Clinical genetics

Lectures for 5th year medical students

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References:

1- Nelson Text Book of Pediatrics

2- Illustrated Text Book of Pediatrics

Lecture 1 inheritance pattern Dr. Miami

Objective

To understand different modes of inheritance, interpretation of pedigree, with clinical examples

Inheritance pattern

Inheritance patterns trace the transmission of genetically encoded traits, conditions or diseases to offspring. There are several modes of inheritance:

- **Single Gene or Mendelian**
- **Multifactorial**
- **Mitochondrial**

- **Single Gene Inheritance:**
- Genetic conditions caused by a mutation in a single gene follow predictable patterns of inheritance within families. There are four types of Mendelian inheritance patterns:

Autosomal dominant Autosomal recessive
X-linked recessive X-linked dominant

Autosomal: the gene responsible for the phenotype is located on one of the 22 pairs of autosomes (non-sex determining chromosomes).

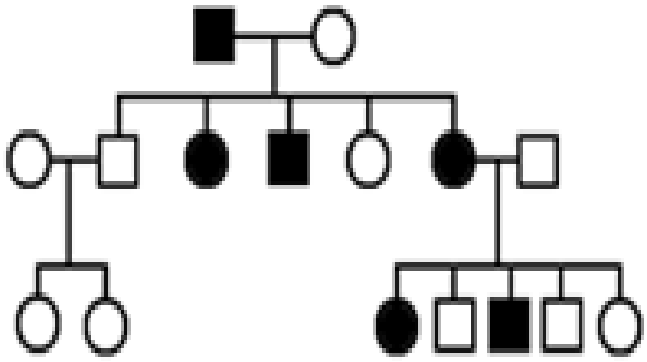
X-linked: the gene that encodes for the trait is located on the X chromosome.

Dominant: conditions that are manifest in heterozygotes (individuals with just one copy of the mutant allele).

Recessive: conditions are only manifest in individuals who have two copies of the mutant allele (are homozygous).

Autosomal Dominant

Dominant conditions are expressed in individuals who have just one copy of the mutant allele. The pedigree illustrates the transmission of an autosomal dominant trait. Affected males and females have an equal probability of passing on the trait to offspring. Affected individuals have one normal copy of the gene and one mutant copy of the gene, thus each offspring has a 50% chance on inheriting the mutant allele. The disorder is transmitted in a vertical pattern appearing in multiple generations and there is male to male transmission. For many patients with AD disorder there is no history of an affected family member, the patient may represent a new mutation or the condition demonstrates incomplete penetrance meaning that not all individuals who carry the mutation have phenotypic manifestations

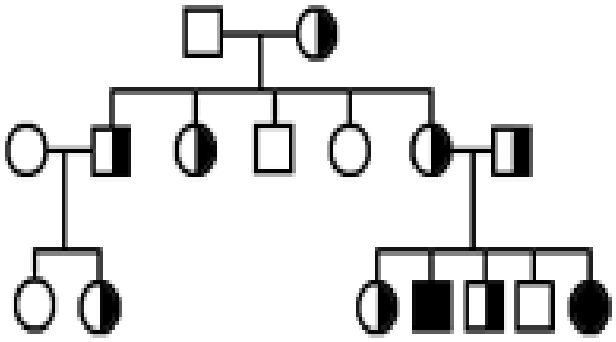


Autosomal Dominant Conditions:

- **Huntington Disease**
- **acondroplasia (short-limbed dwarfism)**
- **polycystic kidney disease**

Autosomal Recessive

Recessive conditions are clinically manifest only when an individual has two copies of the mutant allele. When just one copy of the mutant allele is present, an individual is a carrier of the mutation, but does not develop the condition. Females and males are affected equally by traits transmitted by autosomal recessive inheritance. When two carriers mate, each child has a 25% chance of being homozygous (unaffected); a 25% chance of being homozygous mutant (affected); or a 50% chance of being heterozygous (unaffected carrier).



Autosomal recessive diseases:

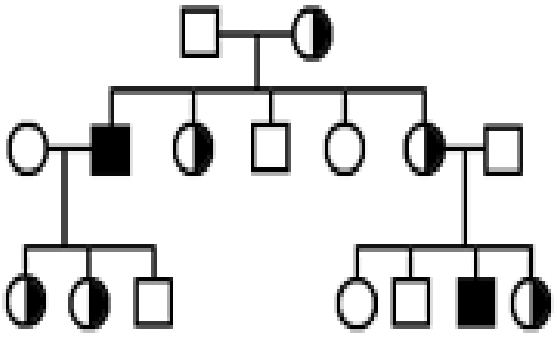
- **Cystic fibrosis**
- **SCA, Thalassemia**
- **hemochromatosis**
- **phenylketonuria (PKU)**

Pseudo dominant inheritance

Refers to the observation of apparent dominant (parent to child) transmission of a known AR disorder. This occurs when a homozygous affected individual has a partner who is a heterozygous carrier, most likely occurs with sickle cell anemia and congenital deafness.

