Mendelian disorders

Inheritance Patterns

The laws of inheritance were postulated by Gregor Mendal (1822 –1884) from his studies on garden pea. Genetic disorders due to single gene defect (monogenic disorders) classically follow the mendelian law of inheritance with few exceptions.

Mendelian law of inheritance:

1. Every trait is determined by two copies of the gene(called alleles), which are located at the same locus on homologous chromosome. Exception is sex chromosomes (XY) in males, where the trait is determined by single allele.
2. The dominant phenotypic trait requires only one allele. Hence it is expressed in heterozygous state and also in homozygous state.
3. The recessive trait expression requires homozygous gene pair (both the alleles have to be identical.
4. Codominance is expression of both the traits of a heterozygous gene pair. Example Blood group genes. (A and B genes are dominant; O is recessive)

Blood group Inheritance:

Blood group	Antigens present	Genotype
A	A antigen	OA (heterozygous) AA (homozygous)
B	B antigen	OB,BB
AB	A antigen B antigen	AB (heterozygous, Codominance)
O	No antigens	OO (homozygous)

Classification of Mendelian disorders

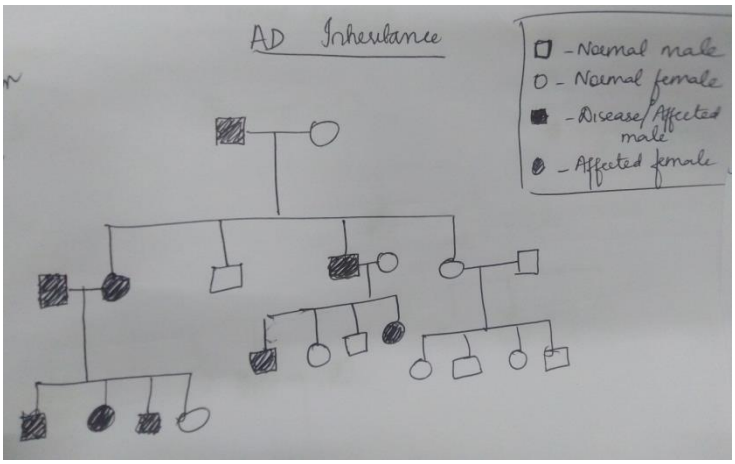
1. Autosomal Inheritance
    a. Autosomal Dominant
    b. Autosomal Recessive
2. Sex-linked Inheritance
    a. X-linked Recessive
    b. X-linked Dominant

Note: Mutations in Y chromosome affects the spermatogenesis causes infertility in the affected males. Hence no Y linked inheritance disorders are known.

The characteristic features of each group of disorders are described briefly.

Autosomal Dominant Disorders

- The gene involved is located in the autosomal chromosome. So males and females are equally affected.
- The disease can manifest in heterozygous and in homozygous state.
- Age of onset is delayed.
- Pedegree (family tree)



- One of the parent is usually affected.
- When the affected person marries a normal person, there is 50% chance of the offspring inheriting the disease
- All the generations will have some affected person
- Variations in penetrance and expressivity seen.

  Penetrance is given as percentage. 75% penetrance means only 75% of the individuals with inherited mutation will express the disease. The remaining 25% are phenotypically normal.

  Some mutation can have one or more phenotypic expression. Example: Neurofibromatosis Type I can manifest as multiple brown colored macules(café-au-lait spots), Lisch nodules in iris, freckles in axilla and groin, neurofibromas of skin , gliomas of optic nerve and skeletal deformities. The individuals who inherit the NFI gene , can vary in the expression from one to all the characteristics of the disease.
- The mutant gene usually encodes for a structural protein or regulatory protein.

