*Monogenic disorders or Single-gene Diseases*" .

Most of the monogenic disorders are spontaneous and naturally occurring whereas, some are non-spontaneous and due to environmental changes .

Over 10,000 of human genetic diseases are known to be monogenic.

Highly prevalent

Significant recent progress with diagnostic and therapeutic issues

Monogenic Disorders/Single Gene Defects

- These disorders are categorized as “Autosomal” or “Sex-Linked” based upon their origin whether the mutation is in an autosome or in a sex chromosome.
- Monogenic disorders inheritance are as follows;

1. Autosomal Dominant Inheritance (Huntington’s Chorea, Osteogenesis imperfecta , Neurofibromatosis,Tuberous sclerosis)
2. Autosomal Recessive Inheritance (cystic fibrosis, phenylketonuria, homocystinuria, hemochromatosis, sickle cell anemia, thalassemias, alkaptonuria, Tay-sachs disease, Phenylketonuria neurogenic muscular atrophies)

- 3. X-Linked Dominant Inheritance (Vitamin D resistant rickets, Incontinentia pigmenti and Congenital generalized hypertrichosis)

Autosomal Disorders

Both Males and Females affected, and both transmit to both sexes of offspring

- **Recessive**
  - usually rare in population
  - Skips Generations
  - Inbreeding increases risk of recessive traits
- **Dominant**
  - Doesn’t skip generations

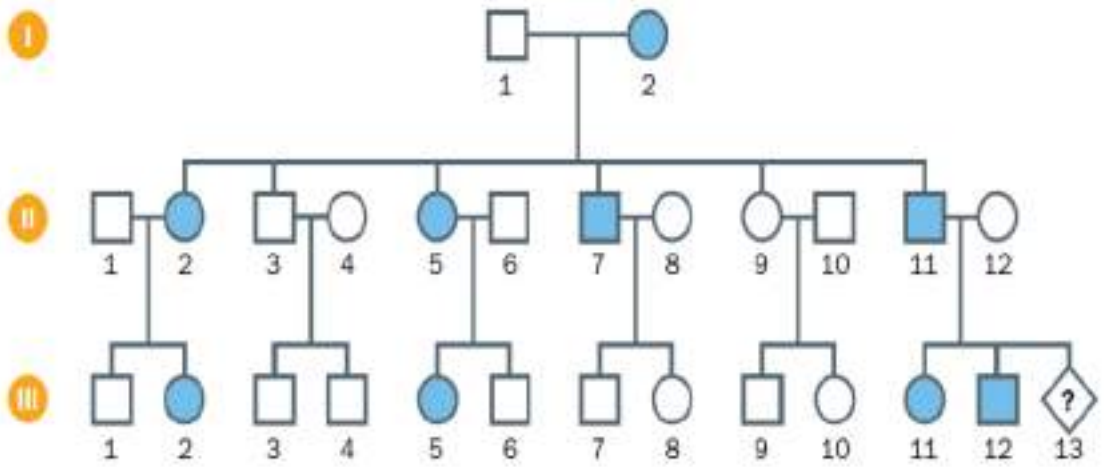
Autosomal Dominant Inheritance

An affected person usually has at least one affected parent (but exceptions are due to new mutations or non-penetranc).

It affects either sex.

It is transmitted by either sex.

A child with one affected and one unaffected parent has a 50% chance of being affected (this assumes that the affected person is heterozygous, which is usually true for rare conditions).



An ideal autosomal dominant pedigree.

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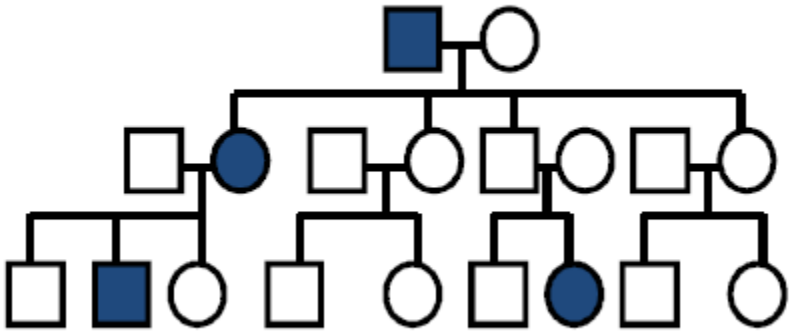
Autosomal Dominant (Non penetrance)

