Human Genetics

Lecture 1

Dr. Abbas Hussein Mugheer

Cell Division

Cell division is fundamental to the growth and propagation of all living organisms. In eukaryotes, somatic cell division involves division of the nuclear contents (mitosis) and the cytoplasm (cytokinesis). Germ cells undergo a specialized form of cell division called meiosis. Meiosis results in production of haploid gametes and also provides the opportunity for genetic recombination.

Cell Cycle

The cell cycle represents a self-regulated sequence of events that controls cell growth and cell division. The goal of the cell cycle is to produce two daughter cells, each containing chromosomes identical to those of the parent cell. Rapidly renewing populations of human cells progress through the full cell cycle in about 24 hours, while other types of cells take longer time.

Phases of the Cell Cycle:

The cell cycle incorporates two principal phases: the **interphase**, and the **M phase (mitosis)**.

A: Interphase:

It represents continuous growth of the cell and is subdivided into three phases, **G_1 (gap1) phase**,**S (synthesis) phase**, and **G_2 (gap 2) phase**.

1: The G_1 phase

It is usually the longest and the most variable phase of the cell cycle, and it begins at the end of M phase. During the **G_1 phase**, the cell gathers nutrients and synthesizes RNA and proteins necessary for DNA synthesis and chromosome replication.

2: The S phase (DNA replication)

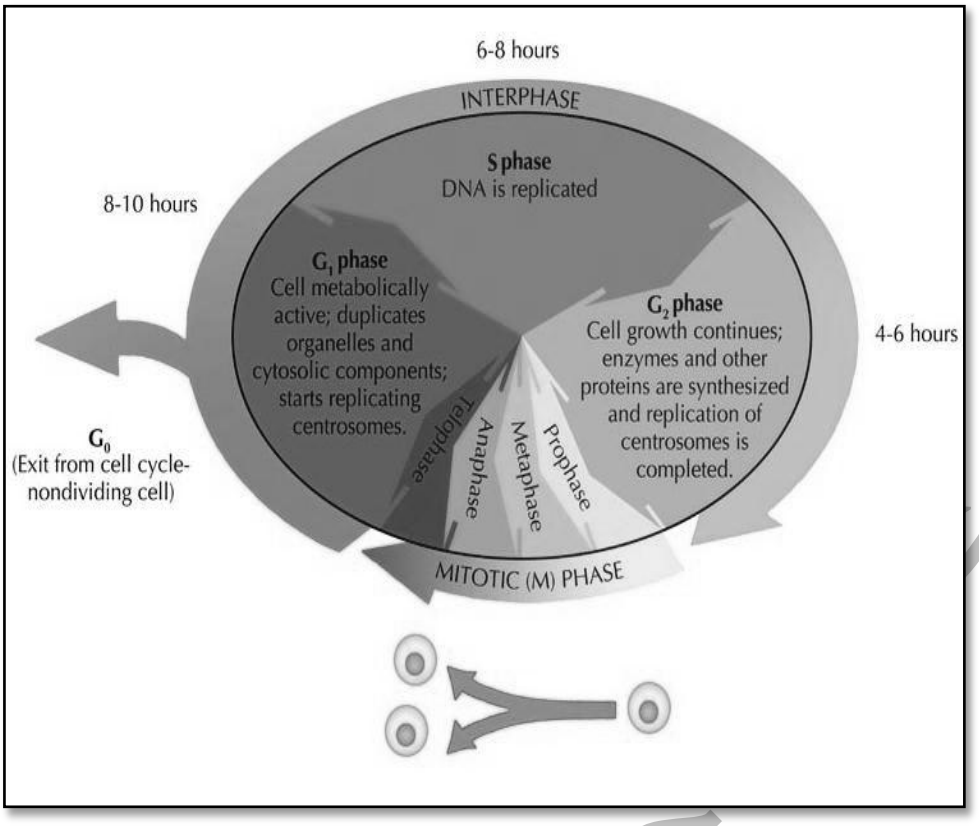
Initiation of DNA synthesis marks the beginning of the **S phase**, which is about 7.5 to 10 hours in duration. The DNA of the cell is doubled during the S phase, and new chromatidsare formed.

3: The G_2 phase (cell preparation for cell division)

During this phase, the cell examines its replicated DNA in preparation for cell division. This is a period of cell growth and reorganization of cytoplasmic organelles before entering the mitotic cycle. The **G_2 phase** may be as short as 1 hour in rapidly dividing cells or of nearly indefinite duration in some polyploid cells and in cells such as the primary oocyte that are arrested in G_2 for extended periods.

B: Mitosis (M) phase

Mitosis nearly always includes both **karyokinesis** (division of the nucleus) and **cytokinesis** (division of the cell) and lasts about 1 hour. Mitosis takes place in several stages described in more detail below. Separation of two identical daughter cells concludes the **M phase**.

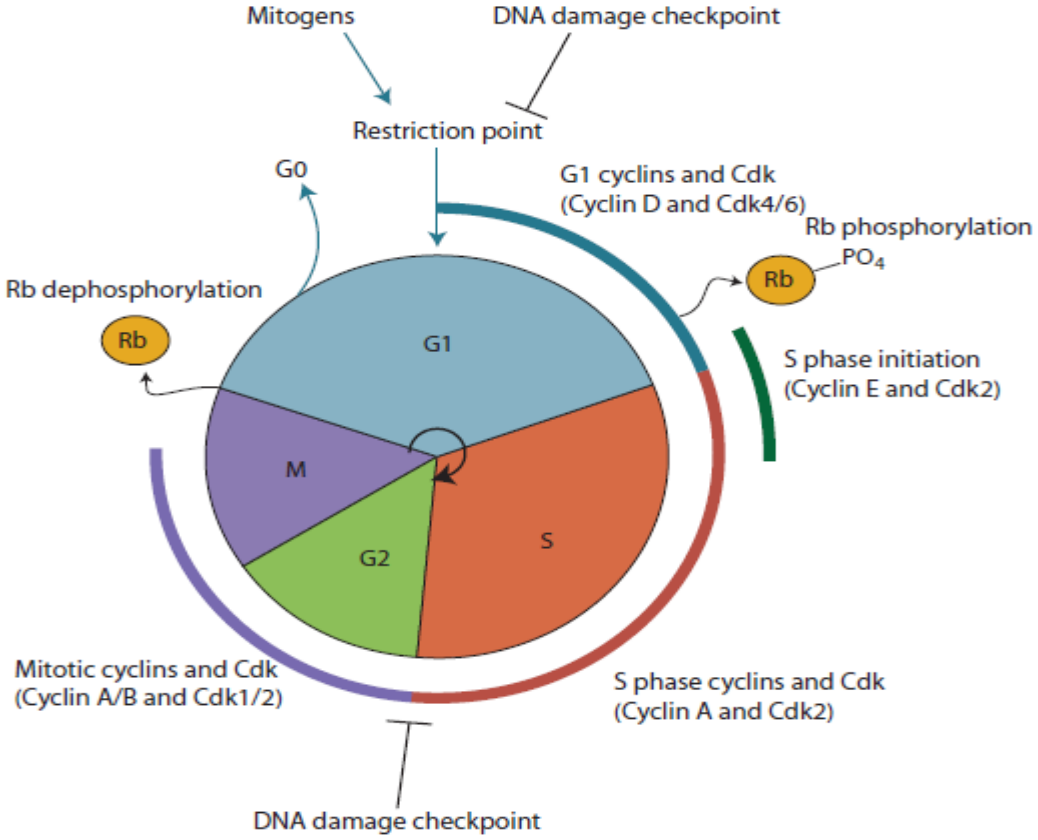


Cell Cycle Checkpoints

Throughout the cell cycle, several internal quality control mechanisms or **checkpoints** represented by biochemical pathways control transition between cell-cycle stages. The cell cycle stops at several checkpoints and can only proceed if certain conditions are met—for example, if the cell has reached a certain size. Checkpoints monitor and modulate the progression of cells through the cell cycle in response to intracellular or environmental signals.

The **restriction checkpoint (or "point of no return")** is the most important checkpoint in the cell cycle. At this checkpoint, the cell self-evaluates its own replicative potential before deciding to either enter the S phase and the next round of cell division or to retire and leave the cell cycle.

A cell that leaves the cycle in the G_1 phase usually begins terminal differentiation by entering the **G_O phase** ("O" stands for "outside" the cycle). Thus, the G_1 phase may last for only a few hours (average 9 to 12 hours) in a rapidly dividing cell, or it may last a lifetime in a nondividing cell.

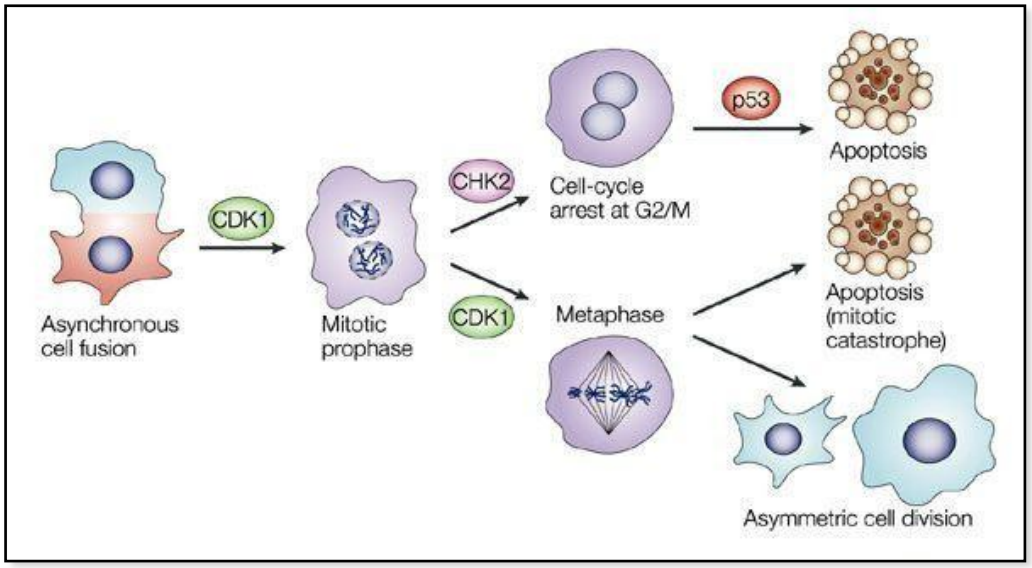


The mitotic catastrophe

Malfunction of any of the checkpoints at the **G_1**, **S**, and **G_2** phases of the cell cycle and the checkpoint at **M** phase may lead to a **mitotic catastrophe**.

Mitotic catastrophe is defined as the failure to arrest the cell cycle before or at mitosis, resulting in abnormal chromosome separation. Under normal conditions, death in these cells will occur by activation of the apoptotic cycle. Cells that fail to execute the apoptotic cycle are likely to divide asymmetrically in the next round of cell division.

This leads to the generation of **aneuploid cells** (cells containing abnormal chromosome numbers). Thus, a mitotic catastrophe may be regarded as one of the mechanisms contributing to **oncogenesis** (tumor cell development).



Mitosis

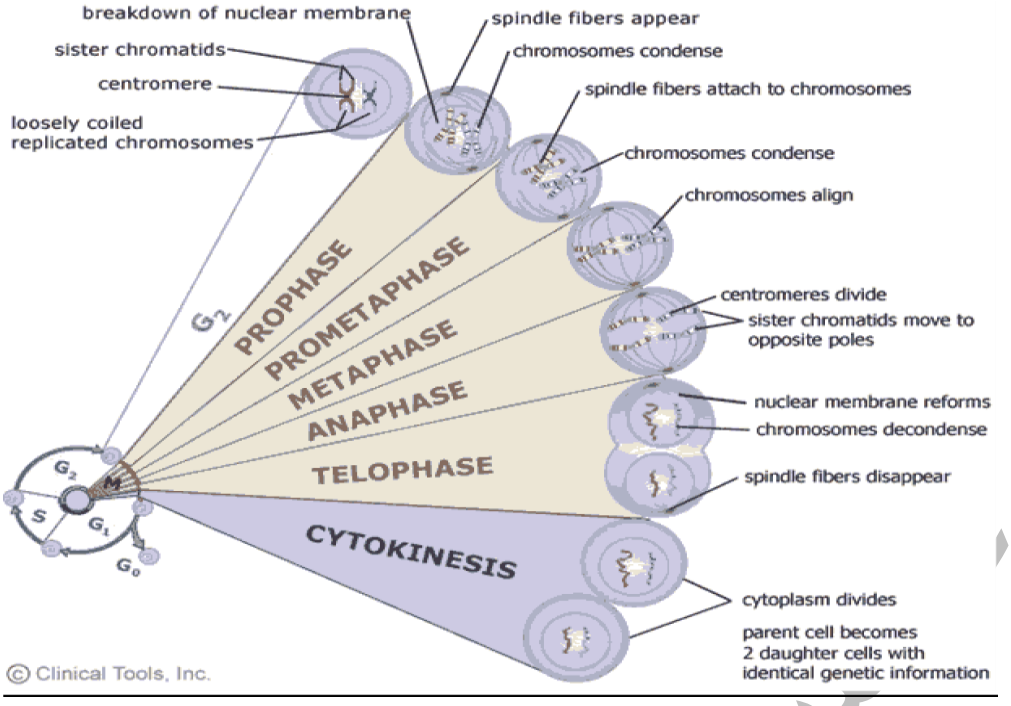
Cell division is a crucial process that increases the number of cells, permits renewal of cell populations, and allows wound repair.

Mitosis is a process of chromosome segregation and nuclear division followed by cell division that produces two daughter cells with the same chromosome number and DNA content as the parent cell.

The process of cell division includes division of both the nucleus (**karyokinesis**) and the cytoplasm (**cytokinesis**).

The process of cytokinesis results in distribution of nonnuclear organelles into two daughter cells.

Before entering mitosis, cells duplicate their DNA in the *S* or *synthesis phase*.



Phases of Mitosis

1. **Prophase:**

- The replicated chromatin condenses and become visible as chromosomes.

Each chromosome can be seen to consist of two **chromatids**.

- The sister chromatids are held together by the ring of proteins at the **centromere**.
- In late prophase, the nuclear envelope begins to disintegrate, and the nucleolus completely disappears.
- In addition, a highly specialized protein complex called a **kinetochore** appears on each chromatid opposite to the centromere.

2. **Metaphase:**

- Formation of the mitotic spindle, consisting of three types of microtubules, that becomes organized around the **centrosomes**, the **astral microtubules**, **the polar microtubules** and the **kinetochore microtubules**. When a kinetochore is finally captured by a kinetochore microtubule, it is pulled toward the centrosomes.
- Kinetochore microtubules and their associated motor proteins direct the movement of the chromosomes to a plane in the middle of the cell, called the **equatorial** or **metaphase plate**.

3. **Anaphase:**

- Separation of sister chromatids. This separation occurs when the proteins that have been holding the chromatids together break down.

- The separated chromatids are pulled to opposite poles of the cell by the sliding along the kinetochore microtubules toward the centrosomes.

4. **Telophase:**

- Reconstitution of a nuclear envelope around the chromosomes at each pole.

The chromosomes uncoil and become indistinct.

- The nucleoli reappear, and the cytoplasm divides (cytokinesis) to form two daughter cells.

Cytokinesis

Cytokinesis begins with the furrowing of the plasma membrane midway between the poles of the mitotic spindle. The separation at the **cleavage furrow** is achieved by a **contractile ring** consisting of a very thin array of actin filaments positioned around the perimeter of the cell. As the ring tightens, the cell is pinched into two daughter cells.

Because the chromosomes in the daughter cells contain identical copies of the duplicated DNA, the daughter cells are genetically identical and contain the same kind and number of chromosomes. The daughter cells are **(2d)** in DNA content and **(2n)** in chromosome number.

Meiosis

Meiosis involves two sequential nuclear divisions followed by cell divisions that produce gametes (sex cells) containing half the number of chromosomes and half the DNA found in somatic cells.
The **zygote** (the cell resulting from the fusion of an ovum and a sperm) and all the somatic cells derived from it are **diploid (2n)** in chromosome number (46 chromosomes in human); thus, their cells have two copies of every chromosome and every gene encoded on this chromosome.
These chromosomes are called **homologous chromosomes** because they are similar but not identical; one set of chromosomes is of maternal origin, the other is from paternal origin.
The **gametes**, having only one member of each chromosome pair, are described as **haploid (1n)**.
During gametogenesis, reduction in chromosome number to the haploid state (23 chromosomes in humans) occurs through **meiosis**.
This reduction is necessary to maintain a constant number of chromosomes in a given species.
Reduction in chromosome number to **(1n)** in the first meiotic division is followed by reduction in DNA content to the haploid **(1d)** amount in the second meiotic division.
During meiosis, the chromosome pair may exchange chromosome segments, thus altering the genetic composition of the chromosomes. This genetic exchange, called **crossing-over**, and the random assortment of each member of the chromosome pairs into haploid gametes give rise to infinite genetic diversity.

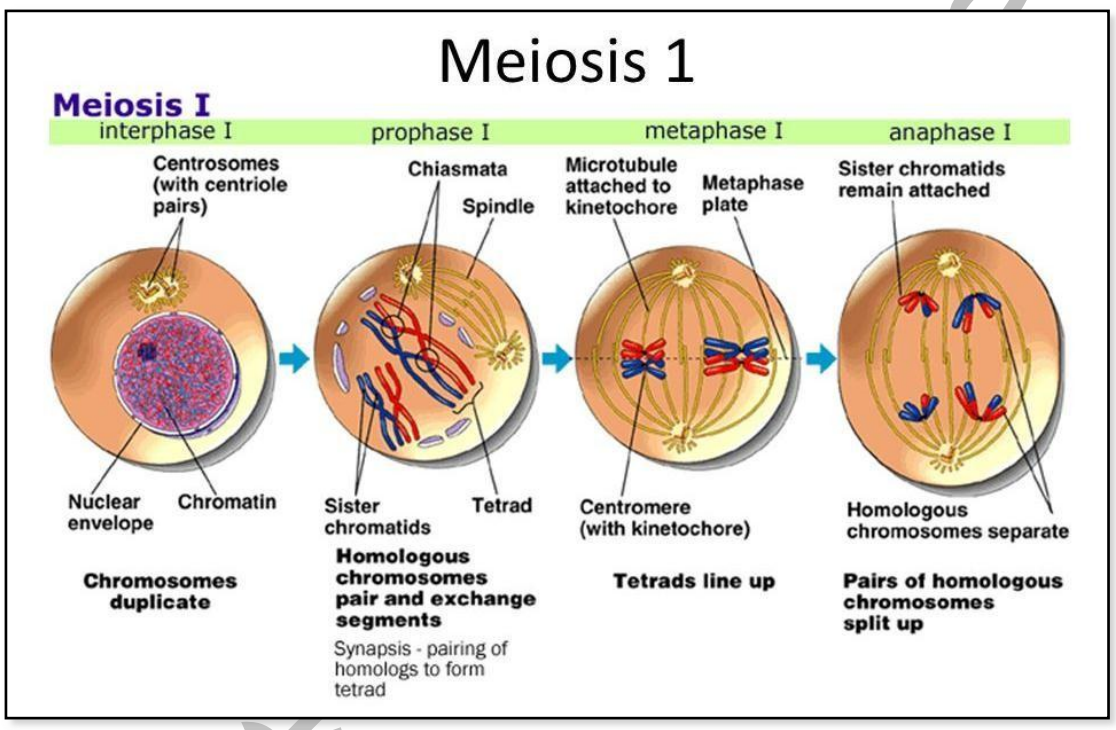
Differences in Meiosis between Male & Female

The nuclear events of meiosis are the same in males and females, but the cytoplasmic events are markedly different. In males, the two meiotic divisions of a **primary spermatocyte** yield four structurally identical, although genetically unique, haploid **spermatids**. Each spermatid has the capacity to differentiate into a **spermatozoon**.

