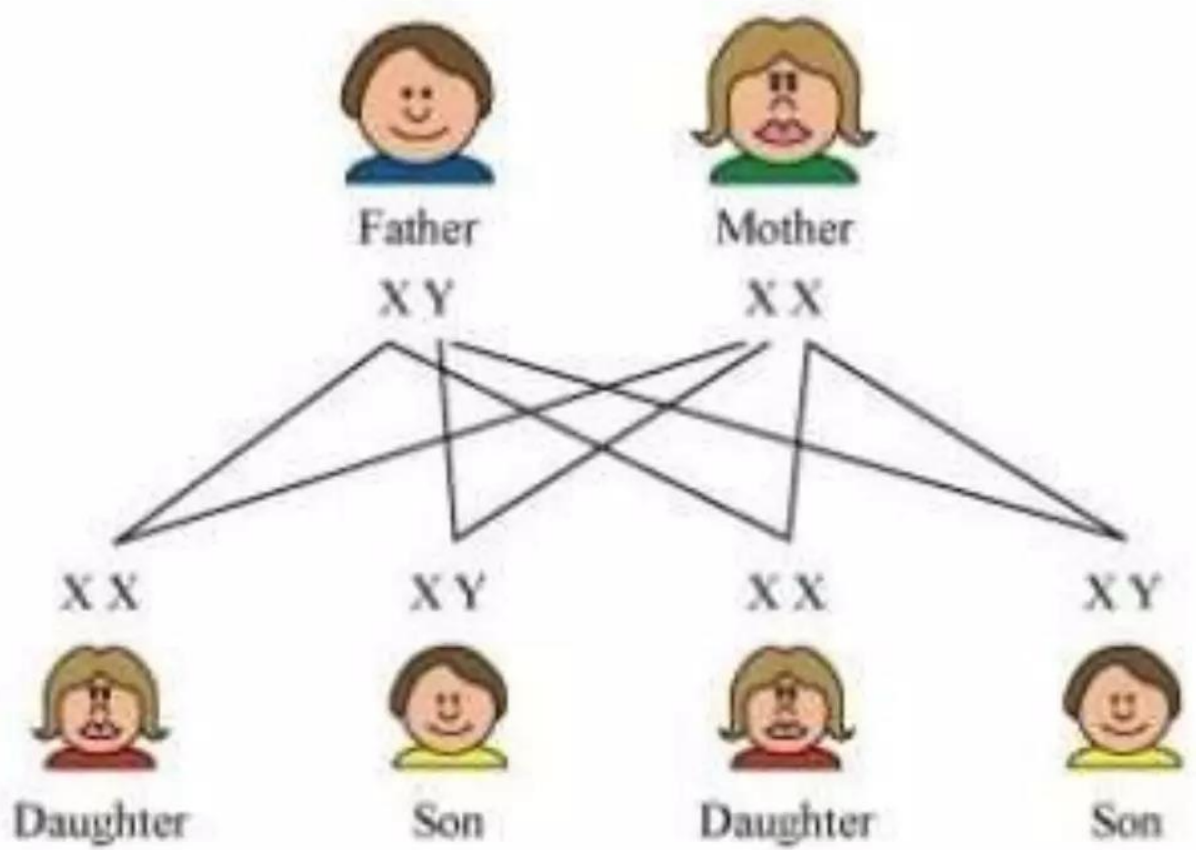
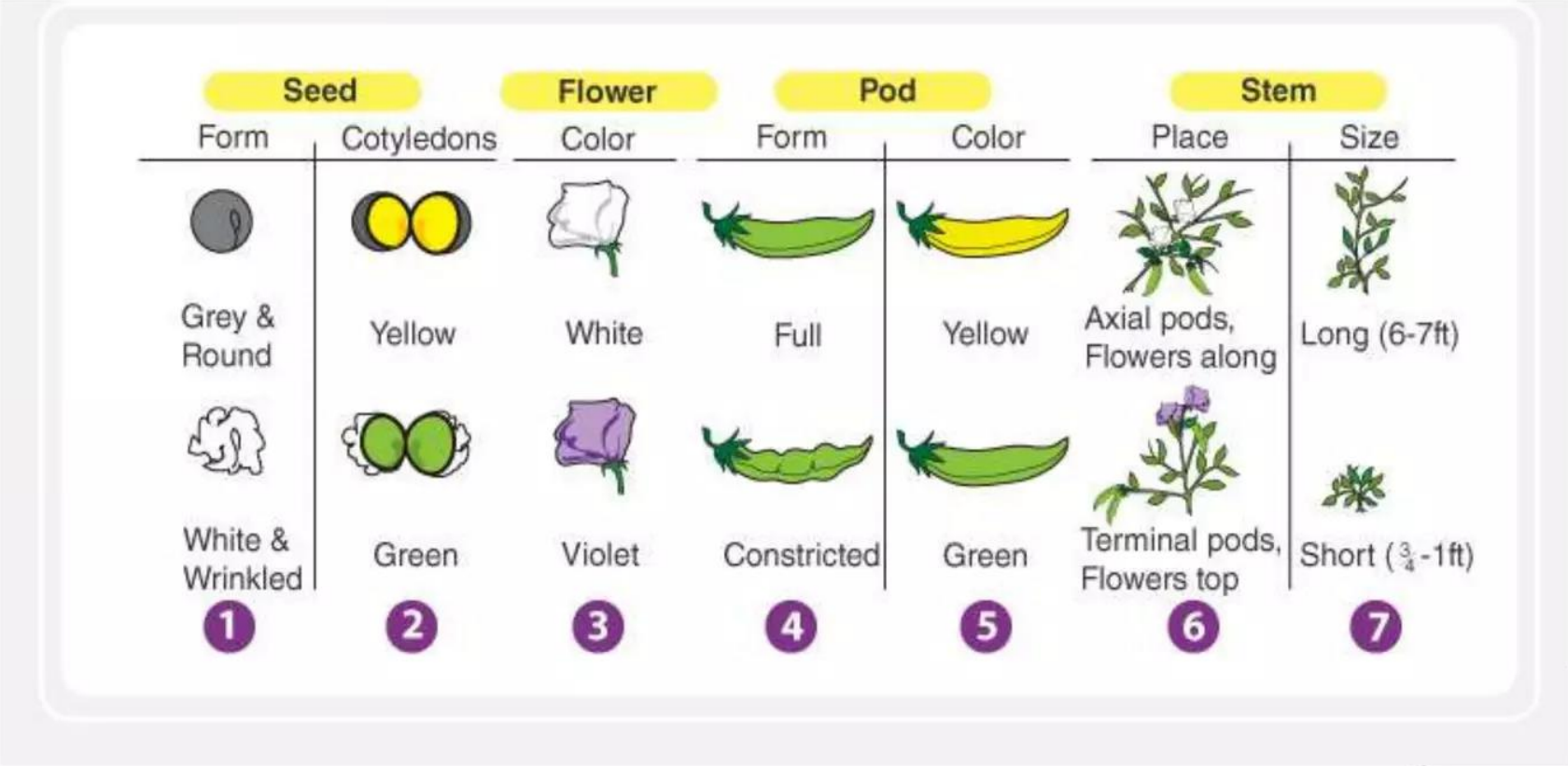
CHROMOSOMES – SEX DETERMINATION



SEX DETERMINATION

- Human body cells have 46 chromosomes arranged in 23 pairs.
- There are 22 pairs of autosomes and one pair of sex chromosomes (allosomes).
- Female have a perfect pair of sex chromosome XX.
- Male have mismatches pair of sex chromosome XY.
- Both male and female contain equal amount of chromosome 23 pair
- Out of 23 pair: 22 pairs are autosomes 1 pair is sex chromosome.

MENDELLIAN THEORY OF INHERITENCE



MENDELLIAN THEORY OF INHERITENCE

- The Law of Inheritance were derived by Austrian Monk named Gregor Mendel.
- He conducted hybridization experiments in garden pea and proposed certain laws which were known as Mendelian law of Genetics.
- Mendel suggested that the genes occurs in pairs one of which recessive and the other one is dominant .
- He stated that genes can be paired in three different ways for each trait: AA, aa, Aa.
- The capital “A” represents the dominant factor and lowercase “a” represents the recessive
- “Aa will occur roughly twice as often as each of the other two as it can be made in two different ways “Aa” , “aA”.

MENDELLIAN THEORY OF INHERITENCE

- Mendelian inheritance is a set of primary statements about the way certain characteristics (e.g. color of hair, eye, skin etc.) are transmitted from parent to their offspring.

- Mendel Law's of Inheritance
  - Law of Dominance
  - Law of Segregation
  - Law of Independent Assortment

GENOTYPE

- Your genotype is a way of expressing the two alleles that you hold for a particular gene
- Human eye color is controlled by one gene in particular, for which there are only 2 available alleles.

  B – codes for phenotypically Brown eyes (dominant)

  b – codes for phenotypically blue eyes (recessive)

- You need only 1 copy of a dominant allele for it to be expressed
- You need 2 copies of a recessive allele for it to be expressed

  BB = Brown eyes

  bb = Blue Eyes

  Bb =Brown eyes

GENOTYPE

- When one possesses identical alleles on the maternal and paternal chromosome, this is referred to as a homozygous genotype.

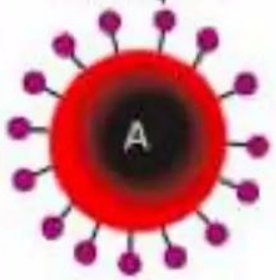
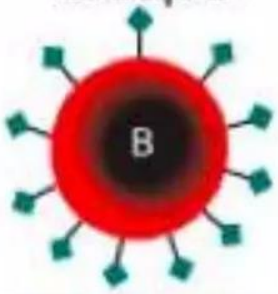
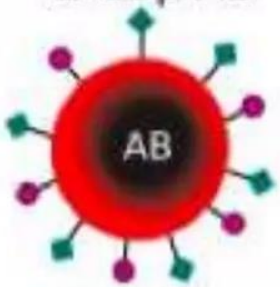
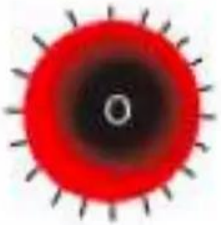
- e.g. BB = homozygous dominant
- e.g. bb = homozygous recessive

- Having two different alleles is a heterozygous genotype.
  - E.g. Bb = Heterozygous
  - The allele for Brown eyes (B) is dominant
  - The allele for Blue eyes (b) is recessive

PHENOTYPE

- The expression of a gene is determined by the combination of dominant and recessive alleles possessed by the individual.
- Trait that is easily seen (observed trait) is called the phenotype.
- The ABO blood group system represents not only a gene with multiple alleles, but also a system of codominance.
- Phenotypic expression is not always visible, it can be physical, biochemical or physiological.

BLOOD GROUPING

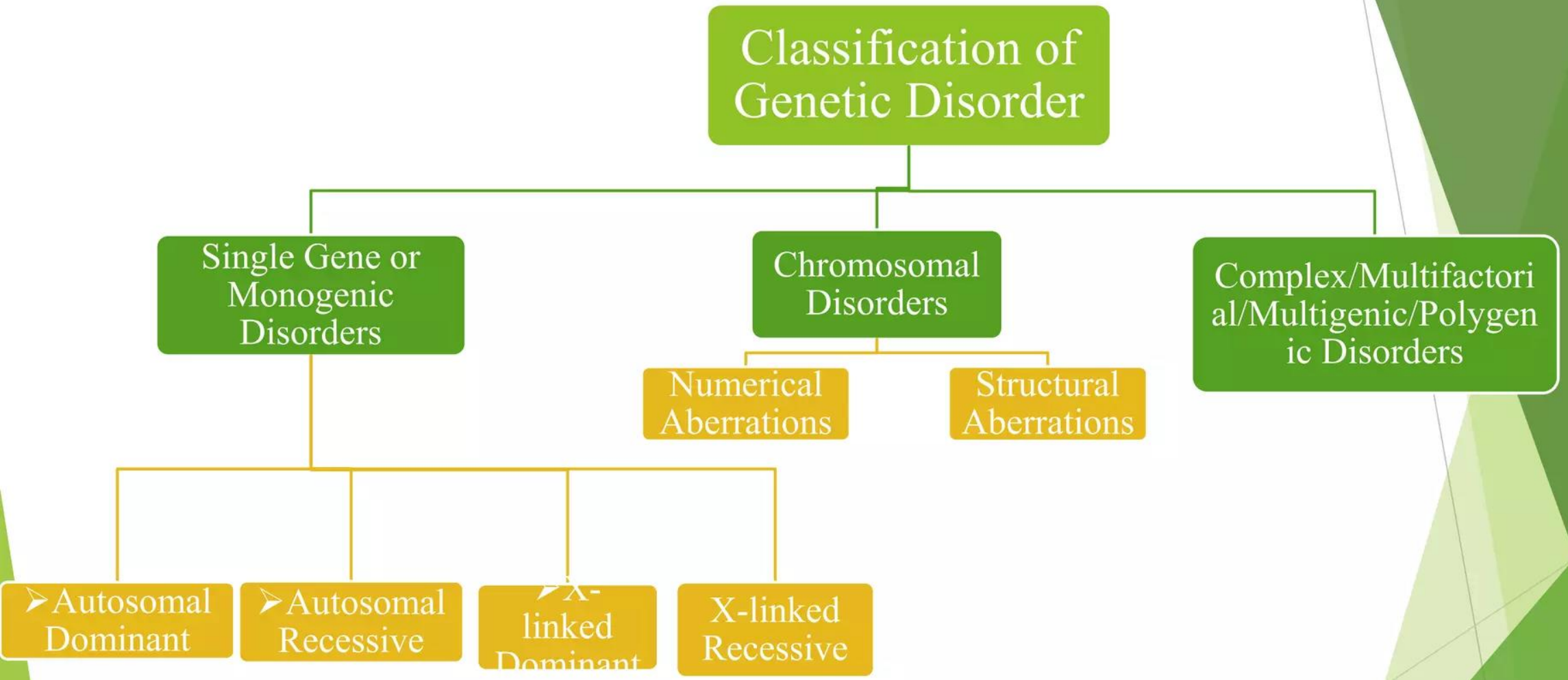
Genotype	AA or AO	BB or BO	AB	OO
Phenotype	Type A Carbohydrate	Type B Carbohydrate	Type A & B Carbohydrates	No Carbohydrate
Blood Group	Group A 	Group B 	Group AB 	Group O 