- An individual who inherits the disease gene does not develop the disorder

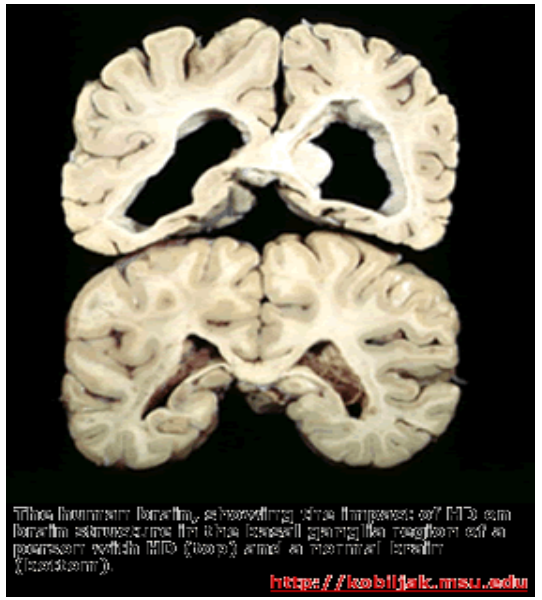
- The disorder appears to **"skip" generations**



Huntington's Disease

- Autosomal, dominant
- Deterioration of brain tissue, usually begins between age 30 and 40.
- No cure, but have medications to cope with symptoms
- People usually die 15-20 years after onset of

  degeneration



Achondroplastic Dwarfism

Achondroplasia is caused by a gene alteration (mutation) in the *FGFR3* gene."[5]

As a result of this gene mutation, individuals with achondroplasia "have short arms and legs, a large head, and characteristic facial features with frontal bossing [pronounced forehead] and midface retrusion [increased concavity of the face].“[

These characteristics may be noticeable upon birth, and infants with this condition usually suffer from hypotonia, or weak muscle tone.[5]

megalocephaly

short limbs

low nasal bridge

caudal narrowing of spinal cord

- **skeletal anomalies**
- **mild hypotonia**
- **normal intelligence**

The Johnston Family

Autosomal Recessive Inheritance

Affected people are usually born to unaffected parents.

Parents of affected people are usually asymptomatic carriers.

There is an increased incidence of parental consanguinity.

It affects either sex.

After the birth of an affected child, each subsequent child has a 25% chance of being affected (assuming that both parents are heterozygous carriers).

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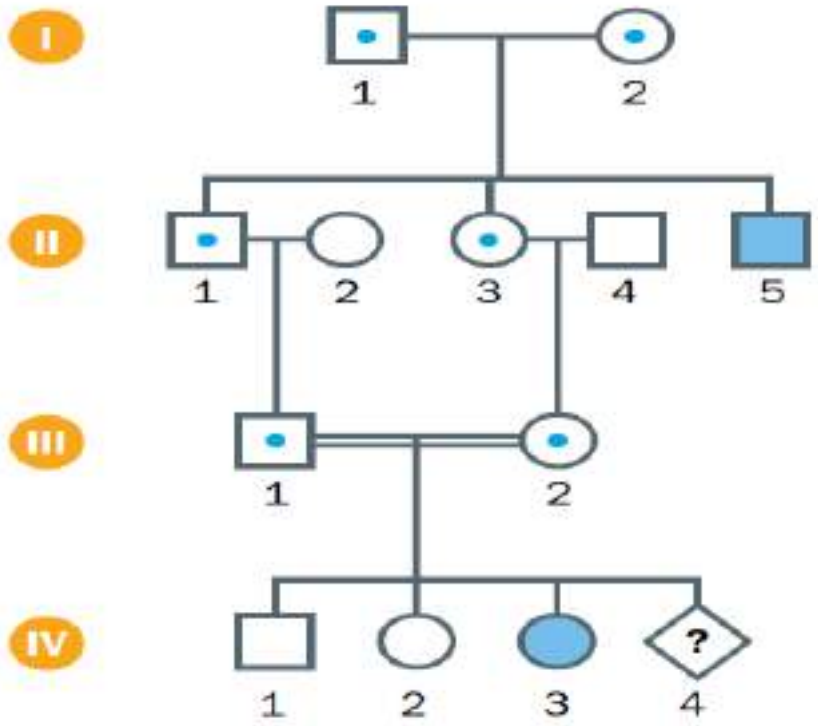

