المحاضرة الثامنة / الوراثة النظري

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المرحلة :الثالثة

القسم:تقنيات المختبرات الطبية

X-linked inheritance

- In humans and other mammals, biological sex is determined by a pair of **sex chromosomes**: XY in males and XX in females.
- Genes on the X chromosome are said to be **X-linked**. X-linked genes have distinctive inheritance patterns because they are present in different numbers in females (XX) and males (XY).
- X-linked human genetic disorders are much more common in males than in females due to the X-linked inheritance pattern.

Introduction

- A human male has two **sex chromosomes**, the X and the Y. Unlike the 44 **autosomes** (non-sex chromosomes), the X and Y don't carry the same genes and aren't considered homologous.
- Instead of an X and a Y, a human female has two X chromosomes. Because sex chromosomes don't always come in homologous pairs, the genes they carry show unique, distinctive patterns of inheritance.

Sex chromosomes in humans

Human X and Y chromosomes determine the biological sex of a person, with XX specifying female and XY specifying male. Although the Y chromosome contains a small region of similarity to the X chromosome

so that they can pair during meiosis, the Y chromosome is much shorter and contains many fewer genes.

To put some numbers to it, the X chromosome has about (800-900) protein-coding genes with a wide variety of functions, while the Y chromosome has just 60−70 protein-coding genes, about half of which are active only in the testes (sperm-producing organs).

The human Y chromosome plays a key role in determining the sex of a developing embryo. This is mostly due to a gene called *SRY* ("sex-determining region of Y"). *SRY* is found on the Y chromosome and encodes a protein that turns on other genes required for male development.

- XX embryos don't have *SRY*, so they develop as female.
- XY embryos do have *SRY*, so they develop as male.

In rare cases, errors during meiosis may transfer *SRY* from the Y chromosome to the X chromosome. If an *SRY*-bearing X chromosome fertilizes a normal egg, it will produce a chromosomally female (XX) embryo that develops as a male. If an *SRY*-deficient Y chromosome fertilizes a normal egg, it will produce a chromosomally male embryo (XY) that develops as a female.

X-linked genes

When a gene being is present on the X chromosome, but not on the Y chromosome, it is said to be **X-linked**. X-linked genes have different inheritance patterns than genes on non-sex chromosomes (autosomes). That's because these genes are present in different copy numbers in males and females.

X-linked genetic disorders

The same principles we see at work in fruit flies can be applied to human genetics. In humans, the alleles for certain conditions (including some forms of color blindness, hemophilia, and muscular dystrophy) are X-linked. These diseases are much more common in men than they are in women due to their X-linked inheritance pattern.

Why is this the case? Let's explore this using an example in which a mother is heterozygous for a disease-causing allele. Women who are heterozygous for disease alleles are said to be **carriers**, and they usually don't display any symptoms themselves. Sons of these women have a 50% chance of getting the disorder, but daughters have little chance of getting the disorder (unless the father also has it), and will instead have a 50% chance of being carriers.

Why is this the case? Recessive X-linked traits appear more often in males than females because, if a male receives a "bad" allele from his mother, he has no chance of getting a "good" allele from his father (who provides a Y) to hide the bad one. Females, on the other hand, will often receive a normal allele from their fathers, preventing the disease allele from being expressed.

Hemophilia

A person with hemophilia may have severe, even life-threatening, bleeding from just a small cut.

Hemophilia is caused by a mutation in either of two genes, both of which are located on the X chromosome. Both genes encode proteins that help blood clot. Let's focus on just one of these genes, calling the functional allele .

In our example, a woman who is heterozygous for normal and hemophilia alleles (X^HX^h) has children with a man who is hemizygous for the normal form (X^HY). Both parents have normal blood clotting, but the mother is a carrier. What is the chance of their sons and daughters having hemophilia?

Punnett square showing the potential genotypes of children produced by a father with normal clotting X^HY) and a heterozygous carrier mother (X^HX^h).