father \ mother	A	B	O
A	AA	AB	AO
B	BA	BB	BO
O	OA	OB	OO

alleles	blood type
A+A	A
A+O	A
A+B	AB
B+B	B
B+O	B
O+O	O

MECHANISM OF INHERITENCE

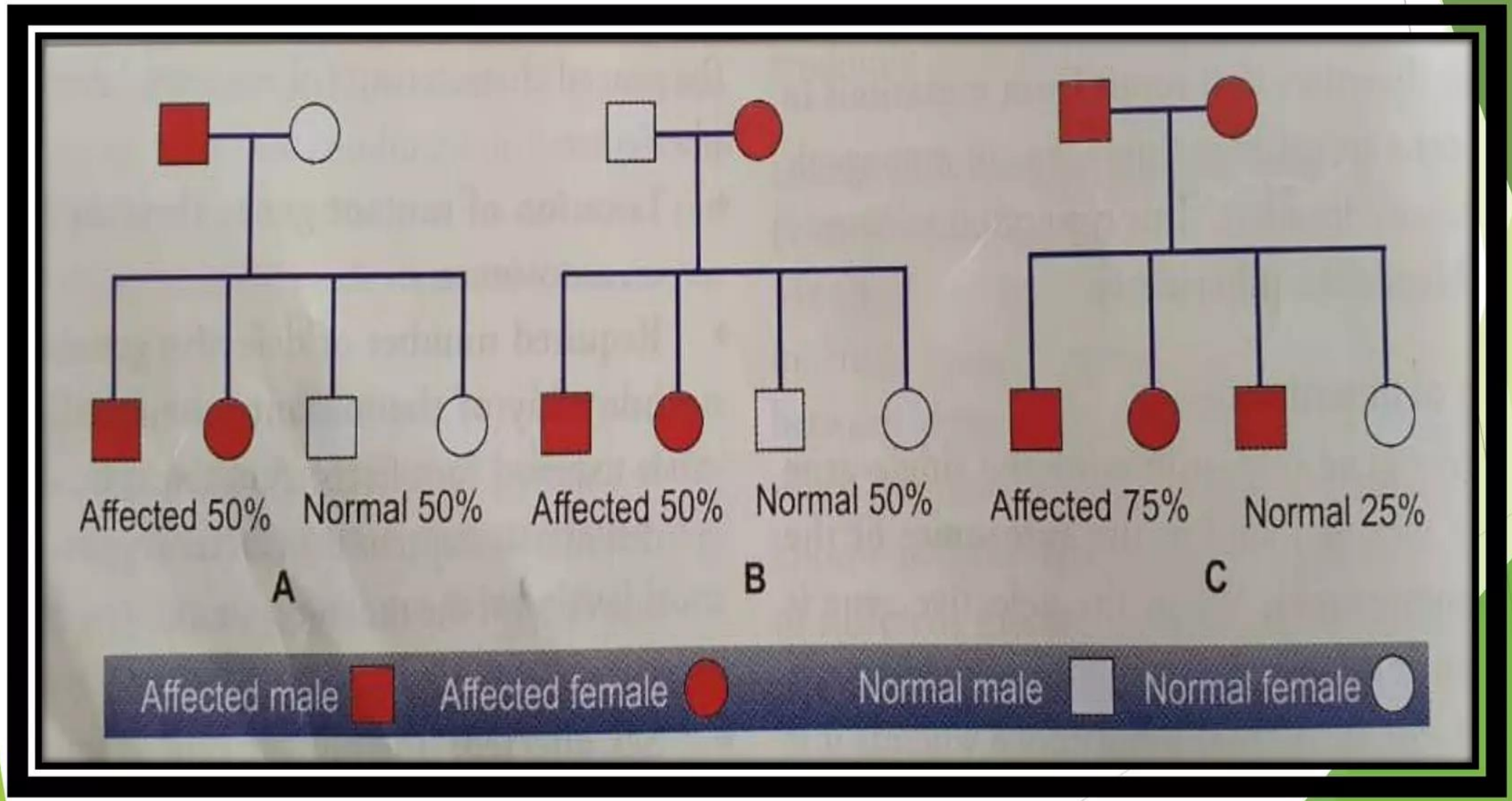
- Mode of inheritance is defined as the manner in which a particular genetic trait or disorder is passed from one generation to the next.


Classification of Genetic Disorder
Single Gene or Monogenic Disorders
Chromosomal Disorders
Complex/Multifactorial/Multigenic/Polygenic Disorders
Numerical Aberrations
Structural Aberrations
Autosomal Dominant
Autosomal Recessive
X-linked Dominant
X-linked Recessive

Single Gene or Monogenic Disorders/Mendelian Disorders

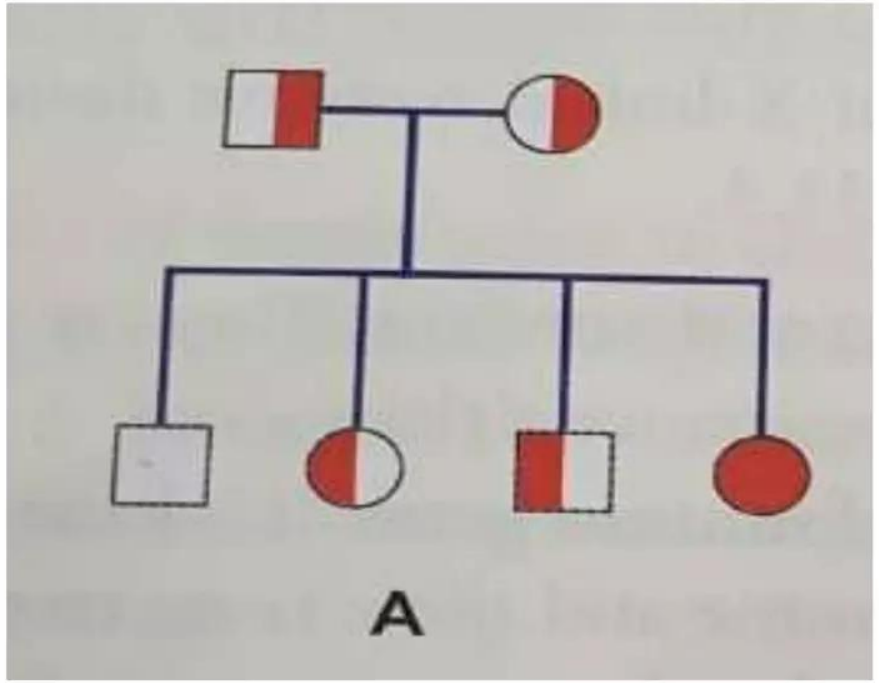
- Genetic Disorders that results from mutations in single gene are called as Single gene or Monogenic Disorders.
- This type of inheritance is called as Mendelian Inheritance.
- Defective gene is responsible for the single gene may be found in the autosomes or the sex chromosomes.
- When the defective gene is found on an autosome, the mode of inheritance is said to be of autosomal inheritance
- If it is on the sex chromosomes, it is said to show sex linked inheritance

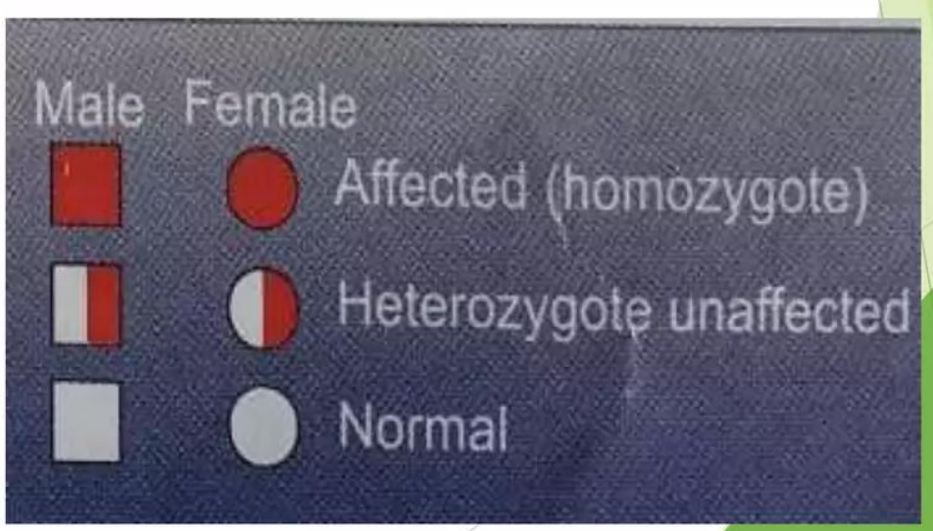
AUTOSOMAL DOMINANT PATTERN OF INHERITANCE



AUTOSOMAL RECESSIVE PATTERN OF INHERITANCE

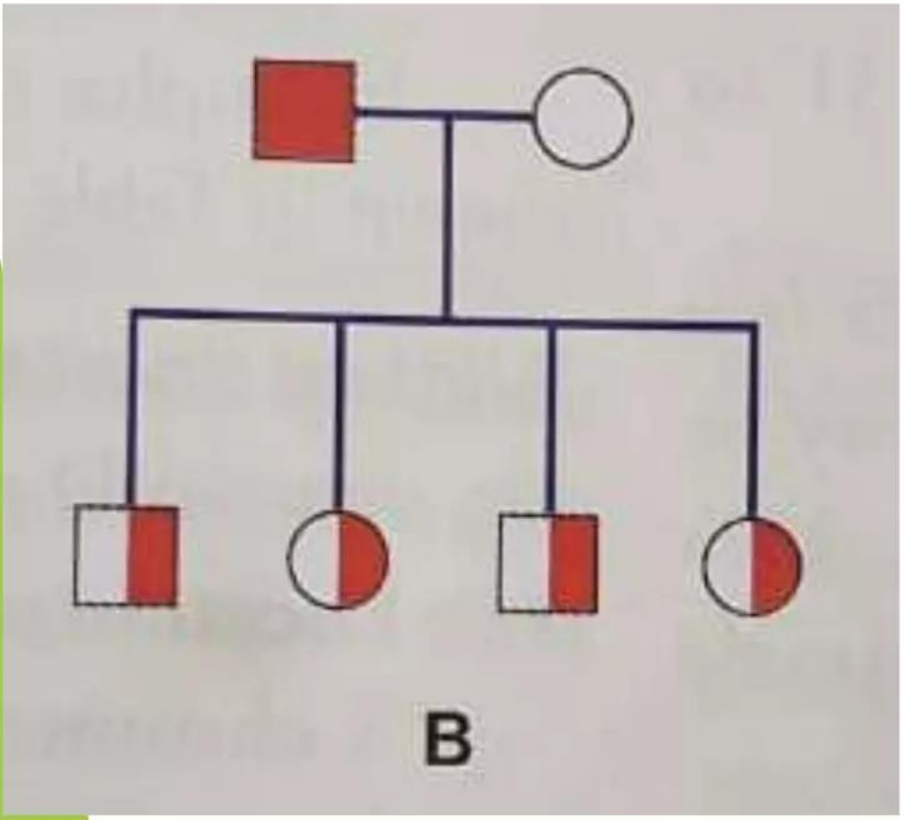
- **When both parents are heterozygous for the condition**: Heterozygous parents carry one mutated gene and normal gene. When two heterozygotes mate, 25% of the children will be affected, 50% will be unaffected heterozygotes and 25% will be normal.

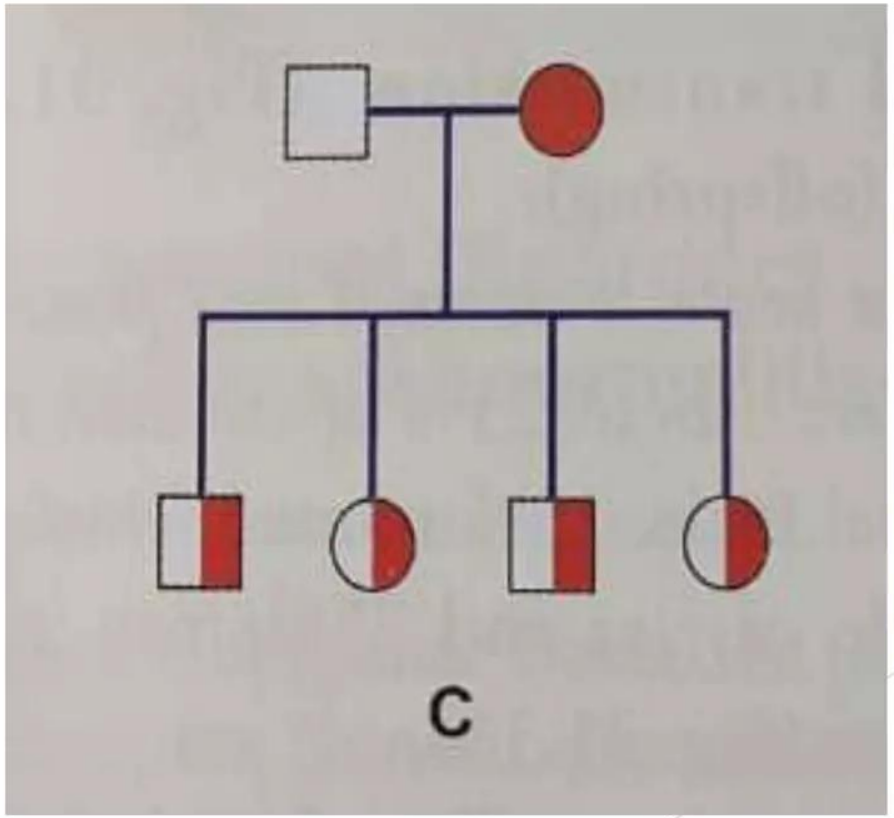


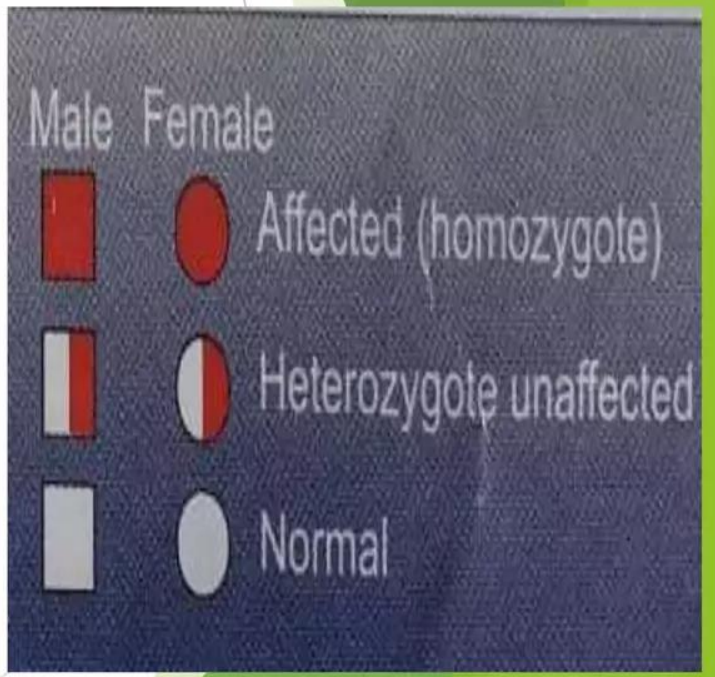


AUTOSOMAL RECESSIVE PATTERN OF INHERITANCE

- **When one parent is affected and the other is normal**: All the children will be unaffected heterozygotes.