In contrast, in females, the two meiotic divisions of a primary oocyte yield one haploid ovum and three haploid polar bodies. The ovum receives most of the cytoplasm and becomes the functional gamete. The polar bodies receive very little cytoplasm and degenerate

Phases of Meiosis

1- **Meiosis** consists of two successive mitotic divisions without the additional **S phase** between the two divisions.
2- During the S phase that precedes meiosis, DNA is replicated forming sister chromatids (two parallel strands of DNA) joined together by the centromere. The DNA content becomes **(4d)**, but the chromosome number remains the same **(2n)**.
3- The cells then undergo a **reductional division (meiosis I)** and an **equatorial division (meiosis II)**.
4- During **meiosis I**, as the name *reductional division* implies, the chromosome number is reduced from diploid **(2n)** to haploid **(1n)**, and the amount of DNA is reduced from the **(4d)** to **(2d)**.
5- No DNA replication precedes **meiosis II**.
6- The division during meiosis II is always equatorial because the number of chromosomes does not change. It remains at **(1n)**, although the amount of DNA represented by the number of chromatids is reduced to **(1d)**.

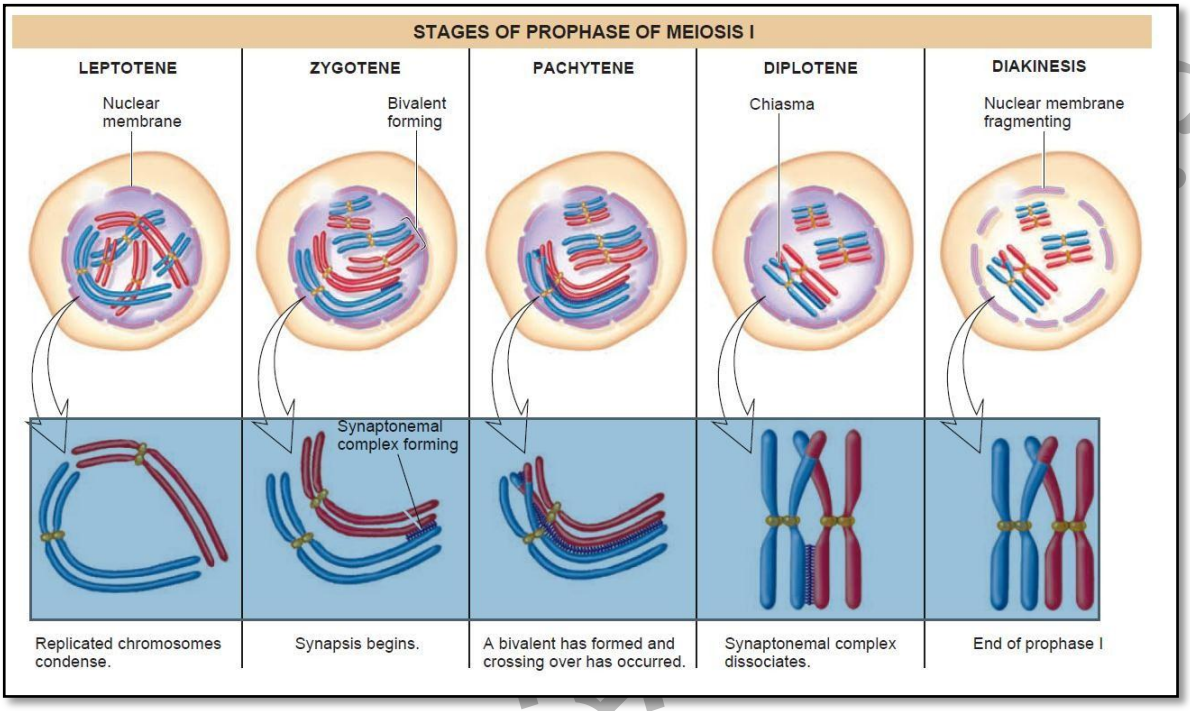


Phases of Meiosis I:

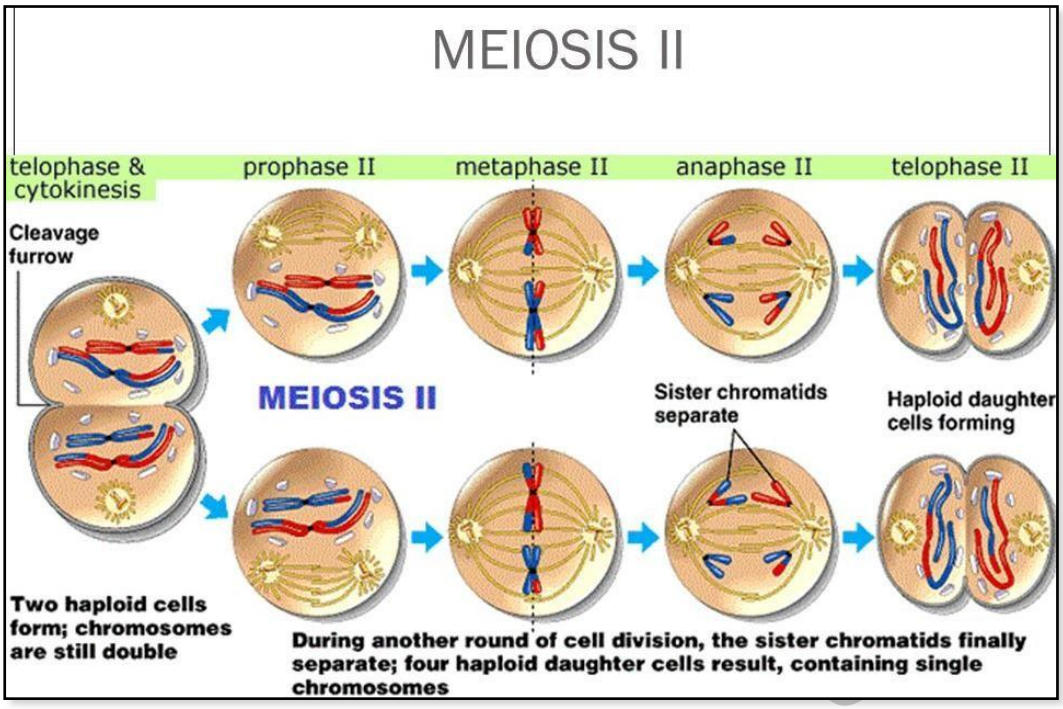
1. **Prophase I:** It is an extended phase that is subdivided into the following five stages:

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(sing. chiasma).
Diplotene: homologous chromosomes start to separate but remain attached by chiasmata. **Diakinesis:** homologous chromosomes continue to separate, and chiasmata move to theends of the chromosomes.



2. **Metaphase I:** Metaphase I is similar to the metaphase of mitosis except that the paired chromosomes are aligned at the **equatorial plate** with one member on either side.
   - ❖ The chiasmata are cut, and the homologous chromosomes separate completely.
   - ❖ The spindle microtubules begin to interact with the chromosomes through the **kinetochore** at the centromere.
   - ❖ The chromosomes undergo movement to ultimately align their centromeres along the equatorial plate with one member of the homologous chromosomes on either side.
3. **Anaphase I**:
   - ❖ The sister chromatids, held together by protein complexes and by the centromere, remain together.
   - ❖ A maternal or paternal member of each homologous pair moves to each pole.
   - ❖ **Segregation** or **random assortment** occurs because the maternal and paternal chromosomes of each pair are randomly aligned on one side or the other of the metaphase plate, thus contributing to genetic diversity.
4. **Telophase I:**
   - ❖ Homologous chromosomes, each consisting of two sister chromatids, are at the opposite poles of the cell.
   - ❖ Reappearance of the nucleolus and nuclear envelope.
   - ❖ At the completion of meiosis I, the cytoplasm divides. Each resulting daughter cell is haploid in chromosome number **(1n)** and contains one member of each homologous chromosome pair. The cell is still diploid in DNA content **(2d)**.



Phases of Meiosis II:

After meiosis I, the cells quickly enter meiosis II without passing through an S phase.

Meiosis II is an equatorial division and resembles mitosis.

During this phase, the sister chromatids will separate at anaphase II and move to opposite poles of the cell.

During meiosis II, the cells pass through **prophase II**, **metaphase II**, **anaphase II**, and **telophase II**.

These stages are essentially the same as those in mitosis except that they involve a haploid set of chromosomes **(1n)** and produce daughter cells that have only haploid DNA content **(1d)**.

Unlike the cells produced by mitosis, which are genetically identical to the parent cell, the cells produced by meiosis are genetically unique.

By the end of meiosis II, each parent cell (2n) give rise to 4 daughter cells with haploid number of chromosomes (1n) and each daughter cell is genetically different from the parent cell.

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Human Chromosome

Chromosomes (named from the Greek word chroma, "color," some, "body") were discovered in the nineteenth century, as threadlike structures in the nucleus of eukaryotic cells that become visible as the cells begin to divide. Each human cell have 46 chromosomes, which occur in 23 pairs.Twenty-two of these chromosome pairs are called autosomes, which are found in both males and females.One pair of chromosomes is called the sex chromosomes, because this pair contains the genes that control gender. Males have the sex chromosomes X and Y, and females have two X chromosomes.Each human cell contains about 2 meters of DNA; yet the cell nucleus is only 5–8 μm in diameter.In eukaryotic cells, very long double-stranded DNA molecules are packaged into chromosomes. The complex task of packaging DNA is accomplished by specialized proteins that bind to and fold the DNA, generating a series of coils and loops that provide increasingly higher levels of organization and prevent the DNA from becoming a tangled, unmanageable mess. Amazingly, the DNA is compacted in a way that allows it to remain accessible to all of the enzymes and other proteins that replicate it, repair it, and control the expression of its genes.

Chromosome History

Ernst Haeckel described the nucleus in 1866 as the centre for passing on elements that determine hereditary characteristics in his work, "Generelle Morphologie". Almost two decades later, German scientist August Weismann found that gametes or sperm and egg cells were different from somatic or body cells. He also suggested that the nucleus is the centre where the genetic material that is responsible for heredity lies. He added that when the sperm and the egg join in fertilization, a new combination of chromosomes is formed. The cell division process (meiosis) that produces gametes containing 23 chromosomes, was first described by Eduoard van Beneden.

Theodor Boveri described two important properties of chromosomes contained within the nucleus. One of these was the uniqueness of each chromosome and the other their potential for passing on chromosomal information through generations. Wilhelm Roux had previously suggested that each chromosome was unique, but it was Boveri who managed to prove this fact in his experiments.

Chromosome Structure

The nucleus of a human cell contains all the genetic material necessary to direct all the functions in the body. The genetic material is arranged into chromosomes, which are structures that assist in the transmission of genetic information from one generation to the next. The instructions in each chromosome are contained within **genes**, which in turn are composed of **DNA**.

Chromosomes Morphology

1-At time of cell division each chromosome can be seen to consist of two identical strands known as chromatids, or sister chromatids, which are the result of DNA replication having taken place during the S phase of the cell cycle.

2-These sister chromatids can be seen to be joined at a primary constriction known as the centromere.

3-Centromeres consist of several hundred kilobases of repetitive DNA and are responsible for the movement of chromosomes at cell division.

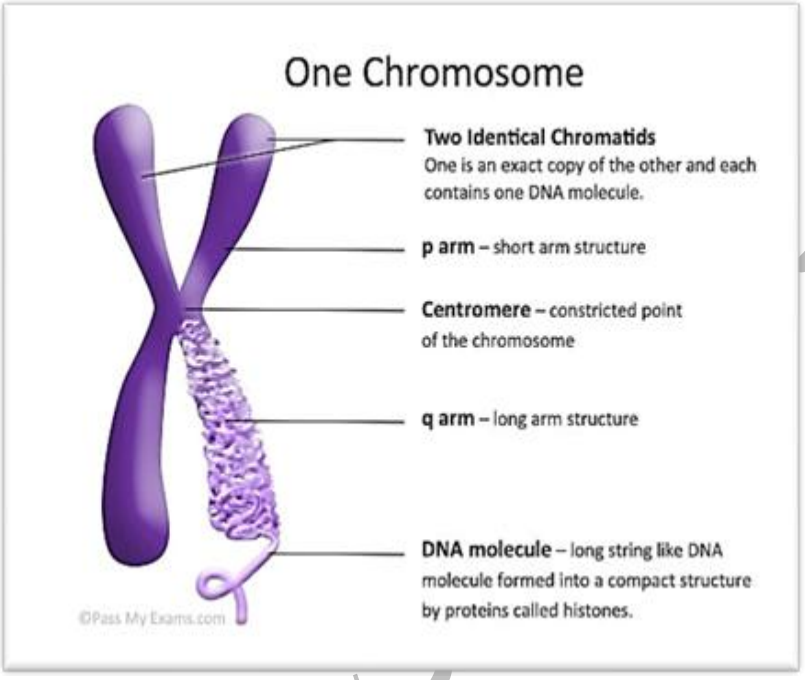
4-The position of the centromere is variable, and thus chromosomes could be acrocentric, submetacentric or metacentric according to the position of centromere.

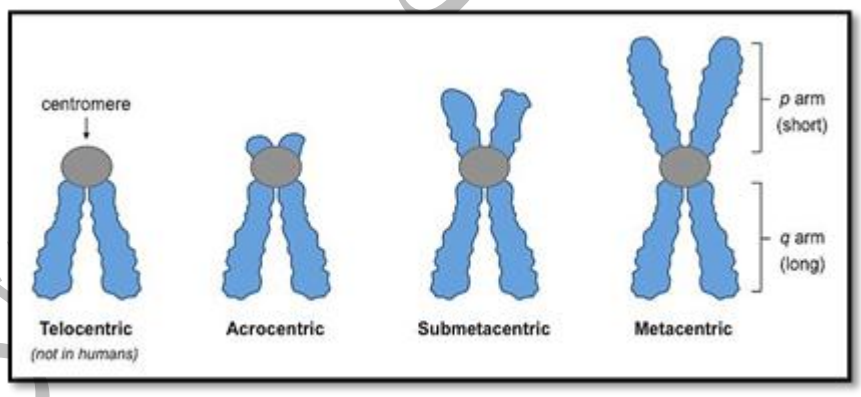
5-Each centromere divides the chromosome into short and long arms, designated p (= petite) and q ('g' = grand), respectively.

6- The tip of each chromosome arm is known as the telomere.

7-Telomeres play a crucial role in sealing the ends of chromosomes and maintaining their structural integrity.

8-Telomeres have been highly conserved throughout evolution and in humans they consist of many tandem repeats of a TTAGGG sequence.





Organizational Levels of Chromosomes Structure

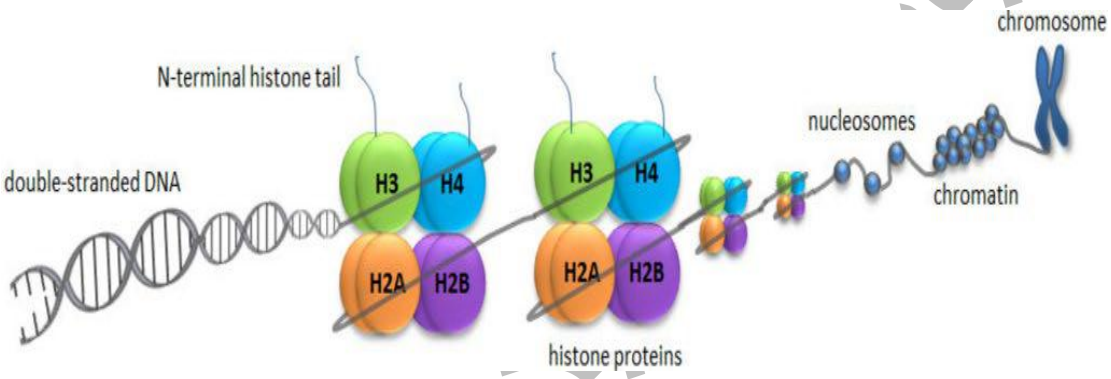
1-The proteins that bind to DNA to form eukaryotic chromosomes are traditionally divided into two general classes: the histones and the nonhistone chromosomal proteins.

2-The complex of histones and non-histone proteins with nuclear DNA is called chromatin.

3- Histones are responsible for the first and most fundamental level of chromatin packing, the nucleosome.

4-Each nucleosome consists of DNA coiled around a core of eight histone proteins (octamer).These proteins are composed of two molecules of each of histones H2A, H2B, H3, and H4.

5-A series of adjacent nucleosomes can be seen in the electron microscope as a series of "beads on a string", with 50-80 bp of linker DNA separating each bead.



6-The nucleosomes are further packed on top of one another to generate a more compact structure, known as the chromatin fiber (30 nm in diameter). This additional packing of nucleosomes into a chromatin fiber depends on a fifth histone called histone H1, which is thought to pull adjacent nucleosomes together into a regular repeating array.

7-The chromatin fiber is folded into a series of loops, and that these loops are further condensed to produce the interphase chromatin (when the cell is not dividing).

8-Finally, this compact string of loops is thought to undergo at least one more level of packing to form the mitotic chromosome at time of cell division.

The chromatin containing the following two types :

A- Euchromatin: region of chromosome have the following properties

1. is compacted during cell division, but relaxes and an open conformation during interphase(protein synthesis phase).

2. contains the majority of the structural genes.

3. active in transcription.

4. staining R-bands .