Pedigree of an autosomal recessive character

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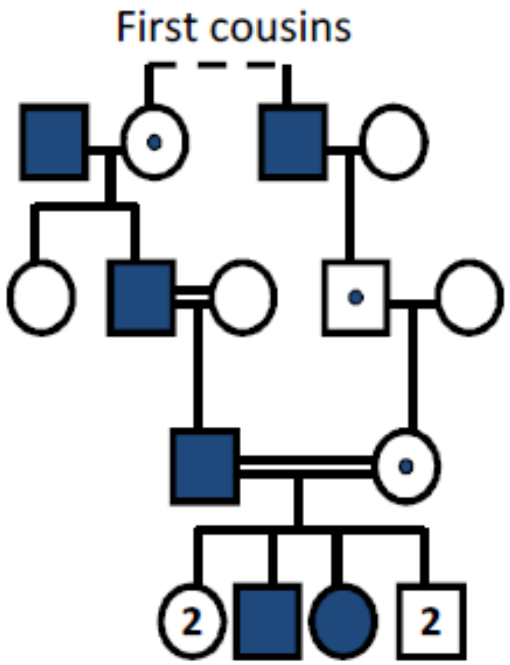
Autosomal Recessive Consanguinity

Increased consanguinity (over general population) is often found between parents of a child with a rare autosomal recessive disorder

Condition may appear to be dominant in a consanguineous family



Autosomal recessive (AR) pedigree

There is an increased incidence of parental consanguinity

Affected children are homozygous for mutant gene

Affected individuals are usually born to unaffected parents

Usually due to mutations that reduce or eliminate the function of the gene product (loss-of-function)

AR Disorders

PKU - phenylketonuria

Galactosemia

Homocystinuria

Cystic fibrosis

Tay-Sachs

Sickle cell anemia

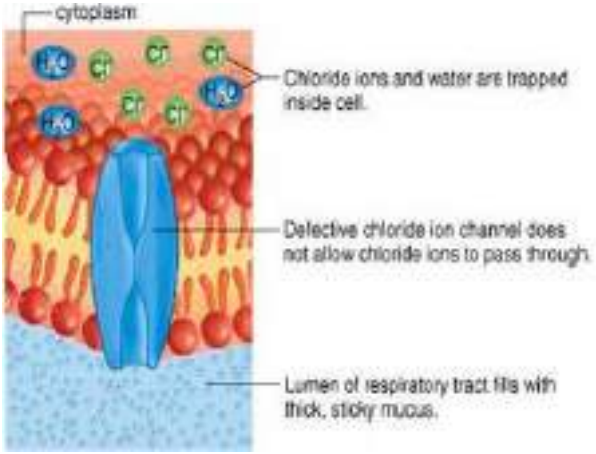
Albinism

- Lack of pigmentation
- Fair skin and hair
- Decreased visual acuity
- Lack of stereoscopic vision
- Mutations in the gene encoding Tyrosinase (lack of Melanin)

Sickle-cell anemia

Irregular red blood cells caused by abnormal hemoglobin
Clog vessels- poor circulation
Internal hemorrhaging
Heterozygous individuals are normal unless dehydrated or experience mild oxygen deprivation

Cystic fibrosis



Most common genetic disorder in Caucasians
Defect in chloride channel proteins in cells
Thick, abnormal mucus production
Lungs, bronchial tubes, pancreatic ducts affected

X-linked Recessive Inheritance

It affects mainly males.

Affected males are usually born to unaffected parents; the mother is normally an asymptomatic carrier but may have affected male relatives.

Females may be affected if the father is affected and the mother is a carrier, or occasionally as a result of nonrandom X-inactivation.