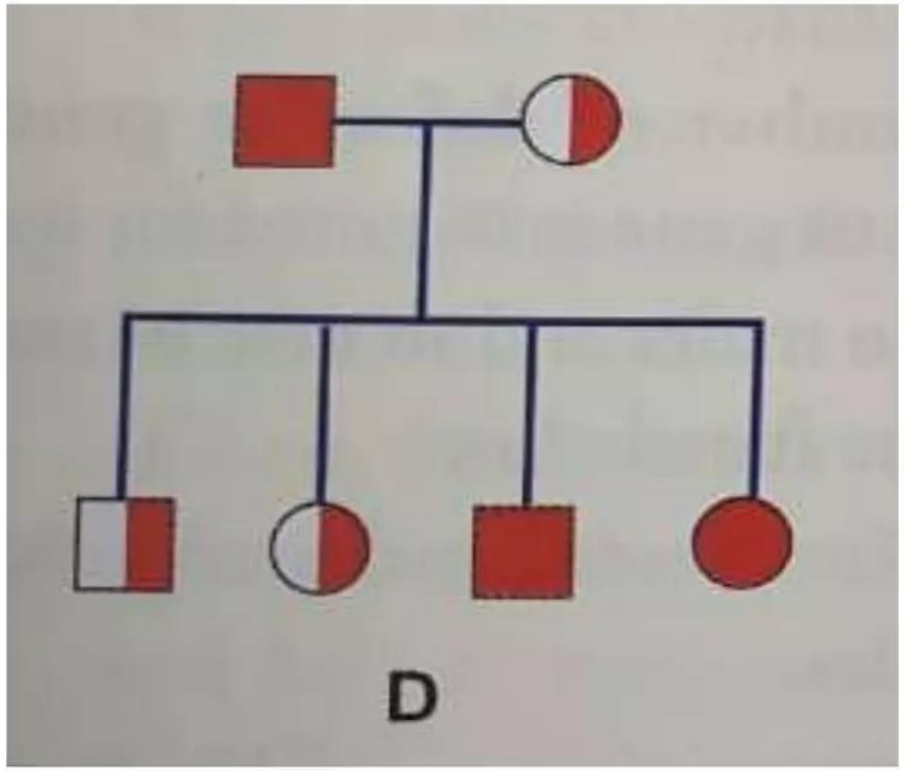


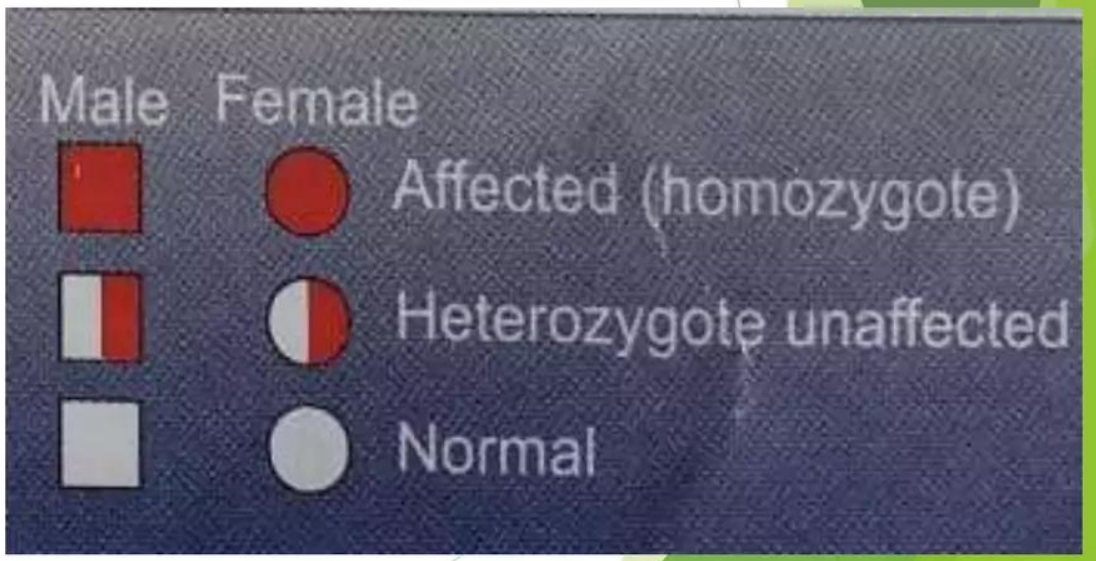




AUTOSOMAL RECESSIVE PATTERN OF INHERITANCE

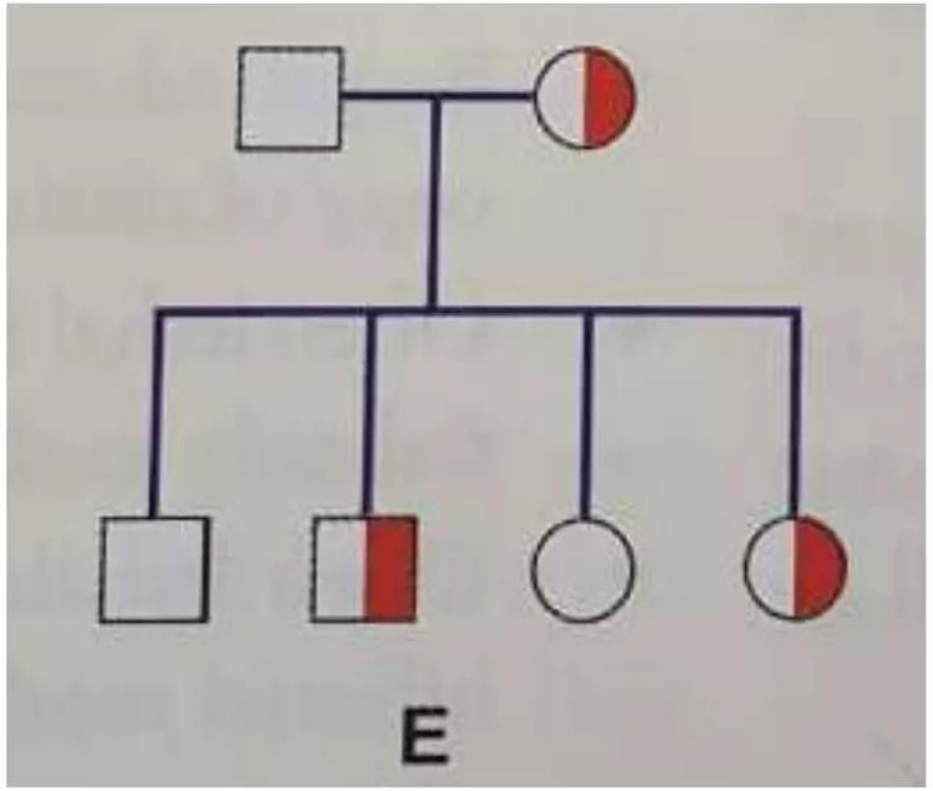
- **When one parent is affected and the other is heterozygote**: The chances are that 50% of children will be unaffected heterozygotes and 50% homozygously affected.

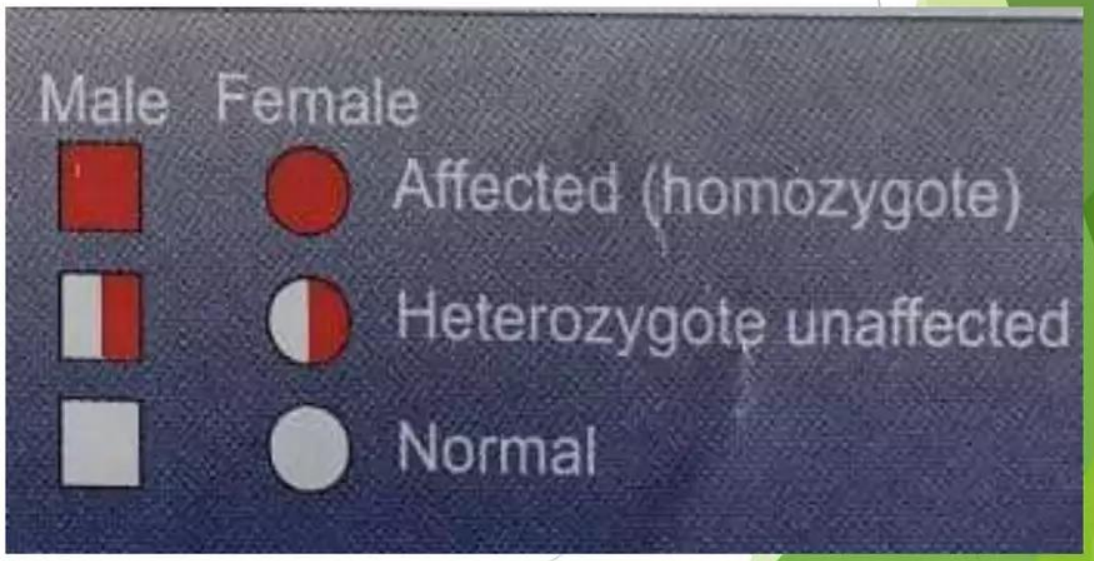




AUTOSOMAL RECESSIVE PATTERN OF INHERITANCE

- **When one parent is normal and the other is heterozygote:** This may result in 50% unaffected heterozygote carriers and 50% normal children.





X LINKED PATTERN OF INHERITANCE

- Almost all sex-linked Mendelian Disorder are X-linked.
- Males with mutations affecting the Y-linked genes are usually infertile.
- Expression of an X-linked disorder is different in males and females. Though X-linked disorders may be inherited either as dominant or recessive, almost all X-linked disorders have recessive pattern of inheritance.
- Females: They inherit one X chromosome from each parent (46 XX). The clinical expression of the X-linked disease in a female is variable, depending on whether it is dominant or recessive.
- Females are rarely affected by X-linked recessive diseases; however they are affected by X-linked dominant disease.
- Males: They inherit only one X chromosome from mother and Y chromosome from father (46 XY). Males have only one X. chromosome and gene mutation affecting X chromosome is fully expressed even with one copy, regardless of whether the disorder is dominant or recessive.

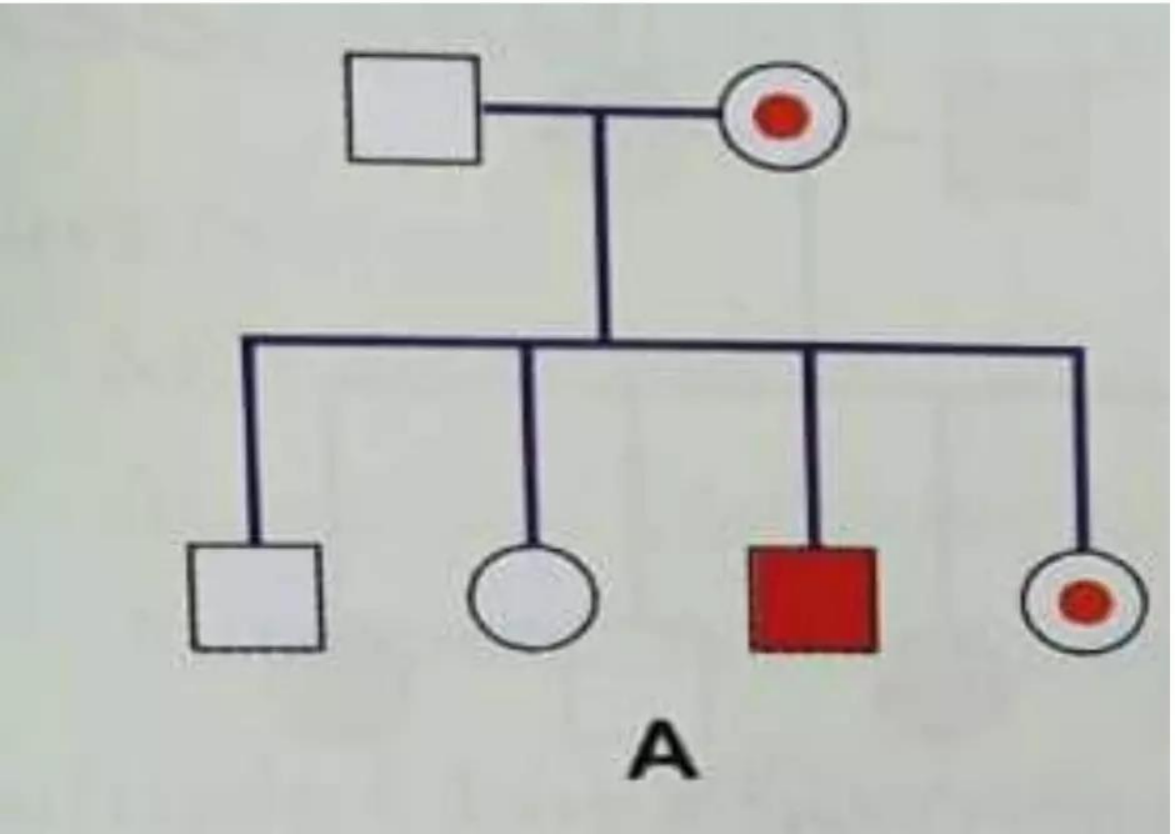
X LINKED RECESSIVE TRAIT

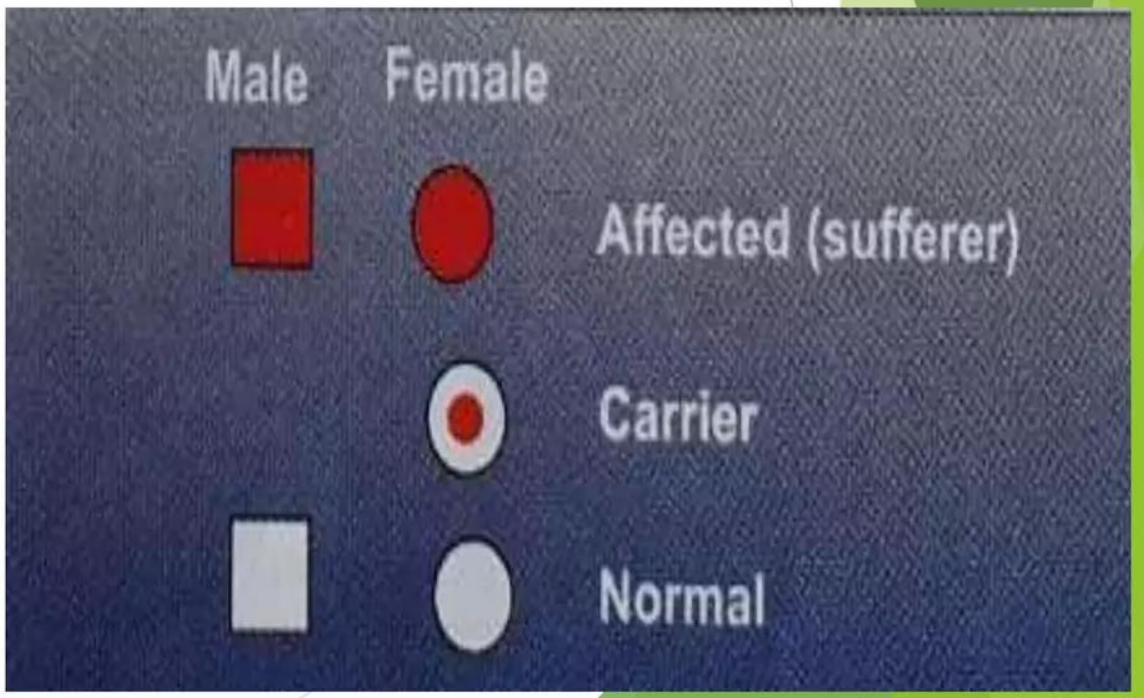
- This pattern of Inheritance constitutes a small number of clinical conditions.
- **Location of mutant gene :** Mutant gene is on the X chromosomes and there is no male to male transmission.
- **Required number of defective gene:** One copy of mutant gene is required for the manifestation of disease in males, but two copies of the mutant gene are needed in females.
- **Sex affected:** Males are more frequently affected than females; daughters of affected male are all asymptomatic carriers.
- **Pattern of inheritance:** Transmission is through female carrier (heterozygous).

X LINKED RECESSIVE TRAIT

Risks of transmission to children (offspring):

- **When male is normal and female is a carrier:** About 25% of children may be normal male, 25% normal female, 25% female carrier and 25% may be male sufferer.