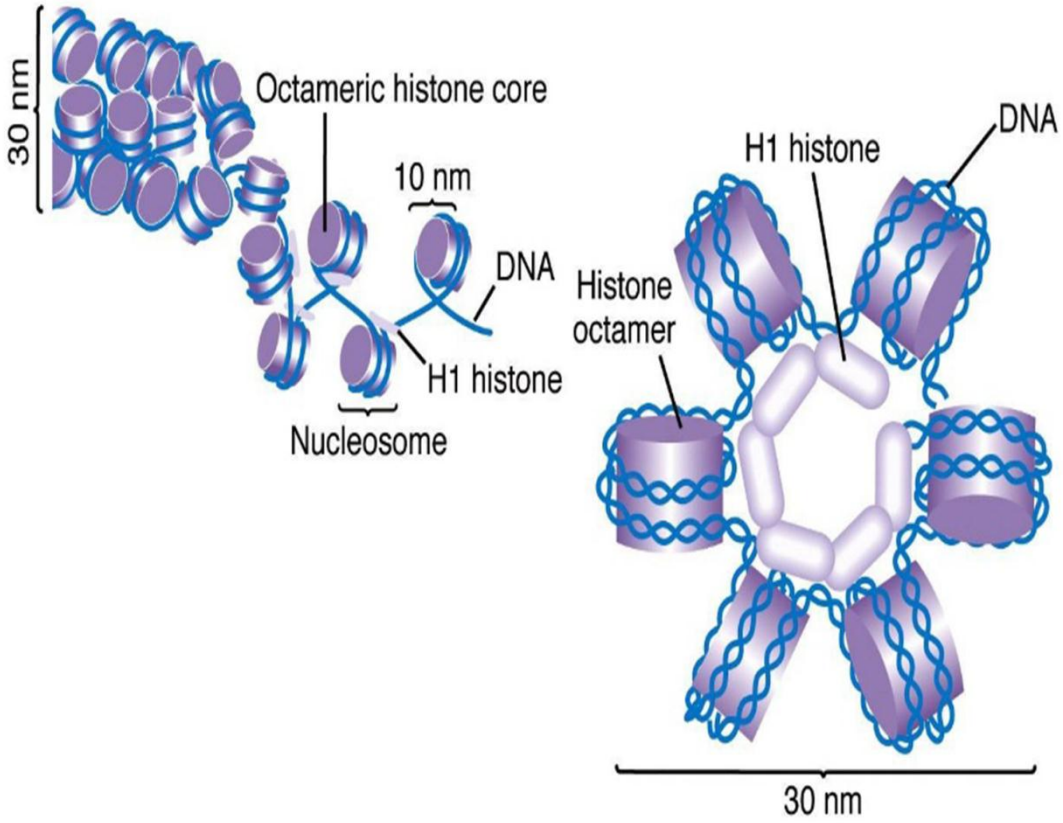
B- **Heterochromatin**: region of chromosome have the following properties:

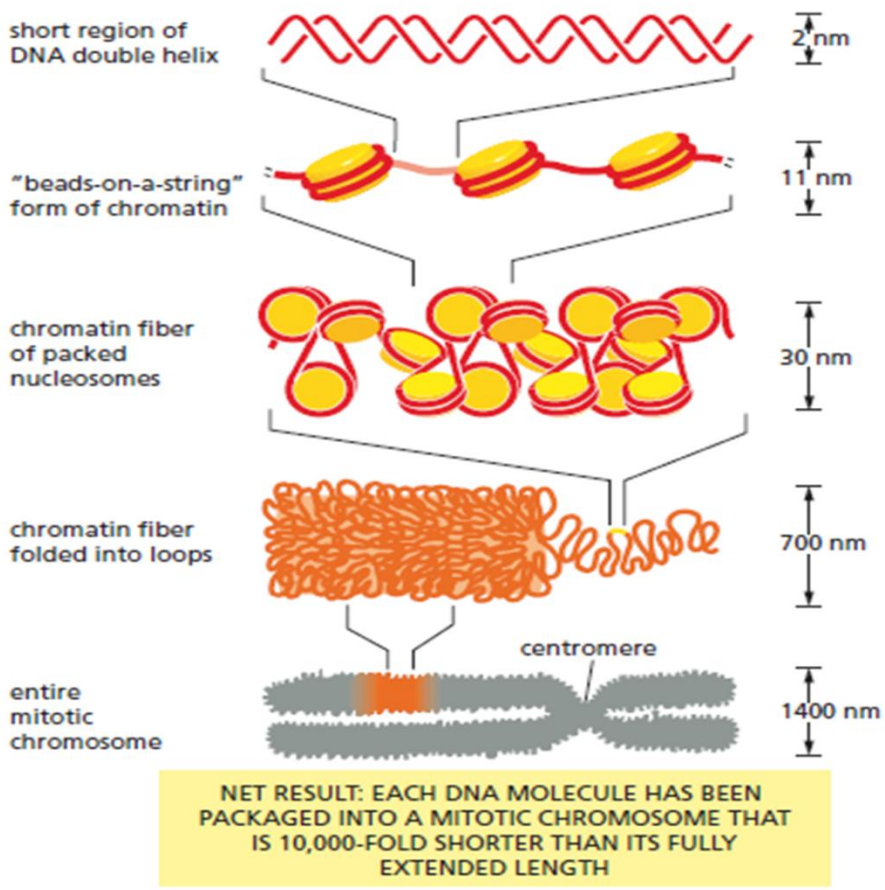
1. is densely compacted at cell division and remains compacted at interphase.

2. is relatively inactive in transcription.

3. Have not any genetic information

4. Found in centromere and telomers





The Regulation of Chromosome Structure

1-The DNA in cells carries enormous amounts of coded information, and cells must be able to get to this information as needed .

2-A cell can alter its chromatin structure to expose localized regions of DNA and allow access to specific proteins and protein complexes, particularly those involved in gene expression and in DNA replication and repair .

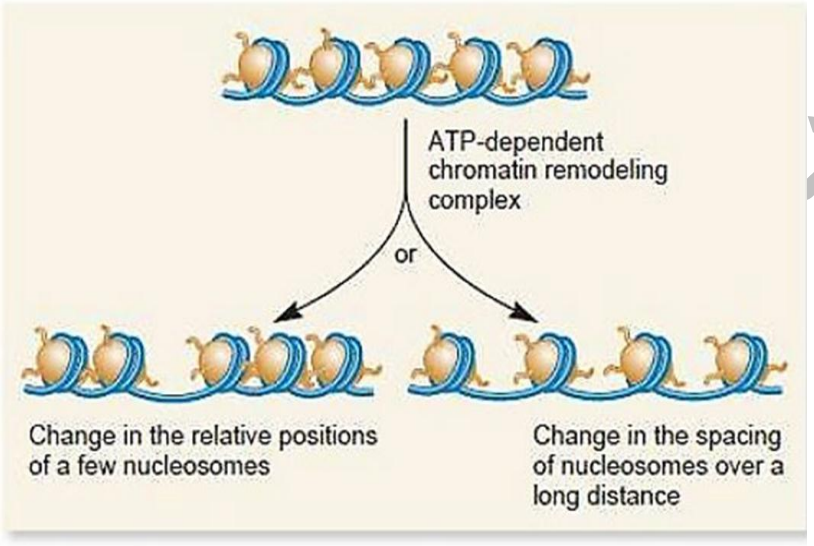
3-The regulation and inheritance of chromatin structure play crucial parts in the development of eukaryotic organisms.

4-Eukaryotic cells have several ways to adjust the local structure of their chromatin rapidly .

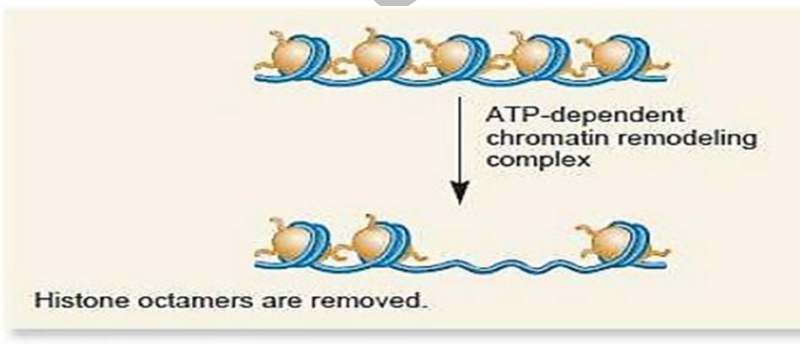
5-One way takes advantage of chromatin-remodelling complexes (protein machines that use the energy of ATP hydrolysis to change the position of the DNA wrapped around nucleosomes). The complexes, which attach to

both the histone octamer and the DNA wrapped around it, can locally alter the arrangement of nucleosomes on the DNA, making the DNA either more accessible or less accessible to other proteins in the cell.

6- Another way of altering chromatin structure relies on the reversible chemical modification of the histones, thereby loosening chromatin structure and allowing access to particular nuclear proteins .



(a) Change in nucleosome position



(b) Histone eviction

The Sex Chromosomes

1- The X and Y chromosomes are known as the sex chromosomes because of their crucial role in sex determination .

2- The X chromosome was originally labeled as such because of uncertainty as to its function when it was realized that in some insects this chromosome is present in some gametes but not in others.

3- In human, the Y chromosome is much smaller than the X and carries only a few genes of functional importance, most notably the testis-determining factor, known as SRY .

4- In the female each ovum carries an X chromosome, whereas in the male each sperm carries either an X or a Y chromosome. As there is a roughly equal chance of either an X-bearing sperm or a Y-bearing sperm fertilizing an ovum, the numbers of male and female conceptions are approximately equal. In fact, slightly more male babies are born than females, although during childhood and adult life, the sex ratio evens out at 1: 1.

Chromosome Number

Precise number of chromosomes typical for a given species. In any given asexually reproducing species, the chromosome number is always the same. In sexually reproducing organisms, the number of chromosomes in the body (somatic) cells typically is diploid (2n; a pair of each chromosome), twice the haploid (1n) number found in the sex cells, or gametes. The haploid number is produced during meiosis. In some sexually reproducing organisms, individuals may be produced from unfertilized eggs and therefore are haploid; an example is a drone (a male bee).

An organism with any multiple of the diploid number of chromosomes is said to be polyploid. Polyploidy is a normal evolutionary strategy among many plant groups but appears to be quite rare in animals. Examples of polyploid plants and animals are the potato (Solanum tuberosum), the African clawed frog (Xenopus laevis), and the plains viscacha rat (Tympanoctomys barrerae; also called red vizcacha rat). In most animals, however, any change from the typical chromosome number for a species may be accompanied by changes—sometimes drastic—in the organism. For instance, in humans, fetuses affected by polyploidy often are spontaneously aborted early in pregnancy.

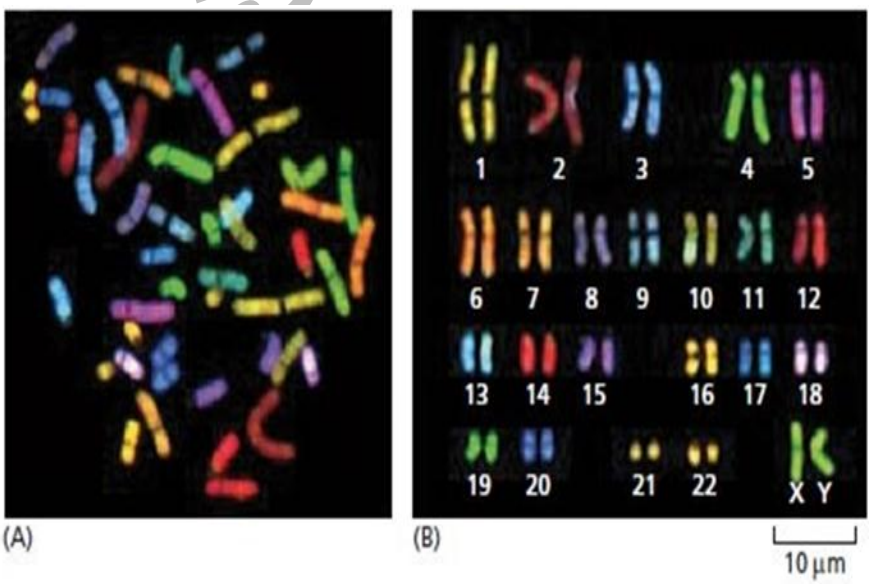
The number of chromosomes does not correlate with the apparent complexity of an animal or a plant: in humans, for example, the diploid number is 2n = 46 (that is, 23 pairs), compared with 2n = 78, or 39 pairs,

in the dog and 2n = 36 (18) in the common earthworm. There is an equally great range of numbers among plants.

Karyotyping

Karyotyping is a test to examine chromosomes in a sample of cells. This test can help identify genetic problems as the cause of a disorder or disease.The test can be performed on almost any tissue, including: Amniotic fluid, Blood and Bone marrow.Tissue from the organ that develops during pregnancy to feed a growing baby (placenta) .To test amniotic fluid, an amniocentesis is done.A bone marrow biopsy is needed to take a sample of bone marrow.

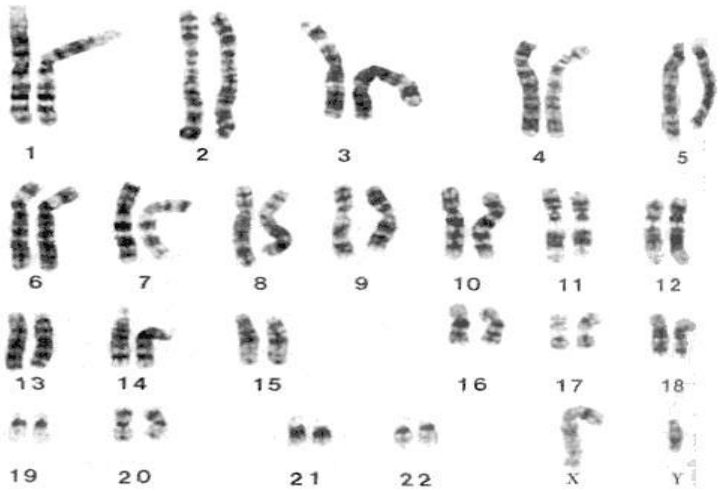
The sample is placed into a special dish or tube and allowed to grow in the laboratory. Cells are later taken from the new sample and stained. The laboratory specialist uses a microscope to examine the size, shape, and number of chromosomes in the cell sample. The stained sample is photographed to show the arrangement of the chromosomes. This is called a karyotype.Certain problems can be identified through the number or arrangement of the chromosomes. Chromosomes contain thousands of genes that are stored in DNA, the basic genetic material.



Chromosome banding

Is a technique used in cytogenetics to produce a visible karyotype by staining condensed chromosomes. It is useful for identifying genetic diseases through the photographic representation of the entire chromosome complement. The metaphase chromosomes are treated with trypsin (to partially digest the chromosome) and stained with Giemsa stain. Heterochromatic regions, which tend to be rich with adenine and thymine (AT-rich) DNA and relatively gene-poor, stain more darkly in G-banding. In contrast, less condensed chromatin (Euchromatin)—which tends to be rich with guanine and cytosine (GC-rich) and more transcriptionally active—incorporates less Giemsa stain, and these regions appear as light bands in G-banding. The pattern of bands is numbered on each arm of the chromosome from the centromere to the telomere. This numbering system allows any band on the chromosome to be identified and described precisely. The reverse of G bands is obtained in R banding. Banding can be used to identify chromosomal abnormalities, such as translocations, because there is a unique pattern of light and dark bands for each chromosome.

It is difficult to identify and group chromosomes based on simple staining because the uniform colour of the structures makes it difficult to differentiate between the different chromosomes. Therefore, techniques like G-banding were developed that made "bands" appear on the chromosomes. These bands were the same in appearance on the homologous chromosomes, thus, identification became easier and more accurate. The less condensed the chromosomes are, the more bands appear when G-banding. This means that the different chromosomes are more distinct in prophase than they are in metaphase



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Chromosomal abnormality:

Chromosomal anomaly, chromosomal aberration, chromosomal mutation, or chromosomal disorder, is a missing, extra, or irregular portion of chromosomal DNA. These can occur in the form of numerical abnormalities, where there is an atypical number of chromosomes, or as structural abnormalities, where one or more individual chromosomes are altered. Chromosome mutation was formerly used in a strict sense to mean a change in a chromosomal segment, involving more than one gene. Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis. Chromosome abnormalities may be detected or confirmed by comparing an individual's karyotype, or full set of chromosomes, to a typical karyotype for the species via genetic testing.

Aneuploidy

Aneuploidy is the second major category of chromosome mutations in which chromosome number is abnormal. An **aneuploid** is an individual organism whose chromosome number differs from the wild type by part of a chromosome set. Generally, the aneuploid chromosome set differs from wild type by only one or a small number of chromosomes. Aneuploids can have a chromosome number either greater or smaller than that of the wild type. Aneuploid nomenclature is based on the number of copies of the specific chromosome in the aneuploid state. For example, the aneuploid condition $2n-1$ is called monosomic ("one chromosome") because only one copy of some specific chromosome is present instead of the usual two found in its diploid progenitor. The aneuploid $2n+1$ is called trisomic, $2n-2$ is nullisomic (lake of both the normal chromosomal pairs, human with this condition will not survive) and $n+1$ is **disomic.**

Aneuploidy originates during cell division when the chromosomes do not separate properly between the two cells. Most cases of aneuploidy

result in miscarriage and the most common extra autosomal chromosomes among live births are 21, 18 and 13.

Mechanism

1. Nondisjunction is the failure of homologous chromosomes or sister chromatids to separate properly during cell division. There are three forms of nondisjunction: failure of a pair of homologous chromosomes to separate in meiosis I, failure of sister chromatids to separate during meiosis II, and failure of sister chromatids to separate during mitosis. Nondisjunction results in daughter cells with abnormal chromosome numbers (aneuploidy).

2. Merotelic attachment occurs when one kinetochore is attached to both mitotic spindle poles. One daughter cell would have a normal complement of chromosomes; the second would lack one.

3. Multipolar spindles: more than two spindle poles form. Such a mitotic division would result in one daughter cell for each spindle pole; each cell may possess an unpredictable complement of chromosomes.

4. Monopolar spindle: only a single spindle pole forms. This produces a single daughter cell with its copy number doubled. a tetraploid intermediate may be produced as the end-result of the monopolar spindle mechanism.

Monosomy. Refers to lack of one chromosome of the normal complement. Partial monosomy can occur in unbalanced translocations or deletions, in which only a portion of the chromosome is present in a single copy (see deletion (genetics)). Monosomy of the sex chromosomes (45,X) causes Turner syndrome.

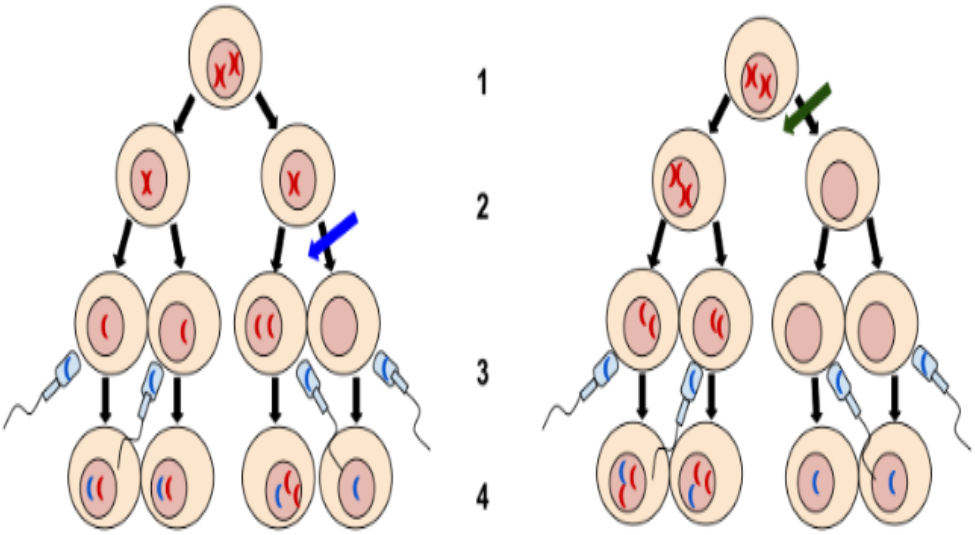
Uniparental Disomic is an aneuploid chromosome complement. In uniparental disomy, both copies of a chromosome come from the same parent (with no contribution from the other parent).

Trisomy refers to the presence of three copies, instead of the normal two, of a particular chromosome. The presence of an extra chromosome 21, which is found in Down syndrome, is called trisomy 21. Trisomy 18 and Trisomy 13, known as Edwards Syndrome and Patau Syndrome,

respectively, are the two other autosomal trisomies recognized in live-born humans. Trisomy of the sex chromosomes is also possible, for example (47,XXX), (47,XXY), and (47,XYY).

Tetrasomy and **pentasomy** are the presence of four or five copies of a chromosome, respectively. Although rarely seen with autosomes, sex chromosome tetrasomy and pentasomy in humans, including XXXX, XXYY, XXXXX, XXXXY and XYYYY.

Mosaicism.the organism evolves as a mixture of cell lines with differing ploidy (number of chromosomes). Mosaicism syndromes can be caused by mitotic nondisjunction in early fetal development Mosaicism may be present in some tissues, but not in others.



1. Meiosis I 2. Meiosis II 3. Fertilization 4. Zygote The left image at the blue arrow is nondisjunction taking place during meiosis II. The right image at the green arrow is nondisjunction taking place during meiosis I. Nondisjunction is when chromosomes fail to separate normally resulting in a gain or loss of chromosomes.

