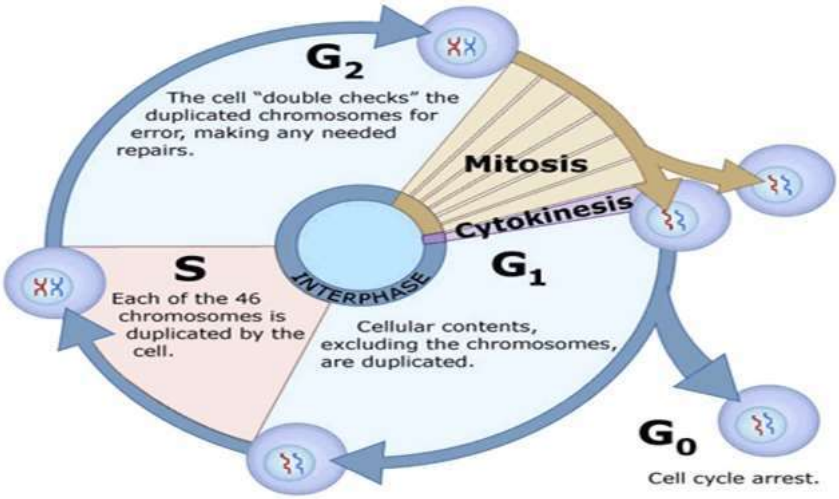
The cell cycle, mitosis and meiosis

The cell cycle

Actively dividing eukaryote cells pass through a series of stages known collectively as the cell cycle: two gap phases (G1 and G2); an S (for synthesis) phase, in which the genetic material is duplicated; and an M phase, in which mitosis partitions the genetic material and the cell divides.



G1 phase: the cell synthesizes mRNA and proteins in preparation for subsequent steps leading to mitosis.

S phase: any problems with DNA replication trigger a 'checkpoint', the phase will on hold until the problem is resolved. Each chromosome now consists of two sister chromatids.

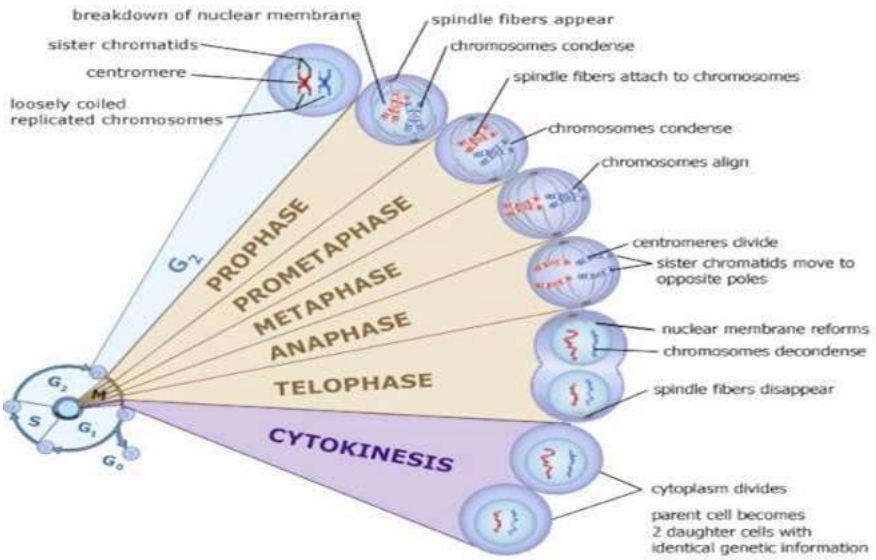
G2 phase: is a period of rapid cell growth and protein synthesis during which the cell prepares itself for mitosis.

M phase: During the mitotic (M) phase, the cell divides its copied DNA and cytoplasm to make two new cells. M phase involves two distinct division-related processes: mitosis and cytokinesis.

Interphase: This is when the cell grows and copies its DNA before moving into mitosis. During mitosis, chromosomes will align, separate, and move into new daughter cells. The interphase takes place between one mitotic (M) phase and the next. The period between mitotic cell divisions that are include G1, S and G2.

Mitosis Cell division:

- Mitosis is a form of eukaryotic cell division that produces two daughter cells with the same genetic component as the parent cell.
- Chromosomes replicated during the S phase are divided in such a way as to ensure that each daughter cell receives a copy of every chromosome.
- In actively dividing animal cells, the whole process takes about one hour.
- The replicated chromosomes are attached to a 'mitotic apparatus' that aligns them and then separates the sister chromatids to produce an even partitioning of the genetic material.
- This separation of the genetic material in a mitotic nuclear division (or karyokinesis) is followed by a separation of the cell cytoplasm in a cellular division (or cytokinesis) to produce two daughter cells.
- In some single-celled organisms mitosis forms the basis of asexual reproduction.
- In diploid multicellular organisms sexual reproduction involves the fusion of two haploid gametes to produce a diploid zygote.
- Mitotic divisions of the zygote and daughter cells are then responsible for the subsequent growth and development of the organism.
- In the adult organism, mitosis plays a role in cell replacement, wound healing and tumour formation.
- Mitosis, although a continuous process, is conventionally divided into five stages: **prophase, prometaphase, metaphase, anaphase and telophase**.



The phases of mitosis:

1. **Prophase:**

- The nuclear membrane breaks down to form a number of small vesicles and the nucleolus disintegrates.
- A structure known as the centrosome duplicates itself to form two daughter centrosomes that migrate to opposite ends of the cell.
- The centrosomes organize the production of microtubules that form the spindle fibres that constitute the mitotic spindle.
- The chromosomes condense into compact structures.
- Each replicated chromosome can now be seen to consist of two identical chromatids (or sister chromatids) held together by a structure known as the centromere.

2. **Prometaphase:**

- The chromosomes, led by their centromeres, migrate to the equatorial plane in the mid-line of the cell at right angles to the axis formed by the centrosomes.
- This region of the mitotic spindle is known as the metaphase plate. The spindle fibers bind to a structure associated with the centromere of each chromosome called a kinetochore.
- Individual spindle fibers bind to a kinetochore structure on each side of the centromere.
- The chromosomes continue to condense.

3. **Metaphase:**

The chromosomes align themselves along the metaphase plate of the spindle apparatus.

4. **Anaphase:**

The centromeres divide and the sister chromatids of each chromosome are pulled apart and move to the opposite ends of the cell, pulled by spindle fibers attached to the kinetochore regions.

The separated sister chromatids are now referred to as daughter chromosomes. (It is the alignment and separation in metaphase and anaphase that is important in ensuring that each daughter cell receives a copy of every chromosome).

5. Telophase:

The final stage of mitosis, in which the nuclear membrane reforms around the chromosomes grouped at either pole of the cell, the chromosomes uncoil and become diffuse, and the spindle fibers disappear.

Cytokinesis

It is the final cellular division to form two new cells. In plants a cell plate forms along the line of the metaphase plate; in animals there is a constriction of the cytoplasm. The cell then enters interphase (the interval between mitotic divisions).

The phases of Meiosis:

Meiosis is the form of eukaryotic cell division that produces haploid sex cells or gametes (which contain a single copy of each chromosome) from diploid cells (which contain two copies of each chromosome).