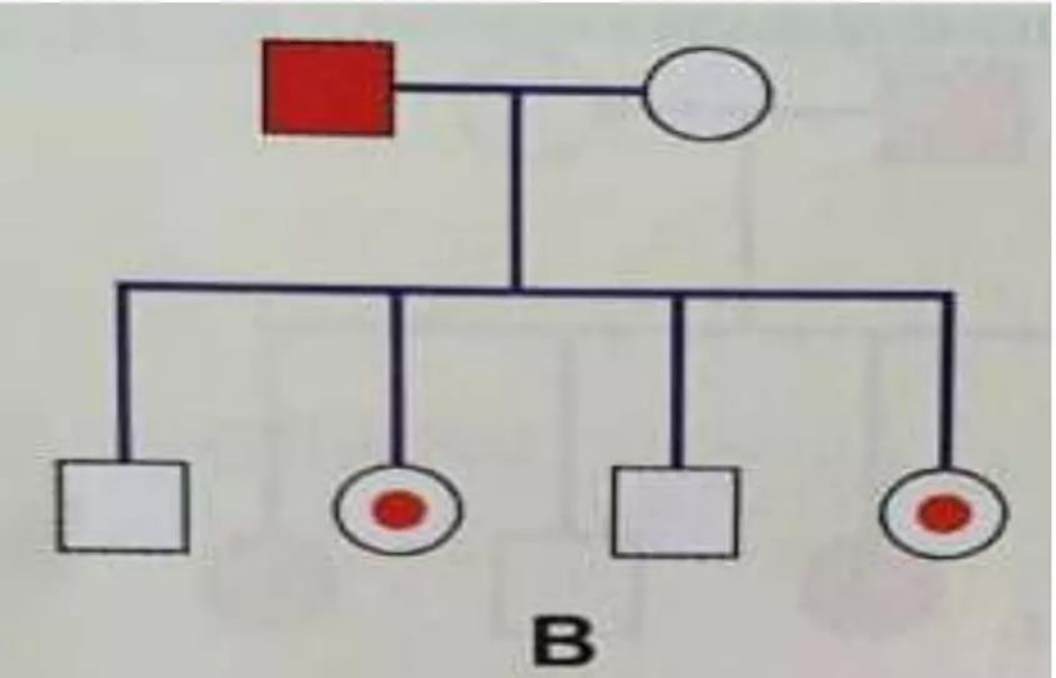


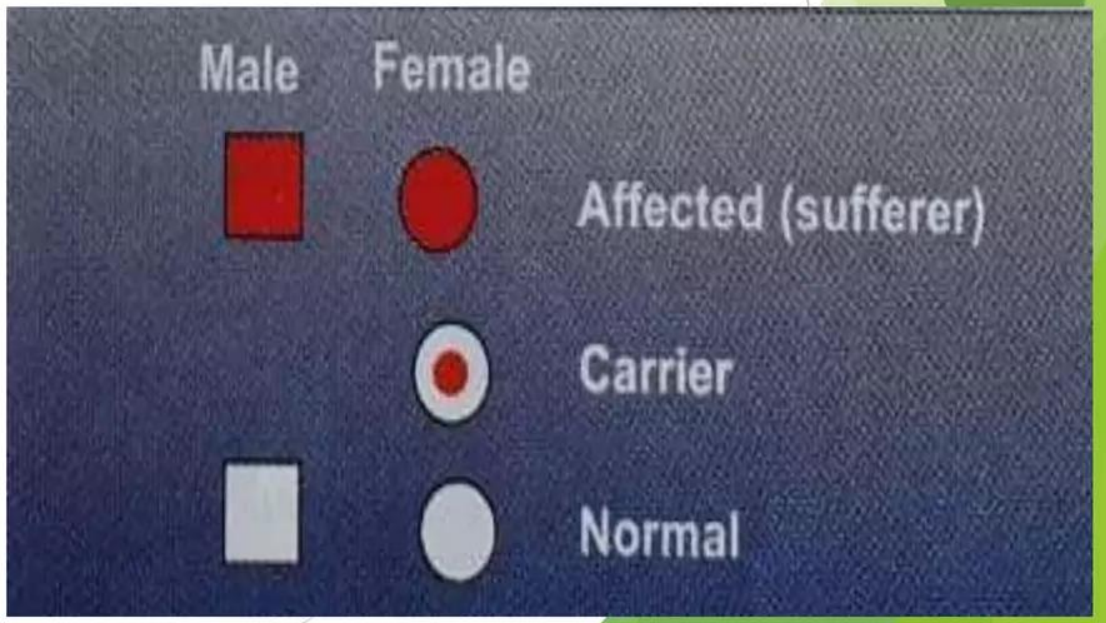


X LINKED RECESSIVE TRAIT

Risks of transmission to children (offspring):

- **When male is affected and female is normal**: An affected male does not transmit the disorder to his sons since he donates only a normal Y chromosome to his son. Thus, all his sons will be normal. An affected male always donates one copy of his abnormal X-chromosome to all his daughters and thus all daughters will be asymptomatic carriers.

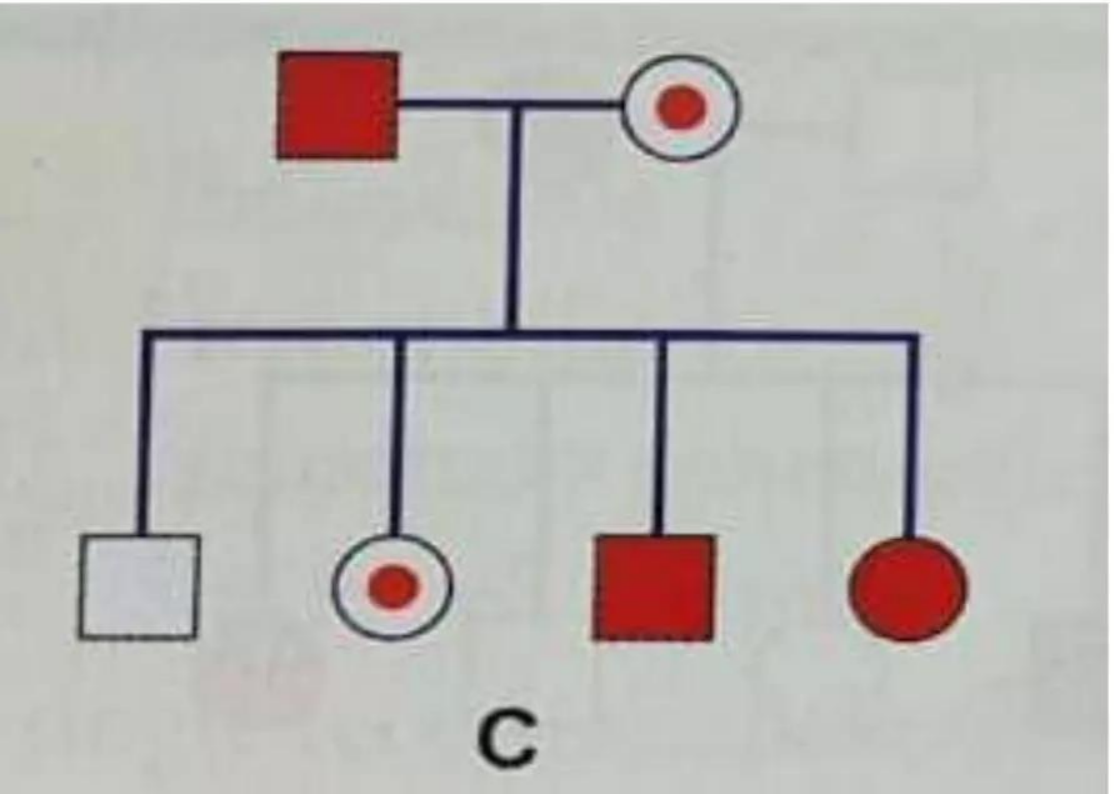


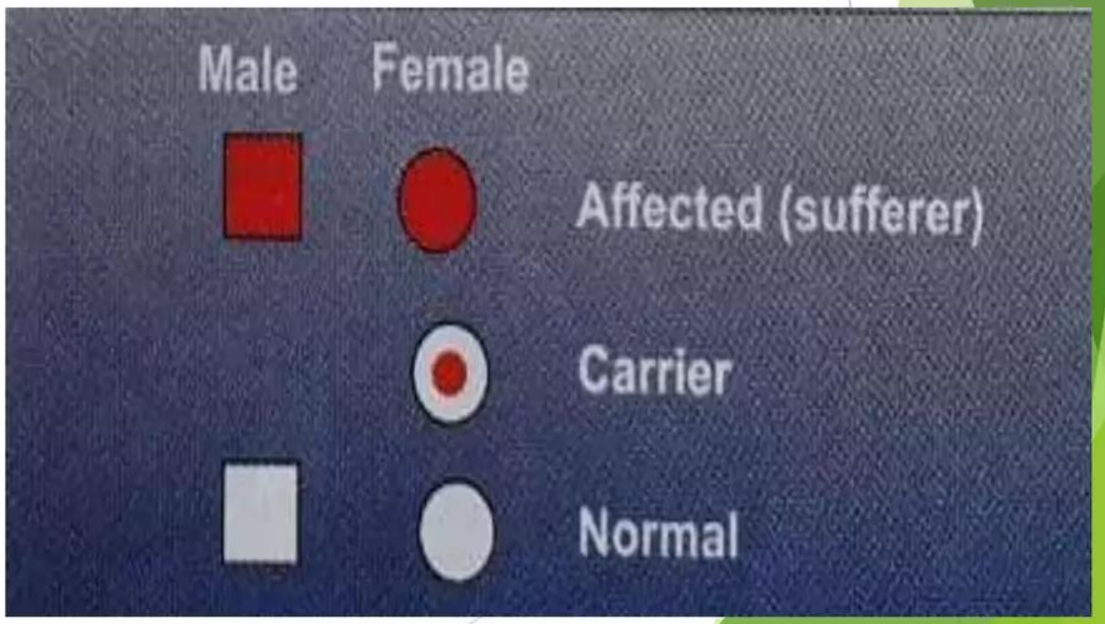


X LINKED RECESSIVE TRAIT

Risks of transmission to children (offspring):

- **When male is affected and female is a carrier:** There are chances of 25% of children being female carrier, 25% affected female, 25% normal male and 25% affected male.

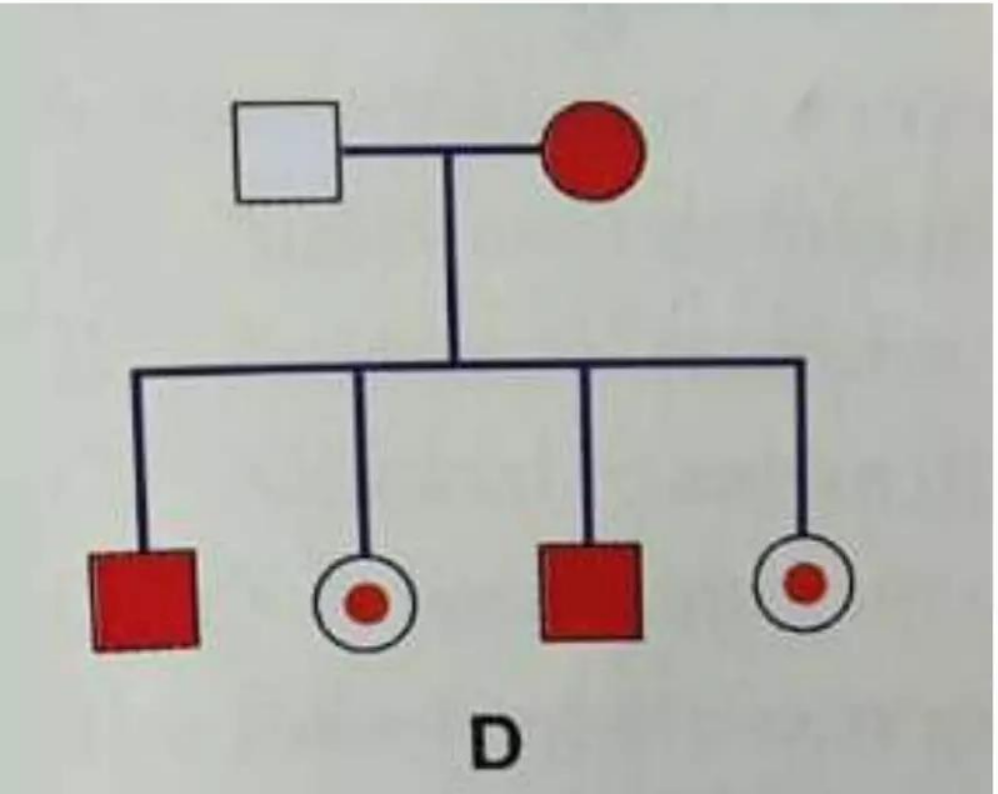


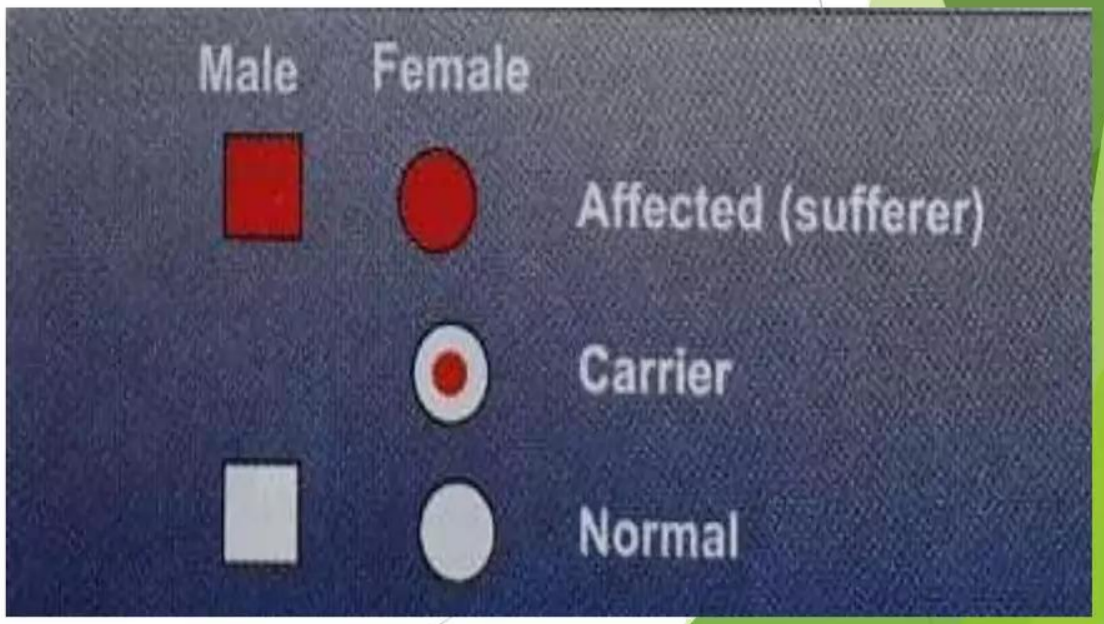


X LINKED RECESSIVE TRAIT

Risks of transmission to children (offspring):

- **When male is normal and female is affected:** 50% of children will be female carriers and 50% may be male sufferers