There is no male-to-male transmission in the pedigree (but matings of an affected male and carrier female can give the *appearance of male-to-male transmission.*

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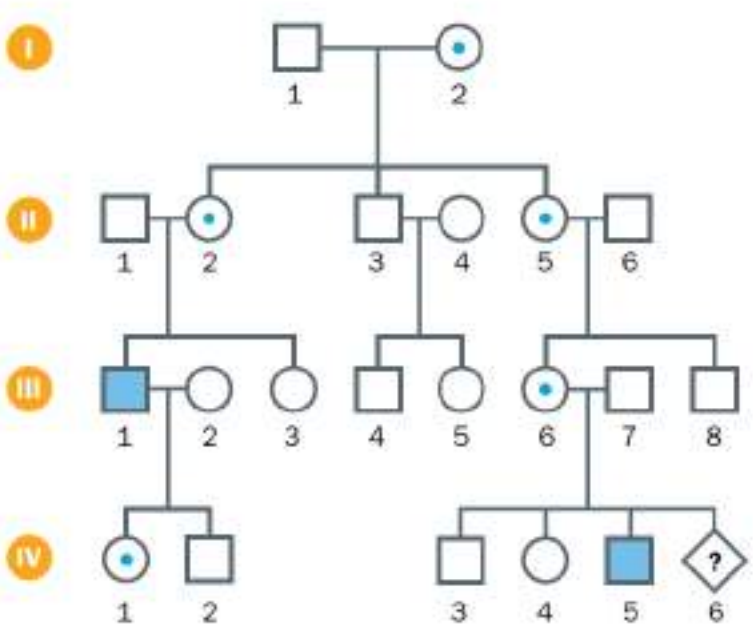

Pedigree pattern of an X-linked recessive condition

Homozygous dominant = normal female (X^AX^A)
Heterozygous dominant = normal female carrier (X^AX^a)
Homozygous recessive = affected female (X^aX^a)

Hemizygous dominant = normal male (X^AY)
Hemizygous recessive = affected male (X^aY)

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- More males are affected
- Passed from affected mothers to all sons
- Affected fathers will only transmit to heterozygous, unaffected daughters
- Very rare to see homozygous recessive females
- To be affected, daughters must inherit it from both parents
- Sons can only inherit it from mother, therefore more males affected than females

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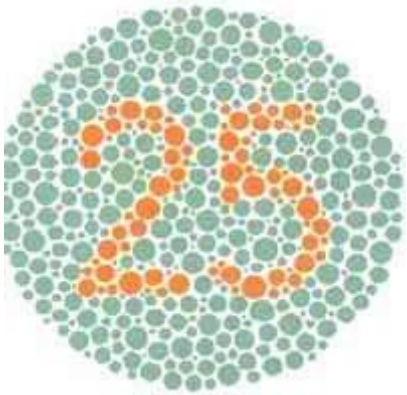
X-linked recessive traits

Glucose-6-Phosphate Dehydrogenase deficiency

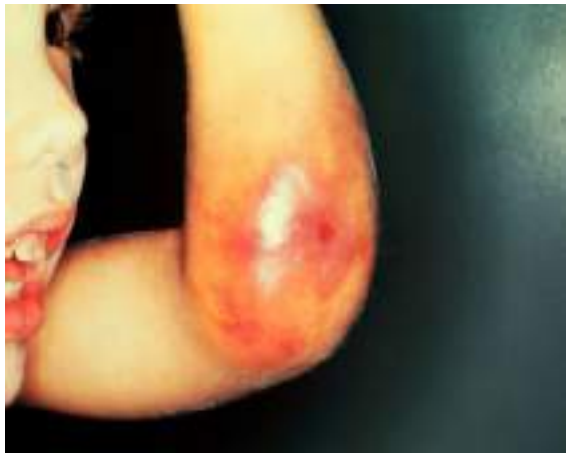
- the most common enzyme disorder worldwide, especially in those of Mediterranean ancestry
- may confer malaria resistance
- hemolytic disorder causes jaundice in infants and (often fatal) sensitivity to fava beans in adults

Red-green color blindness



In most cases, the inability to distinguish red from green, or to see red and green in the same way as most people do, because of an abnormality in the red or green photoreceptors.
About 7 percent of men are red-green color blind, compared to 0.4 percent of women.