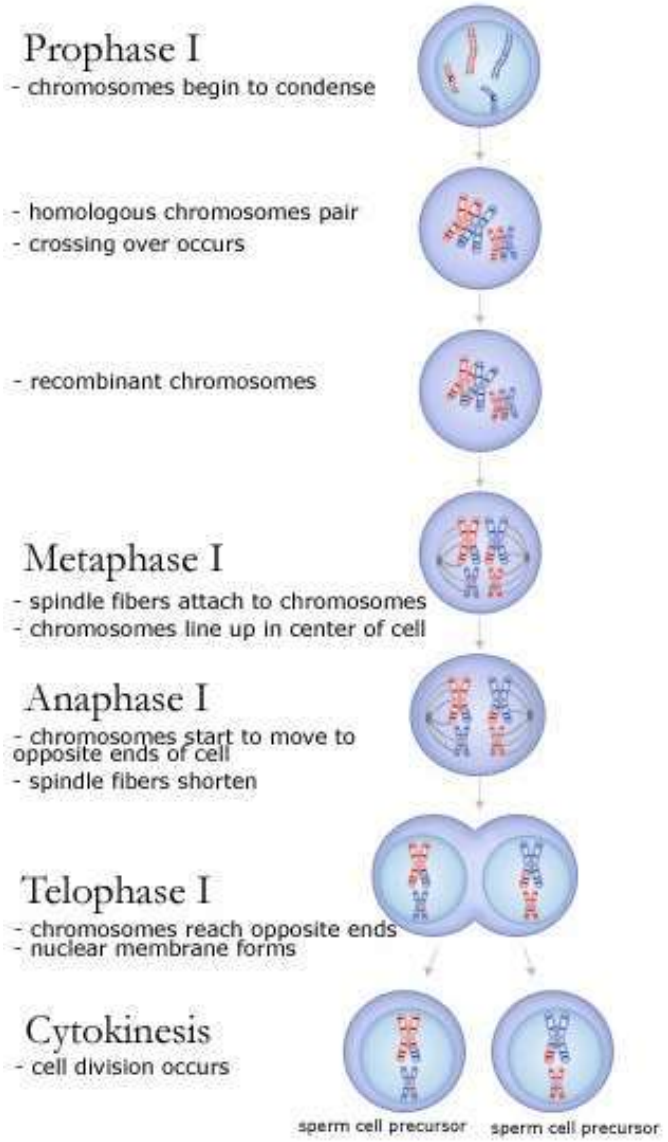
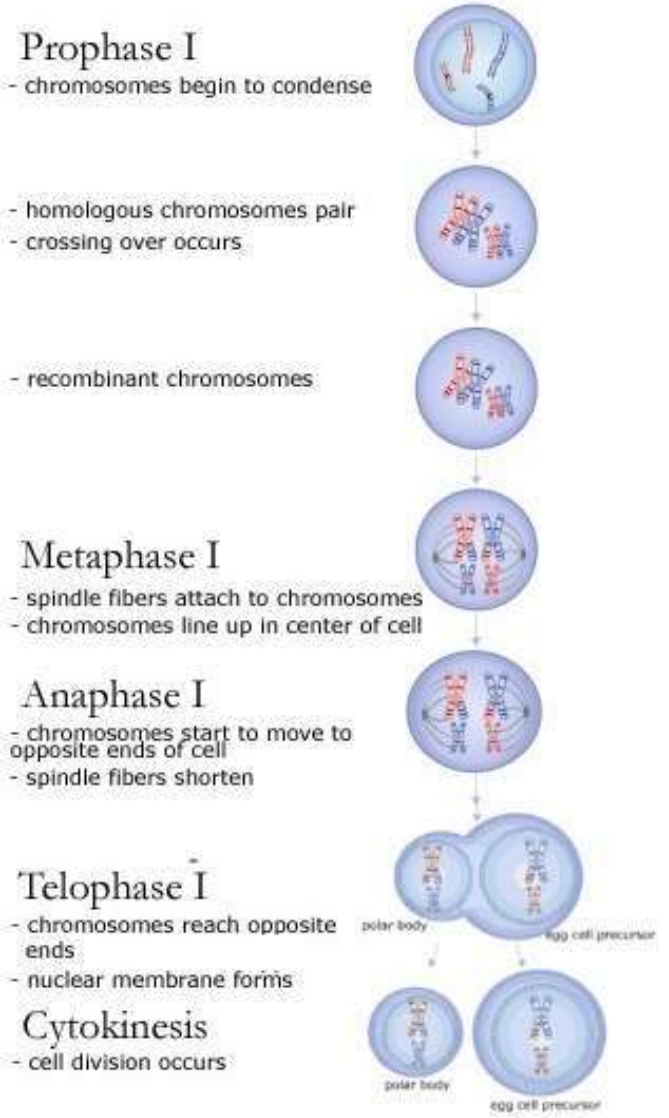
The process takes the form of one DNA replication followed by two successive nuclear and cellular divisions (Meiosis I and Meiosis II).

As in mitosis, meiosis is preceded by a process of DNA replication that converts each chromosome into two sister chromatids.

Meiosis I

Meiosis I separates the pairs of homologous chromosomes.

In Meiosis I a special cell division reduces the cell from diploid to haploid. In male will divide in to two sperm cell precursor, while in female will be polar body and egg cell precursor.

Meiosis I in Males	Meiosis I in Females
	

Prophase I

The homologous chromosomes pair and exchange DNA to form recombinant chromosomes. Prophase I is divided into five phases:

- **Leptotene:** chromosomes start to condense.
- **Zygotene:** homologous chromosomes become closely associated (synapsis) to form pairs of chromosomes (bivalents) consisting of four chromatids (tetrads).
- **Pachytene:** crossing over between pairs of homologous chromosomes to form chiasmata.
- **Diplotene:** homologous chromosomes start to separate but remain attached by chiasmata.
- **Diakinesis:** homologous chromosomes continue to separate, and chiasmata move to the ends of the chromosomes.

Prometaphase I

Spindle apparatus formed, and chromosomes attached to spindle fibres by kinetochores.

Metaphase I

Homologous pairs of chromosomes (bivalents) arranged as a double row along the metaphase plate. The arrangement of the paired chromosomes with respect to the poles of the spindle apparatus is random along the metaphase plate. (This is a source of genetic variation through random assortment, as the paternal and maternal chromosomes in a homologous pair are similar but not identical. The number of possible arrangements is 2n, where n is the number of chromosomes in a haploid set.
Human beings have 23 different chromosomes, so the number of possible combinations is 23.)

Anaphase I

The homologous chromosomes in each bivalent are separated and move to the opposite poles of the cell

Telophase I

The chromosomes become diffuse and the nuclear membrane reforms, and forms the polar body and egg cell precursor for female and/or two sperm cell precursor for male.

Cytokinesis

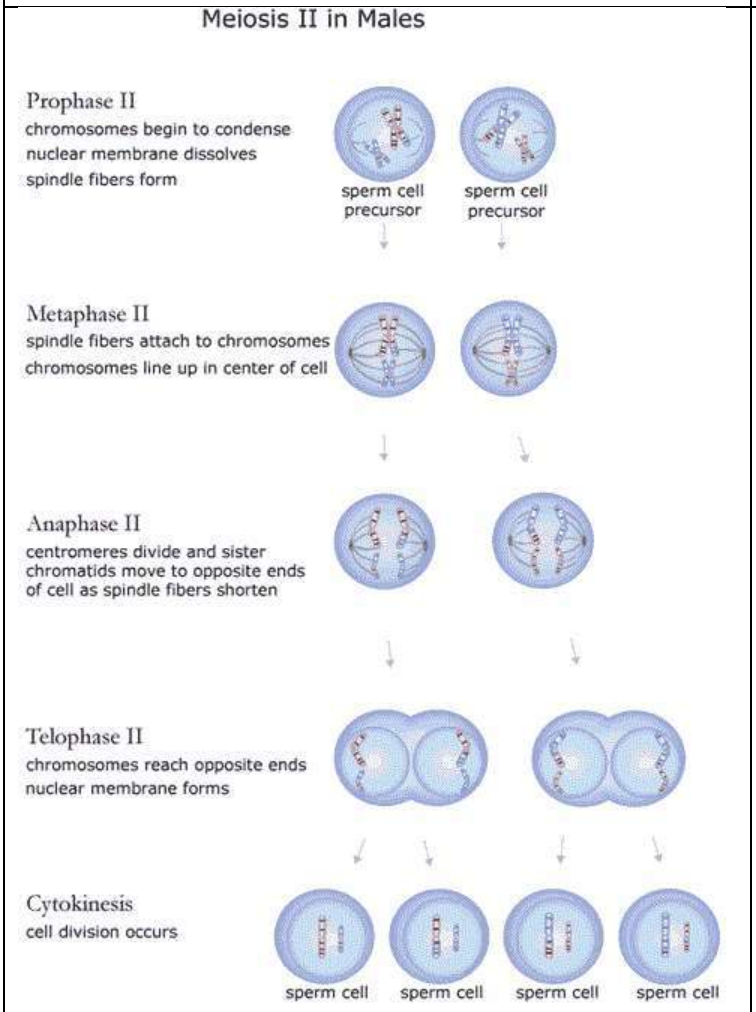
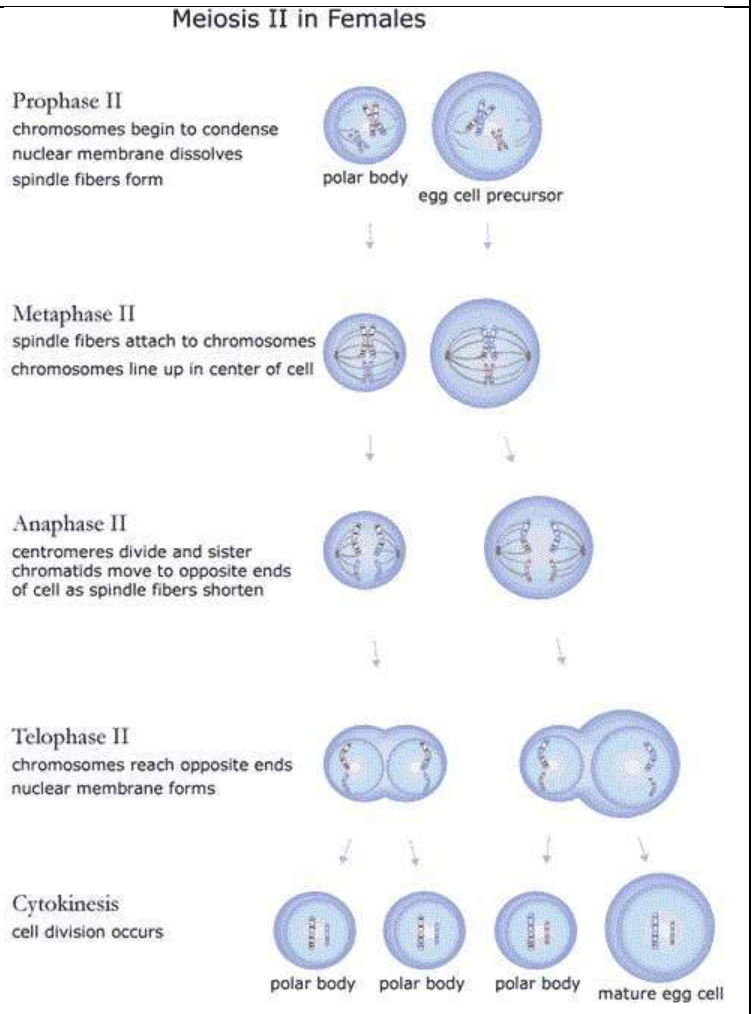
It is the final cellular division to form two new cells, followed by Meiosis II. Meiosis I is a reduction division: the original diploid cell had two copies of each chromosome; the newly formed haploid cells have one copy of each chromosome.