Chromosome structural abnormalities

Structural aberrations include **translocations**, **deletions**, **ring chromosomes**, **duplications**, **isochromosomes,** and **fragile sites**. Most of these result from unequal exchange between homologous repeated sequences on the same or different chromosomes, or when two

chromosome breaks occur close together and enzyme repair mechanisms link the wrong ends.

1- Translocations

A translocation involves transposition of chromosome material usually between chromosomes. Three types of translocation are recognized:

Centric fusion or 'Robertsonian translocations

Centric fusion arises from breaks at or near the centromeres of two chromosomes, followed by their fusion. The carrier of a pair of centrically fused chromosomes may therefore have only 45 chromosomes, but be quite healthy as the overall loss is insignificant.

Reciprocal translocations

Reciprocal translocation involves interchromosomal exchange. X-linked recessive disease can arise in heterozygous females as a consequence of X–autosome translocation. For example, the reciprocal translocation between chromosomes X and 1, interferes with X inactivation, as the translocation breakpoint occurs between that gene and the inactivation centre. Reciprocal translocations can also activate genes in cancers, as in Burkitt lymphoma.

Insertional translocations

Insertional translocation involves insertion of a deleted segment interstitially at another location. It is extremely rare and balanced carriers are usually healthy, but may produce chromosomally unbalanced offspring with either a duplication or a deletion.

2. Deletions

Deletion of part of a chromosome can be interstitial or terminal. Interstitial deletions can arise from two breaks, followed by faulty repair, from unequal crossing-over in a previous meiosis, or as a consequence of a translocation in a parent.

For example, **DiGeorge syndrome**, caused by a deletion at 22q11.22, is formulated: del(22)(q11.22).

A **terminal** deletion of the long arm of Chromosome 1 from band 21 would be formulated: 46,XX,del(1)(q21;qter)

3. Ring chromosomes

If two breaks occur in the same chromosome the broken ends can fuse as a ring. Non-centric rings are lost, but if the ring contains a centromere it can survive subsequent cell division.

4. Duplications

Duplication is the presence of two adjacent copies of a chromosomal segment and can be either 'direct' (tandem), or 'inverted'. Duplications may originate by unequal crossing-over in a previous meiosis, or as a consequence of translocation, inversion, or presence of an isochromosome in a parent. An example is cat eye syndrome involving: dup(22)(p13;q11).

5. Isochromes

An isochromosome has one chromosome arm deleted and the other arm duplicated. The long arm of the X, resulting in Turner syndrome due to short arm monosomy.

6. Fragile sites

A fragile site is an apparent gap in a chromosome. Some are common others are rare and sensitive to folate levels in the medium in which the cells under examination are cultured.

7- Chromosomal inversion

An inversion is a chromosome rearrangement in which a segment of a chromosome is reversed end-to-end. An inversion occurs when a single chromosome undergoes breakage and rearrangement within itself. Inversions are of two types: paracentric and pericentric.

Paracentric inversions do not include the centromere, and both breaks occur in one arm of the chromosome. Pericentric inversions include the centromere, and there is a break point in each arm.

Inversions usually do not cause any abnormalities in carriers, as long as the rearrangement is balanced, with no extra or missing DNA. However, in individuals which are heterozygous for an inversion, there is an increased production of abnormal chromatids (this occurs when crossing-over occurs within the span of the inversion). This leads to lowered fertility, due to production of unbalanced gametes. An inversion does not involve a loss of genetic information, but simply rearranges the linear gene sequence.

Inheritance

Most chromosome abnormalities occur as an accident in the egg cell or sperm, and therefore the anomaly is present in every cell of the body. Some anomalies, however, can happen after conception, resulting in Mosaicism (where some cells have the anomaly and some do not). Chromosome anomalies can be inherited from a parent or be "de novo". This is why chromosome studies are often performed on parents when a child is found to have an anomaly. If the parents do not possess the abnormality it was not initially inherited; however, it may be transmitted to subsequent generations.

Acquired chromosome abnormalities

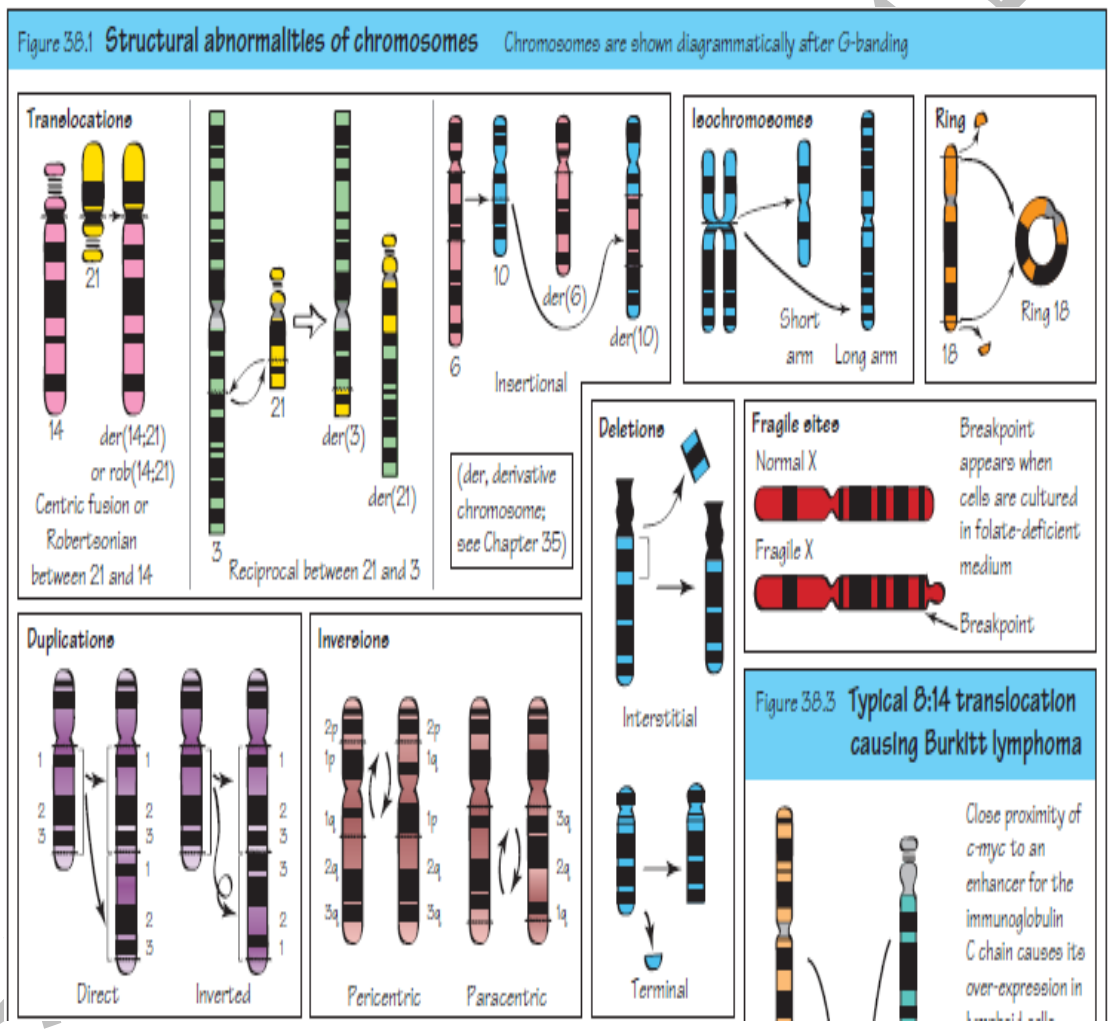
Most cancers, if not all, could cause chromosome abnormalities, with either the formation of hybrid genes and fusion proteins, deregulation of genes and overexpression of proteins, or loss of tumor suppressor genes Furthermore, certain consistent chromosomal abnormalities can turn normal cells into a leukemic cell such as the translocation of a gene, resulting in its inappropriate expression.

DNA damage during spermatogenesis

During the mitotic and meiotic cell divisions of mammalian gametogenesis, DNA repair is effective at removing DNA damages. However, in spermatogenesis the ability to repair DNA damages decreases substantially in the latter part of the process as haploid spermatids undergo major nuclear chromatin remodeling into highly compacted sperm nuclei. The last few weeks of sperm development before fertilization are highly susceptible to the accumulation of sperm DNA damage. Such sperm DNA damage can be transmitted unrepaired

into the egg where it is subject to removal by the maternal repair machinery. However, errors in maternal DNA repair of sperm DNA damage can result in zygotes with chromosomal structural aberrations.

Melphalan is a bifunctional alkylating agent frequently used in chemotherapy. Meiotic inter-strand DNA damages caused by melphalan can escape paternal repair and cause chromosomal aberrations in the zygote by maternal misrepair Thus both pre- and post-fertilization DNA repair appear to be important in avoiding chromosome abnormalities and assuring the genome integrity of the conceptus.



Genetic diseases due to chromosomal abnormalities

Down syndrome

A condition in which a person has an extra chromosome. Chromosomes are small “packages” of genes in the body. They determine

how a baby's body forms and functions as it grow during pregnancy and after birth. Typically, a baby is born with 46 chromosomes. Babies with Down syndrome have an extra copy of one of these chromosomes, chromosome 21. A medical term for having an extra copy of a chromosome is 'trisomy.' Down syndrome is also referred to as Trisomy 21. This extra copy changes how the baby's body and brain develop, which can cause both mental and physical challenges for the baby

Klinefelter syndrome

Where boys and men are born with an extra X chromosome. Chromosomes are packages of genes found in every cell in the body. There are 2 types of chromosome, called the sex chromosomes that determine the genetic sex of a baby. These are named either X or Y.

Usually, a female baby has 2 X chromosomes (XX) and a male has 1 X and 1 Y (XY). But in Klinefelter syndrome, a boy is born with an extra copy of the X chromosome (XXY).

The X chromosome is not a "female" chromosome and is present in everyone. The presence of a Y chromosome denotes male sex.

Boys and men with Klinefelter syndrome are still genetically male, and often will not realise they have this extra chromosome, but occasionally it can cause problems that may require treatment.

Klinefelter syndrome affects around 1 in every 660 males.

Edwards' syndrome

Also known as trisomy 18, is a rare but serious condition.

Edwards' syndrome affects how long a baby may survive. Sadly, most babies with Edwards' syndrome will die before or shortly after being born.

A small number (about 13 in 100) babies born alive with Edwards' syndrome will live past their 1st birthday.

Each cell in your body usually contains 23 pairs of chromosomes, which carry the genes you inherit from your parents.

A baby with Edwards' syndrome has 3 copies of chromosome number 18 instead of 2. This affects the way the baby grows and develops.

Turner syndrome,

A condition that affects only females, results when one of the X chromosomes (sex chromosomes) is missing or partially missing. Turner syndrome can cause a variety of medical and developmental problems, including short height, failure of the ovaries to develop and heart defects.

Turner syndrome may be diagnosed before birth (prenatally), during infancy or in early childhood. Occasionally, in females with mild signs and symptoms of Turner syndrome, the diagnosis is delayed until the teen or young adult years.

Cri du chat syndrome

A rare genetic disorder due to a partial chromosome deletion on chromosome 5. Its name is a French term ("cat-cry" or "call of the cat") referring to the characteristic cat-like cry of affected children. It was first described by Jérôme Lejeune in 1963. The condition affects an estimated 1 in 50,000 live births across all ethnicities and is more common in females by a 4:3 ratio

Patau's syndrome

A serious rare genetic disorder caused by having an additional copy of chromosome 13 in some or all of the body's cells. It's also called trisomy 13.

Each cell normally contains 23 pairs of chromosomes, which carry the genes you inherit from your parents.

But a baby with Patau's syndrome has 3 copies of chromosome 13, instead of 2.

This severely disrupts normal development and, in many cases, results in miscarriage, stillbirth or the baby dying shortly after birth.

Babies with Patau's syndrome grow slowly in the womb and have a low birth weight, along with a number of other serious medical problems.

Williams's syndrome

Caused by the loss (deletion) of genetic material from a specific region of chromosome 7. The deleted region includes 25 to 27 genes, and researchers believe that a loss of several of these genes contributes to the characteristic features of this disorder.

Triple X syndrome,

Also called trisomy X or 47,XXX, is a genetic disorder that affects about 1 in 1,000 females. Females normally have two X chromosomes in all cells — one X chromosome from each parent. In triple X syndrome, a female has three X chromosomes.

Many girls and women with triple X syndrome don't experience symptoms or have only mild symptoms. In others, symptoms may be more apparent — possibly including developmental delays and learning disabilities. Seizures and kidney problems occur in a small number of girls and women with triple X syndrome

XYY syndrome

A rare chromosomal disorder that affects males. It is caused by the presence of an extra Y chromosome. Males normally have one X and one Y chromosome. However, individuals with this syndrome have one X and two Y chromosomes. Affected individuals are usually very tall.

Human Genetics
Lecture 4
Dr. Abbas Hussein Mugheer

Patterns of Inheritance

The basic laws of inheritance are important in understanding patterns of disease transmission. The inheritance patterns of single gene diseases are often referred to as Mendelian since Gregor Mendel first observed the different patterns of gene segregation for selected traits in garden peas and was able to determine probabilities of recurrence of a trait for subsequent generations. If a family is affected by a disease, an accurate family history will be important to establish a pattern of transmission. In addition, a family history can even help to exclude genetic diseases, particularly for common diseases where behavior and environment play strong roles.

Most genes have one or more versions due to mutations or polymorphisms referred to as alleles. Individuals may carry a 'normal' allele and/or a 'disease' or 'rare' allele depending on the impact of the mutation/polymorphism (e.g., disease or neutral) and the population frequency of the allele. Single-gene diseases are usually inherited in one of several patterns depending on the location of the gene and whether one or two normal copies of the gene are needed for the disease phenotype to manifest.

The expression of the mutated allele with respect to the normal allele can be characterized as dominant, co-dominant, or recessive. There are five basic modes of inheritance for single-gene diseases: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and mitochondrial.

Genetic heterogeneity is a common phenomenon with both single-gene diseases and complex multi-factorial diseases. It should not be surprising that multiple affected family members may experience different levels of disease severity and outcomes. This effect may be due to other genes influencing the disease phenotype or different mutations in the same gene resulting in similar, but not identical phenotypes.

Genotype: refers to the genes of an individual, in regard to specific trait.

Trait: is a specific characteristic of an organism. Traits can be determined by genes or the environment, or more commonly by interactions between them. The genetic contribution to a trait is called the genotype. The outward expression of the genotype is called the phenotype.

Locus: is the specific physical position of a gene on a chromosome.

Allele: is an alternate form of a gene. For example, if the trait the gene codes for is eye color, one allele contains the information for blue eyes while a different allele may produce brown eyes

Alleles are often classified as being either dominant or recessive. In general, dominant alleles mask (hide) the expression of recessive alleles .

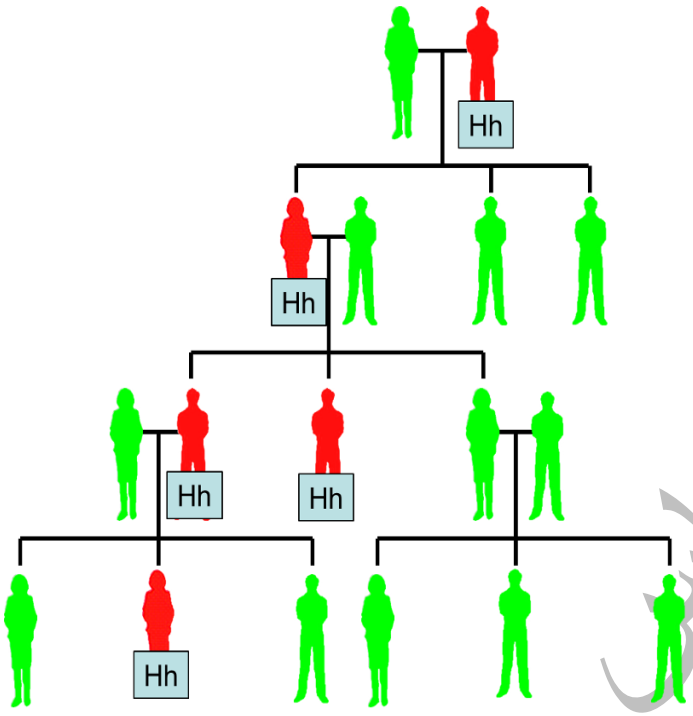
Therefore, if an allele is dominant, only one copy of that allele needs to be present for that trait to appear (or be expressed). If an allele is recessive, both of the chromosomes must possess the recessive allele for it to be expressed in the individual .

The terms dominant and recessive do not indicate the prevalence (or frequency) of a trait in the population but instead, what is happening in the cell at the level of gene expression. A dominant allele may be very rare in a population, and the recessive alleles may be the most prevalent.

An uppercase letter is usually assigned for dominant allele, and lowercase letters are used for recessive alleles .

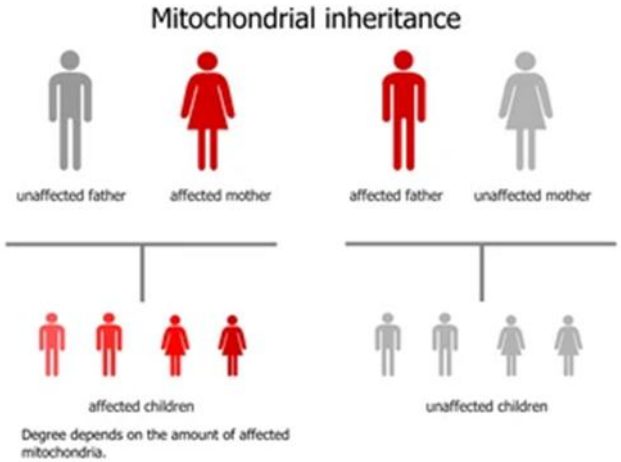
Dominant Inheritance

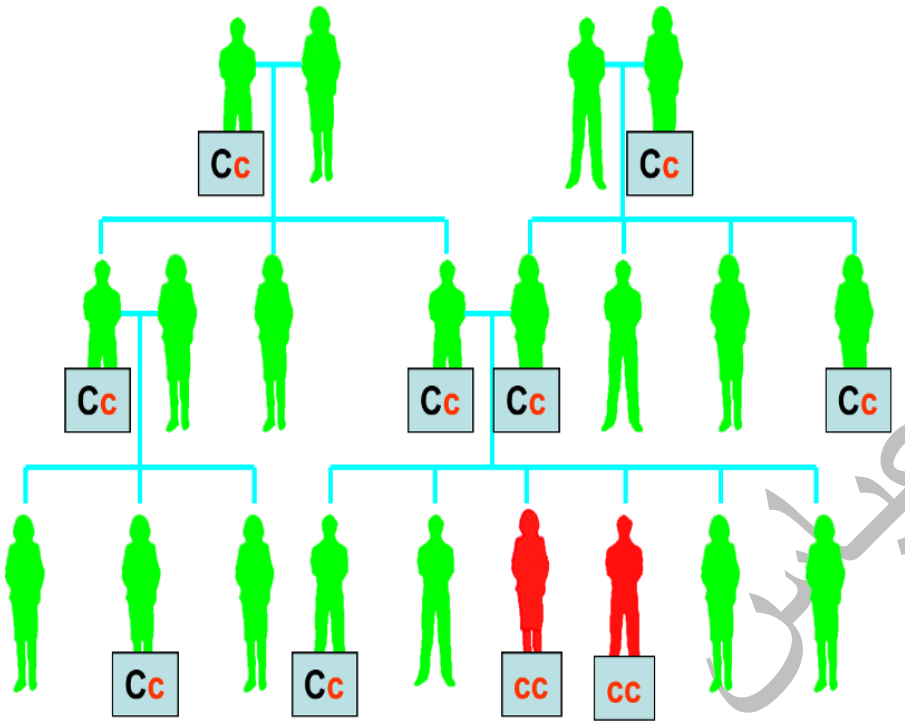
Some diseases are inherited, and the pattern of appearance within a family tree will depend on whether the faulty allele is dominant or recessive compared to the normal allele. For example, the allele for Huntington's disease is dominant. If a heterozygous (Hh) man with Huntington's disease and a normal woman (hh) have children, some of them (about half on average) will have the disease (individuals shown in red). With a dominant allele like this, the disease occurs fairly frequently in the family tree.