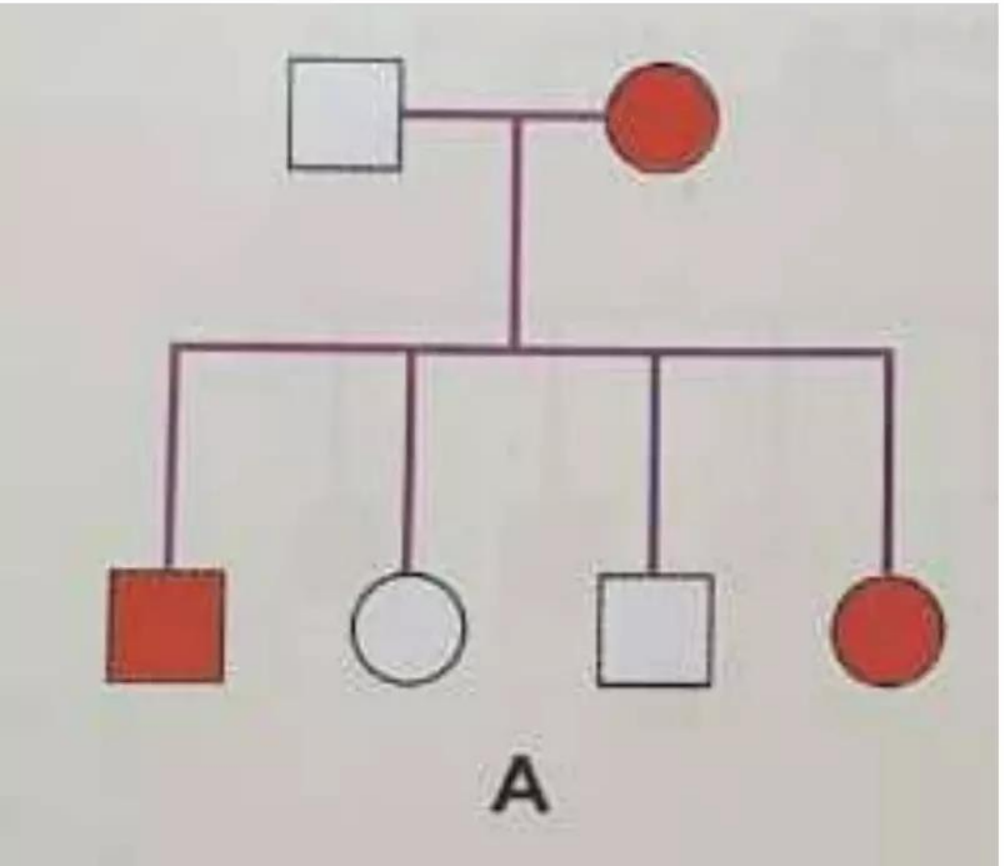
X LINKED DOMINANT DISORDERS

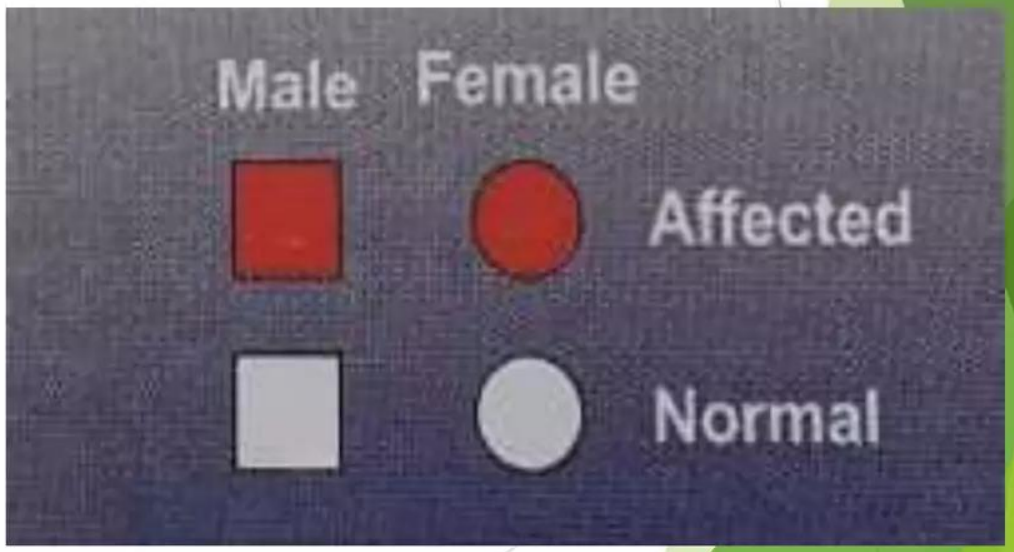
- They are very rare, e.g. vitamin D resistance rickets.
- **Location of mutant gene:** It is located on the X chromosome and there is no transmission from affected male to son.
- **Required number of defective gene:** One copy of mutant gene is required for its effect.
- Often lethal in males and so may be transmit ted only in the female line.
- Often lethal in affected males and they have affected mothers.
- There is no carrier state. These are more frequent in females than in males.

X LINKED DOMINANT DISORDERS

Risks of transmission to children (offspring):

- **When female is affected and the male is normal:** They transmit the disorder to 50% of their sons and 50% of their daughters.

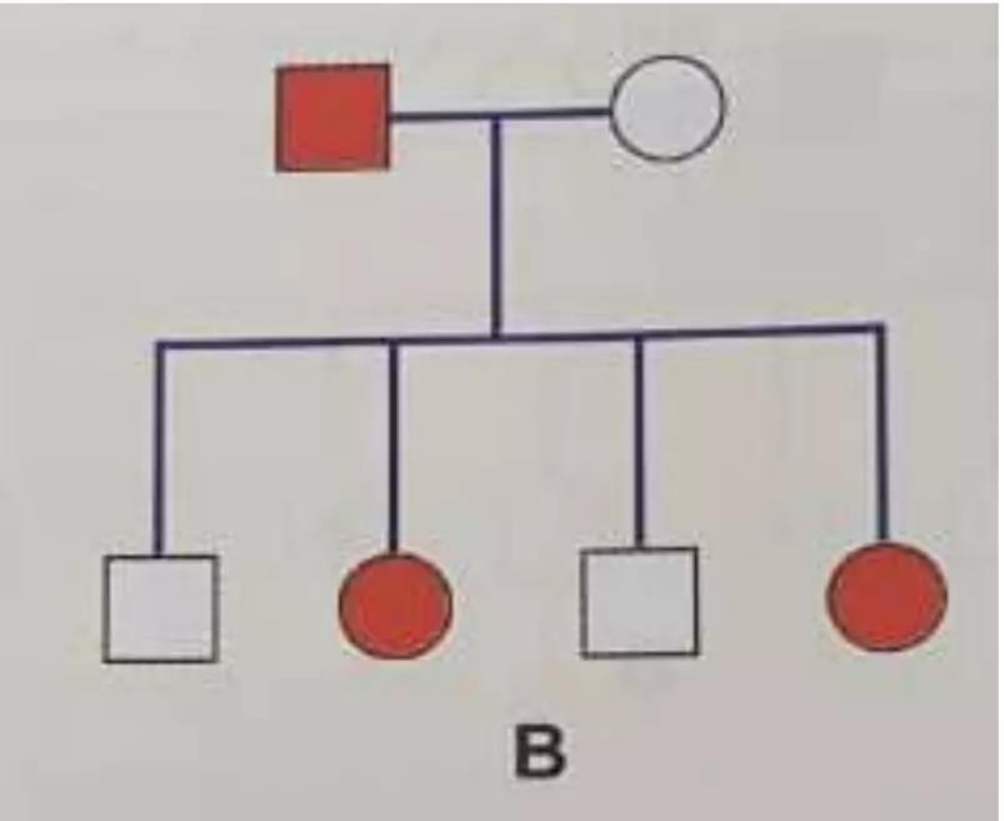


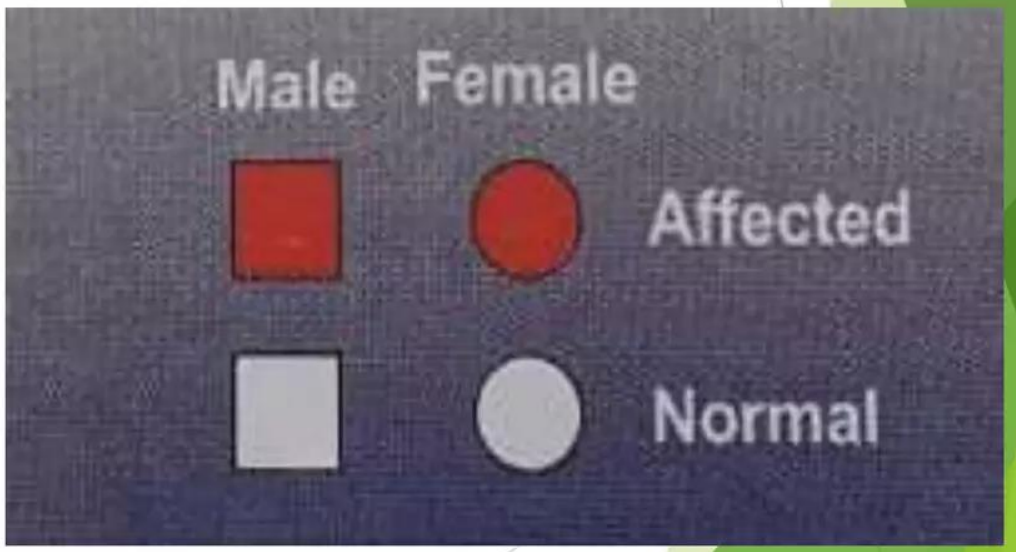


X LINKED DOMINANT DISORDERS

Risks of transmission to children (offspring):

- **When male is affected and the female is normal:** They transmit to all their daughters but none to their sons.

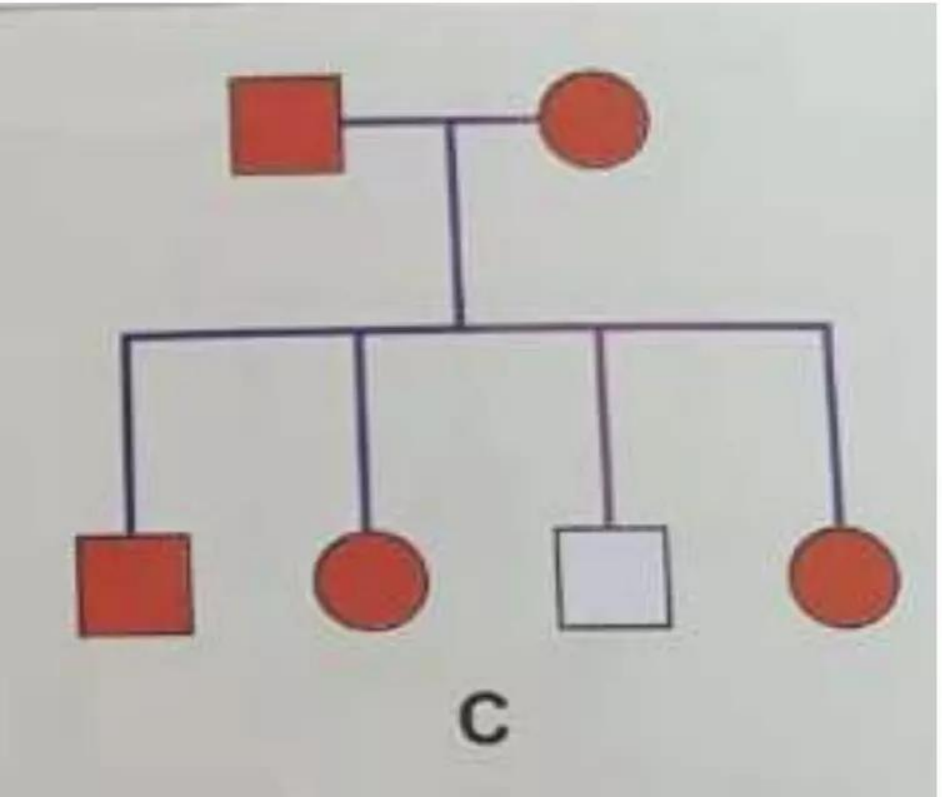


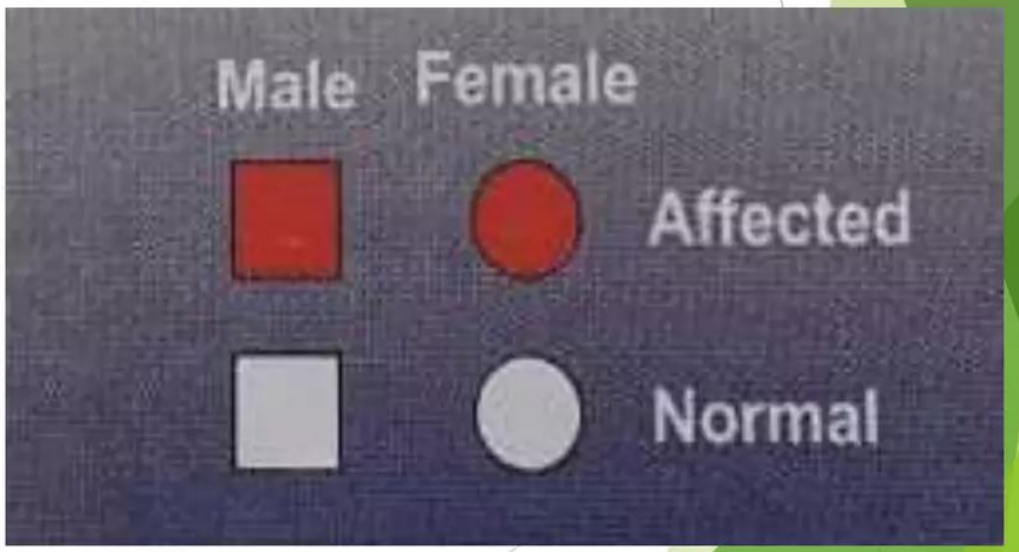


X LINKED DOMINANT DISORDERS

Risks of transmission to children (offspring):

- **When both male and female are affected:** All the females will be affected and half of males will be affected





CHROMOSOMAL ABERRATIONS

- **Chromosomal aberrations, or abnormalities, are changes to the structure or number of chromosomes, which are strands of condensed genetic material.**
- Humans typically have 23 pairs of chromosomes, of which 22 pairs are autosomal, numbered 1 through 22. The last pair of chromosomes are sex chromosomes, which determine an individual's sex assignment.
- At birth, most people with XY sex chromosomes are assigned male, and most individuals with XX are assigned female.
- In general, each parent contributes one set of chromosomes to their offspring, which collectively make up the 23 pairs of chromosomes.
- **A change to any of the chromosomes, in number or structure, creates a chromosomal aberration and may cause medical disorders.**

CHROMOSOMAL ABERRATIONS

- The chromosomal aberrations/disorders may be broadly classified as
  - Numerical chromosomal aberrations
  - Structural chromosomal aberrations
- Both may involve either the autosomes or the sex chromosomes.

NUMERICAL CHROMOSOMAL ABERRATIONS

- Normal cells are diploid containing 46 chromosomes, 22 pairs of autosomes and 1 pair of sex chromosomes.
- The total number of chromosomes may be either increased or decreased. The deviation from the normal number of chromosomes is called as numerical chromosomal aberrations.