The list of Mendelian disorders are given in Table

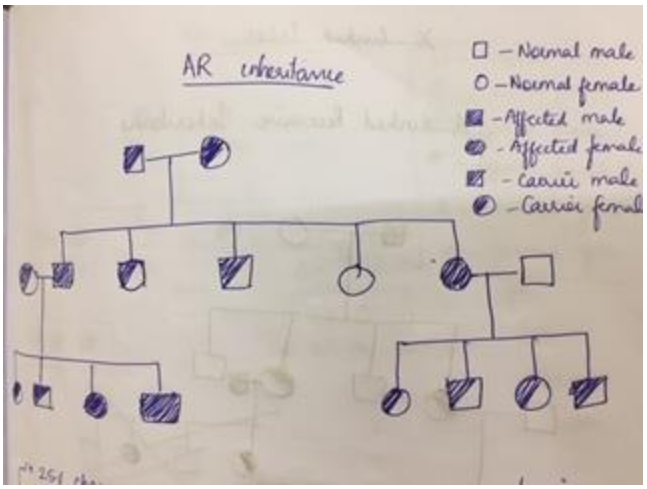
Mendelian Disorders

Inheritance / System	Autosomal Dominant	Autosomal Recessive	X- linked Recessive

Nervous	- Huntingtons disease - Neurofibromatosis - Myotonic Dystrophy	- Friedrich ataxia - Spinal Muscular Atrophy	Fragile X Syndrome
Hematology	- Heriditary Spherocytosis - von Willebrand disease	- Sickle cell anaemia - Thalassemia	Hemophilia A & B Glucose 6 phosphate dehydrogenase deficiency
MusculoSkeletal	- Marfan syndrome - Ehler Danlos syndrome (some variants) - Osteogenesis Imperfecta - Achondroplasia	Ehler Danlos syndrome (some variants)	Duchenne Muscular Dystrophy
Metabolic	- Familial Hypercholesterolemia - Acute Intermittent Porphyria	- Cystic Fibrosis - Phenylketonuria - Galactosemia - Homocystinuria - Lysosomal storage diseases - Glycogen Storage diseases - α 1 Antitrypsin deficiency - Wilson disease - Hemochromatosis - Alkaptonuria	- Diabetes Insipidus - Lesch Nyhan syndrome
Renal	Autosomal Dominant Polycystic Kidney Disease	Autosomal Recessive Polycystic Kidney Disease	
Gastrointestinal	Familial Polyposis Coli		
Immunity			- Chronic Granulomatous Disease -Agammaglobulinemia -Wiskott Aldrich Syndrome

Autosomal Recessive disorders:

- Most metabolic diseases show Autosomal Recessive Inheritance.
- The disease can manifest only in homozygous state. It is characterized by complete penetrance and full expression.
- The onset of symptoms occur early in life.
- The pedigree is shown below



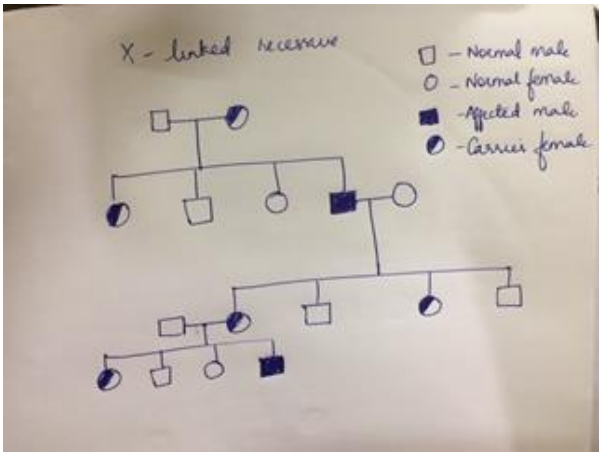
- Both males and females are affected
- Parents are usually normal (heterozygotes). Skip in generation seen.
- The siblings of affected person has 25% (1 in 4) chance of inheriting the disease
- More common in consanguinous marriage.
- If the affected person marries a normal individual, none of the offsprings are affected.
- Onset of symptoms occur early in life

X- LINKED INHERITANCE:

- Female have two X chromosomes, hence the X- linked traits can be dominant or recessive
- Males having one X chromosome are **hemizygous** and they express the trait, regardless of whether it is dominant or recessive .

X-linked Recessive disorders:

- The pedigree

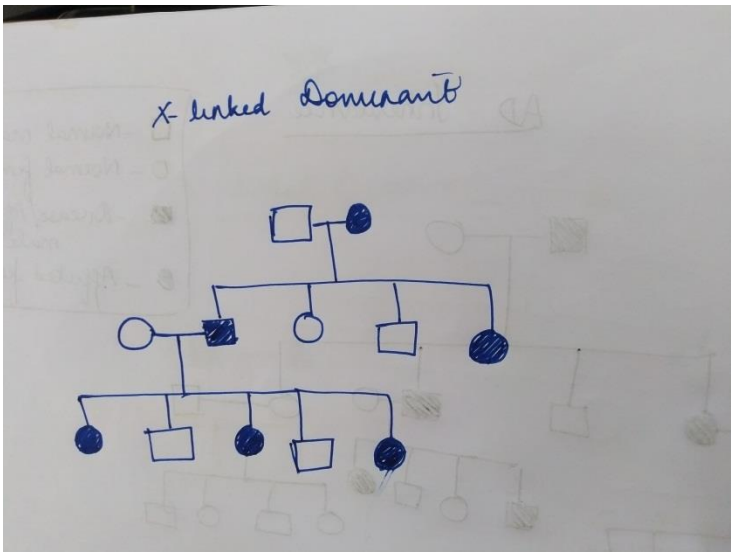


- Males are commonly affected.

- The affected male does not transmit the disease to his sons; but all his daughters are carriers.
- The carrier females do not manifest the disease, but have 50% (1in 2) chance of transmitting the disease to her sons and 50 % chance of daughters being carriers.
- Very rarely, because of random inactivation of the normal X chromosome (Lyon hypothesis) can result in disease manifestation in heterozygous (carrier) female.

X- linked Dominant inheritance:

They are very rare. The pedigree is shown



- Females are affected twice more than males.
- The affected female, transmits the disease to half of the children (50 % chance in both male and females)
- The affected male transmits the disease to all his daughters but none of his sons are affected.
- Examples: Vitamin D resistant(Familial hypophosphatemic) rickets and Ornithine transcarbamylase deficiency.