Meiosis II

Meiosis II separates each chromosome into two chromatids. The events of Meiosis II are analogous to those of a mitotic division, although the number of chromosomes involved has been halved. Finally it forms the three polar body and mature egg cell for female and/or four sperm for male.

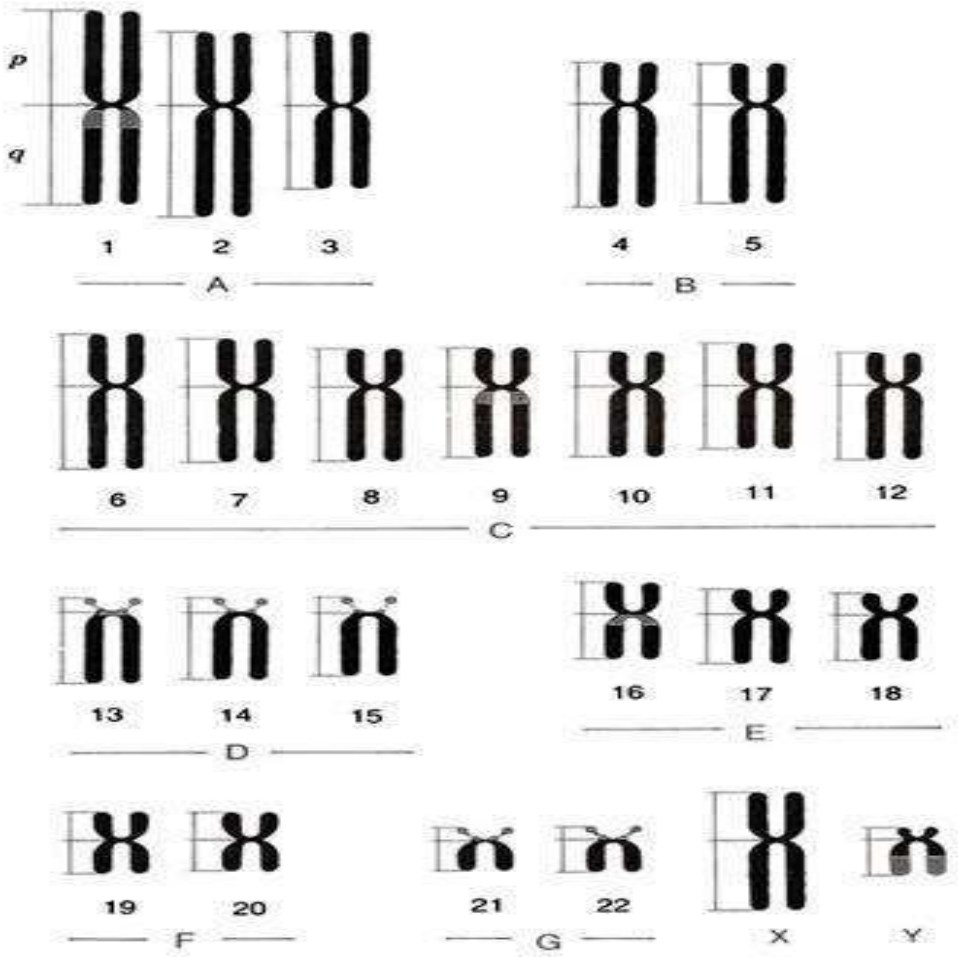
Meiosis generates genetic diversity through:

- The exchange of genetic material between homologous chromosomes during Meiosis I
- The random alignment of maternal and paternal chromosomes in Meiosis I
- The random alignment of the sister chromatids at Meiosis II

Meiosis II in Males	Meiosis II in Females
	

Karyotyping

The term karyotype refers to the chromosomal pattern inside the nucleus of an animal cell (eukaryote), as well as to describe the set of chromosomes in a species or in an individual organism.



A karyotype will be shared by organisms from the same species, but the following intra-species variations are seen:-

1. The karyotype of males and females may differ. For instance, in humans the male karyotype contains an X and Y chromosome while in human females there are two X chromosomes.
2. There are karyotypic differences between body (somatic) cells and gametes. The sperm and egg cells each contain half the amount of chromosomes a somatic cell contains, and only make a complete cell with the full number of 46 chromosomes when they combine during fertilization.

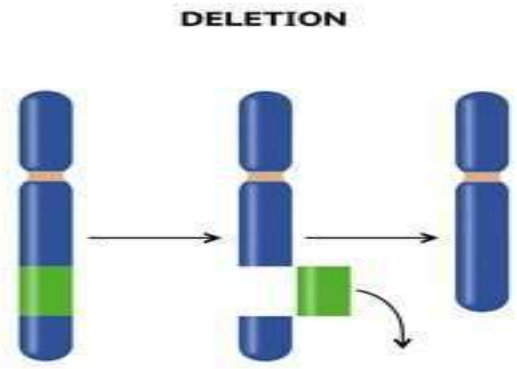
3. Karyotypes may also differ within a population due to genetic polymorphism.
4. The karyotype of a species may vary by geographical location and racial differences are also seen.
5. Genetic abnormalities may also give rise to abnormal and different karyotypes.

Chromosome abnormalities:

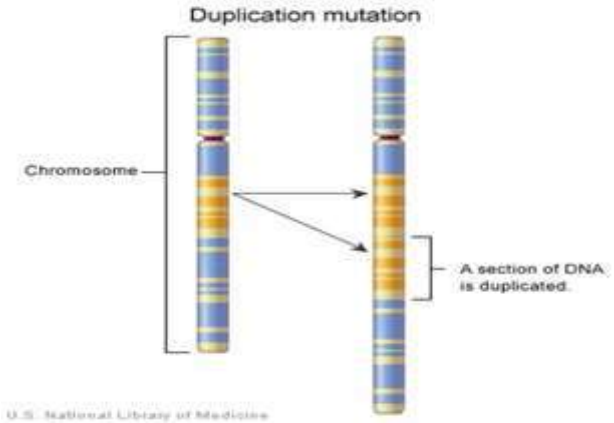
Mutations that cause change in the structure or number of chromosomes are called chromosomal aberration. These are of two types:-

A- Structural Abnormalities: (change in the structure of gene sequence).

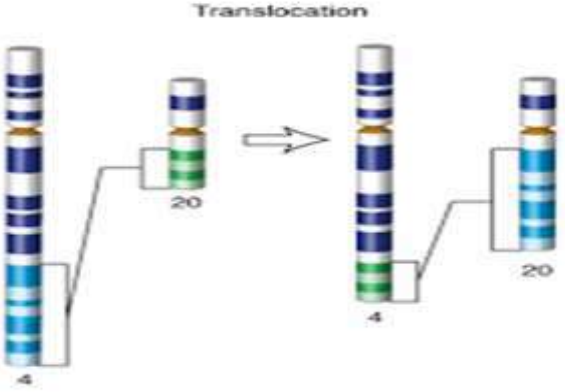
A chromosome's structure can be altered in several ways:-



- **Deletions:** A portion of the chromosome is missing or deleted.

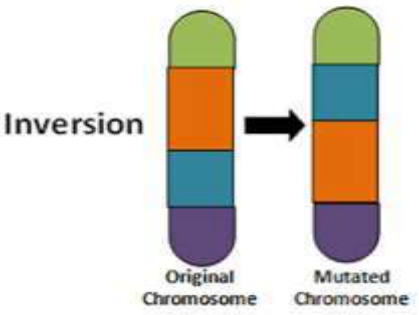


- **Duplications:** A portion of the chromosome is duplicated, resulting in extra genetic material.

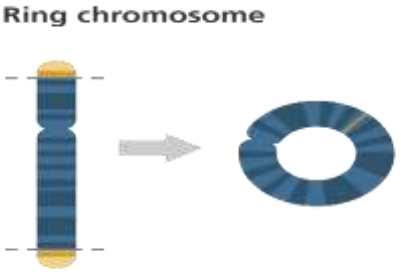


- **Translocations:** A portion of one chromosome is transferred to another chromosome

- **Inversions:** A portion of the chromosome has broken off, turned upside down, and reattached. As a result, the genetic material is inverted.



- **Rings:** A portion of a chromosome has broken off and formed a circle or ring. This can happen with or without loss of genetic material.



Most chromosome abnormalities occur as an accident in the egg or sperm. In these cases, the abnormality is present in every cell of the body. Some abnormalities, however, happen after conception; then some cells have the abnormality and some do not. Chromosome abnormalities can be inherited from a parent (such as a translocation) or be "de novo" (new to the individual).

B- Numerical Abnormalities:

a. Aneuploidy : Variation in the number of particular chromosomes within a set

1- Hyperploidy- gain of chromosome/s

- Trisomy: 2n + 1
- Double trisomy: 2n + 1 +1
- Tetrasomy: 2n + 2

When an individual has more than two chromosomes instead of a pair, the condition is called trisomy. An example of a condition caused by numerical abnormalities is Down syndrome, which is marked by mental retardation, learning difficulties, a characteristic facial. An individual with Down syndrome has three copies of chromosome 21 rather than two; for that reason, the condition is also known as Trisomy 21.