TYPES OF NUMERICAL CHROMOSOMAL ABERRATIONS

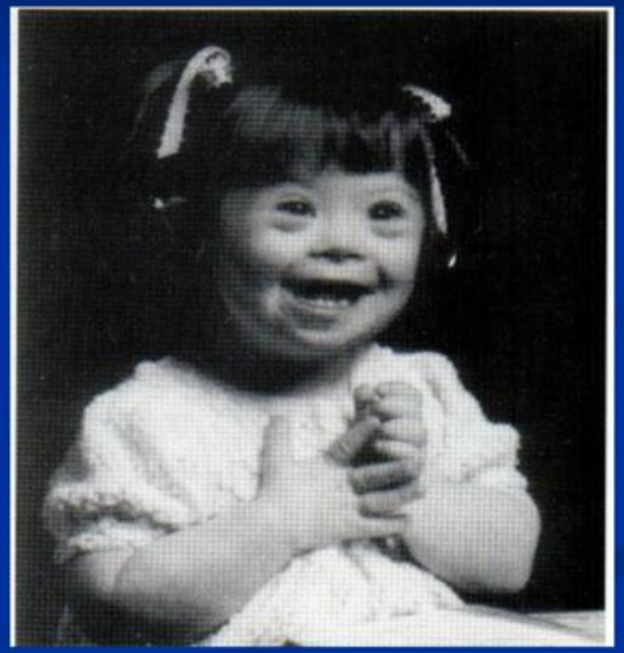
NUMERICAL CHROMOSOMES ABERRATIONS
➢ Aneuploidy ➢ Monosomy ➢ Trisomy ➢ Tetrasomy
➢ Polyploidy ➢ Triploidy ➢ Tetraploidy
➢ Different Cell Lines: Mosaicism

ANEUPLOIDY

- It is defined as a chromosome number that is not a multiple of 23 (the normal haploid number). It is caused by either loss or gain of one or more chromosomes. Aneuploidy may result from nondisjunction or anaphase lag.
- **Trisomy:** Numerical abnormalities with the presence of one extra chromosome are referred to as trisomy. It may involve either sex chromosomes or autosomes. For examples, patients with Down's syndrome have three copies of chromosome 21(47 XX, +21), hence Down's syndrome is often known as trisomy 21. Others are Patau syndrome (trisomy 13) and Edward's syndrome (trisomy 18).

Down syndrome (Trisomy 21)

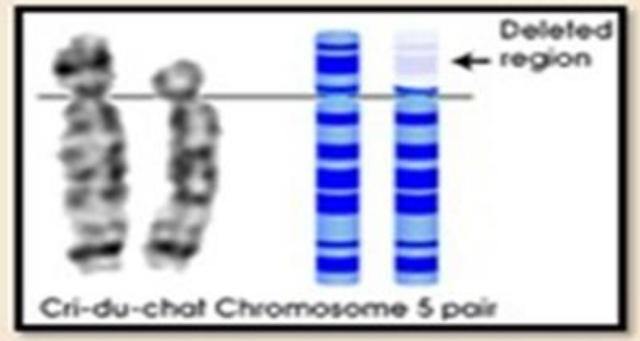
- 1:800 of birth
- Mental deficiency ,heart defects ..
- Round face
- Short digits
- some fertility



Example: *Cri-du-chat* syndrome

krē-dü-ˈshä-

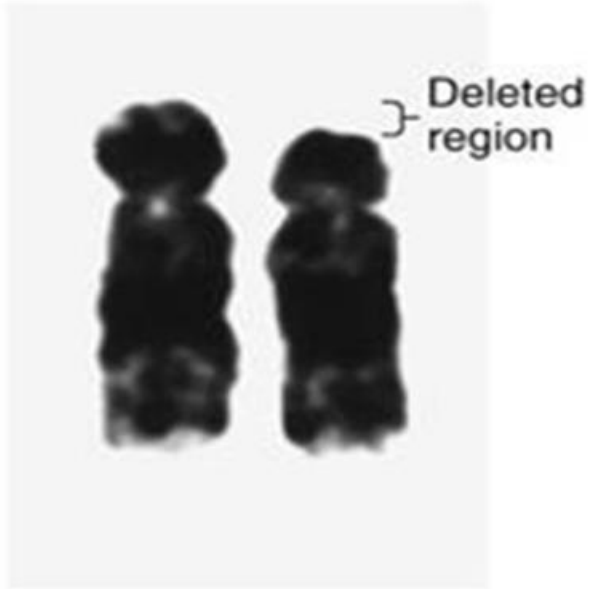
1. due to deletion of a section of the short arm of chromosome 5



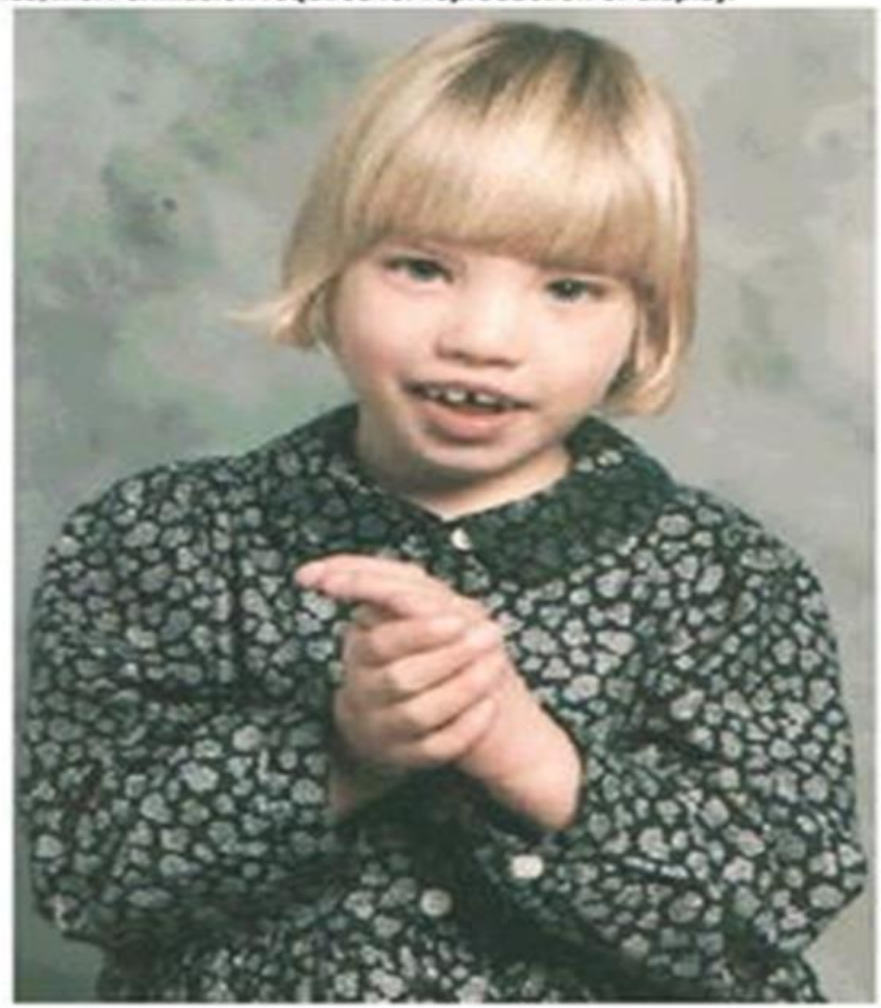
2. characteristics:
   - small head
   - unusual facial features
   - mentally retarded
   - cries like the mew of a cat

3. Usually dies in infancy/ early childhood

Cri-du-chat Syndrome



(a) Chromosome 5



(b) A child with cri-du-chat syndrome

ANEUPLOIDY

- **Monosomy:** Numerical abnormalities with the absence or loss of one chromosome are referred to as monosomy. It may involve autosomes or sex chromosomes. Monosomy of autosomes is almost incompatible with survival because of loss of too much genetic information. Example for monosomy of sex chromosomes is Turner syndrome, in which the girl is born with only one X-chromosome (45 XO) instead of normal XX (46 XX).

Duplications

- A chromosomal duplication is usually caused by abnormal events during recombination

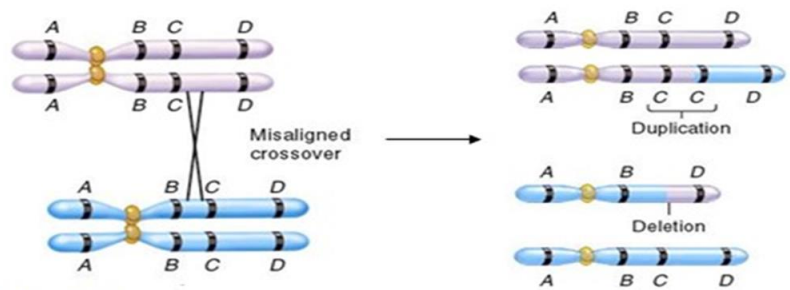
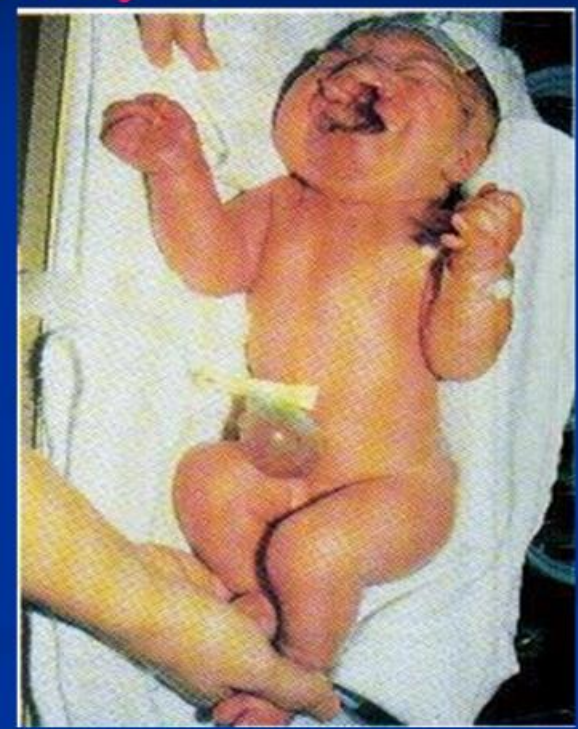


Figure 8.5

Female with trisomy 13

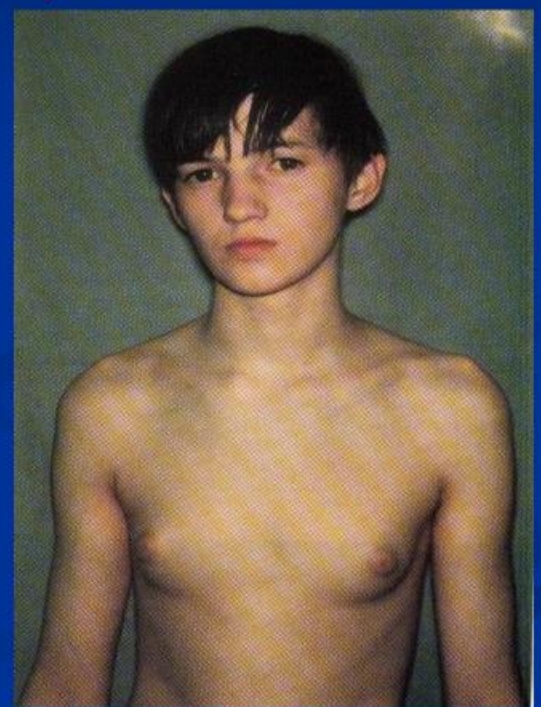
- 1:25000 of birth
- Mental deficiency,,
  Bilateral cleft lip &palate
- Low set malformed ears
- Polydactyly



Trisomy 13; Patau Syndrome
47; + 13

Young male with Klinefelter syndrome (XXY trisomy)

- 1:1080 of birth
- Presence of breasts
- Gynecomastia (excessive development of male mammary glands)
- Small testes ,aspermatogenesis due to hyalinization of seminiferous tubules
- Less intelligent



47, XXY; Klinefelter Syndrome

POLYPLOIDY

- Polyploidy is chromosome number that is a multiple greater than two of the haploid number (multiples of haploid number 23). Triploidy is three times the haploid number (69), tetraploidy is four times the haploid number (92). **Polyploidy is incompatible with life and usually results in spontaneous abortion.**

DIFFERENT CELL LINES

- Changes in chromosome number in an individual may not necessarily be present in all cells but may be found in some cells.
- Mosaicism is defined as the presence of two or more populations of cells with different chromosomal complement in an individual.
- Mitotic errors during early development. occasionally give rise to mosaicism. It can involve sex chromosomes or autosomes.

STRUCTURAL CHROMOSOMAL ABRERRATION

- A second type of chromosomal aberrations is due to alterations in the structure of one or more chromosomes.
- They may occur either during mitosis or meiosis.
- Structural changes in chromosomes can be balanced or unbalanced.
- Balanced aberration is generally harmless, because there is no loss or gain of chromosomal material.
- In unbalanced aberrations, chromosomal material is either gained or lost.

TYPES OF STRUCTURAL CHROMOSOMAL ABRERRATION

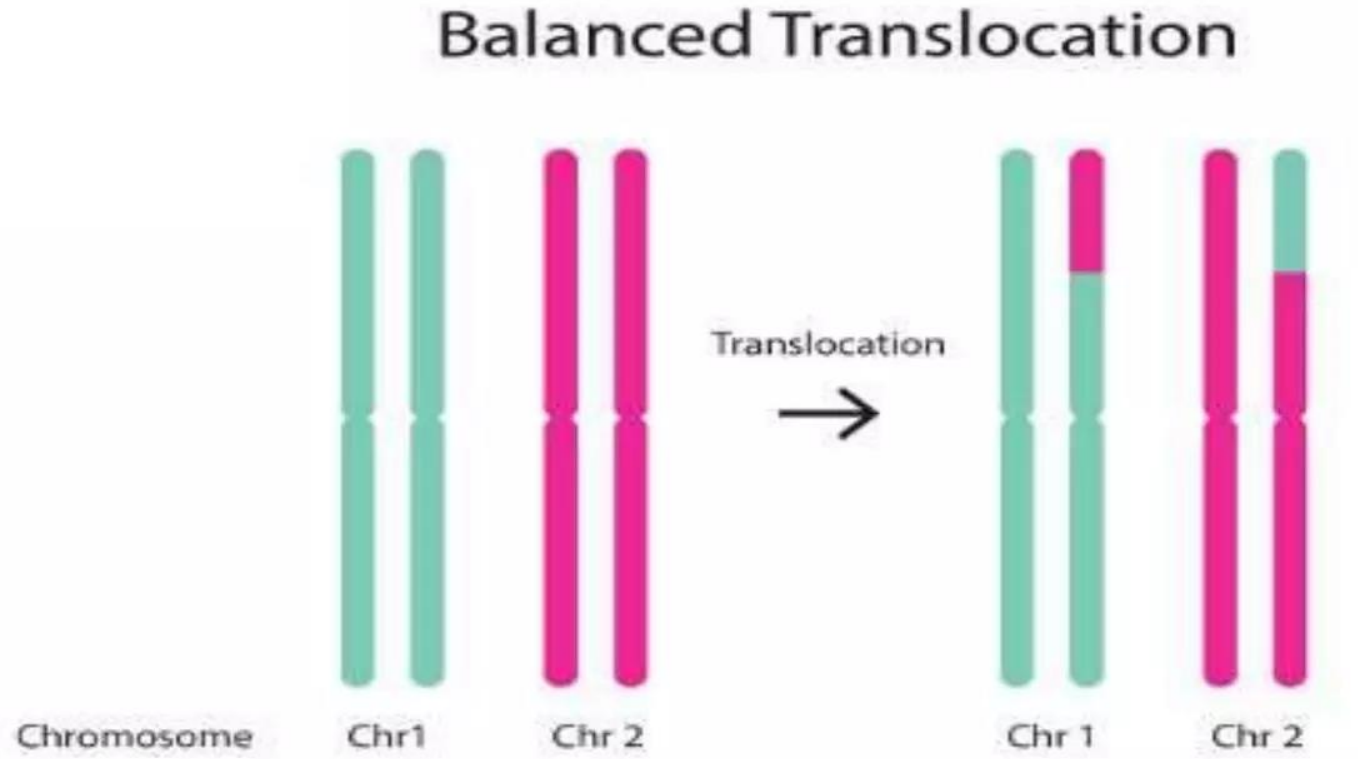
STRUCTURAL CHROMOSOMES ABERRATIONS
➢ Translocations (exchange) ➢ Balanced Reciprocal ➢ Robertsonian Translocation
➢ Inversions ➢ Paracentric ➢ Pericentric
➢ Isochromosomes
➢ Deletions (loss)
➢ Ring Chromosomes
➢ Insertions

TRANSLOCATION

- It is a structural alteration be tween two chromosomes in which segment of one chromosome gets detached and is transferred to another chromosome. There are two types of translocations –
  - Balanced reciprocal translocation
  - Robertsonian Translocation

Balanced reciprocal translocation

- It is characterized by single breaks in each of two chromosomes with ex change of genetic material distal to the break. There is no loss of genetic material.



