Lecture-4

Mendelian Inheritance

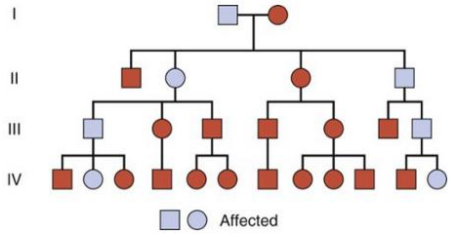
Mendelian Inheritance

- Within a population, there may be a number of alleles for a given gene.
- Individuals that have two copies of the same allele are referred to as homozygous for that allele; individuals that have copies of different alleles are known as heterozygous for that allele.
- The inheritance patterns observed will depend on whether the allele is found on an autosomal chromosome (autosomal inheritance) or a sex chromosome (sex-linked inheritance).
- Inheritance pattern also depends on whether the allele is dominant or recessive.

Autosomal Dominant

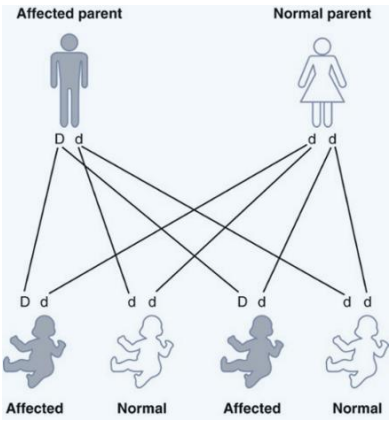
- Alteration in **one copy of the gene** (heterozygous) is sufficient to impair cell function, leading to disease.
- The alteration is located on an **autosome.**
- Each generation has affected persons
- Males and females are affected in roughly equal proportions.
- All forms of transmission present (male to female, male to male, female to male and female to female).

Family tree of autosomal dominant trait



Autosomal Dominant

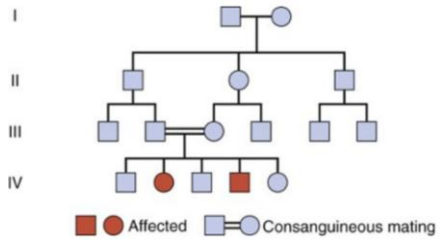
- Each gamete from an individual with a dominant trait or disorder will contain either the normal allele or the mutant allele.
- In the figure, the dominant mutant allele is shown as 'D' and the normal allele as 'd'.
- Any child born to a person affected with a dominant trait or disorder has a 1 in 2 (50%) chance of inheriting it and being similarly affected.



Autosomal Recessive

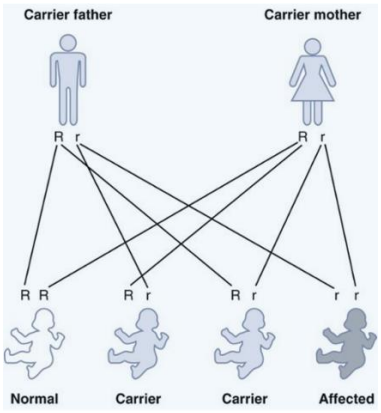
- The phenotype (disorder) is observed only when both the copies of gene have mutant alleles (**homozygous)**.
- Individuals heterozygous for such mutant alleles show no features of the disorder and are perfectly healthy; they are described as **carriers**.
- It is not possible to trace an autosomal recessive trait or disorder through the family, as all the affected individuals in a family are usually in a single **sibship** (i.e., brothers and sisters).
- Both males and females have the condition in roughly equal proportions.
- Consanguinity increases the chance that a condition presenting in a child might be due to both parents being carriers for the same recessive gene alteration.

Family tree of autosomal recessive trait



Autosomal Recessive

- A person with an autosomal recessive condition must have inherited one gene alteration from each parent.
- In the figure, R=normal dominant allele and r=recessive mutant allele and each parental gamete carries either the mutant or the normal allele.
- At conception each child of parents who are both carriers has a chance to be:
  - Normal: 1 in 4 (25%)
  - Carrier: 2 in 4 (50%)
  - Affected: 1 in 4 (25%)

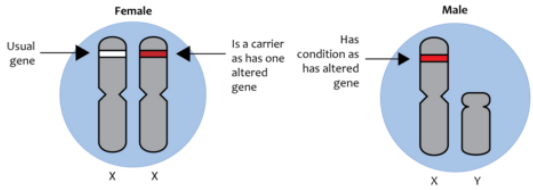


Sex-Linked Inheritance

- Sex-linked inheritance refers to the pattern of inheritance shown by genes that are located on either of the sex chromosomes.
- Genes carried on the X chromosome are referred to as being **X-linked**.
- Genes carried on the Y chromosome are referred to as exhibiting **Y-linked** or **holandric inheritance**.
- The X chromosome carries hundreds of genes, and many of these are not connected with the determination of sex.
- The smaller Y chromosome contains a number of genes responsible for the initiation and maintenance of maleness, but it lacks copies of most of the genes that are found on the X chromosome.
- A number of medical conditions in humans are associated with genes on the X chromosome, including hemophilia, muscular dystrophy and color blindness.