Recessive Inheritance

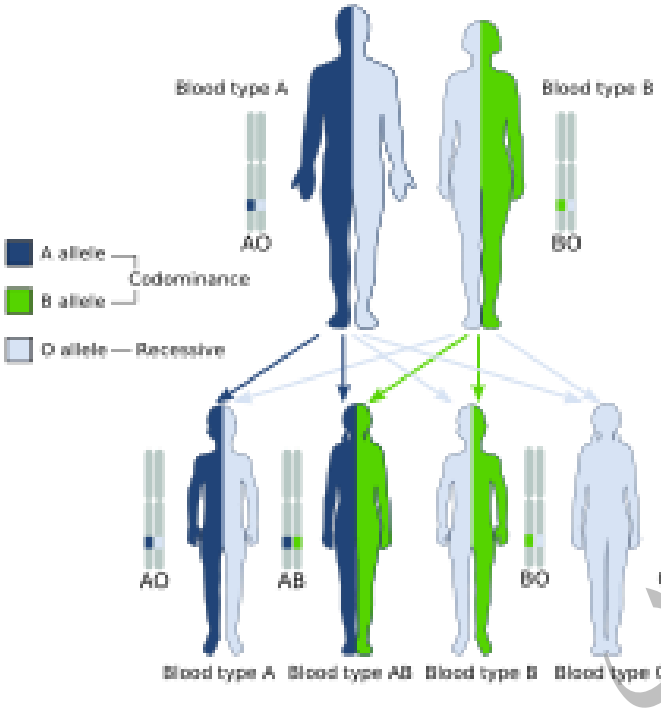
Cystic fibrosis is caused by a recessive allele, meaning that individuals who are heterozygous for the cystic fibrosis allele (shown as Cc below) will not manifest any signs or symptoms of cystic fibrosis. As a result, the cystic fibrosis allele can be passed along a family tree with only sporadic appearance of individuals who have signs and symptoms of cystic fibrosis because they are homozygous for the recessive allele (cc).





Co-dominance

Co-dominance occurs when the contributions of both alleles are visible in the phenotype and neither allele masks another. For example, in the ABO blood group system, chemical modifications to a glycoprotein (the H antigen) on the surfaces of blood cells are controlled by three alleles, two of which are co-dominant to each other (I^A, I^B) and dominant over the recessive i at the ABO locus. The I^A and I^B alleles produce different modifications. The enzyme coded for by I^A adds an N-acetylgalactosamine to a membrane-bound H antigen. The I^B enzyme adds a galactose. The i allele produces no modification. Thus the I^A and I^B alleles are each dominant to i (I^AI^A and I^Ai individuals both have type A blood, and I^BI^B and I^Bi individuals both have type B blood), but I^AI^B individuals have both modifications on their blood cells and thus have type AB blood, so the I^A and I^B alleles are said to be co-dominant.



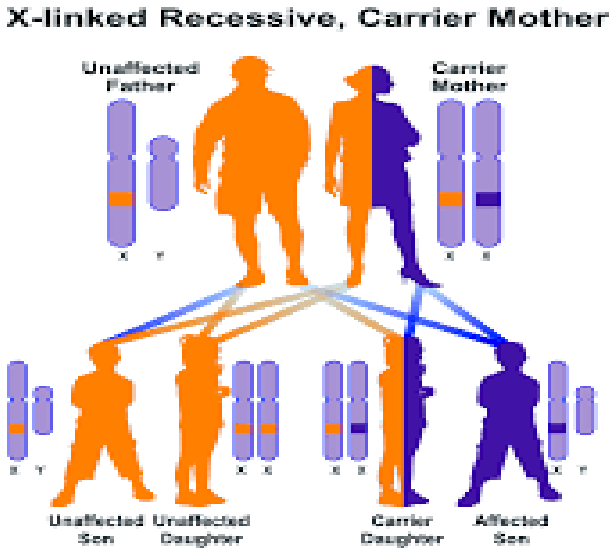
Another example occurs at the locus for the beta-globin component of hemoglobin, where the three molecular phenotypes of HbA/HbA, HbA/HbS, and HbS/HbS are all distinguishable by protein electrophoresis. (The medical condition produced by the heterozygous genotype is called sickle-cell trait and is a milder condition distinguishable from sickle-cell anemia, thus the alleles show incomplete dominance with respect to anemia, see above). For most gene loci at the molecular level, both alleles are expressed co-dominantly, because both are transcribed into RNA.

Co-dominance, where allelic products co-exist in the phenotype, is different from incomplete dominance, where the quantitative interaction of allele products produces an intermediate phenotype. For example, in co-dominance, a red homozygous flower and a white homozygous flower will produce offspring that have red and white spots. When plants of the F1 generation are self-pollinated, the phenotypic and genotypic ratio of the F2 generation will be 1:2:1 (Red: Spotted: White). These ratios are the same as those for incomplete dominance. Again, this classical terminology is inappropriate – in reality such cases should not be said to exhibit dominance at all.

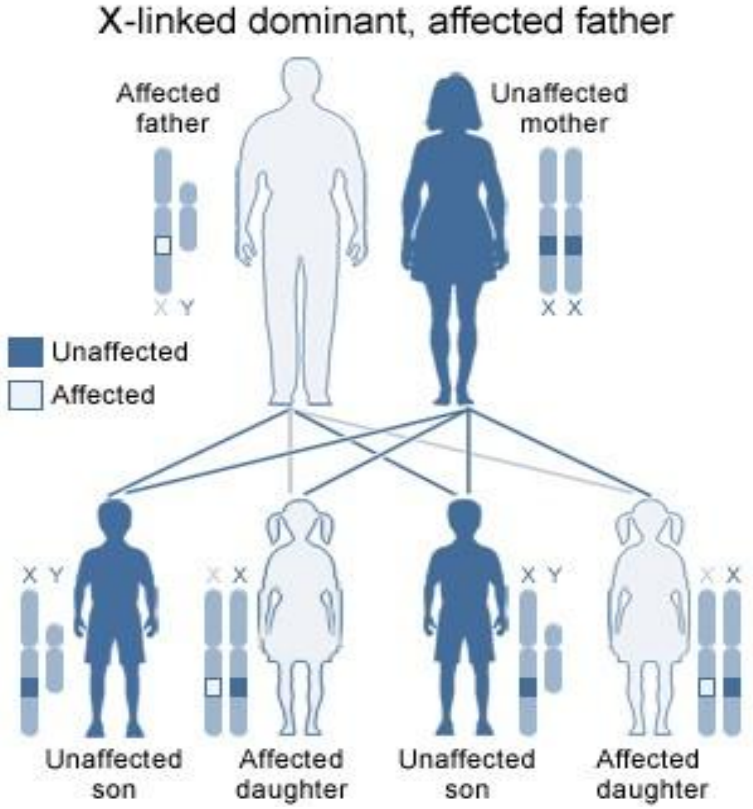
X-linked inheritance

One of the ways a genetic trait or condition caused by a mutated (changed) gene on the X chromosome can be passed down (inherited) from parent to child. In X-linked recessive inheritance, a daughter inherits a single mutated gene on the X chromosome from one of her parents. The X chromosome she inherits from the other parent will usually cancel the effect of the mutation, and she most likely will not have the genetic condition. If she inherits a mutated copy of the gene from both parents, she will be affected with the condition. Fathers cannot pass X-linked recessive conditions to their sons. When a son inherits a mutated gene on the X chromosome from his mother, the genetic condition is more likely to occur. X-linked recessive conditions most often occur in males.

X-linked recessive inheritance is a way a genetic trait or condition can be passed down from parent to child through mutations (changes) in a gene on the X chromosome. In males (who only have one X chromosome), a mutation in the copy of the gene on the single X chromosome causes the condition. Females (who have two X chromosomes) must have a mutation on both X chromosomes in order to be affected with the condition. If only the father or the mother has the mutated X-linked gene, the daughters are usually not affected and are called carriers because one of their X chromosomes has the mutation but the other one is normal. Sons will be affected if they inherit the mutated X-linked gene from their mother. Fathers cannot pass X-linked recessive conditions to their sons.

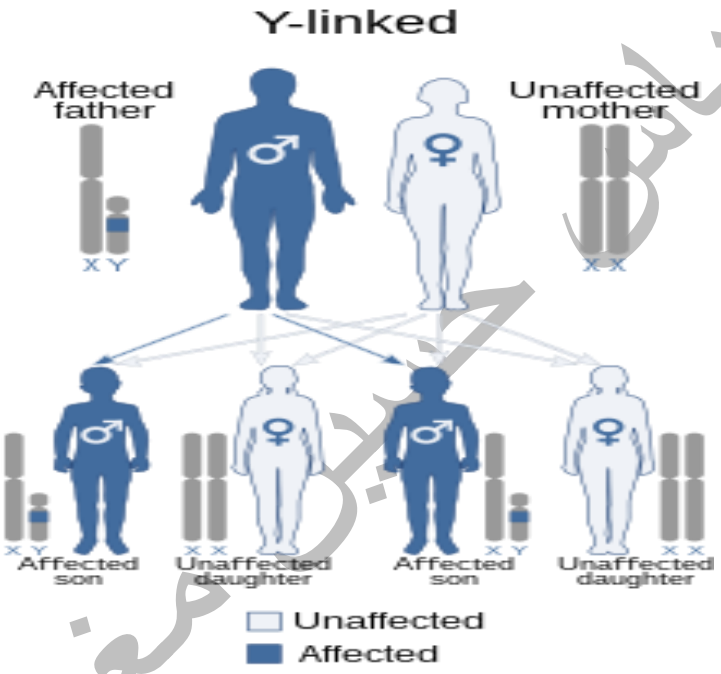


X--linked dominant inheritance refers to genetic conditions associated with mutations in genes on the X chromosome. A single copy of the mutation is enough to cause the disease in both males (who have one X chromosome) and females (who have two X chromosomes).



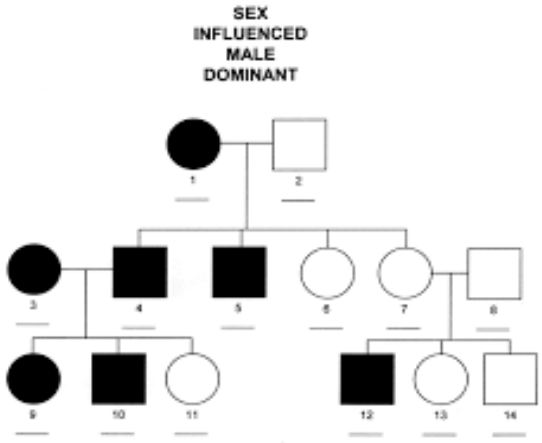
Y-linked inheritance

A condition is considered 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. This is partly because the Y chromosome is small and contains fewer genes than the autosomal chromosomes or the X chromosome. It is estimated to contain about 200 genes Such as, some cases of Swyer syndrome



Sex Influenced Traits

Modes of inheritance can vary greatly depending on what gene is being expressed. In sex influenced traits, autosomal traits are influenced by the sex of the individual. For example, in the gene that leads to baldness, it is dominant in men. This means if they have the big "P" they are going to have the trait for baldness. In females, the trait is recessive. This means it is much less likely for the female to exhibit the trait. They would need to big "P"s to exhibit the trait. Although the trait is not coded on the sex chromosomes, Y and X, it is influenced by the traits expressed. Due to the difference in inheritance, there is a probability a man would exhibit the trait is larger than a female exhibiting the trait.



Sex-limited genes

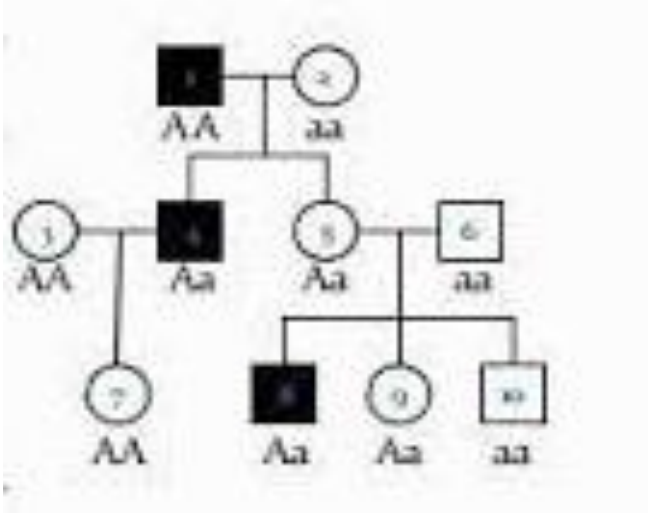
Genes that are present in both sexes of sexually reproducing species but are expressed in only one sex and have no penetrance, or are simply 'turned off' in the other. In other words, sex-limited genes cause the two sexes to show different traits or phenotypes, despite having the same genotype. This term is restricted to autosomal traits, and should not be confused with sex-linked characteristics, which have to do with genetic differences on the sex chromosomes (see sex-determination system). Sex-limited genes are also distinguished from sex-influenced genes, where the same gene will show differential expression in each sex. Sex-influenced genes commonly show a dominant/recessive relationship, where the same gene will have a dominant effect in one sex and a recessive effect in the other (for example, male pattern baldness). However, the resulting phenotypes caused by sex-limited genes are present in only one sex and can be seen prominently in various species that typically show high sexual dimorphism.

Sex-limited genes are responsible for sexual dimorphism, which is a phenotypic (directly observable) difference between males and females of the same species regardless of genotype. These differences can be reflected in size, color, behavior (ex: levels of aggression), and morphology. Examples of sex-limited genes are genes which control horn development in sheep: while both males and females possess the same genes controlling horn development, they are only expressed in males. Sex-limited genes are also responsible for some female beetles' inability

to grow exaggerated mandibles, research that is discussed in detail later in this article.

Modern study of sex-limited genes includes research on epigenetics, which is the study of inheritable phentotypic changes with no change in DNA sequence. Modern research suggests that a substantial portion of the expression of sex-limited genes and sexual dimorphism may be influenced by certain epigenetic marks.

The purpose of sex-limited genes is to resolve sexual conflict. These genes try to resolve the "push-pull" between males and females over trait values for optimal phenotype. Without these genes, organisms would be forced to settle on an average trait value, incurring costs on both sexes. With these genes, it is possible to 'turn off' the genes in one sex, allowing both sexes to attain (or at least, approach very closely) their optimal phenotypes. This phenotypic variation can play a key role in the evolution of various species and their sexual differentiation.



The genetic basis of sex

Mammalian sex determination normally depends on the presence and appropriate expression of the SRY (Sex Determining Region, Y) gene. Mutations in this gene can cause failure of testicular development resulting in male to female sex reversal. However, there is increasing evidence for the existence of X-linked and autosomal genes necessary for sex determination or differentiation. The Steroidogenic factor 1 (SF-1) and Wilms' tumor 1 (WT-1) genes are clearly involved in early gonadal

development whilst mutations in the SRY-related gene SOX9 are associated with campomelic dysplasia and XY sex reversal. Pedigree analysis of human SRY-negative XX males suggests the existence of at least one autosomal testis determining locus (TDFA). In addition, rearrangements of chromosomes 9, 10 and the X have occasionally been associated with 46, XY gonadal dysgenesis leading to female gender assignment.

Human Genetics
Lecture 5
Dr. Abbas Hussein Mugheer

Mutation

A mutation is a change in the DNA sequence of an organism. Mutations can result from errors in DNA replication during cell division, exposure to mutagens or a viral infection. Germline mutations (that occur in eggs and sperm) can be passed on to offspring, while somatic mutations (that occur in body cells) are not passed on.

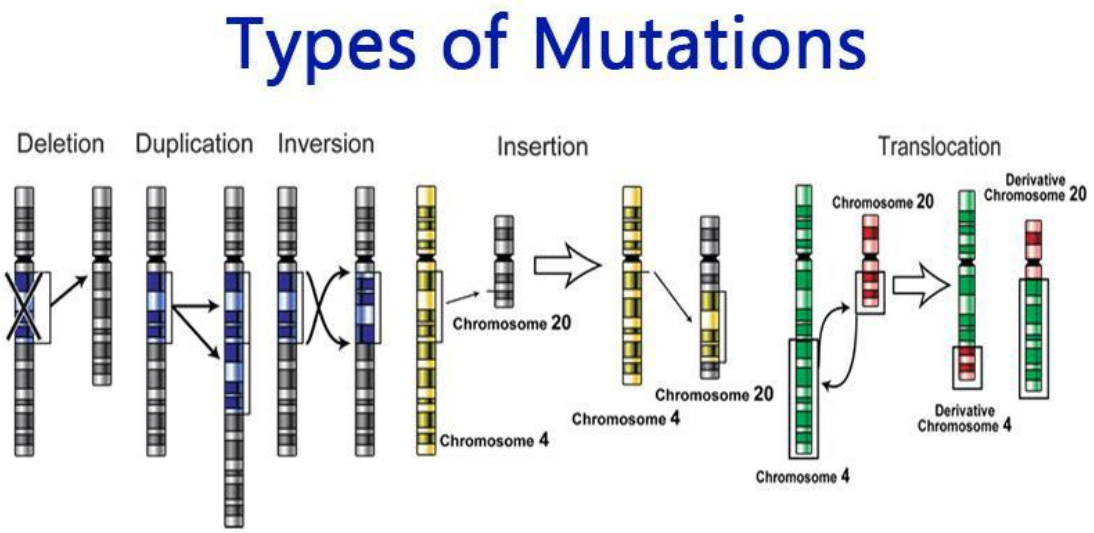
Mutations are happening in our cells all the time, but almost none of these affect our health. This is very different than what we often see in science fiction in movies. In real life, a mutation is never so beneficial that it turns a person into a superhero or does something bizarre like cause them to grow wings. There are many reasons that mutations usually don't have major consequences. One reason is that our cells have very sophisticated machinery for repairing mutations very quickly. So there's not enough time for them to cause problems. Another is that most mutations occur in somatic cells like muscle cells or skin cells and can only affect the cell where the mutation occurred and cells that grow from that cell. On the other hand, when mutations occur in germline cells, eggs and sperm, they will be present in every cell that develops from that egg or sperm, an entire person, and can have larger effects.

Mutation is a process that produces a gene or chromosome that differs from the wild type. The mutation may result due to changes either on the gene or the chromosome itself.

Thus, broadly mutation maybe:

1. **Gene mutation** where the allele of a gene changes.

2. **Chromosome mutation** where segments of chromosomes, whole chromosomes, or entire sets of chromosomes change.



Types of Mutations

There are various schemes for classification of different kind of mutations. Depending on:

A. The Type of Cell Involved

1. **Somatic mutations**

- Mutations that are in the somatic tissues of the body.
- Mutations are not transmitted to progeny.
- The extent of the phenotypic effect depends upon whether the mutation is dominant or recessive (dominant mutations generally have a greater effect).
- The extent of the phenotypic effect depends upon whether it occurs early or late in development (early arising mutations have a greater effect).