Hemophilia



a group of hereditary disorders in which affected individuals fail to make enough of certain proteins needed to form blood clots.

X-linked Dominant Inheritance

It affects either sex, but more females than males.

Usually at least one parent is affected.

Females are often more mildly and more variably affected than males (because of X-inactivation).

The child of an affected female, regardless of its sex, has a 50% chance of being affected.

For an affected male, all his daughters but none of his sons are affected.

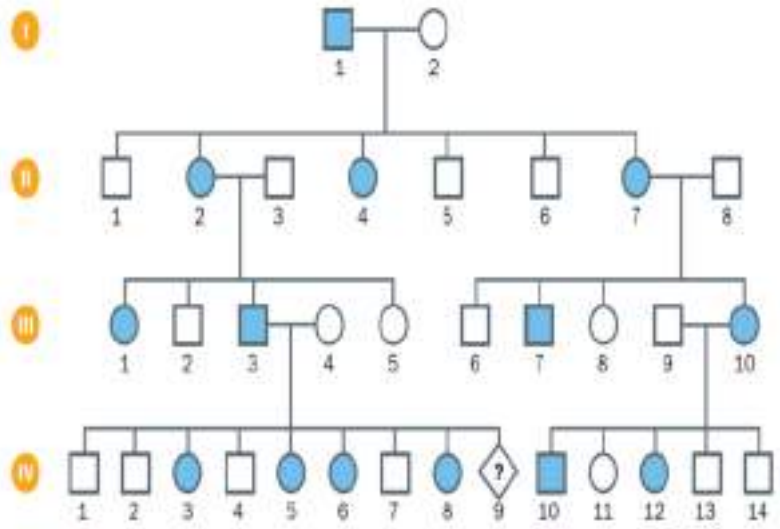
X-Linked Dominant

- Males and females both affected
- Can be passed to both offspring, however often see more females affected because of male lethality
- Affected fathers to every single daughter
    - Affected males pass the trait only to daughters
    - Females can pass trait to both daughters and sons

For rare conditions, females are about 2x as likely to be affected than males.

May be lethal in males and usually milder, but variable, in females.

Affected males pass the gene to all of their daughters, who will be affected, and to none of their sons (NO male-to-male transmission)



Pedigree pattern of an X-linked dominant condition

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Congenital generalized hypertrichosis (CGH) Xq24-27.1.

Congenital generalized hypertrichosis (CGH), is the type of X-linked dominant; the gene that is mutated is found on the X chromosome.

X-linked congenital generalized hypertrichosis is a rare congenital (present at birth) skin disease.

It is characterized by hair overgrowth on the entire body in males, and mild and asymmetric hair overgrowth in females.

It is associated with mild facial abnormalities (including nasal openings that are tipped upwards and moderate protrusion of the jaw) and occasional teeth anomalies and deafness.

https://en.wikipedia.org/wiki

Vitamin D resistant rickets

Frequency: 1/20,000

Growth retardation and childhood rickets,reduced serum phosphate.

Treatable with large doses of vitamin D (or its active metabolite calcitrol0 and oral phosphate.

X-linked dominant trait with locus at Xp21-22; presymptomatic detection possible using linked RFLPs.

Y-linked (Holandric)