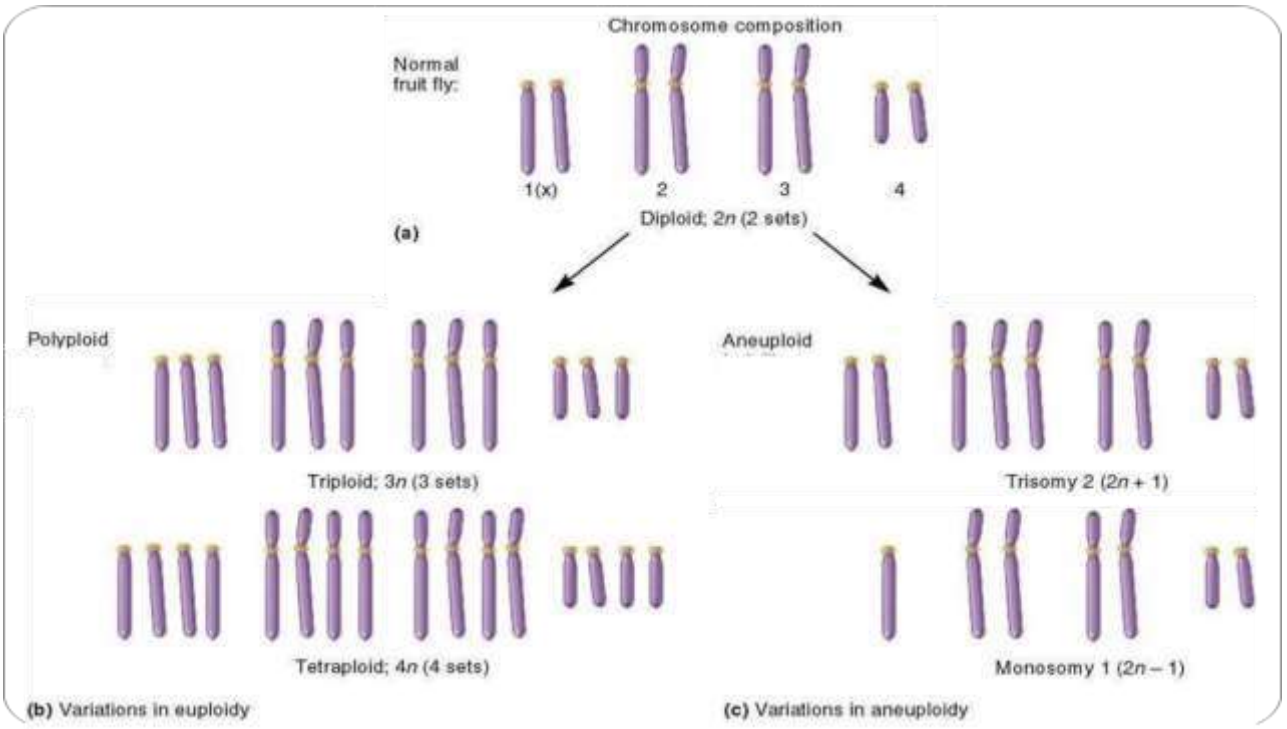
2- Hypoploidy- loss of chromosome/s

- Monosomy: 2n -1
- Double monosomy: 2n -1-1
- Nullisomy: 2n -2

When an individual is missing one of the chromosomes from a pair, the condition is called monosomy. An example of monosomy, in which an individual lacks a chromosome, is Turner syndrome. In Turner syndrome, a female is born with only one sex chromosome, an X, and is usually shorter than average and unable to have children, among other difficulties.

b. Polyploidy: Condition in which the cells have more than 2 homologous sets of chromosome:

- Triploid (3n)
- Tetraploid (4n)
- Pentaploid (5n)



Chromosome abnormalities usually occur when there is an:

- **Error in cell division:** (mitosis or and meiosis)

Errors in cell division can result in cells with too few or too many copies of a chromosome.

- **Maternal Age:** Older women are at higher risk of giving birth to babies with chromosome abnormalities than younger women. Because men produce new sperm throughout their lives, paternal age does not increase risk of chromosome abnormalities.

Genetic diseases due to Chromosomal abnormalities

A chromosome disorder results from a change in the number or structure of chromosomes. Any deviation from the normal karyotype is known as a chromosome abnormality. While some chromosome abnormalities are harmless, some are associated with clinical disorders.

A. Structural abnormalities

This is when large sections of DNA are missing from or are added to a chromosome.

1. Deletion

a. Prader-Willi syndrome /Angelman syndrome: m Due to microdeletion from short arm of chromosome 15**.**

Clinical features:

a. They have short stature and very small hands and feet in comparison to body.
b. Rapid weight gain and increasing obesity.
c. Low muscle tone and almond-shaped eyes.
d. Mental retardation or learning disabilities.
e. Incomplete sexual development.
f. Angelman Syndrome is also known as **happy puppet syndrome** because of the child's sunny outlook and jerky movements.

b. Cri-du-chat or (cat's cry syndrome): It is caused by deletion from tip of short arm of chromosome 5p.

Clinical features:

a. They have a high-pitched cry.
b. Poor muscle tone, a small head size and low birth weight.
c. Problems with language.
d. Delays in walking and problems with feeding.
e. Hyperactivity and severe intellectual disability.

2. Duplications

Pallister-Killian syndrome: Due to part of the 12 chromosome is duplicated.

Clinical features:

a. Babies have severe intellectual disability and poor muscle tone.
b. Coarse facial features and a prominent forehead.
c. They tend to have a very thin upper lip, with a thicker lower lip and a short nose.
d. People have a shortened life span but may live into their 40s.

3. Translocation:

There are two main types of translocations:

i. Reciprocal (also known as non-Robertsonian): Caused by exchange of material between non-homologous chromosomes. Two detached fragments of two different chromosomes are switched. For example is (**Chronic Myelogenous Leukemia)**.

Chronic Myelogenous Leukemia (chronic granulocytic leukemia (CGL)): is translocation of genetic material between chromosome 9 and chromosome 22.

It is characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood.

ii. Robertsonian: Occurs when two non-homologous chromosomes get attached, meaning that given two healthy pairs of chromosomes, one of each pair "sticks" and blends together homogeneously. For example is **(Translocation in Down's syndrome)**.

Translocation in Down's syndrome: The extra chromosome 21 or part of it may be attached to chromosome 14, sometimes to 13, 15 or 22. In some cases, two chromosomes 21 can be attached to each other.

4. Inversion:

Inv(9)(p12q13): The abnormalities on chromosome 9.

It is considered to have no harmful effects, but there is some evidence it leads to an increased risk for miscarriage for about 30% of affected couples.

5. Rings:

Ring chromosome 14 syndrome: Occurs when the chromosome 14 become ring shape.

Clinical features:

a. Seizures, intellectual disability and learning problems.
b. Development may be delayed such as speech, sitting, standing and walking.

B. Numerical Abnormalities:

1. Aneuploidy:

a. Hyperploidy:

Down syndrome also known as trisomy 21: The abnormalities on chromosome 21.

Clinical features:

a. Physical growth delays and intellectual disability, and characteristic facial features.
b. The average IQ of a young adult with Down syndrome is 50, equivalent to the mental ability of an (8-9) year old child.

b. Hypoploidy:

Turner syndrome: The abnormalities on chromosome 45.

It is also known as 45,X or 45,X0 is a genetic condition in which a female is partially or completely missing an X chromosome.

Clinical features:

a. Short neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth.
b. Not develop menstrual periods and breasts without hormone treatment and are unable to have children without reproductive technology.
c. Heart defects, diabetes, and low thyroid hormone.
d. Vision and hearing problems.

2. Polyploidy

Triploid syndrome: It is a chromosomal disorder in which a fetus has three copies of every chromosome instead of the normal two.

Clinical features:

a. Common central nervous system defects.
b. Skeletal manifestations include cleft lip/palate and hypertelorism.
c. Congenital heart defects, hydronephrosis and meningocele.

The pattern of genetic inheritance (Mendel's laws)

Inheritance is the process of how a child receives genetic information from the parent. The whole process of heredity is dependent upon inheritance and it is the reason that the offspring's are similar to the parents and because of that, the members of the same family possess similar characteristics.

The people start to understand the inheritance in a proper way were in the middle of 19th century. This knowledge about inheritance was become possible by a scientist named Gregor Mendel who creates specific laws to understood inheritance known as Mendel's laws of 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, while the 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 or a sex chromosome, and on whether the allele is dominant or recessive.

Dominant inheritance

Dominant trait is when only one allele is required for the trait to be observed. Dominant allele will hide a recessive allele, if present. A dominant allele is denoted by a capital letter (A versus a). Because of each parent provides one allele, the possible combination are (AA), (Aa), (aa). Offspring whose genotype is either (AA) or (Aa) will have the dominant trait expressed phenotypically, while (aa) individuals express the recessive trait for instant:

D= Dominant trait, d= Other trait but not dominant.