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 disease, 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 daughters will inherit one copy of the mutant allele from him (carriers). There is no male to male transmission. A female may exhibit signs of X-linked trait in the presence of sex chromosome abnormality (45,xo)

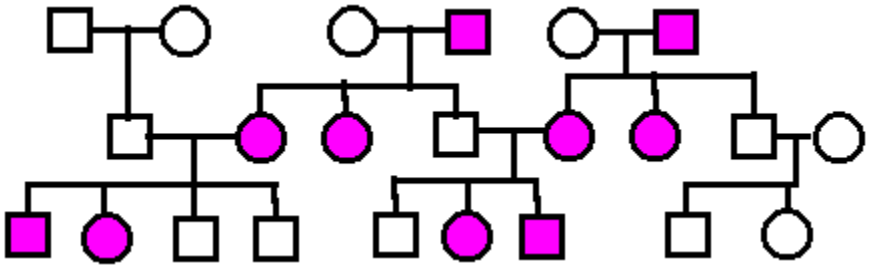


X-linked Recessive Disorders:

- **Duchenne muscular dystrophy**
- **hemophilia A**
- **X-linked severe combined immune disorder (SCID)**
- **some forms of congenital deafness**

X-linked Dominant

Because the gene is located on the X chromosome, there is no transmission from father to son, but there can be transmission from father to daughter (all daughters of an affected male will be affected since the father has only one X chromosome to transmit). Children of an affected woman have a 50% chance of inheriting the X chromosome with the mutant allele. X-linked dominant disorders are clinically manifest when only one copy of the mutant allele is present.



X-linked Dominant Disorders

- **some forms of retinitis pigmentosa**
- **Chondrodysplasia Punctata**
- **hypophosphatemic rickets**

Multifactorial Inheritance

Most diseases have multifactorial inheritance patterns. As the name implies, multifactorial conditions are not caused by a single gene, but rather are a result of interplay between genetic factors and environmental factors. Diseases with multifactorial inheritance are not genetically determined, but rather a genetic mutation may predispose an individual to a disease. Other genetic and environmental factors contribute to whether or not the disease develops.

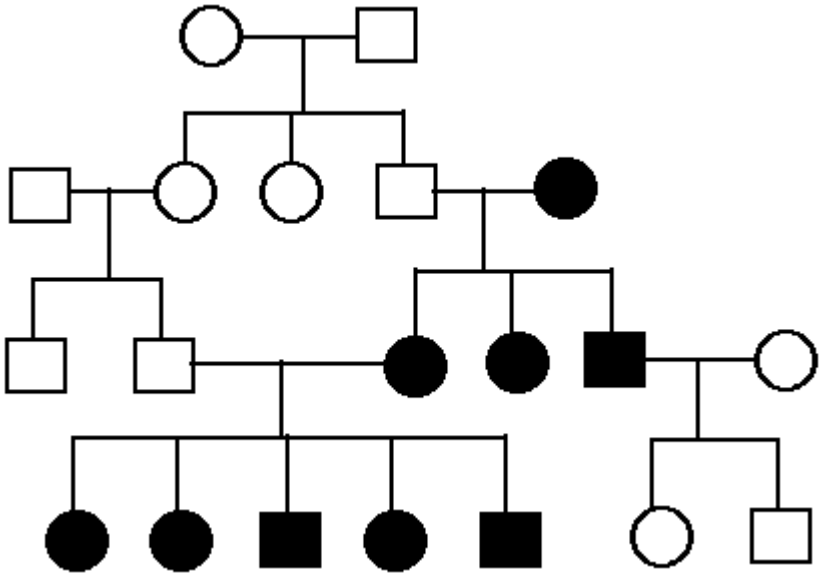
Numerous genetic alterations may predispose individuals to the same disease (genetic heterogeneity). For instance coronary heart disease risk factors include high blood pressure, diabetes, and hyperlipidemia. All of those risk factors have their own genetic and environmental components. Thus multifactorial inheritance is far more complex than Mendelian inheritance and is more difficult to trace through pedigrees.

Conditions with multifactorial inheritance:

- Alzheimers disease
- heart disease
- some cancers
- neural tube defects
- schizophrenia
- insulin-dependent diabetes mellitus
- intelligence

Mitochondrial Inheritance

Mitochondria are organelles found in the cytoplasm of cells. Mitochondria are unique in that they have multiple copies of a circular chromosome. Mitochondria are only inherited from the mother's egg, thus only females can transmit the trait to offspring, however they pass it on to all of their offspring. The primary function of mitochondria is conversion of molecule into usable energy. Thus many diseases transmitted by mitochondrial inheritance affect organs with high-energy use such as the heart, skeletal muscle, liver, and kidneys



Examples of mitochondrial inheritance:

1- DAD= Diabetes Mellitus And Deafness
2- Mitochondrial Myopathy
3- MELAS = Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, Stroke like symptoms