2. **Germinal mutations**

- Mutations that are in the germ tissues of the body.
- Mutations may be transmitted to progeny
- Dominant mutations are seen in first generation after the mutation occurs
- If a female gamete containing an X-linked mutation is fertilized, the males will show the mutant phenotype

- Recessive mutations will only be seen upon the chance mating with an individual carrying the recessive allele too; thus, the recessive mutation may remain hidden for many generations

B. Mode of Origin

(1) Spontaneous mutations

The spontaneous mutations occur suddenly in the nature and their origin is unknown. They are also called "background mutation" and have been reported in many organisms such as, Oenothera, maize, bread molds, microorganisms (bacteria and viruses), Drosophila, mice, man, etc.

(2) Induced mutations

Besides naturally occurring spontaneous mutations, the mutations can be induced artificially in the living organisms by exposing them to abnormal environment such as radiation, certain physical conditions (i.e., temperature) and chemicals.

C. Direction of Mutation

According to their mode of direction following types of mutations have been recognized:

1. Forward mutations

In an organism when mutations create a change from wild type to abnormal phenotype, then that type of mutations are known as forward mutations. Most mutations are forward type.

2. Reverse or back mutations

The forward mutations are often corrected by error correcting mechanism, so that an abnormal phenotype changes into wild type phenotype.

D. Size and Quality

According to size following two types of mutations have been recognized:

1. Point mutation

When heritable alterations occur in a very small segment of DNA molecule, i.e., a single nucleotide or nucleotide pair, then this type of mutations are called "point mutations". The point mutations may occur due to following types of subnucleotide change in the DNA and RNA.

– Deletion mutations. The point mutation which is caused due to loss or deletion of some portion (single nucleotide pair) in a triplet codon of a cistron or gene is called deletion mutation.

– Insertion or addition mutation. The point mutations which occur due to addition of one or more extra nucleotides to a gene or cistron are called insertion mutations.

The mutations which arise from the insertion or deletion of individual nucleotides and cause the rest of the message downstream of the mutation to be read out of phase are called **frameshift mutations.**

– Substitution mutation. A point mutation, in which a nucleotide of a triplet is replaced by another nucleotide, is called substitution mutation.

2. Multiple mutations or gross mutations.

When changes involving more than one nucleotide pair, or entire gene, then such mutations are called gross mutations. The gross mutations occur due to rearrangements of genes within the genome. It may be:

1. The rearrangement of genes may occur within a gene. Two mutations within the same functional gene can produce different effects depending on gene whether they occur in the cis or trans position.

2. The rearrangement of gene may occur in number of genes per chromosome. If the numbers of gene replicas are non-equivalent on the homologous chromosomes, they may cause different types of phenotypic effects over the organisms.

3. Due to movement of a gene locus new type of phenotypes may be created, especially when the gene is relocated near heterochromatin. The movement of gene loci may take place due to following method:

(i) Translocation. Movement of a gene may take place to a non-homologous chromosome and this is known as translocation.

(ii) Inversion. The movement of a gene within the same chromosome is called inversion.

E. Phenotypic Effects

1. **Morphological mutations** are mutations that affect the outwardly visible properties of an organism (i.e. curly ears in cats)

2. **Lethal mutations** are mutations that affect the viability of the organism (i.e. Manx cat).

3. **Conditional mutations** are mutations in which the mutant allele causes the mutant phenotype only in certain environments (called the restrictive condition).

In the permissive condition, the phenotype is no longer mutant.

Example. Siamese cat – mutant allele causes albino phenotype at the restrictive temperature of most of the cat body but not at the permissive temperature in the extremities where the body temperature is lower.

4. **Biochemical mutations** are mutations that may not be visible or affect a specific morphological characteristic but may have a general effect on the ability to grow or proliferate. For example, the bacterium Escherichia coli do not require the amino acid tryptophan for growth because they can synthesize tryptophan. However, there are E. coli mutants that have mutations in the trip genes. These mutants are auxotrophic for tryptophan, and tryptophan must be added to the nutrient medium for growth.

F. Magnitude of Phenotypic Effect

According to their phenotypic effects following kinds of mutations may occur:

1. **Dominant mutations**

The mutations which have dominant phenotypic expression are called dominant mutations. For example, in man the mutation disease aniridia (absence of iris of eyes) occurs due to a dominant mutant gene.

2. **Recessive mutations**

Most types of mutations are recessive in nature and so they are not expressed phenotypically immediately. The phenotypic effects of mutations of a recessive gene are seen only after one or more generations, when the mutant gene is able to recombine with another similar recessive gene.

3. Isoalleles

Some mutations alter the phenotype of an organism so slightly that they can be detected only by special techniques. Mutant genes that give slightly modified phenotypes are called isoalleles. They produce identical phenotypes in homozygous or heterozygous combinations.

G. Loss of Function or Gain of Function

1. **Loss of function mutation**

Loss of function mutation is also called inactivating mutations, result in the gene product having less or no function (being partially or wholly inactivated).

2. **Gain of function mutations**

The gain of function mutations also called activating mutations, changes the gene product such that its effect gets stronger (enhanced activation) or even is superseded by a different and abnormal function.

H. Type of Chromosome Involved

According to the types of chromosomes, the mutations may be of following two kinds:

1. **Autosomal mutations.** This type of mutation occurs in autosomal chromosomes.

2. **Sex chromosomal mutations.** This type of mutation occurs in sex chromosomes.

I. Chromosomal Mutation and Types

• The changes in the genome involving chromosome parts, whole chromosomes, or whole chromosome sets are called chromosome aberrations or chromosome mutations.

• Chromosome mutations have proved to be of great significance in applied biology— agriculture (including horticulture), animal husbandry and medicine.

Chromosome mutations are inherited once they occur and are of the following types

a. Structural changes in chromosomes:

1. **Changes in number of genes**

(a) Loss: **Deletion** which involves loss of a broken part of a chromosome.

(b) Addition: **Duplication** which involves addition of a part of chromosome.

2. **Changes in gene arrangement:**

(a) Rotation of a group of genes 1800 within one chromosome: **Inversion** in which broken segment reattached to original chromosome in reverse order.

(b) Exchange of parts between chromosomes of different pairs: **Translocation** in which the broken segment becomes attached to a non-homologous chromosome resulting in new linkage relations.

b. Changes in number of chromosomes:

1. Euploidy

• It involves the loss, or gain, of whole chromosome set.

• The term euploidy (Gr., eu = even or true; ploid = unit) designates genomes containing chromosomes that are multiples of some basic number (x).

• The euploids are those organisms which contain balanced set or sets of chromosomes in any number.

• The number of chromosomes in a basic set is called the monoploid number, x.

• Those euploid types whose number of sets is greater than two are called polyploid.

• Thus, 1x is monoploid, 2x is diploid; and the polyploid types are 3x (triploid), 4x (tetraploid), 5x (pentaploid), 6x (hexaploid) and so on.

• Mutation due to Euploidy refers to the state of having a chromosome number that is an exact multiple of a basic chromosome set. This means the number of chromosome sets is increased in euploidy.

Polyploidy

Addition of one or more sets of chromosomes.

They may be further:

(a) Autopolyploidy. The autopolyploidy involves polyploidy, in which the same basic set of chromosomes are multiplied.

(b) Allopolyploidy. The polyploidy results due the doubling of chromosome number in a F1 hybrid which is derived from two distinctly different species. The resultant species is called an allopolyploid.

2. Aneuploidy

• It involves the loss, or gain, of a part of the chromosome set.

• It refers to a condition in which one or a few chromosomes are added or deleted from the normal chromosome number. Hence, the number of chromosomes in aneuploidy can be greater or smaller than the number of chromosomes in the wild type.

• Various types of aneuploidy can be identified as: nullisomy, monosomy, and trisomy.

1. **Nullisomy (2n-2)** is the loss of both chromosomes of the homologous pair. This conditions may be lethal in most organisms.

2. **Monosomy (2n-1)** is the loss of a single chromosome of the homologous pair.

3. **Trisomy** is the gain of an extra chromosome (2n+1). Klinefelter syndrome (44+XXY/XYY) and Down syndrome are examples of trisomy.

Missense mutation A base change that converts one codon into another. Many missense mutations are silent because the encoded amino acid remains the same or the amino acid substitution is sufficiently subtle so as not to compromise activity of the enzyme. Missense mutations that have a marked effect often lie in the active site or grossly disrupt protein folding.

Nonsense mutation a base change that converts a codon within the coding sequence into a stop codon. Note that there is only a limited set of sense codons that can be converted to a stop codon by a single base change. Nonsense mutations lead to a truncated protein product. Nonsense mutations that lie early in the gene sequence will completely inactivate the gene. Sometimes nonsense mutations that lie late in the gene sequence will not disrupt gene function.

Frameshift mutation the addition or deletion of a base or bases such that the coding sequence is shifted out of register. Note that addition or deletion of a multiple of three bases does not cause a frameshift. After the frameshift mutation is encountered, missense codons will be read up to the first stop codon. Like nonsense mutations, frameshift mutations usually lead to complete inactivation of the gene.

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Mutagens

Chemical mutagens were not demonstrated to cause mutation until the 1940s, when Charlotte Auerbach and J. M. Robson found that mustard gas can cause mutations in fruit flies. A large number of chemical mutagens have since been identified, especially after the development of the Ames test in the 1970s by Bruce Ames that screens for mutagens and allows for preliminary identification of carcinogens. Early studies by Ames showed around 90% of known carcinogens can be identified in Ames test as mutagenic (later studies however gave lower figures), and ~80% of the mutagens identified through Ames test may also be carcinogens. Mutagens are not necessarily carcinogens. Sodium azide for example may be mutagenic (and highly toxic), but it has not been shown to be carcinogenic.

Mutagens Types

Mutagens may be of physical, chemical or biological origin. They may act directly on the DNA, causing direct damage to the DNA, and most often result in replication error. Some however may act on the replication mechanism and chromosomal partition. Many mutagens are not mutagenic by themselves, but can form mutagenic metabolites through cellular processes, for example through the activity of the cytochrome P450 system and other oxygenases such as cyclooxygenase. Such mutagens are called promutagens.

Physical mutagens

Ionizing radiations: such as X-rays, gamma rays and alpha particles cause DNA breakage and other damages. The most common lab sources include cobalt-60 and cesium-137.

Ultraviolet radiations with wavelength above 260 nm are absorbed strongly by bases, producing pyrimidine dimers, which can cause error in replication if left uncorrected.

Radioactive decay: such as ^{14}C in DNA which decays into nitrogen.

DNA reactive chemicals

A DNA adduct (at center) of the mutagenic metabolite of benzo[a]pyrene from tobacco smoke.

A large number of chemicals may interact directly with DNA. However, many such as PAHs, aromatic amines, benzene are not necessarily mutagenic by themselves, but through metabolic processes in cells they produce mutagenic compounds.

Reactive oxygen species (ROS): These may be superoxide, hydroxyl radicals and hydrogen peroxide, and large number of these highly reactive species is generated by normal cellular processes, for example as by-products of mitochondrial electron transport, or lipid peroxidation. As an example of the latter, 15-hydroperoxyicosatetraenocic acid, a natural product of cellular cyclooxygenases and lipoxygenases, breaks down to form 4-hydroxy-2(E)-nonenal, 4-hydroperoxy-2(E)-nonenal, 4-oxo-2(E)-nonenal, and cis-4,5-epoxy-2(E)-decanal; these bifunctional electrophiles are mutagenic in mammalian cells and may contribute to the development and/or progression of human cancers. A number of mutagens may also generate these ROS. These ROS may result in the production of many base adducts, as well as DNA strand breaks and crosslinks.

Deaminating agents: for example nitrous acid which can cause transition mutations by converting cytosine to uracil.

Polycyclic aromatic hydrocarbons (PAH): when activated to diol-epoxides can bind to DNA and form adducts.

Alkylating agents: such as ethylnitrosourea. The compounds transfer methyl or ethyl group to bases or the backbone phosphate groups. Guanine when alkylated may be mispaired with thymine. Some may cause DNA crosslinking and breakages. Nitrosamines are an important group of mutagens found in tobacco, and may also be formed in smoked meats and fish via the interaction of amines in food with nitrites added as preservatives. Other alkylating agents include mustard gas and vinyl chloride.

Aromatic amines and amides have been associated with carcinogenesis since 1895 when German physician Ludwig Rehn observed high incidence of bladder cancer among workers in German synthetic aromatic amine dye industry. 2-Acetylaminofluorene, originally used as a pesticide but may also be found in cooked meat, may cause cancer of the bladder, liver, ear, intestine, thyroid and breast.

Alkaloid from plants: such as those from Vinca species, may be converted by metabolic processes into the active mutagen or carcinogen.

Bromine and some compounds that contain bromine in their chemical structure.

Sodium azide, an azide salt that is a common reagent in organic synthesis and a component in many car airbag systems

Psoralen combined with ultraviolet radiation causes DNA cross-linking and hence chromosome breakage.

Benzene, an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber and dyes.

Base analogs

Base analog: This can substitute for DNA bases during replication and cause transition mutations. Some examples are 5 bromo uracil and 2 amino purine.

Intercalating agents

Intercalating agents, such as ethidium bromide and proflavine, are molecules that may insert between bases in DNA, causing frameshift mutation during replication. Some such as daunorubicin may block transcription and replication, making them highly toxic to proliferating cells.

Metals

Many metals, such as arsenic, cadmium, chromium, nickel and their compounds may be mutagenic, but they may act, however, via a number of different mechanisms. Arsenic, chromium, iron, and nickel

may be associated with the production of ROS, and some of these may also alter the fidelity of DNA replication. Nickel may also be linked to DNA hypermethylation and histone deacetylation, while some metals such as cobalt, arsenic, nickel and cadmium may also affect DNA repair processes such as DNA mismatch repair, and base and nucleotide excision repair.

Biological agents

Transposon: a section of DNA that undergoes autonomous fragment relocation/multiplication. Its insertion into chromosomal DNA disrupts functional elements of the genes.

Virus – Virus DNA may be inserted into the genome and disrupts genetic function. Infectious agents have been suggested to cause cancer as early as 1908 by Vilhelm Ellermann and Oluf Bang, and 1911 by Peyton Rous who discovered the Rous sarcoma virus.

Bacteria : some bacteria such as Helicobacter pylori cause inflammation during which oxidative species are produced, causing DNA damage and reducing efficiency of DNA repair systems, thereby increasing mutation.

Carcinogen

Any substance that causes cancer is known as a carcinogen. But simply because a substance has been designated as a carcinogen does not mean that the substance will necessarily cause cancer. Many factors influence whether a person exposed to a carcinogen will develop cancer, including the amount and duration of the exposure and the individual's genetic background. Cancers caused by involuntary exposures to environmental carcinogens are most likely to occur in subgroups of the population, such as workers in certain industries who may be exposed to carcinogens on the job.

Cancer is any disease in which normal cells are damaged and do not undergo programmed cell death as fast as they divide via mitosis. Carcinogens may increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, which interferes with biological processes, and induces the uncontrolled, malignant

division, ultimately leading to the formation of tumors. Usually, severe DNA damage leads to programmed cell death, but if the programmed cell death pathway is damaged, then the cell cannot prevent itself from becoming a cancer cell.

There are many natural carcinogens. Aflatoxin B1, which is produced by the fungus Aspergillus flavus growing on stored grains, nuts and peanut butter, is an example of a potent, naturally occurring microbial carcinogen. Certain viruses such as hepatitis B and human papilloma virus have been found to cause cancer in humans. The first one shown to cause cancer in animals is Rous sarcoma virus, discovered in 1910 by Peyton Rous. Other infectious organisms which cause cancer in humans include some bacteria (e.g. Helicobacter pylori) and helminths (e.g. Opisthorchis viverrini and Clonorchis sinensis).

Co-carcinogens are chemicals that do not necessarily cause cancer on their own but promote the activity of other carcinogens in causing cancer. After the carcinogen enters the body, the body makes an attempt to eliminate it through a process called biotransformation. The purpose of these reactions is to make the carcinogen more water-soluble so that it can be removed from the body. However, in some cases, these reactions can also convert a less toxic carcinogen into a more toxic carcinogen.

Radiation induced cancer

Higher-energy radiation, including ultraviolet radiation (present in sunlight), x-rays, and gamma radiation, generally is carcinogenic, if received in sufficient doses. For most people, ultraviolet radiations from sunlight are the most common cause of skin cancer. In Australia, where people with pale skin are often exposed to strong sunlight, melanoma is the most common cancer diagnosed in people aged 15–44 years.

Substances or foods irradiated with electrons or electromagnetic radiation (such as microwave, X-ray or gamma) are not carcinogenic. In contrast, non-electromagnetic neutron radiation produced inside nuclear reactors can produce secondary radiation through nuclear transmutation.

In prepared food

Chemicals used in processed and cured meat such as some brands of bacon, sausages and ham may produce carcinogens. For example, nitrites used as food preservatives in cured meat such as bacon have also been noted as being carcinogenic with demographic links, but not causation, to colon cancer. Cooking food at high temperatures, for example grilling or barbecuing meats, may also lead to the formation of minute quantities of many potent carcinogens that are comparable to those found in cigarette smoke (i.e., benzo[a]pyrene). Charring of food looks like coking and tobacco pyrolysis, and produces carcinogens. There are several carcinogenic pyrolysis products, such as polynuclear aromatic hydrocarbons, which are converted by human enzymes into epoxides, which attach permanently to DNA. Pre-cooking meats in a microwave oven for 2–3 minutes before grilling shortens the time on the hot pan, and removes heterocyclic amine (HCA) precursors, which can help minimize the formation of these carcinogens.

In cigarettes

There is a strong association of smoking with lung cancer; the risk of developing lung cancer increases significantly in smokers. A large number of known carcinogens are found in cigarette smoke. Potent carcinogens found in cigarette smoke include polycyclic aromatic hydrocarbons (PAH, such as benzo(a)pyrene), benzene, and nitrosamine.

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Cancer and Genetics

Oncogene

An oncogene is a mutated gene that has the potential to cause cancer. Before an oncogene becomes mutated, it is called a proto-oncogene, and it plays a role in regulating normal cell division. Cancer can arise when a proto-oncogene is mutated, changing it into an oncogene and causing the cell to divide and multiply uncontrollably. Some oncogenes work like an accelerator pedal in a car, pushing a cell to divide again and again. Others work like a faulty brake in a car parked on a hill, also causing the cell to divide unchecked.

The name of oncogene suggests it is a gene that can cause cancer. Initially, oncogenes were identified in viruses, which could cause cancers in animals. Later, it was found that oncogenes can be mutated copies of certain normal cellular genes also called proto-oncogenes. Intact proto-oncogenes play important functions, regulating normal cellular growth, division, and apoptosis, which is the name for programmed or controlled cell death. Oncogenes or mutated copies of the proto-oncogenes may lead to uncontrolled cell growth and the escape from cell death, which may result in cancer development.