Parent with dominant trait Parent without the trait

Dd dd

Children Dd dd

Dd= children with the trait (50%)

dd= children without the trait (50%)

Recessive inheritance

Recessive trait is when two copies of a recessive allele are required for the trait to be observed. Recessive allele are denoted by a lowercase letter (a versus A). Only individuals with an (aa) genotype will express a recessive trait. Offspring must receive one recessive allele from each parent to express phenotypically.

r= Recessive trait, R= Other trait but not Recessive

Carrier parent who does not express trait Carrier parent who does not express trait

Rr Rr

children RR Rr Rr rr

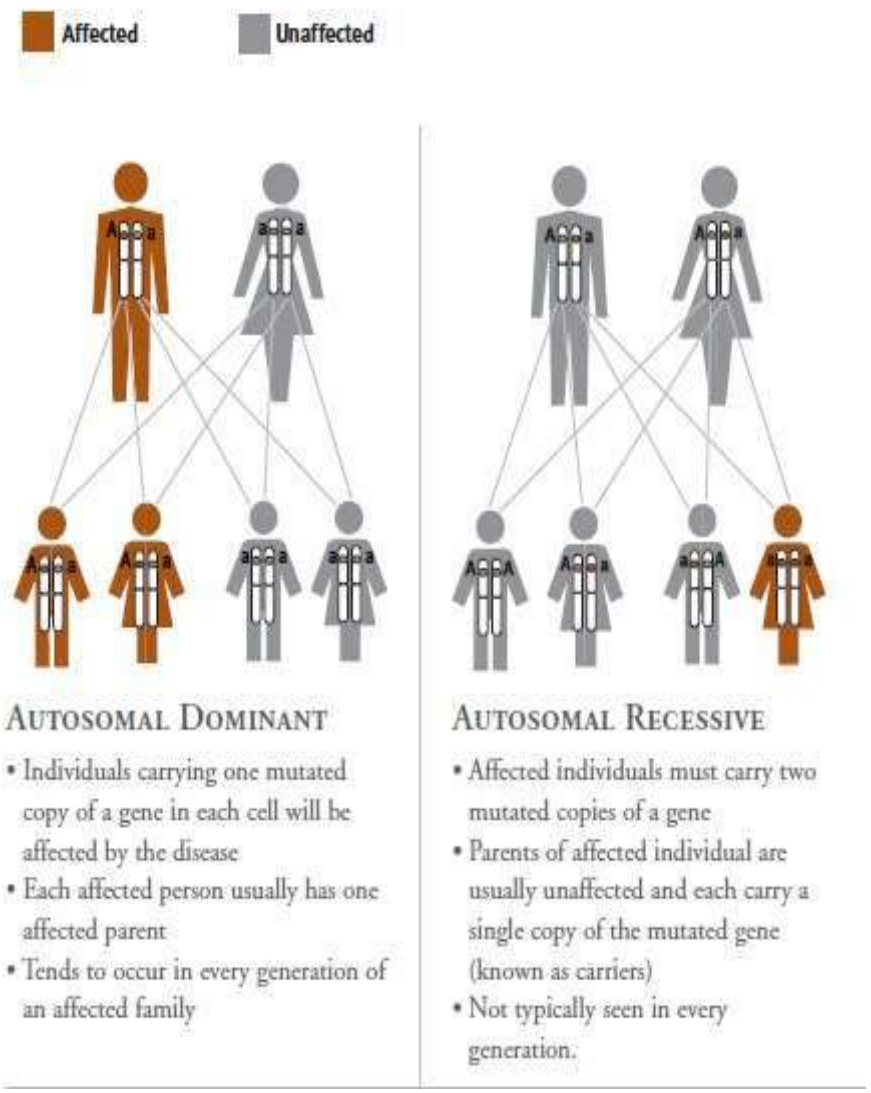
Children with recessive trait =rr (one in four or 25%)

Children who are carriers of a recessive trait like their parents= Rr (two in four or 50%)

Children who do not get the a recessive trait from either parent RR (one in four or 25%)

There are five patterns of genetic inheritance:

1. Autosomal dominant
2. Autosomal recessive
3. X-linked dominant
4. X- linked recessive
5. Y-linked



1. Autosomal Dominants Inheritance

If the phenotype associated with a given version of a gene is observed when an individual has only one copy, the allele is said to be autosomal dominant. The phenotype will be observed whether the individual has one copy of the allele (is heterozygous) or has two copies of the allele (is homozygous). Huntington's disease is the example of autosomal dominants inheritance.

Huntington's disease:

Huntington's disease is a rare, inherited disease that causes the progressive breakdown (degeneration) of nerve cells in the brain. Huntington's disease has a broad impact on a person's functional abilities and usually result in movement, thinking (cognitive) and psychiatric disorders. The signs and symptoms of most people with Huntington's disease

develop in their 30s to 40s, but the disease begins before age 20, the condition is called is juvenile Huntington's disease.

Symptoms:

1- Movement disorders.
2- Cognitive disorders.
3- Psychiatric disorders.

2. Autosomal Recessive Inheritance

If the phenotype associated with a given version of a gene is observed only when an individual has two copies, the allele is said to be autosomal recessive. The phenotype will be observed only when the individual is homozygous for the allele concerned. An individual with only one copy of the allele will not show the phenotype, but will be able to pass the allele on to subsequent generations. As a result, an individual heterozygous for an autosomal recessive allele is known as a carrier.

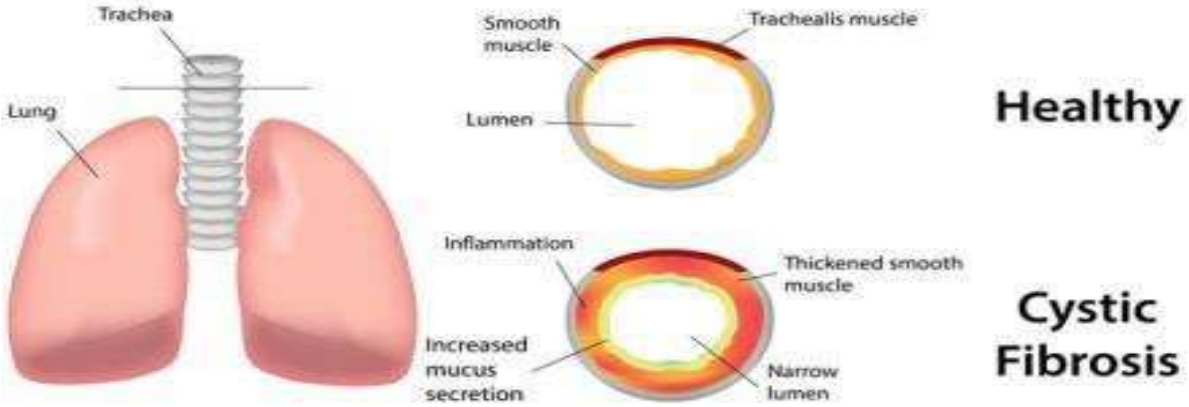
Cystic Fibroses:

Cystic fibrosis is an inherited disorder that causes severe damage to the lungs, digestive system and other organs in the body. Cystic fibrosis affects the cells that produce mucus, sweat and digestive juices. These recreated fluids are normally thin and slippery, but in people with cystic fibrosis, a defective gene causes the secretion to become sticky and thick. Instead of action as a lubricate, the secretion plug up tubes, ducts and passageway, especially in the lungs and pancreas.

Symptoms:

Lung infections or pneumonia.
Wheezing.
Coughing with thick mucus.
Bulky, greasy bowel movements.
Constipation or diarrhea.
Trouble gaining weight or poor height growth.
Very salty sweat.

Cystic Fibrosis



The pattern of genetic inheritance (Mendel's laws)

3. X-linked Recessive Inheritance

X-linked recessive inheritance is a mode of inheritance in which a mutation in a gene on the X chromosome causes the phenotype to be always expressed in males (who are necessarily homozygous for the gene mutation because they have one X and one Y chromosome) and in females who are homozygous for the gene mutation. Females with one copy of the mutated gene are carriers.

It is general features are:

- A single copy of the trait is enough to express in male while two for females.
- Both males and females affected, and more commonly expressed in males than females?
- Affected fathers cannot pass X-linked recessive traits to their sons because fathers give Y chromosomes to their sons.
- X-linked recessive traits tend to skip generations, meaning that an affected grandfather will not have an affected son, but could have an affected grandson through his daughter.

a. Red-green color blindness:

Red-green color blindness means that a person cann't distinguish shades of red and green (usually blue-green) due to the absence or mutation of the red or green retinal photoreceptors.

b. Hemophilia A:

Hemophilia A is a disorder where the blood cannot clot properly due to a deficiency of a clotting factor called Factor VIII. This result in abnormally heavy bleeding that will not stop, even from a small cut. People with hemophilia A bruise easily and can have internal bleeding into their joints and muscles. Treatment is available by infusion of Factor VIII (blood transfusion).

4. X-linked Dominant Inheritance

X-linked dominant inheritance occurs when a gene responsible for a trait is located on the X chromosome. The gene acts in a dominant manner. This means that both males and females can display the trait when they have only one copy of the gene from a parent.

Some X-linked dominant disorders are so severe that males with the genetic disorder may die before birth. Therefore, there may be an increased rate of miscarriages in the family or fewer male children than expected.

For an X-linked dominant disorder: If the father carries the abnormal X gene, all of his daughters will inherit the disease and none of his sons will have the disease. That is because daughters always inherit their father's X chromosome. If the mother carries the abnormal X gene, half of all their children (daughters and sons) will inherit the disease tendency. The following features are necessary to establish the clinical diagnosis.

- A single copy of the mutation is enough to cause the disease in both males and female.
- Both males and females affected, affected females are more in numbers?
- Affected fathers cannot pass X-linked dominant traits to their sons because fathers give Y chromosomes to their sons.
- X-linked dominant traits tend to appear in every generation.

a. Incontinentia Pigmenti IP:

IP is extremely rare. The main features occur in the skin where a blistering rash occurs in newborns. This is followed by the blisters becoming raised, like warts. Next, brown swirls appear in the skin, followed by the appearance of light-colored swirls. The result is a "marble-cake like" appearance on the skin.

b. Fragile X syndrome:

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities.

Affected individuals usually have delayed development of speech by age 2.