X-Linked Recessive Inheritance

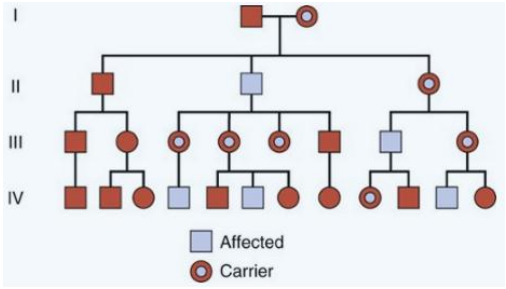
- Only males are usually affected. As males have only one X chromosome, if they have a gene alteration on their X chromosome they will develop the condition.
- Females rarely show signs of X-linked recessive conditions as they have a second unaltered copy of the gene to compensate for an altered gene.
- Transmitted through unaffected heterozygous females (carriers) to their sons.
- Males cannot transmit the disorder to their sons (no male-to-male transmission)
- Hemizygous (only one allele) males can transmit the affected gene to their carrier daughters.



X-Linked Recessive Inheritance

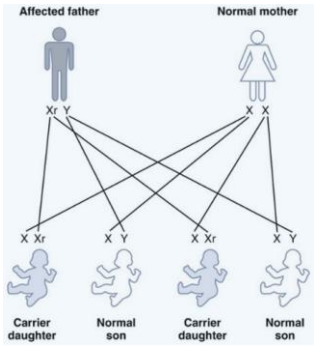
- Queen Victoria was a carrier of hemophilia, and her carrier daughters, who were healthy, introduced the gene into the Russian and Spanish royal families.
- Fortunately, Queen Victoria's son, Edward VII, did not inherit the gene and so could not transmit it to his descendants.

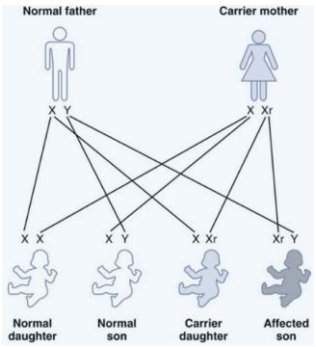
Family tree of X-linked recessive trait



X-Linked Recessive Inheritance

- A male transmits his X chromosome to each of his daughters and his Y chromosome to each of his sons.
- If a male affected with hemophilia has children with a normal female, then all of his daughters will be **obligate carriers** but none of his sons will be affected.
- For a carrier female having children with a normal male, each son has a 1 in 2 (50%) chance of being affected and each daughter has a 1 in 2 (50%) chance of being a carrier.

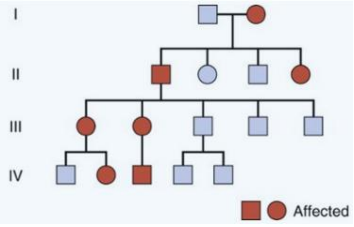




X-Linked Dominant Inheritance

- The disease is manifest in the heterozygous female as well as in the male who has the mutant allele on his single X chromosome.
- Affected males tend to have more significant disease than affected females.
- Affected male transmits the trait to all his daughters but to none of his sons.
- Therefore, in families there is an excess of affected females.
- Disorders inherited in this manner are relatively rare.
- Examples are vitamin D–resistant rickets, Charcot-Marie-Tooth disease, and incontinentia pigmenti.

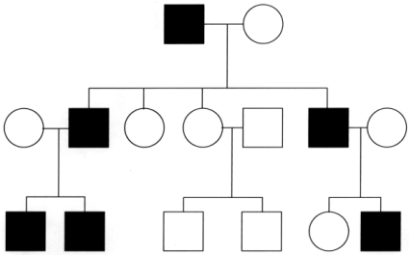
Family tree of X-linked dominant trait



Y-Linked Inheritance

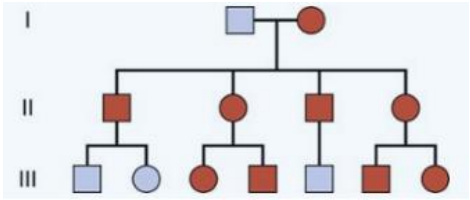
- Only males are affected.
- An affected male transmits Y-linked traits to all of his sons but to none of his daughters.
- Example is male infertility.

Family tree of Y-linked inheritance



Mitochondrial Inheritance

- Each cell contains thousands of copies of mitochondrial DNA with more being found in cells that have high energy requirements, such as brain and muscle.
- Mitochondria are inherited only from the mother (maternal inheritance).
- Both males and females are affected, but only females can transmit the disease.
- The organs most susceptible to mitochondrial mutations are central nervous system, skeletal muscle and heart because of their high energy demand.
- Because mitochondrial proteins are also encoded by nuclear genes. Mutations in these genes can also cause mitochondrial disorders.



Mitochondrial Inheritance

- In most persons, mtDNA from different mitochondria is identical (**homoplasmy)**.
- If a mutation occurs in mtDNA, there will be two populations of mitochondrial DNA (**heteroplasmy)**.
- The range of phenotypic severity in persons affected with mitochondrial disorders is associated with the extent of mutant mtDNA.