Only males are affected

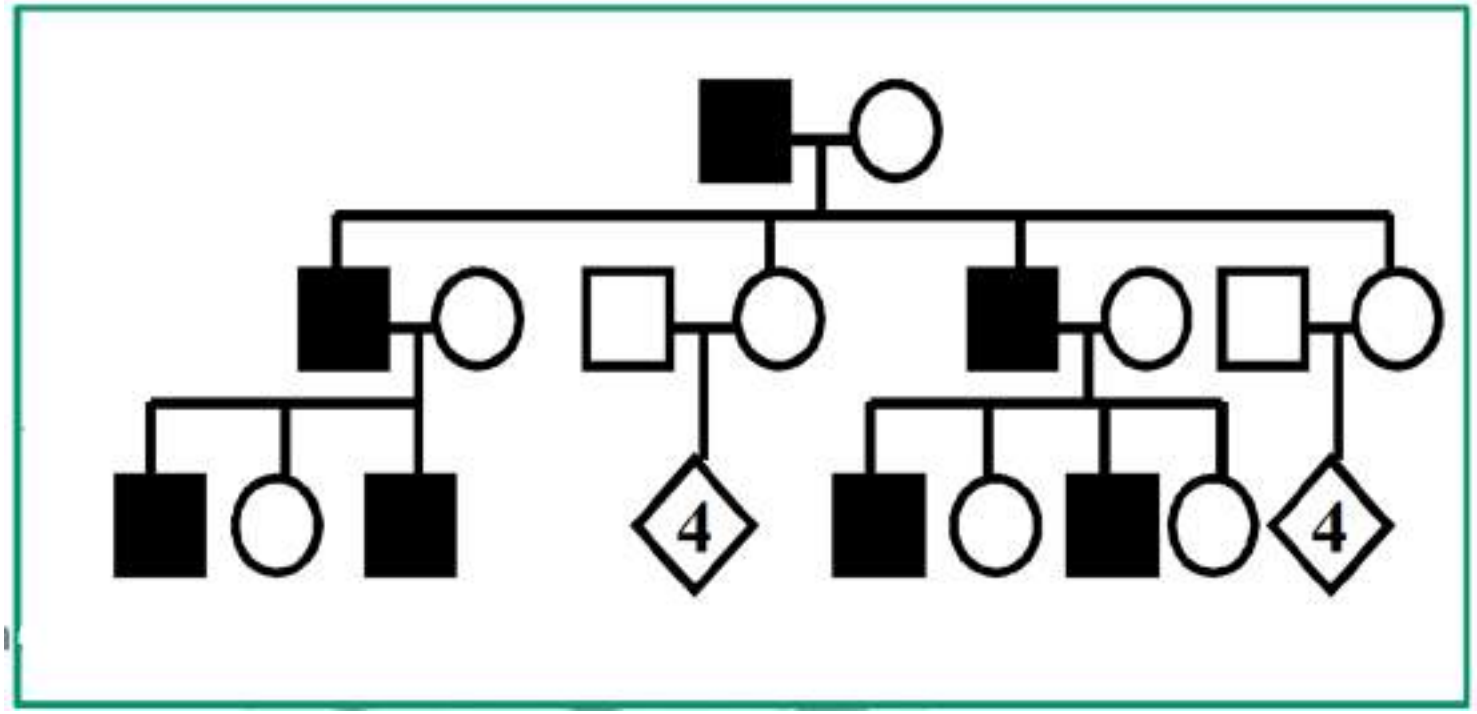
Affected males pass the

disease gene to all their sons and to none of their daughters.

All sons of an affected man are affected.

Example-

Hair on pinna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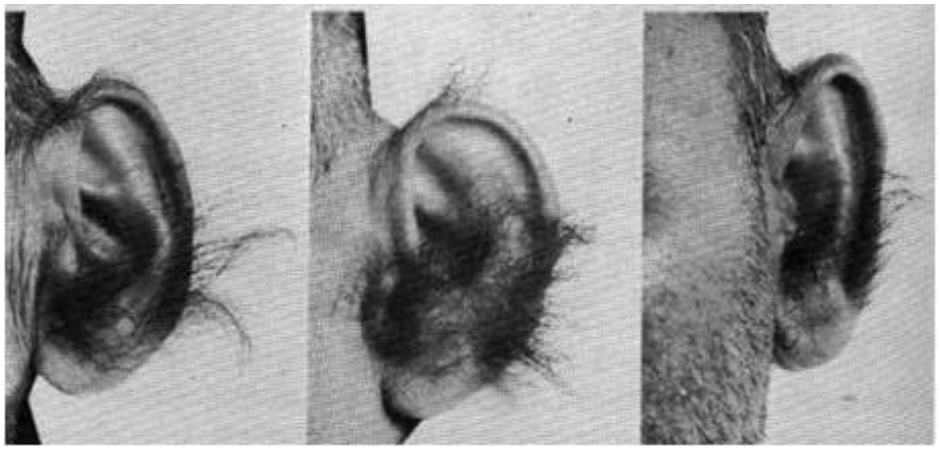

Mitochondrial Inheritance

It affects **both sexes.**

It is usually inherited from an affected mother (but is often caused by *de novo mutations, with the mother* unaffected).