5. Y-linked

A condition is considered Y-linked if the altered gene that causes the disorder is located on the Y chromosome, one of the two sex chromosomes in each of a male's cells. Because only males have a Y chromosome, in Y-linked inheritance, a variant can only be passed from father to son.

a. Y chromosome infertility

Y chromosome infertility is a condition that affects the production of sperm and causes male infertility, which means it is difficult or impossible for affected men to father children. Men with Y chromosome infertility do not have any other signs or symptoms related to the condition.

Some men with Y chromosome infertility who have mild to moderate affects may eventually father a child naturally or with assisted reproductive technologies.

b. Swyer syndrome

People with Swyer syndrome have female external genitalia and some female internal reproductive structures. These individuals usually have a uterus and fallopian tubes, but their gonads (ovaries or testes) are not functional. Instead, the gonads are small and underdeveloped and contain little gonadal tissue. These structures are called **streak gonads**. The streak gonadal tissue is at risk of developing cancer that is often hard-to-detect, so it is usually removed surgically. Swyer syndrome is also called **46,XY complete gonadal dysgenesis**.

Hormone replacement therapy is important for bone health and helps reduce the risk of low bone density and fragile bones. Women with Swyer syndrome do not produce eggs (ova), but if they have a uterus, they may be able to become pregnant with a donated egg or embryo.

Pedigree Analysis

A pedigree is a visual chart that depicts a family history or the transmission of a specific trait though several generations. They can be interesting to view and can be important tools in determining patterns of inheritance of specific traits. The pedigree shows the relationships between family members and indicates which individuals express or silently carry the trait in question.

Pedigrees are used primarily by genetic counselors when helping couples decide to have children when there is evidence of a genetically inherited disorder in one or both families. They are also used when trying to determine the predisposition of someone to carry a hereditary disease for example, familial breast cancer.

A pedigree is a representation of our family tree. It shows how individuals within a family are related to each other. We can also indicate which individuals have a particular trait or genetic condition.

There are standard ways to draw pedigrees so that we can all look at a pedigree and understand it. We use squares to represent males and circles to represent females. We then can number our generations with roman numerals, so the top generation would be generation one, or Roman numeral I.

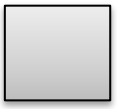
We use the following shapes:-

Clear Square to represent uninfected male or the trait is not appearing on the male.

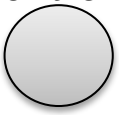
Clear Circle to represent uninfected female or the trait is not appearing on the female.

Circle with point in the middle of the circle to represent the female is carrier that trait but it is not appearing on the female.

Dark Square to represent infected male or the trait is appearing on the male.



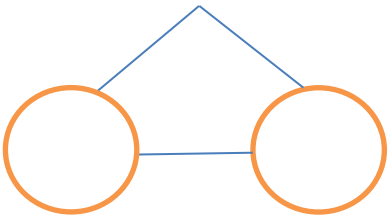
Dark Circles to represent infected female or the trait is appearing on the female.



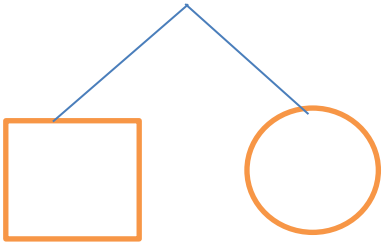
Square with a slash inside to represent dead male.

Circle with a slash inside to represent dead female.

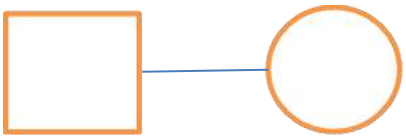
The shape bellows to represent identical twins.



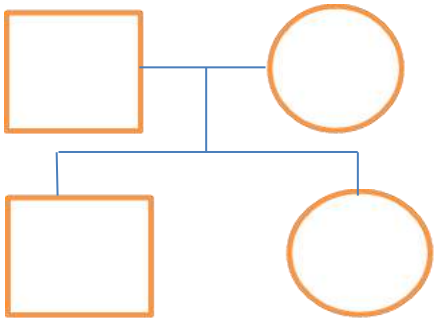
The shape bellows to represent non-identical twins.



The shape bellows to represent mating parents.



The shape bellows to represent mating parents and offspring in the birth order (first generation).



Along this line, we'd indicate males and females. We would indicate marriages between individuals with a horizontal line connecting the two individuals. If an individual has a genetic trait, we would blacken those individuals in or shade them, and the individuals carrying the trait are also represented by a point in the middle of the square for the male and a point in the middle of the circle for the female

Example: Mating between male infected with Hemophilia A, with female carrier for that disorder, by pedigree analysis:

1. Tracking the path of that disorder in the 1st generation.

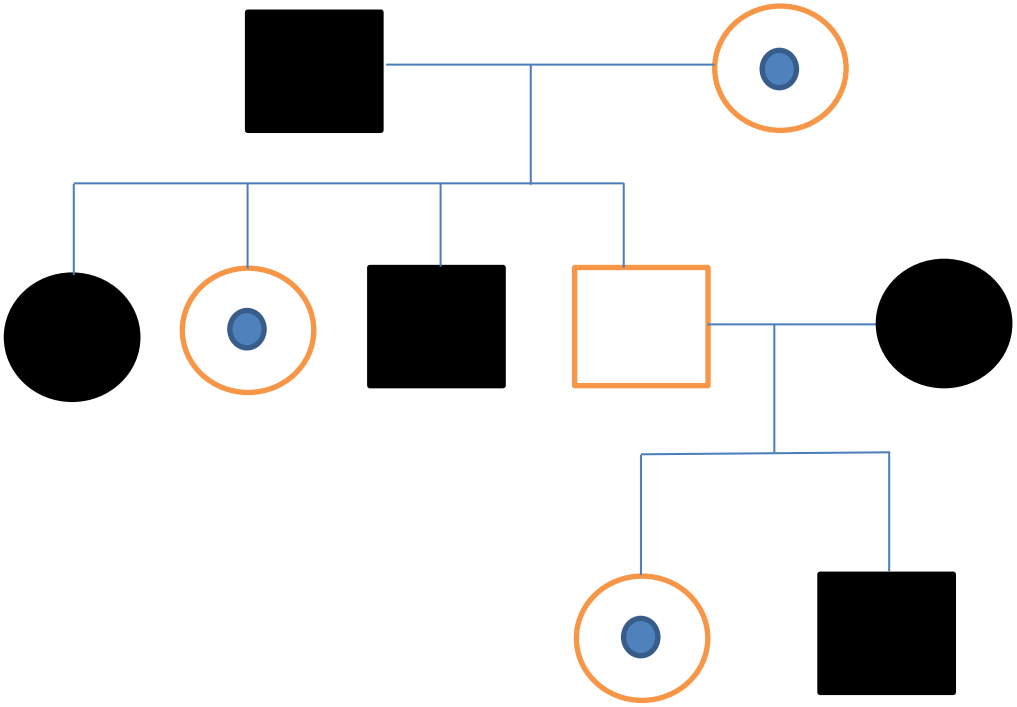
2. Then mating between uninfected male from the 1st generation with infected female from another family.

1. X^oY x XX^o

XX^O X^OX^O XY X^OY

2. XY x X^OX^O

XX^O X^OY



Example: Mating between male infected with swyer syndrome, with female, by pedigree analysis:

1. Tracking the path of that trait in the 1st generation.

2. Then mating between the male in the 1st generation with female from another family.

Non Mendlean Inheritance

Non-Mendelian inheritance refers to the inheritance of traits that have a more complex genetic basis than one gene with two alleles and complete dominance. It is any pattern in which traits do not segregate in accordance with Mendel's laws.

Conditions of non-Mendelian inheritance:

1. Multiple allele traits

Multiple allele traits are controlled by a single gene with more than two alleles. An example of a human multiple allele trait is ABO blood type, for which there are three common alleles: A, B, and O.

ABO Blood Group	
Genotype	Phenotype(blood type)
AA	A
AO	A
BB	B
BO	B
OO	O
AB	AB

2. Codominance

Codominance occurs when two alleles for a gene are expressed equally in the phenotype of heterozygotes. A human example of codominance also occurs in the ABO blood type, in which the A and B alleles are codominant.

3. Incomplete dominance

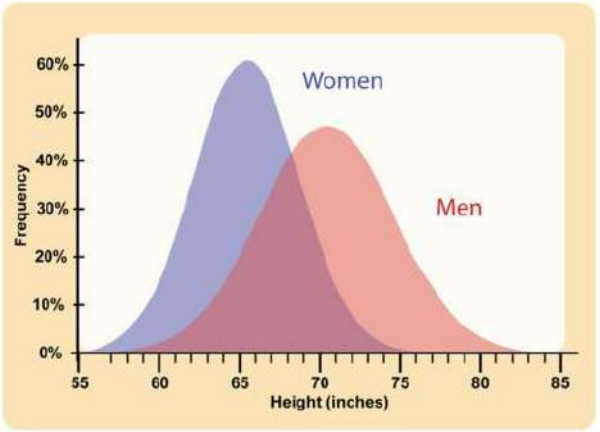
Another relationship that may occur between alleles for the same gene is incomplete dominance. This occurs when the dominant allele is not completely dominant. In this case, an intermediate phenotype results in heterozygotes who inherit both alleles. Generally, this happens when the two alleles for a given gene both produce proteins, but

one protein is not functional. As a result, the heterozygote individual produces only half the amount of normal protein as is produced by an individual who is homozygous for the normal allele for example of incomplete dominance in humans is Tay Sachs disease. Another example is hair type, there are genes for straight and curly hair, and if an individual is heterozygous, they will typically have the phenotype of wavy hair.