The proto-oncogene can become an oncogene by a relatively small modification of its original function. There are three basic methods of activation:

(First) A mutation within a proto-oncogene, or within a regulatory region (for example the promoter region), can cause a change in the protein structure, causing

1- An increase in protein (enzyme) activity
2- loss of regulation

(Second) An increase in the amount of a certain protein (protein concentration), caused by

1- An increase of protein expression (through misregulation)

2- An increase of protein (mRNA) stability, prolonging its existence and thus its activity in the cell

3- Gene duplication (one type of chromosome abnormality), resulting in an increased amount of protein in the cell

(Third) A chromosomal translocation (another type of chromosome abnormality)

There are 2 different types of chromosomal translocations that can occur:

1. translocation events which relocate a proto-oncogene to a new chromosomal site that leads to higher expression
2. translocation events that lead to a fusion between a proto-oncogene and a 2nd gene (this creates a fusion protein with increased cancerous/oncogenic activity)

The genetic basis of cancer

Cancer is essentially a genetic disease resulting from congenital or acquired alterations in some cells of the patient. Such changes may occur in particular oncogenes and are responsible for the tumor phenotype of the affected population of cells. Oncogenes function by continuous positive action in the mitogenic pathway, and may become activated by point mutations, chromosomal rearrangements, gene amplification or viral insertion events. In contrast, unaltered tumor-suppressor genes are responsible for suppressing the neoplastic phenotype, and their inactivation by deletion or mutation permits cancerous development in the affected cells. The genetic model of carcinogenesis is thus based on the idea that mutations at the DNA level create a functional imbalance between the oncogenes and the tumor-suppressor genes, resulting in uncontrolled clonal proliferation. It is likely that the clinical importance of these recent findings will soon be realized and utilized in the development of therapies and diagnostic procedures that will directly benefit the patient

Chromosome and cancer

Two prominent features of cancer cells are abnormal numbers of chromosomes (aneuploidy) and large-scale structural rearrangements of chromosomes. These chromosome aberrations are caused by genomic instabilities inherent to most cancers. Aneuploidy arises through chromosomal instability (CIN) by the persistent loss and gain of whole

chromosomes. Chromosomal rearrangements occur through chromosome structure instability (CSI) as a consequence of improper repair of DNA damage. The mechanisms that cause CIN and CSI differ, but the phenotypic consequences of aneuploidy and chromosomal rearrangements may overlap considerably. Both CIN and CSI are associated with advanced stage tumors with increased invasiveness and resistance to chemotherapy, indicating that targeted inhibition of these instabilities might slow tumor growth. Here, we review recent efforts that define the mechanisms and consequences of CIN and CSI.

Tumor suppressor gene

A tumor suppressor gene (TSG), or anti-oncogene, is a gene that regulates a cell during cell division and replication. If the cell grows uncontrollably, it will result in cancer. When a tumor suppressor gene is mutated, it results in a loss or reduction in its function. In combination with other genetic mutations, this could allow the cell to grow abnormally. The loss of function for these genes may be even more significant in the development of human cancers, compared to the activation of oncogenes.

TSGs can be grouped into the following categories: caretaker genes, gatekeeper genes, and more recently landscaper genes. Caretaker genes ensure stability of the genome via DNA repair and subsequently when mutated allow mutations to accumulate. Meanwhile, gatekeeper genes directly regulate cell growth by either inhibiting cell cycle progression or inducing apoptosis. Lastly landscaper genes regulate growth by contributing to the surrounding environment, when mutated can cause an environment that promotes unregulated proliferation. The classification schemes are evolving as medical advances are being made from fields including molecular biology, genetics, and epigenetics.

Q1: Is cancer a genetic disease?

Genetic changes that cause cancer can be inherited or arise from certain environmental exposures. Genetic changes can also happen because of errors that occur as cells divide.
Credit: National Cancer Institute

Yes, cancer is a genetic disease. It is caused by changes in genes that control the way cells grow and multiply. Cells are the

building blocks of your body. Each cell has a copy of your genes, which act like an instruction manual.

Genes are sections of DNA that carry instructions to make a protein or several proteins. Scientists have found hundreds of DNA and genetic changes (also called variants, mutations, or alterations) that help cancer form, grow, and spread.

Cancer-related genetic changes can occur because:

- random mistakes in our DNA happen as our cells multiply
- our DNA is altered by carcinogens in our environment, such as chemicals in tobacco smoke, UV rays from the sun, and the human papillomavirus (HPV)
- they were inherited from one of our parents

DNA changes, whether caused by a random mistake or by a carcinogen, can happen throughout our lives and even in the womb. While most genetic changes aren't harmful on their own, an accumulation of genetic changes over many years can turn healthy cells into cancerous cells. The vast majority of cancers occur by chance as a result of this process over time.

Q 2: Is cancer hereditary?

Cancer itself can't be passed down from parents to children. And genetic changes in tumor cells can't be passed down. But a genetic change that increases the risk of cancer can be passed down (inherited) if it is present in a parent's egg or sperm cells.

For example, if a parent passes a mutated BRCA1 or BRCA2 gene to their child, the child will have a much higher risk of developing breast and several other cancers.

That's why cancer sometimes appears to run in families. Up to 10% of all cancers may be caused by inherited genetic changes.

Inheriting a cancer-related genetic change doesn't mean you will definitely get cancer. It means that your risk of getting cancer is increased.

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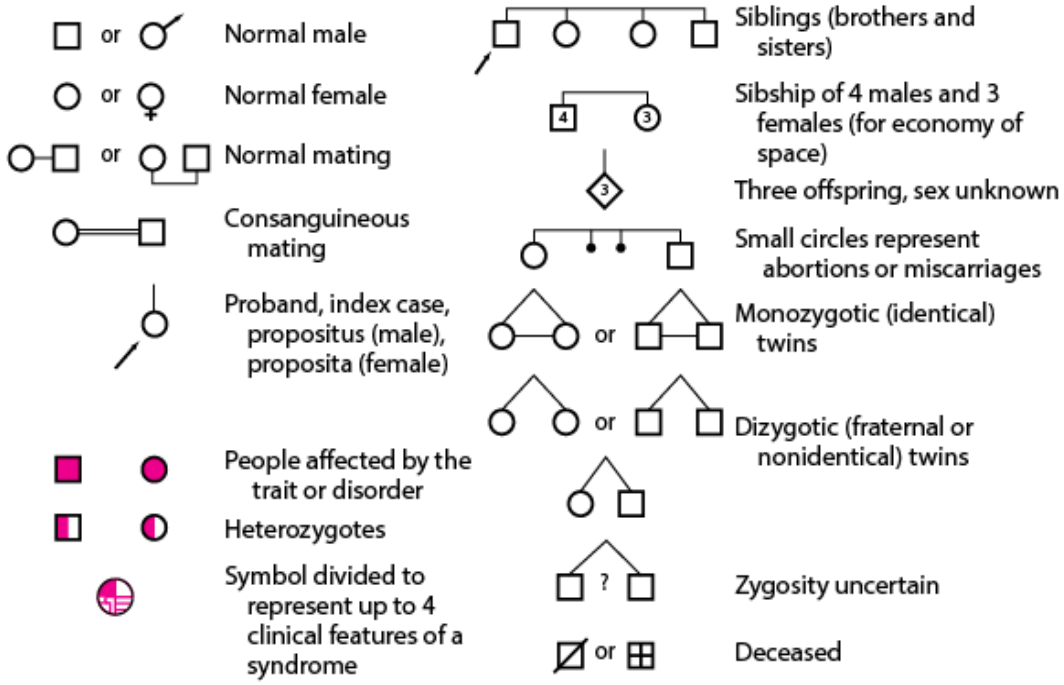
Family pedigree

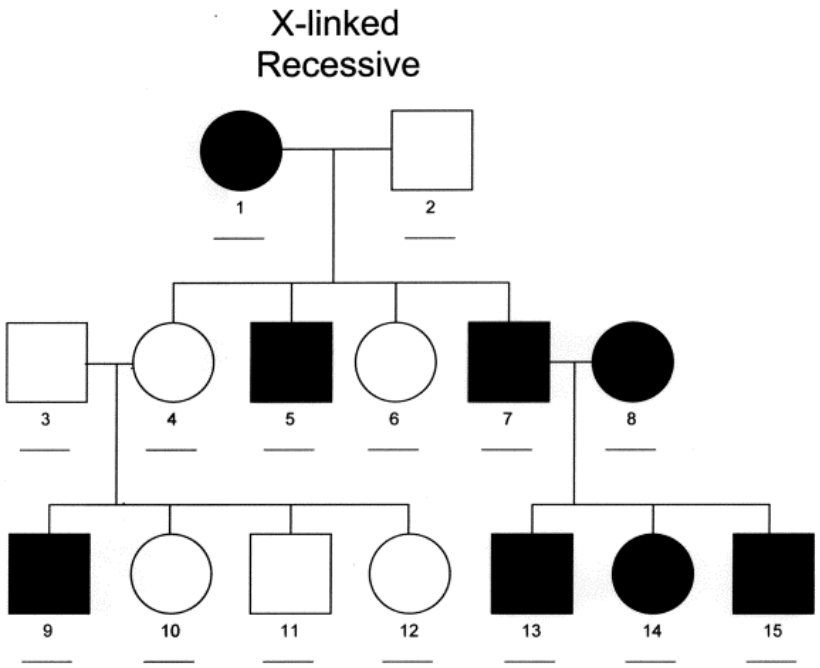
A pedigree, as related to genetics, is a chart that diagrams the inheritance of a trait or health condition through generations of a family. The pedigree particularly shows the relationships among family members and, when the information is available, indicates which individuals have a trait(s) of interest.

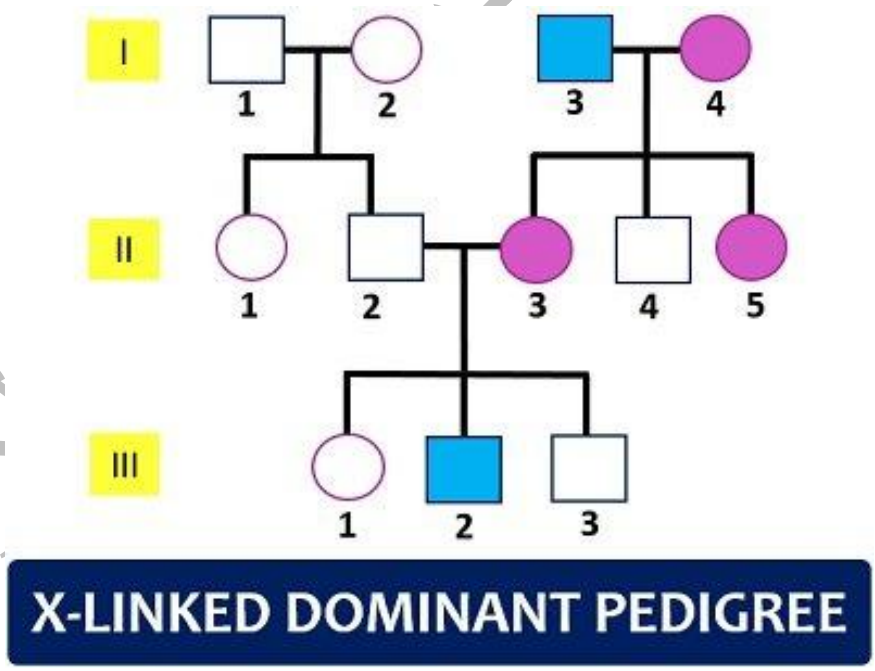
A pedigree is a map that depicts the different members of a family and their connections. It is a graph, and it makes assessing who is connected and their relationships such as parent, sibling, and cousin apparent by visual inspection. A pedigree can also help determine how a trait or condition might be passed down through the generations and what might accompany it.

Symbols

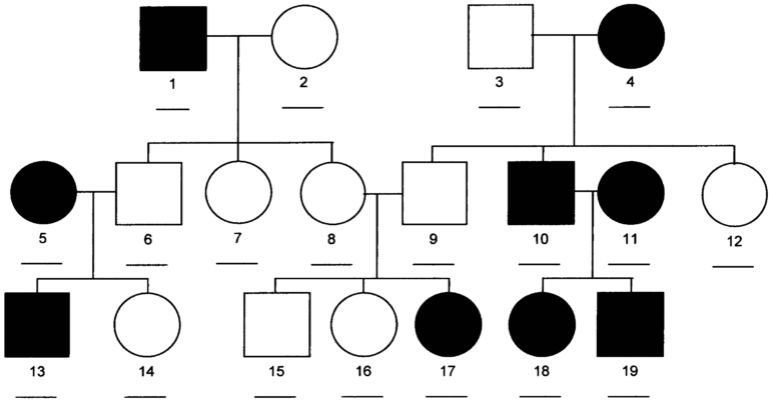


Determination the type of inheritance

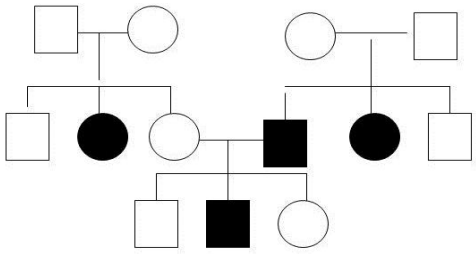


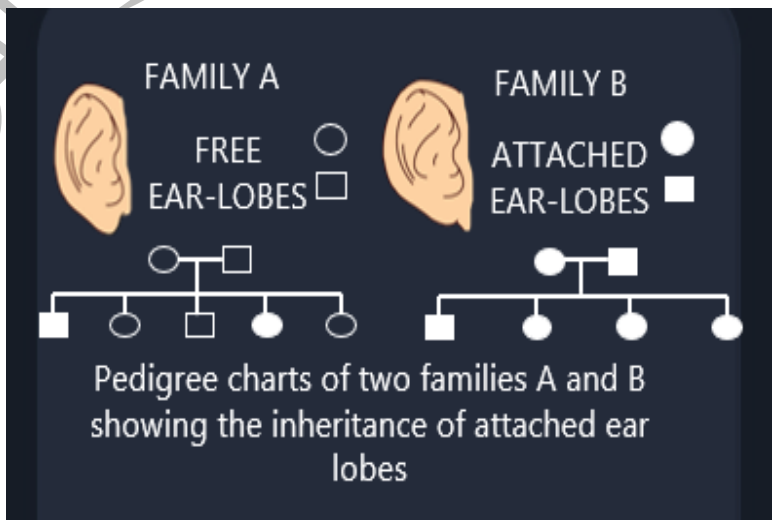


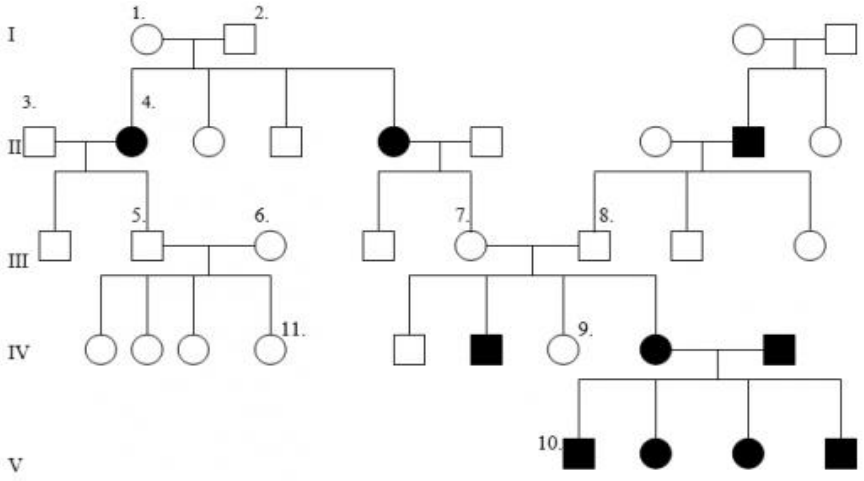
AUTOSOMAL RECESSIVE



- Dominant or Recessive?

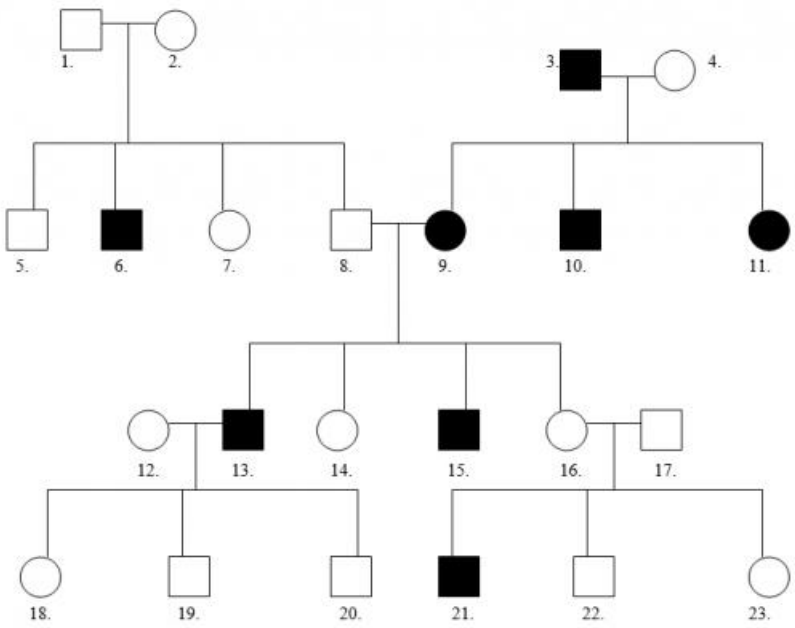






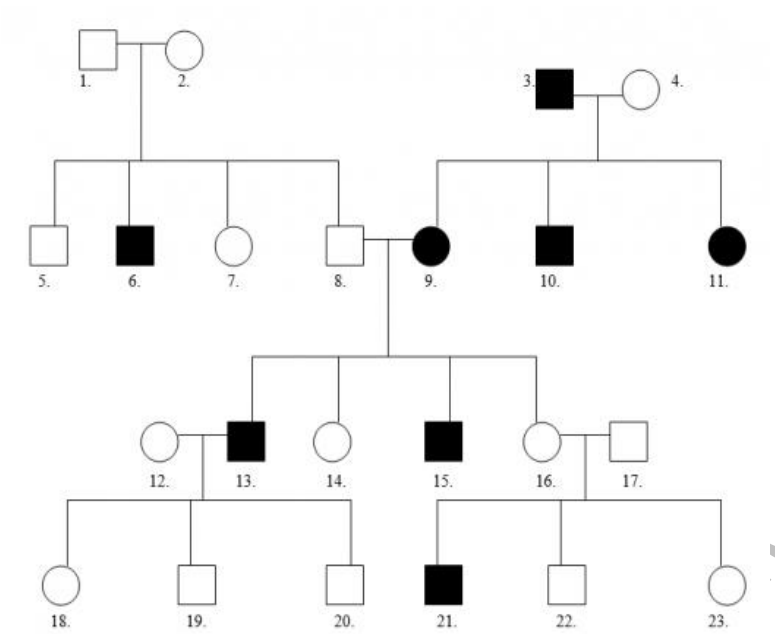
Q1: In the above pedigree, the affected individuals are shown shaded. None of the marriage partners from outside these two families are heterozygous for the trait. What is the inheritance pattern for this trait?

A. Autosomal dominant
B. Autosomal recessive
C. Sex linked dominant
D. Sex linked recessive



Q2: What pattern of inheritance does this pedigree demonstrate?

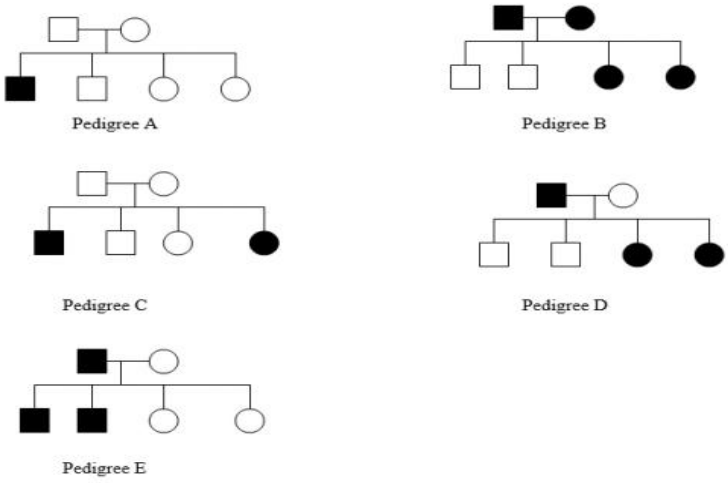
A. Autosomal
B. Sex linked



Q3: What pattern of inheritance does this pedigree demonstrate? (HINT: Look carefully... practice with genotypes if necessary)

A. Dominant

B. Recessive



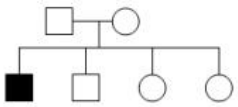
Q4: Indicate the pattern of inheritance observed for pedigree B.