It is not transmitted by a father to any of his children.

Clinical manifestations are often highly variable.

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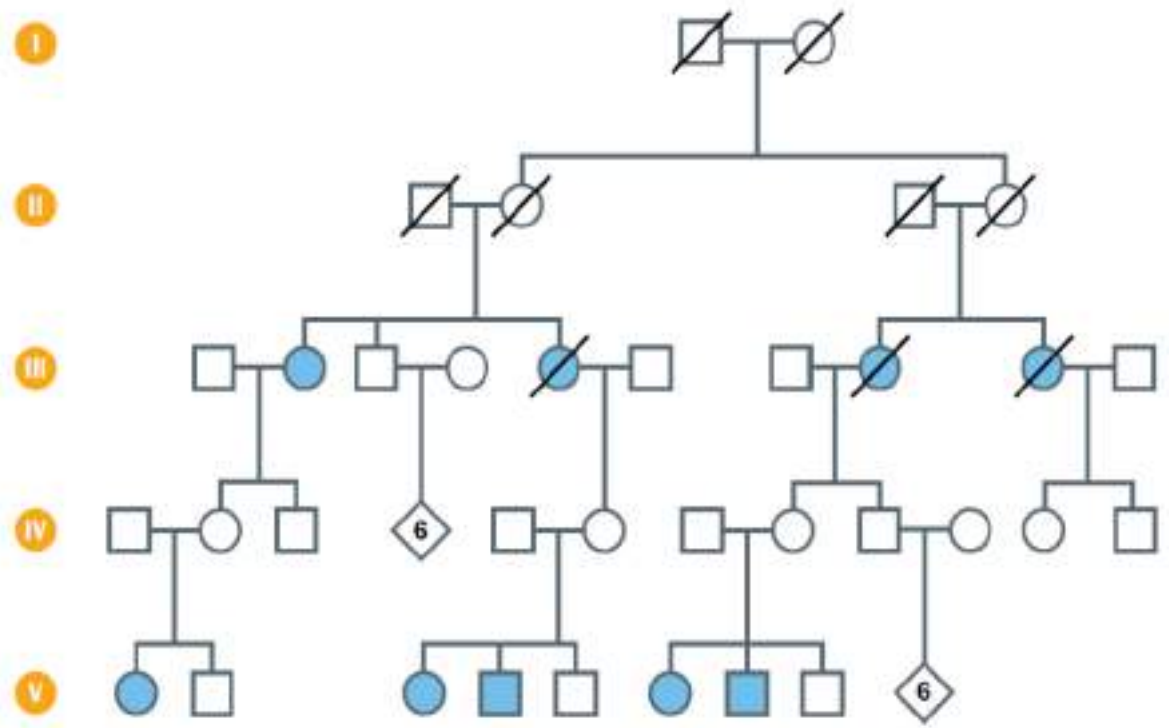

Pedigree of a mitochondrially determined condition

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Common mitochondrial DNA mutations and Mitochondrial diseases

Mitochondrial Encephalomyopathy With Lactic Acidosis and Stroke (MELAS)

Myoclonic Epilepsy with Ragged Red Fibres(MERRF)

Leber Hereditary Optic Neuropathy (LHON)

External Ophthalmoplegia

Kearns-sayre Syndrome

Chronic Progressive External Ophthalmoplegia

Neurogenic Weakness Ataxia with Retinitis Pigmentosa(NARP)

Suggested Reading

•Human Molecular Genetics – Tom Stratchen & Andrew P. Read. Pub: John Wiley & Sons.

•An introduction to Genetic Analysis– Griffith, Miller, Suzuki, Lewontin, Gelbard. Pub: W.H. Freeman & Co.

•Genomes 2 – T.A. Brown, Pub: Wiley-Liss. John W. & Sons.

•Emery's Elements of Medical Genetics (1998)– R.F. Mueller, I.D. Young, Pub: Churchill

•An Introduction to Human Molecular Genetics (1999)– J.J. Pasternak, Pub: Fitzgerald Science