4. Polygenic traits

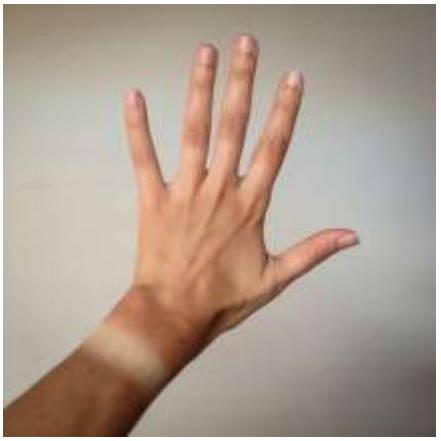
Many human traits are controlled by more than one gene. These traits are called polygenic traits. The alleles of each gene have a minor additive effect on the phenotype. There are many possible combinations of alleles, especially if each gene has multiple alleles.

An example of a human polygenic trait is adult height. Several genes, each with more than one allele, contribute to this trait, so there are many possible adult heights. One adult's height might be 1.65 m, and another adult's height might be 1.75 m. Adult height of males on average being somewhat taller than females. The majority of people fall near the middle of the range of heights for their sex.



5. Environmental Effects on Phenotype

Many traits are affected by the environment, as well as by genes. This may be especially true for polygenic traits. Skin color is an example of polygenic trait. There is a wide range of skin colors in people worldwide. In addition to differences in genes, differences in exposure to ultraviolet (UV) light cause some variation. The exposure to UV light darkens the skin.



6. Pleiotropy

Pleiotropy refers to the situation in which a gene affects more than one phenotypic trait. A human example of pleiotropy occurs with sickle cell anemia. People who inherit two recessive alleles for this disorder have abnormal red blood cells and may exhibit multiple other phenotypic effects, such as stunting of physical growth, kidney failure, and strokes.

7. Epistasis

Epistasis is the situation in which one gene affects the expression of other genes. An example of epistasis is albinism, in which the albinism mutation negates the expression of skin color genes.

DNA Mutation and Repair

A mutation, which may arise during replication and/or recombination, is a permanent change in the nucleotide sequence of DNA. Damaged DNA can be mutated either by substitution, deletion or insertion of base pairs. Mutations, for the most part, are harmless except when they lead to cell death or tumor formation. Because of the lethal potential of DNA mutations cells have evolved mechanisms for repairing damaged DNA.
A gene mutation is a change in one or more genes. Some mutations can lead to genetic disorders or illnesses. If a parent carries a gene mutation in their egg or sperm, it can pass to their child. These hereditary (or inherited) mutations are in almost every cell of the person's body throughout their life. Hereditary mutations include cystic fibrosis, hemophilia, and sickle cell disease.
Other mutations can happen on their own during a person's life. These are called sporadic, spontaneous, or new mutations. They affect only some cells. Damage from the sun's ultraviolet radiation or exposure to some types of chemicals can lead to new mutations. These mutations are not passed from parents to their children.

A gene can mutate because of:

- A change in one or more nucleotides of DNA.
- A change in many genes.
- Loss of one or more genes.
- Rearrangement of genes or whole chromosomes.

Types of DNA Mutations

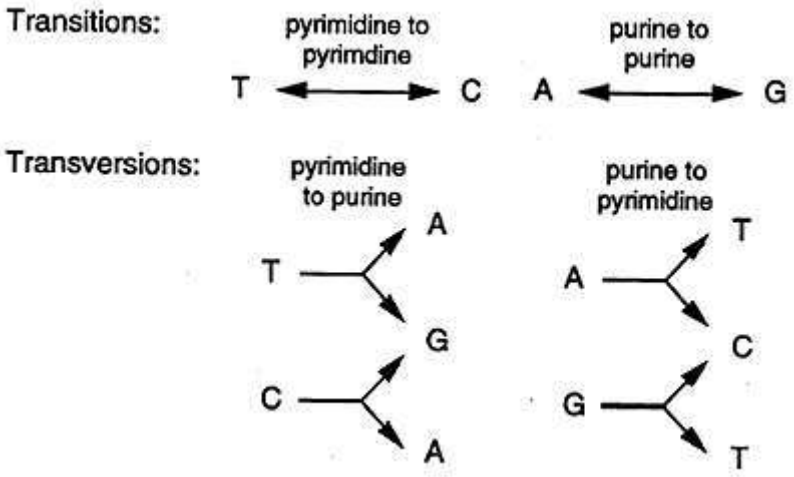
There are three types of DNA Mutations: base substitutions, deletions and insertions.

1. Base Substitutions

Single base substitutions are called point mutation, recall the point mutation Glu -----> Val which causes sickle-cell disease. Point mutations are the most common type of mutation and there are two types.

Transition: this occurs when a purine is substituted with another purine or when a pyrimidine is substituted with another pyrimidine.

Transversion: when a purine is substituted for a pyrimidine or a pyrimidine replaces a purine.



Point mutations that occur in DNA sequences encoding proteins are either silent, missense or nonsense.

Silent: If abase substitution occurs in the third position of the codon there is a good chance that a synonymous codon will be generated. Thus the amino acid sequence encoded by the gene is not changed and the mutation is said to be silent.

Missence: When base substitution results in the generation of a codon that specifies a different amino acid and hence leads to a different polypeptide sequence. Depending on the type of amino acid substitution the missense mutation is either conservative or nonconservative. For example if the structure and properties of the substituted amino acid are very similar to the original amino acid the mutation is said to be conservative and will most likely have little effect on the resultant proteins structure / function. If the substitution leads to an amino acid with very different structure and properties the mutation is nonconservative and will probably be deleterious (bad) for the resultant proteins structure / function (ex. the sickle cell point mutation).

Nonsense: When a base substitution results in a stop codon ultimately truncating translation and most likely leading to a nonfunctional protein.

2. Deletions:

A deletion, resulting in a frame-shift, results when one or more base pairs are lost from the DNA. If one or two bases are deleted the translational frame is altered resulting in a garbled message and nonfunctional product.

3. Insertions:

The insertion of additional base pairs may lead to frame-shifts depending on whether or not multiples of three base pairs are inserted.

- Combinations of insertions and deletions leading to a variety of outcomes are also possible.

Causes of DNA Mutations

1. Errors in DNA Replication

DNA polymerase will incorporate a noncomplementary base into the daughter strand. During the next round of replication the missincorporated base would lead to a mutation.

2. Errors in DNA Recombination

DNA often rearranges itself by a process called recombination which proceeds via a variety of mechanisms. Occasionally DNA is lost during replication leading to a mutation.

3. Chemical Damage to DNA

Many chemical mutagens, some exogenous, some man-made, some environmental, are capable of damaging DNA. Many chemotherapeutic drugs and intercalating agent drugs function by damaging DNA.

4. Radiation

Gamma rays, X-rays, even UV light can interact with compounds in the cell generating free radicals which cause chemical damage to DNA.

DNA Repair Mechanisms

Damaged DNA can be repaired by several different mechanisms.

1. Mismatch Repair

Mismatch repair is a process that corrects mismatched nucleotides in the otherwise complementary paired DNA strands, arising from DNA replication errors and recombination, as well as from some types of base modifications.

2. Nucleotide Excision Repair (NER)

Nucleotide excision repair is the main pathway to remove bulky DNA lesions, such as those formed by UV light, environmental mutagens, and some cancer chemotherapeutic adducts from DNA.

3. Direct Repair of Damaged DNA

Sometimes damage to a base can be directly repaired by specialized enzymes without having to excise the nucleotide.

4. Recombination Repair

This mechanism enables a cell to replicate past the damage and fix it later.

Regulation of Damage Control of DNA

DNA repair is regulated in mammalian cells by a sensing mechanism that detects DNA damage and activates a protein called p53. p53 is a transcriptional regulatory factor that controls the expression of some gene products that affect cell cycling, DNA replication and DNA repair. Some of the functions of p53, which are just being determined, are: stimulation of the expression of genes encoding p21 and Gaad45. Loss of p53 function can be deleterious, about 50% of all human cancers have a mutated p53 gene.

Some examples of the diseases resulting from defects in DNA repair mechanisms.

1. Xeroderma pigmentosum
2. Cockayne's syndrome
3. Hereditary nonpolyposis colorectal cancer

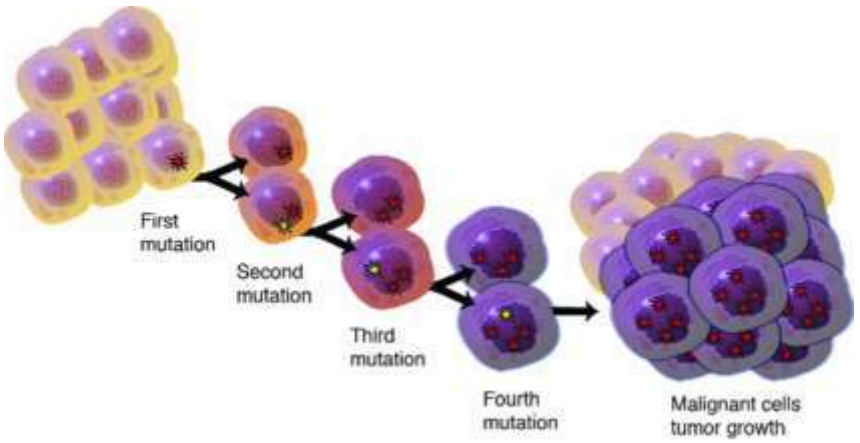
The Genetic Basis of Cancer

Genes are in the DNA of each cell in your body. They control how the cell functions, including:

- How quickly it grows
- How often it divides
- How long it lives

Researchers estimate that each cell contains 30,000 different genes. Within each cell, genes are located on chromosomes. Genes control how your cells work by making proteins. The proteins have specific functions and act as messengers for the cell. Each gene must have the correct instructions for making its protein. This allows the protein to perform the correct function for the cell.