A. Autosomal dominant

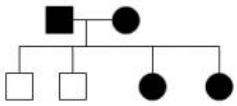
B. Autosomal recessive

C. Sex linked dominant

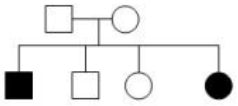
D. Sex linked recessive



Pedigree A



Pedigree B



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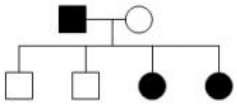

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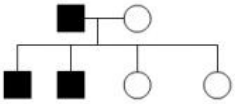
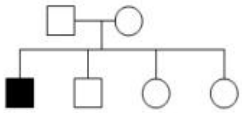


Pedigree E

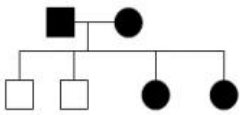
Q5: Indicate the pattern of inheritance observed for pedigree A.

A. Dominant

B. Recessive



Pedigree A



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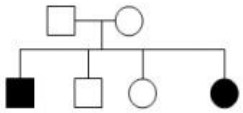
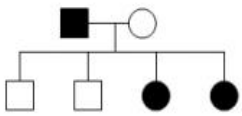
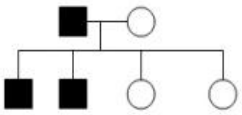


Pedigree C



Pedigree D



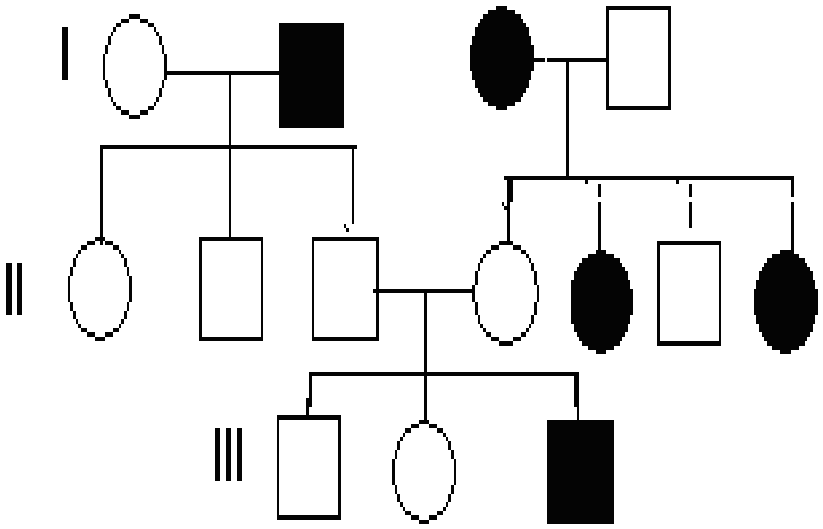
Pedigree E

Q6: Indicate the pattern of inheritance observed for pedigree E.

A. Autosomal

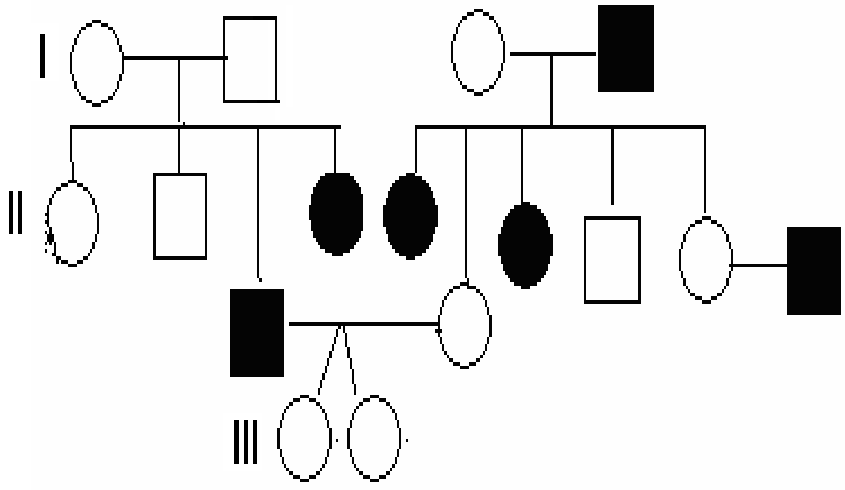
B. X-Linked

C. Y-Linked



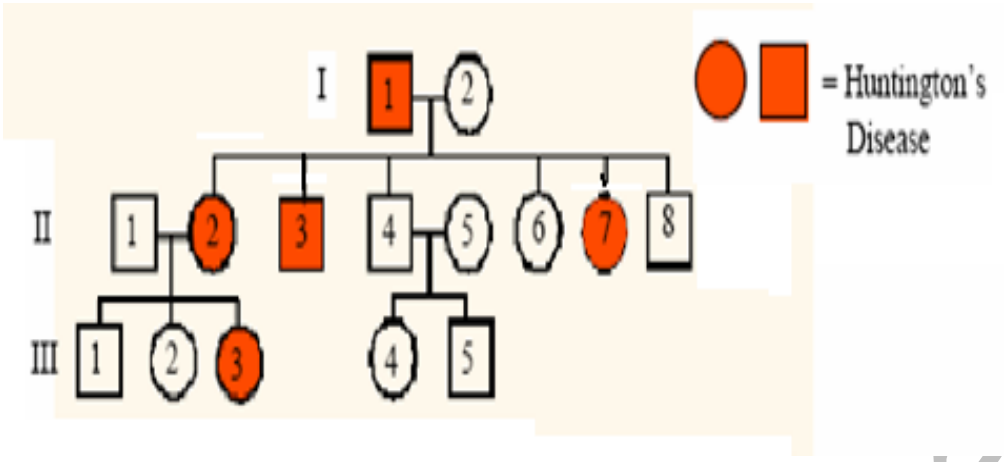
Q7: What pattern of inheritance is shown in the pedigree?

A. Autosomal dominant
B. Autosomal recessive
C. Sex linked dominant
D. Sex linked recessive



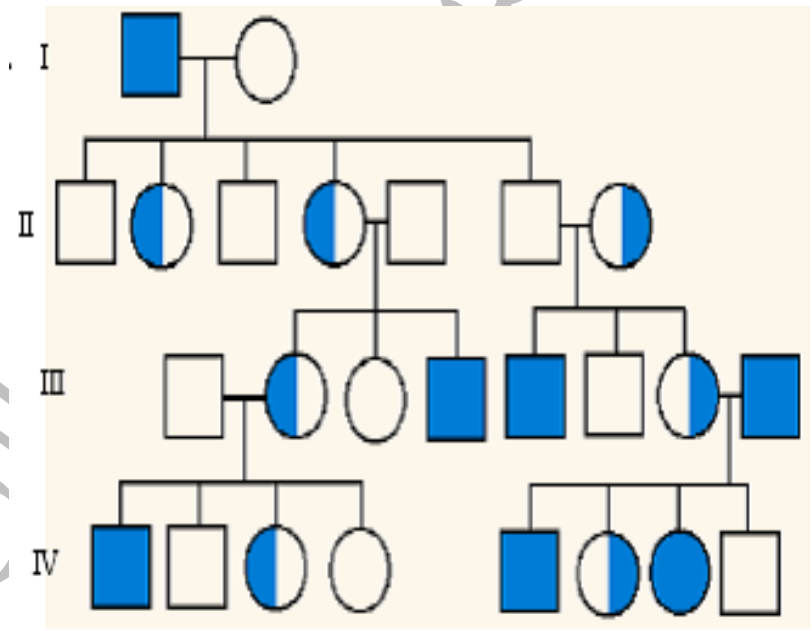
Q8: What pattern of inheritance is shown in the pedigree?

A. Autosomal dominant
B. Autosomal recessive
C. Sex linked dominant
D. Sex linked recessive



Q9: What pattern of inheritance is shown in the pedigree?

A. Autosomal dominant
B. Autosomal recessive
C. Sex linked dominant
D. Sex linked recessive



Q10: What pattern of inheritance is shown in the pedigree?

A. Autosomal dominant
B. Autosomal recessive
C. Sex linked dominant
D. Sex linked recessive

Human Genetics
Lecture 9
Dr. Abbas Hussein Mugheer

Genetic Counseling

The process of helping people understands and adapt to the medical, psychological, and familial implications of the genetic contributions to disease**.**

Genetic counseling gives information about how genetic conditions might affect you or your family. The genetic counselor or other healthcare professional will collect your personal and family health history. They can use this information to determine how likely it is that you or your family member has a genetic condition. Based on this information, the genetic counselor can help you decide whether a genetic test might be right for you or your relative.

These are eight indications for referral to genetic counseling:

1. Family history of a known or suspected genetic disorder
2. Known carrier of a genetic condition
3. Consanguinity (blood relationship of parents, first cousins, or closer)
4. Fetal structural anomaly on prenatal ultrasound
5. Abnormal screening test result either traditional serum screening or cell-free DNA screening.
6. Known teratogenic exposure
7. Recurrent pregnancy loss (3 or more first-trimester losses, stillbirth, or neonatal or fetal loss with structural anomalies)
8. Patient request for additional information regarding genetic test options

Reasons for Genetic Counseling

Based on personal and family health history, doctor can refer to genetic counseling. There are different stages in life when might be referred for genetic counseling:

1-Planning for Pregnancy: Genetic counseling before you become pregnant can address concerns about factors that might affect your baby during infancy or childhood or your ability to become pregnant, including:

a-Genetic conditions that run in your family or your partner's family

b-History of infertility, multiple miscarriages, or stillbirth

c-Previous pregnancy or child affected by a birth defect or genetic condition

2-During Pregnancy: Genetic counseling while you are pregnant can address certain tests that may be done during your pregnancy, any detected problems, or conditions that might affect your baby during infancy or childhood, including:

a-History of infertility, multiple miscarriages, or stillbirth

b-Previous pregnancy or child affected by a birth defect or genetic condition

c-Abnormal test results, such as a blood test, ultrasound, Chorionic Villus Sampling (CVS), or amniocentesis

d-Maternal infections, such as Cytomegalovirus (CMV), and other exposures such as medicines, drugs, chemicals, and x-rays

e-Genetic screening that is recommended for all pregnant women, which includes cystic fibrosis, sickle cell disease, and any conditions that run in your family or your partner's family

3-Caring for Children: Genetic counseling can address concerns if your child is showing signs and symptoms of a disorder that might be genetic, including:

a-Abnormal newborn screening results

b-Birth defects

c-Intellectual disability or developmental disabilities

d-Autism spectrum disorders (ASD)

e-Vision or hearing problems

4-Managing Your Health: Genetic counseling for adults includes specialty areas such as cardiovascular, psychiatric, and cancer. Genetic counseling can be helpful if you have symptoms of a condition or have a

family history of a condition that makes you more likely to be affected with that condition, including

a-Hereditary breast and ovarian cancer (HBOC) syndrome

b-Lynch syndrome (hereditary colorectal and other cancers)

c-Familial hypercholesterolemia

d-Muscular dystrophy and other muscle diseases

e-Inherited movement disorders such as Huntington's disease

f-Inherited blood disorders such as sickle cell disease

Following your genetic counseling session, you might decide to have genetic testing. Genetic counseling after testing can help you better understand your test results and treatment options, help you deal with emotional concerns, and refer you to other healthcare providers and advocacy and support groups.

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. Specifically, 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

There are a variety of non-invasive and invasive techniques available for prenatal diagnosis. Each of them can be applied only during specific time

periods during the pregnancy for greatest utility. The techniques employed for prenatal diagnosis include:

1-Ultrasonography

2-Amniocentesis

3-Chorionic villus sampling

4-Fetal blood cells in maternal blood

5-Maternal serum alpha-fetoprotein

6-Maternal serum beta-HCG

7-Maternal serum unconjugated estriol

8-Pregnancy-associated plasma protein A

9-Inhibin A

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. The developing embryo can first be visualized at about 6 weeks gestation. Recognition of the major internal organs and extremities to determine if any are abnormal can best be accomplished between 16 to 20 weeks gestation.

Although an ultrasound examination can be quite useful to determine the size and position of the fetus, the size and position of the placenta, the amount of amniotic fluid, and the appearance of fetal anatomy, there are limitations to this procedure. Subtle abnormalities may not be detected until later in pregnancy, or may not be detected at all. A good example of this is Down syndrome (trisomy 21) where the morphologic abnormalities are often not marked, but only subtle, such as increased nuchal translucency (the subcutaneous space between skin surface and underlying cervical spine).

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. Enough amniotic fluid is present for this to be accomplished starting about 14 weeks gestation. For prenatal diagnosis, most amniocenteses are performed between 14 and 20 weeks gestation. However, an ultrasound examination always proceeds amniocentesis in order to determine gestational age, the position of the fetus and placenta, and determine if enough amniotic fluid is present. Within the amniotic fluid are fetal cells (mostly derived from fetal skin) which can be\ grown in culture for chromosome analysis, biochemical analysis, and molecular biologic analysis.

In the third trimester of pregnancy, the amniotic fluid can be analyzed for determination of fetal lung maturity. This is important when the fetus is below 35 to 36 weeks gestation, because the lungs may not be mature enough to sustain life following birth. This is because the lungs are not producing enough surfactant. After birth, the infant could develop respiratory distress syndrome from hyaline membrane disease. The amniotic fluid can be analyzed by looking for an appropriate number of lamellar bodies. Other tests for fetal lung maturity include: fluorescence polarization (fpol), lecithin:sphingomyelin (LS) ratio, and for phosphatidyl glycerol (PG). These tests have poor positive predictive value for respiratory distress, so the decision to do amniocentesis can be made by consideration of issues around gestational age and urgency of delivery.

Risks with amniocentesis are uncommon, but include fetal loss and maternal Rh sensitization. The increased risk for fetal mortality following amniocentesis is about 0.5% above what would normally be expected. Rh negative mothers can be treated with RhoGam. Contamination of fluid from amniocentesis by maternal cells is highly unlikely. If oligohydramnios is present, then amniotic fluid is difficulk to obtain. It is sometimes possible to instill saline into the amniotic cavity and then remove fluid for analysis.

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. An alternative approach is transabdominal. The introduction of

the catheter allows sampling of cells from the placental chorionic villi. These cells can then be analyzed by a variety of techniques. The most common test employed on cells obtained by CVS is chromosome analysis to determine the karyotype of the fetus. The cells can also be grown in culture for biochemical or molecular biologic analysis. CVS can be safely performed between 9.5 and 12.5 weeks gestation.

CVS has the disadvantage of being an invasive procedure, and it has a small but significant rate of morbidity for the fetus; this loss rate is about 0.5 to 1% higher than for women undergoing amniocentesis. Rarely, CVS can be associated with limb defects in the fetus. The possibility of maternal Rh sensitization is present. There is also the possibility that maternal blood cells in the developing placenta will be sampled instead of fetal cells and confound chromosome analysis.

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. Ordinarily, only a very small number of fetal cells or cell free DNA enter the maternal circulation in this fashion (not enough to produce a positive Kleihauer-Betke test for fetal-maternal hemorrhage). The sequencing of maternal plasma cell-free DNA (cfDNA testing) can detect fetal autosomal aneuploidy, but without the risks that invasive procedures inherently have. Fluorescence in-situ hybridization (FISH) is another technique that can be applied to identify particular chromosomes of the fetal cells recovered from maternal blood and diagnose aneuploid conditions such as the trisomies and monosomy X. The problem with this technique is that it is difficult to get large amounts of fetal DNA. There may not be enough to reliably determine anomalies of the fetal karyotype or assay for other abnormalities.

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. Ordinarily, only a small amount of AFP gains access to the amniotic fluid and crosses the placenta to maternal blood. However, when there is a fetal defect in the body wall, such as a neural tube defect from failure of part of the embryologic neural tube to close, then there is a means for escape of more AFP into the amniotic fluid. Neural tube

defects include anencephaly (failure of closure at the cranial end of the neural tube) and spina bifida (failure of closure at the caudal end of the neural tube). The incidence of such defects is less than 1 per 1000 in the United States. Also, if there is an omphalocele or gastroschisis (both are defects in the fetal abdominal wall), the MSAFP will be higher.

In order for the MSAFP test to have the greatest utility, the gestational age must be known with certainty. This is because the amount of MSAFP increasses with gestational age (as the fetal liver size and the amount of AFP produced increase). Also, the race of the mother and presence of gestational diabetes are important to know, because the MSAFP can be affected by these factors. The MSAFP is typically reported as multiples of the median (MoM). The greater the MoM, the more likely a defect is present. The MSAFP has the greatest sensitivity between 16 and 18 weeks gestation, but can still be useful between 15 and 22 weeks gestation.

However, the MSAFP can be elevated for a variety of reasons which are not related to fetal neural tube or abdominal wall defects, so this test is not 100% specific. The most common cause for an elevated MSAFP is a wrong estimation of the gestational age of the fetus.

Using a combination of MSAFP screening and ultrasonography, almost all cases of anencephaly can be found, and most cases of spina bifida. Neural tube defects can be distinguished from other fetal defects (such as abdominal wall defects) by use of the acetylcholinesterase test performed on amniotic fluid obtained by amniocentesis--if the acetylcholinesterase is elevated along with MSAFP then a neural tube defect is likely. If the acetylcholinesterase is not detectable, then some other fetal defect is suggested.

NOTE: Prevention of many neural tube defects can be accomplished by supplementation of the maternal diet with just 4 mg of folic acid per day, but this vitamin supplement must be taken a month before conception and through the first trimester.

The MSAFP can also be useful in screening for Down syndrome and other trisomies. The MSAFP tends to be lower when triosmy 21 or other chromosomal abnormalities is present.

Maternal serum beta-HCG

This test is most commonly used as a test for pregnancy. Beginning about a week following conception and implantation of the developing embryo into the uterus, the trophoblast will produce enough detectable beta-HCG (the beta subunit of human chorionic gonadotropin) to diagnose pregnancy. Thus, by the time the first menstrual period is missed, the beta-HCG will virtually always be elevated enough in maternal urine to provide a positive pregnancy test. The beta-HCG can also be quantified in serum from maternal blood, and 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.

Later in pregnancy, in the middle to late second trimester, the beta-HCG can be used in conjunction with the MSAFP to screen for chromosomal abnormalities, and Down syndrome in particular. An elevated beta-HCG coupled with a decreased MSAFP suggests Down syndrome.

Very high levels of HCG suggest trophoblastic disease (molar pregnancy). The absence of a fetus on ultrasonography along with an elevated HCG suggests a hydatidiform mole. The HCG level can be used to follow up treatment for molar pregnancy to make sure that no trophoblastic disease, such as a choriocarcinoma, persists.

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. The substrate for estriol begins as dehydroepiandrosterone (DHEA) produced in the fetus. This is further metabolized in the placenta to estriol. The estriol crosses to the maternal circulation and is excreted by the maternal kidney in urine or by the maternal liver in the bile. The measurement of serial estriol levels in the third trimester will give an indication of general well-being of the fetus. If the estriol level drops, then the fetus is threatened and delivery may be necessary emergently. Estriol tends to be lower when Down syndrome is present or when there is adrenal hypoplasia with anencephaly.

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. An increased level of inhibin-A is associated with an increased risk for trisomy 21. A high inhibin-A may also be associated with risk for preterm delivery.

Pregnancy-associated plasma protein A (PAPP-A)

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