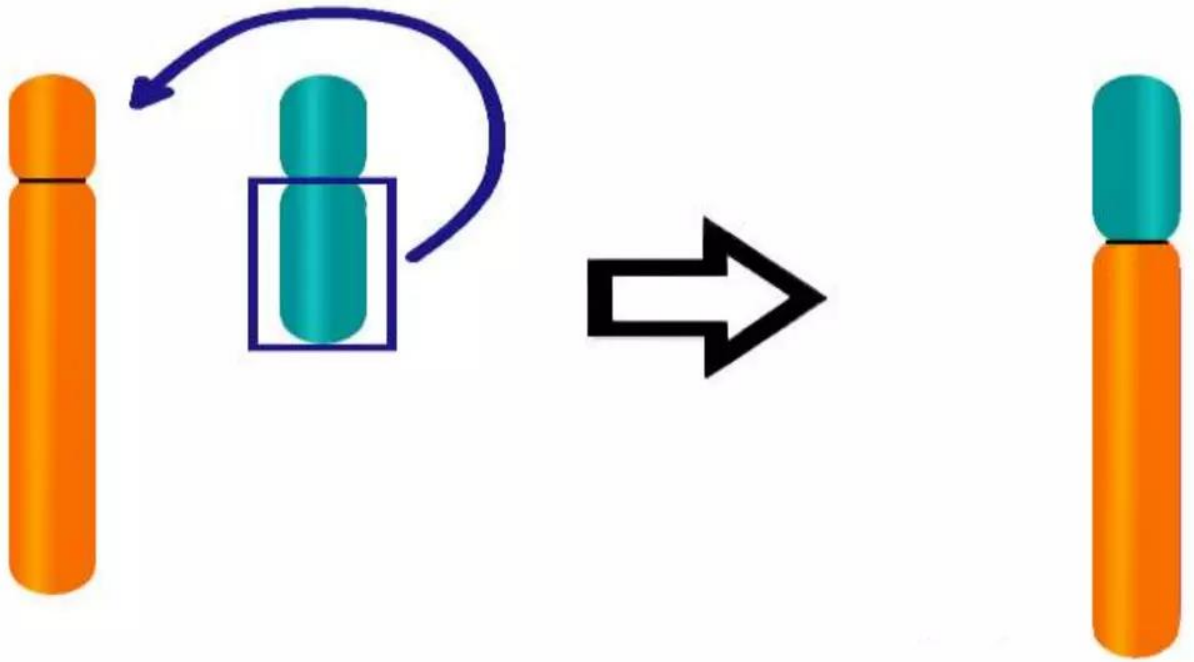
Robertsonian Translocation

- It is a translocation between two acrocentric chromosomes. The breaks occur close to the centromeres of each chromosome. Transfer of the segments leads to one very large chromosome and one extremely small one.
- The small one is because of fusion of short arms of both chromosomes which lack a centromere and is lost in subsequent divisions. This loss is compatible with life.

Robertsonian Translocation

Before translocation

After translocation



The two chromosomes stick together, resulting in 35 rather than 36 chromosomes.

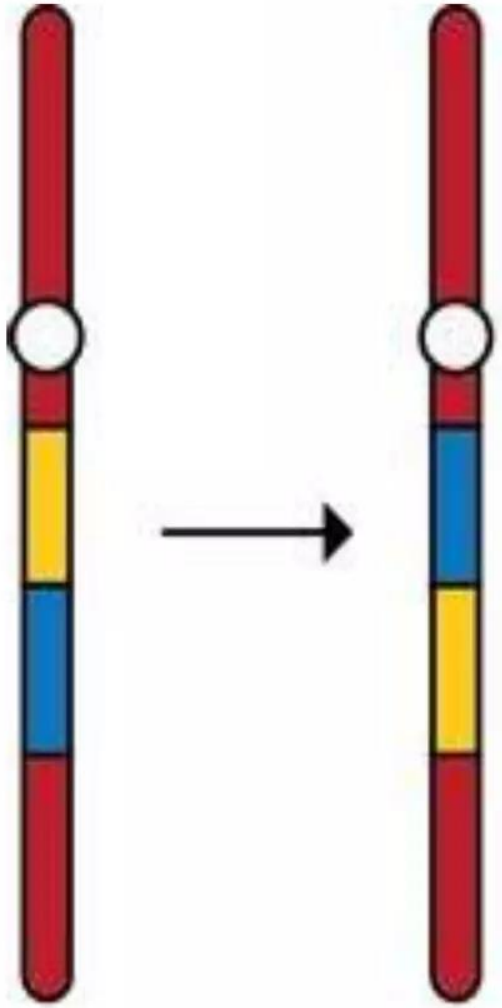
INVERSION

- It involves two breaks within a single chromosome, the affected segment inverts with reattachment of the inverted segment. The genetic material is transferred within the same chromo some.
- There are two types of inversion namely
  - Paracentric
  - Pericentric.

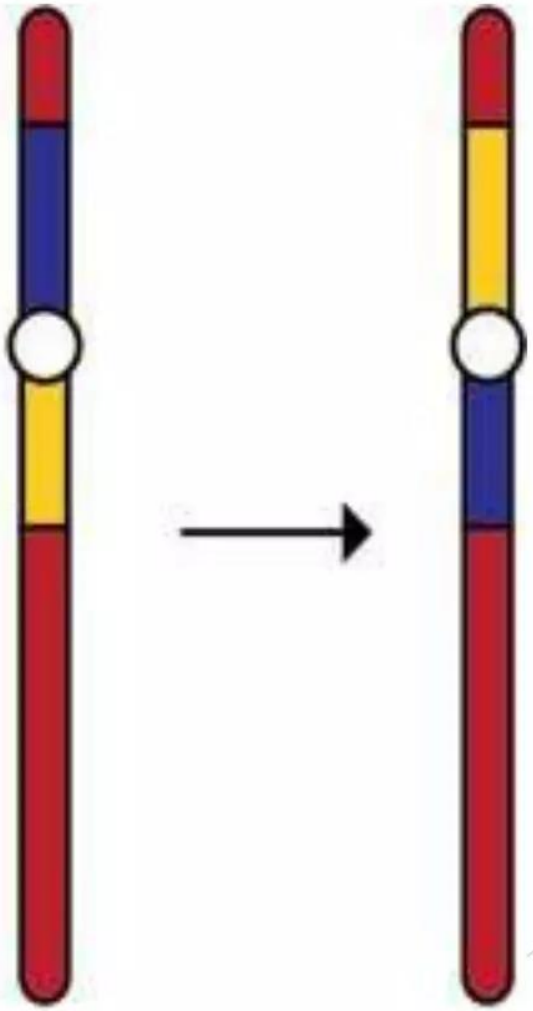
- Paracentric inversions result from breaks on the same arm (either the short arm or the long arm) of the chromosome.

- Pericentric inversions results from breaks on the opposite sides of the centromere where both the short and long arms are involved.

INVERSION



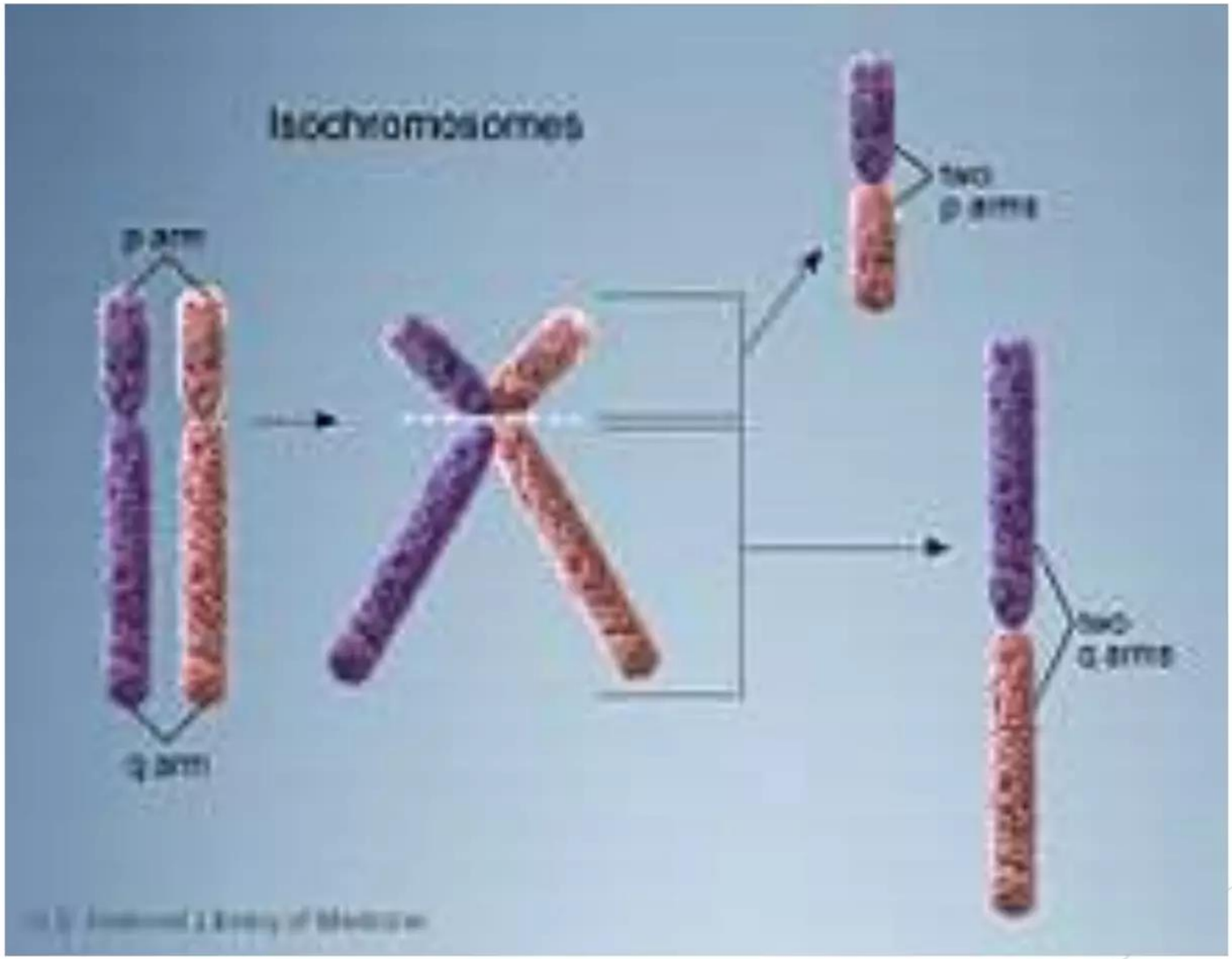
Paracentric inversion



Pericentric inversion

ISOCHROMOSOME

- They are formed due to faulty centromere division.
- Normally, centromeres divide in a plane parallel to long axis of the chromosome.
- If a centromere divides in a plane transverse to the long axis, it results in pair of isochromosomes. One pair consists of two short arms and the other of two long arms.


Isochromosomes

DELETION

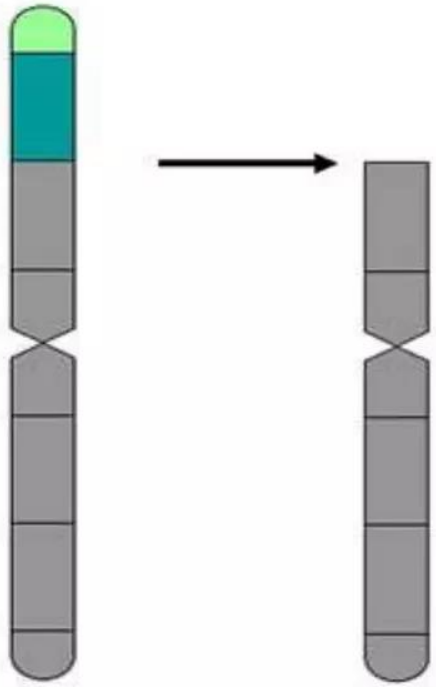
- It is the loss of a part of a chromosome.
- It is of two types namely: interstitial (middle) and terminal (rare).

- Interstitial Deletion - It occurs when there are two breaks within a chromosome arm. This is followed by loss of the chromosomal material between the breaks and fusion of the broken ends of the remaining portion of the chromosome.

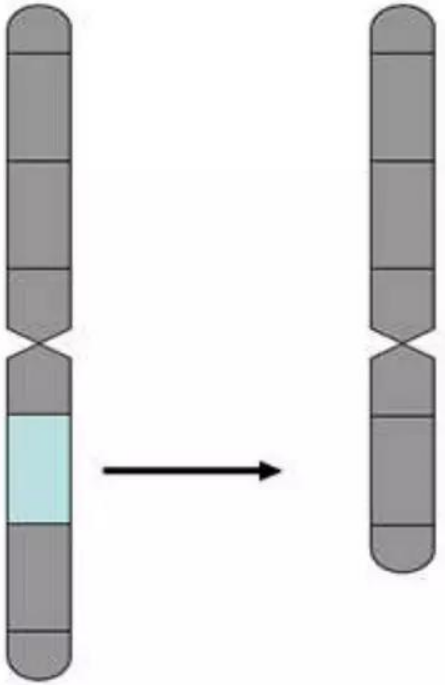
- Terminal Deletion - It results from a single break at the terminal part in a chromosome arm, producing a shortened chromosome bearing a deletion and a fragment with no centromere. The fragment is then lost at the next cell division.