All cancers begin when one or more genes in a cell mutate. A mutation is a change. It creates an abnormal protein. Or it may prevent a protein's formation. An abnormal protein provides different information than a normal protein. This can cause cells to multiply uncontrollably and become cancerous.



There are 2 basic types of genetic mutations for cancer (carcinogenic):

a. Acquired mutations: These are the most common cause of cancer. They occur from damage to genes in a particular cell during a person's life. For example, this could be a breast cell or a colon cell, which then goes on to divide many times and form a tumor. A tumor is an abnormal mass. Cancer that occurs because of acquired mutations is called sporadic cancer. Acquired mutations are not found in every cell in the body and they are not passed from parent to child.

Factors that cause these mutations include:

- Tobacco
- Ultraviolet (UV) radiation
- Viruses
- Age

b. Germline mutations: These are less common. A germline mutation occurs in a sperm cell or egg cell. It passes directly from a parent to a child at the time of conception. As the embryo grows into a baby, the mutation from the initial sperm or egg cell is copied into every cell within the body. Because the mutation affects reproductive cells, it can pass from generation to generation.

Cancer caused by germline mutations is called inherited cancer. It accounts for about 5% to 20% of all cancers.

Mutations and cancer

Mutations happen often. A mutation may be beneficial, harmful, or neutral. This depends where in the gene the change occurs. Typically, the body corrects most mutations.

A single mutation will likely not cause cancer. Usually, cancer occurs from multiple mutations over a lifetime. That is why cancer occurs more often in older people. They have had more opportunities for mutations to build up.

Types of genes linked to cancer

Many of the genes that contribute to cancer development fall into broad categories:

1. **Tumor suppressor genes:** These are protective genes. Normally, they limit cell growth by:
   - Monitoring how quickly cells divide into new cells
   - Repairing mismatched DNA
   - Controlling when a cell dies

When a tumor suppressor gene mutates, cells grow uncontrollably. And they may eventually form a tumor.

Examples of tumor suppressor genes include BRCA1, BRCA2, and p53 or TP53.

Germline mutations in BRCA1 or BRCA2 genes increase a woman's risk of developing hereditary breast or ovarian cancers and a man's risk of developing hereditary prostate or breast cancers. They also increase the risk of pancreatic cancer and melanoma in women and men.

The most commonly mutated gene in people with cancer is p53 or TP53. More than 50% of cancers involve a missing or damaged p53 gene. Most p53 gene mutations are acquired. Germline p53 mutations are rare, but patients who carry them are at a higher risk of developing many different types of cancer.

2. **Oncogenes:** These turn a healthy cell into a cancerous cell. Mutations in these genes are not known to be inherited.

Two common oncogenes are:

- HER2, a specialized protein that controls cancer growth and spread. It is found in some cancer cells. For example, breast and ovarian cancer cells.

- The RAS family of genes, which makes proteins involved in cell communication pathways, cell growth, and cell death.

3. **DNA repair genes:** These fix mistakes made when DNA is copied. Many of them function as tumor suppressor genes. BRCA1, BRCA2, and p53 are all DNA repair genes.

If a person has an error in a DNA repair gene, mistakes remain uncorrected. Then, the mistakes become mutations. These mutations may eventually lead to cancer, particularly mutations in tumor suppressor genes or oncogenes.

Mutations in DNA repair genes may be inherited or acquired. Lynch syndrome is an example of the inherited kind. BRCA1, BRCA2, and p53 mutations and their associated syndromes are also inherited.

Challenges in understanding cancer genetics

Researchers have learned a lot about how cancer genes work. But many cancers are not linked with a specific gene. Cancer likely involves multiple gene mutations. Moreover, some evidence suggests that genes interact with their environment. This further complicates our understanding of the role genes play in cancer.

Researchers continue to study how genetic changes affect cancer development. This knowledge has led to improvements in cancer care, including early detection, risk reduction, the use of targeted therapy, and survival.

Cancer genetics may help doctors find better ways to:

- Predict a person's risk of cancer
- Diagnose cancer
- Treat cancer

Genetic Screening and Prenatal Diagnosis

Prenatal diagnosis employs a variety of techniques to determine the health and condition of an unborn fetus. Without knowledge gained by prenatal diagnosis, there could be an untoward outcome for the fetus or the mother or both. Congenital anomalies account for 20 to 25% of perinatal deaths.

Prenatal diagnosis is helpful for:

1. Managing the remaining weeks of the pregnancy.
2. Determining the outcome of the pregnancy.
3. Planning for possible complications with the birth process.
4. Planning for problems that may occur in the newborn infant.
5. Deciding whether to continue the pregnancy.
6. Finding conditions that may affect future pregnancies.

The techniques employed for prenatal diagnosis include:

1. Ultrasonography

This is a non-invasive procedure that is harmless to both the fetus and the mother. High frequency sound waves are utilized to produce visible images from the pattern of the echos made by different tissues and organs, including the baby in the amniotic cavity. It is used for:

a. The size and position of the fetus.
b. The size and position of the placenta.
c. The amount of amniotic fluid.
d. The appearance of fetal anatomy.

2. Amniocentesis

This is an invasive procedure in which a needle is passed through the mother's lower abdomen into the amniotic cavity inside the uterus. It is used for:

a. Grown in culture for chromosome analysis.
b. Biochemical analysis.
c. Molecular biologic analysis.

3. Chorionic Villus Sampling (CVS)

In this procedure, a catheter is passed via the vagina through the cervix and into the uterus to the developing placenta under ultrasound guidance. It is used for:

a. Sampling of cells from the placental chorionic villi.
b. Chromosome analysis to determine the karyotype of the fetus.
c. Culturing for biochemical or molecular biologic analysis.

4. Maternal blood sampling for fetal DNA

This technique makes use of the phenomenon of fetal blood cells gaining access to maternal circulation through the placental villi. It is used for:

a. Sampling of fetal DNA.
b. Detect fetal autosomal aneuploidy.
c. Identify particular chromosomes of the fetal.
d. Diagnose aneuploid conditions.

5. Maternal serum alpha-fetoprotein (MSAFP)

The developing fetus has two major blood proteins (albumin and alpha-fetoprotein (AFP)). Since adults typically have only albumin in their blood, the MSAFP test can be utilized to determine the levels of AFP from the fetus. It is used for:

a. Fetal defect in the body wall, such as abnormal neural tube.
b. Identify the defects in the fetal abdominal wall.
c. Identify the gestational age.
d. The race of the mother and presence of gestational diabetes.
e. Screening for Down syndrome and other trisomies.

6. Maternal serum beta-HCG

This test is most commonly used as a test for pregnancy. This can be useful early in pregnancy when threatened abortion or ectopic pregnancy is suspected, because the amount of beta-HCG will be lower than expected. It is useful for:

a. Down syndrome will suggest if occur an elevated beta-HCG coupled with a decreased MSAFP.

b. Trophoblastic disease (molar pregnancy) will suggest if a very high levels of HCG.
c. Hydatidiform mole will suggest if the absence of a fetus on ultrasonography along with an elevated HCG.

7. Maternal serum unconjugated estriol

The amount of unconjugated estriol in maternal serum is dependent upon a viable fetus, a properly functioning placenta, and maternal well-being. It is useful for:

a. If the fetus is threatened and delivery may be necessary emergently when the estriol level drops.
b. Estriol tends to be lower when Down syndrome is present.
c. Estriol tends to be lower when there is adrenal hypoplasia with anencephaly.

8. Pregnancy-associated plasma protein A (PAPP-A)

PAPP-A is a protein produced by the placenta. It is needed for the implantation process and to maintain a healthy placenta (afterbirth). PAPP-A is a marker measured as part of the combined pregnancy screening blood test. It is useful for:

a. Low levels of PAPP-A in maternal serum during the first trimester may be associated with fetal chromosomal anomalies including trisomies 13, 18, and 21.
b. Low PAPP-A levels in the first trimester may predict an adverse pregnancy outcome, including a small for gestational age (SGA) baby or stillbirth.
c. A high PAPP-A level may predict a large for gestational age (LGA) baby.

9. Inhibin-A

Dimeric inhibin-A is secreted by the placenta and by the maternal ovarian corpus luteum. Dimeric inhibin-A can be measured in maternal serum. It is useful for:

a. An increased level of inhibin-A is associated with an increased risk for trisomy 21.
b. A high inhibin-A may also be associated with risk for preterm delivery.
c. Dimeric inhibin-A as a marker for Down's syndrome in early pregnancy.

Triple Test it is comprises (AFP, hCG, uE3 (unconjugated oestriol))

Condition	MSAFP	uE3	HCG
Neural tube defect	Increased	Normal	Normal
Trisomy 21	Low	Low	Increased
Trisomy 18	Low	Low	Low
Molar pregnancy	Low	Low	Very High
Multiple gestation	Increased	Normal	Increased
Fetal death (stillbirth)	Increased	Low	Low

Quadruple test it is comprises (Triple test+ Inhibin A estimation).

Double Test it is comprises of Low pregnancy associated plasma proteins-A (PAPP-A) level and raised serum Beta-hCG during 1st trimester.