Types of Deletion

Terminal

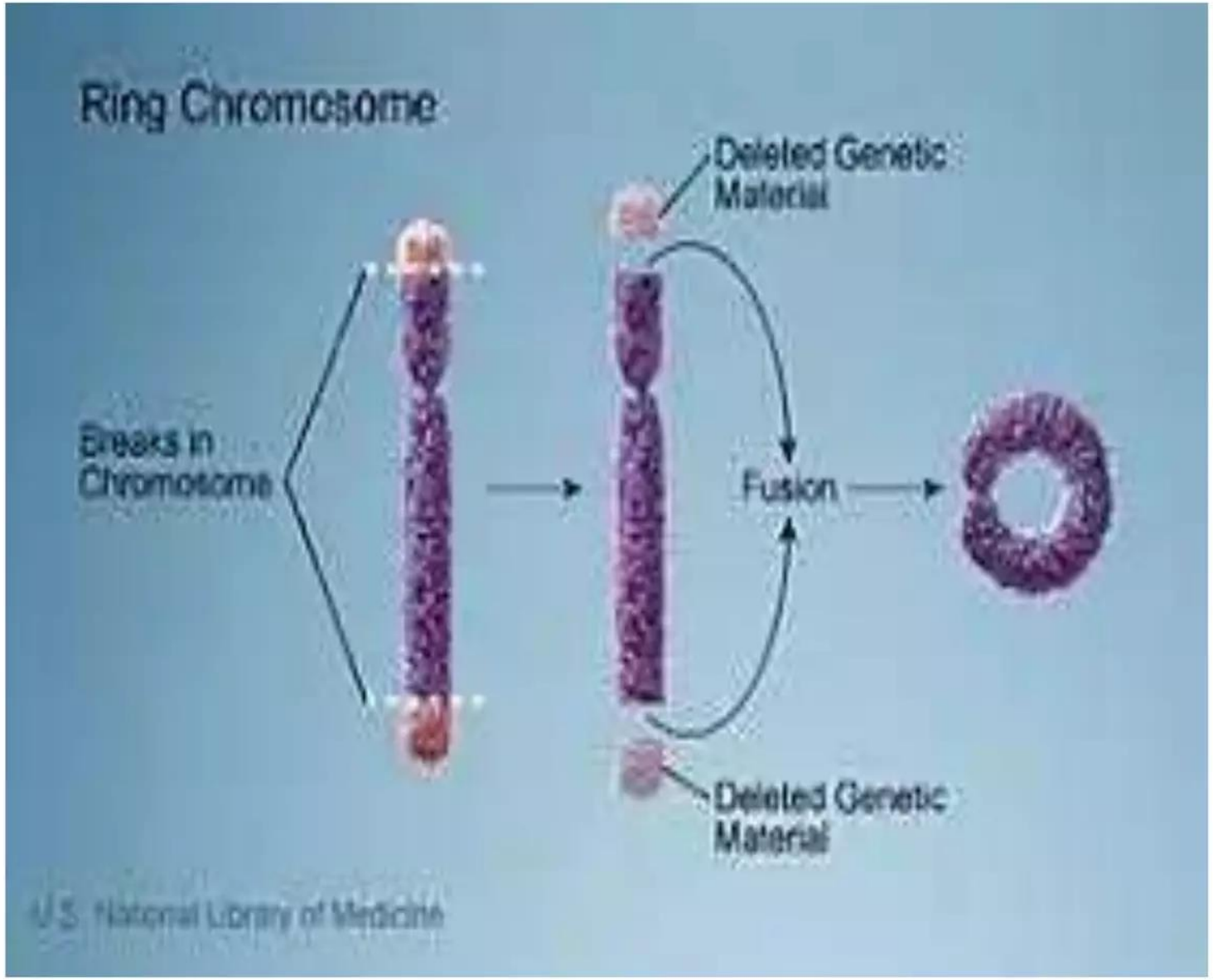


Interstitial



RING CHROMOSOME

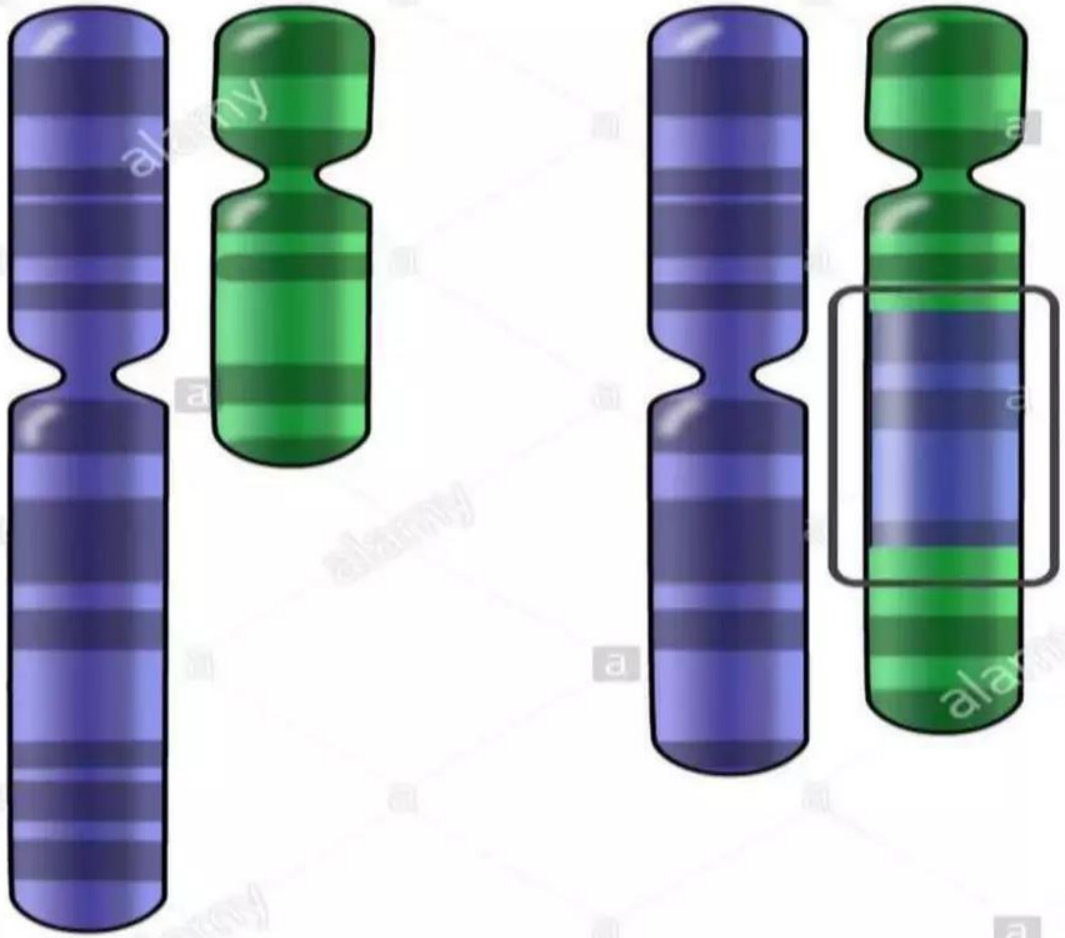
- It is a special form of deletion. Ring chromosomes are formed by a break at both the ends of a chromosome.
- There is deletion of the acentric fragments formed due to break and end-to-end fusion of the remaining centric portion of the chromosome at the cut ends resulting in a ring chromosome.
- The consequences depend on the amount of genetic material lost due to the break.
- Loss of significant amount of genetic material will result in phenotypic abnormalities.


Ring Chromosome
Deleted Genetic Material
Breaks in Chromosome
Fusion
Deleted Genetic Material
U.S. National Library of Medicine

INSERTION

- It is a form of nonreciprocal translocation in which a fragment of chromosome is transferred and inserted into a nonhomologous chromosome.
- Two breaks occur in one chromo some which releases a chromosomal fragment.
- This fragment is inserted into another chromosome following one break in the receiving chromosome, to insert this fragment.

INSERTION



MUTATIONS

- A mutation is defined as a permanent change in the genetic material (DNA) which results in a disease. The term mutation was coined by Muller in 1927.

- Causes
  - Spontaneous mutation: Majority of mutations occurs spontaneously due to errors in DNA replication and repair.
  - Induced mutation: Mutations can be caused due to exposure to mutagenic agents like chemicals, viruses, and ultraviolet or ionizing radiation.

- If the genetic material change/variant does not cause obvious effect upon phenotype, it is termed as polymorphism. A polymorphism is defined as genetic variation that exists in population with a frequency of >1%.

CLASSIFICATION OF MUTATIONS

- Depending on the Cell Involved Mutations are divided into two types:
  - Germ cell mutations: Mutations that affect the germ cells are transmitted to the progeny/ descendants and can give rise to inherited diseases.
  - Somatic cell mutations: Mutations involving the somatic cells can produce cancers and some congenital malformations. These mutations are not inherited and are known as de novo mutations.

CLASSIFICATION OF MUTATIONS

- Depending on the Nature
  - Numerical mutation: There is either gain or loss of whole chromosome (trisomy/monosomy). These usually develop during gametogenesis and are known as genomic mutations.
  - Structural Chromosomal Mutations The rearrangement of genetic material causes structural change. Structural mutations may be visible during karyotyping or submicroscopic. The submicroscopic gene mutations can result in partial or complete deletion of a gene or more often, a single nucleotide base.

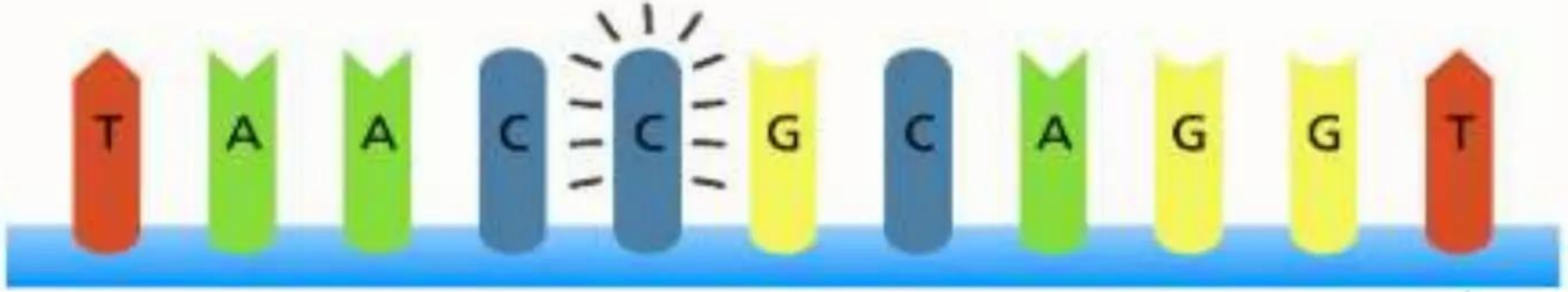
CLASSIFICATION OF MUTATIONS

- **Point Mutation** - When a nucleotide base is replaced by a different nucleotide base within a gene, it is known as point mutation. Majority of point mutation occur in the coding region of a gene and cause failure of translation and synthesis of the particular gene product.

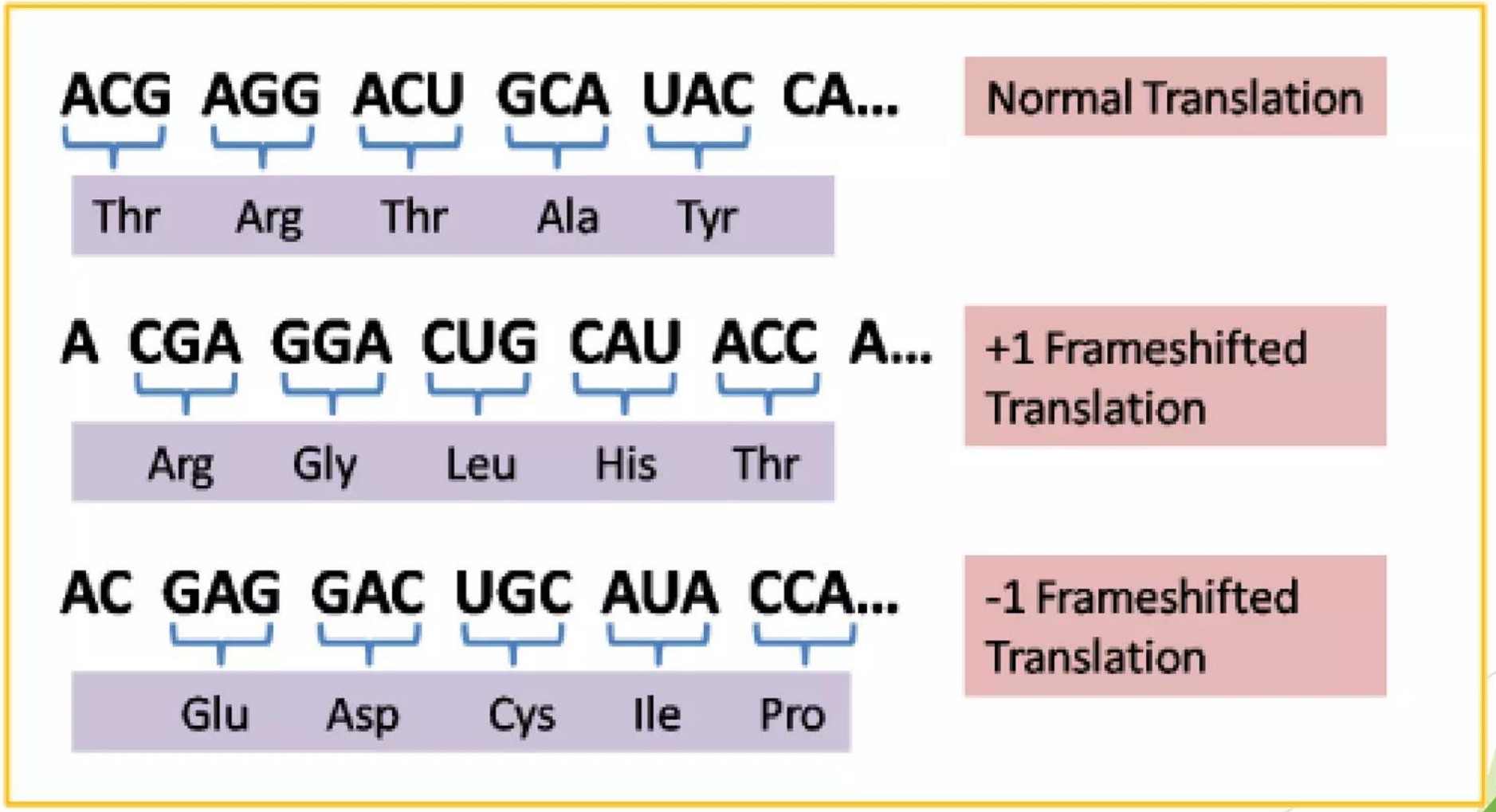
- **Frame Shift Mutation -** This is due to insertion or deletion of one or more nucleotides. If the number of nucleotide bases inserted or deleted is not a multiple of 3, the code will be changed. They are known as frameshift mutation. When deletions involve a large segment of DNA, the coding region of a gene may be entirely removed.

Original sequence

Point mutation



Frame Shift Mutation



CLASSIFICATION OF MUTATIONS

- **Trinucleotide repeat mutation:** The DNA contains several repeat sequences of three nucleotides (trinucleotide). When they are repeated directly adjacent to each other (one right after the other), they are known as tandem repeats. When the repetitive trinucleotide sequences reach above a particular threshold, they can expand (amplify) or contract. The amplification is more common. These trinucleotide-repeat mutation are dynamic (i.e. the degree of amplification increases during gametogenesis).

MUTATIONS WITHIN NONCODING SEQUENCE

- Transcription of DNA is initiated and regulated by promoter and enhancer sequences. Point mutations or deletions of these regulatory regions result in either marked reduction or total lack of transcription.