- None of the daughters will have hemophilia (zero chance of the disorder). That's because, in order to have the disorder, they must get X^h allele from both their mother and their father. There is 0 chance of the daughters getting an X^h allele from their father, so their overall chance of having hemophilia is zero.
- The sons get a Y from their father instead of an X, so their only copy of the blood clotting gene comes from their mother. The mother is heterozygous, so half of the sons, on average, will get an X^h allele and have hemophilia (1/2 chance of the disorder).

X-linked recessive inheritance is a mode of inheritance in which a mutation in a gene on the X chromosome causes the phenotype to be expressed in males (who are necessarily hemizygous for the gene mutation because they have one X and one Y chromosome) and in females who are homozygous for the gene mutation, see zygosity.

X-linked inheritance means that the gene causing the trait or the disorder is located on the X chromosome. Females have two X chromosomes, while males have one X and one Y chromosome. Carrier females who have only one copy of the mutation do not usually express the phenotype, although differences in X chromosome inactivation can lead to varying

degrees of clinical expression in carrier females since some cells will express one X allele and some will express the other. The current estimate of sequenced X-linked genes is 499 and the total including vaguely defined traits is 983.

Some scholars have suggested discontinuing the terms dominant and recessive when referring to X-linked inheritance due to the multiple mechanisms that can result in the expression of X-linked traits in females, which include cell autonomous expression, skewed X-inactivation, clonal expansion, and somatic mosaicism.

Most common

The most common X-linked recessive disorders are:

- **Red-green color blindness**, a very common trait in humans and frequently used to explain X-linked disorders. Between seven and ten percent of (1-7 %) men and 0.49% to 1% of women are affected. Its commonness may be explained by its relatively benign nature. It is also known as daltonism.
- **Hemophilia A**, a blood clotting disorder caused by a mutation of the Factor VIII gene and leading to a deficiency of Factor VIII. It was once thought to be the "royal disease" found in the descendants of Queen Victoria. This is now known to have been Hemophilia B (see below).
- **Hemophilia B**, also known as **Christmas Disease**, a blood clotting disorder caused by a mutation of the Factor IX gene and leading to a deficiency of Factor IX. It is rarer than hemophilia A. As noted above, it was common among the descendants of Queen Victoria.

- **Duchenne muscular dystrophy**, which is associated with mutations in the dystrophin gene. It is characterized by rapid progression of muscle degeneration, eventually leading to loss of skeletal muscle control, respiratory failure, and death.
- **Becker's muscular dystrophy**, a milder form of Duchenne, which causes slowly progressive muscle weakness of the legs and pelvis.
- **X-linked ichthyosis**, a form of ichthyosis caused by a hereditary deficiency of the steroid sulfatase (STS) enzyme. It is fairly rare, affecting one in 2,000 to one in 6,000 males.
- **X-linked agammaglobulinemia (XLA)**, which affects the body's ability to fight infection. XLA patients do not generate mature B cells. B cells are part of the immune system and normally manufacture antibodies (also called immunoglobulins) which defends the body from infections (the humoral response). Patients with untreated XLA are prone to develop serious and even fatal infections.
- **Glucose-6-phosphate dehydrogenase deficiency**, which causes nonimmune hemolytic anemia in response to a number of causes, most commonly infection or exposure to certain medications, chemicals, or foods. Commonly known as "favism", as it can be triggered by chemicals existing naturally in broad (or fava) beans.

X-linked dominant inheritance, sometimes referred to as **X-linked dominance**, is a mode of genetic inheritance by which a dominant gene is carried on the X chromosome. As an inheritance pattern, it is less common than the X-linked recessive type. In medicine, X-linked dominant inheritance indicates that a gene responsible for a genetic disorder is located on the X chromosome, and only one copy of the allele is sufficient to cause the disorder when inherited from a parent

who has the disorder. In this case, someone who expresses an X-linked dominant allele will exhibit the disorder and be considered affected.

X-linked dominant traits do not necessarily affect males more than females (unlike X-linked recessive traits). The exact pattern of inheritance varies, depending on whether the father or the mother has the trait of interest. All fathers that are affected by an X-linked dominant disorder will have affected daughters but not affected sons. However, if the mother is also affected then sons will have a chance of being affected, depending on whether a dominant or recessive X chromosome is passed on. When the son is affected, the mother will always be affected.

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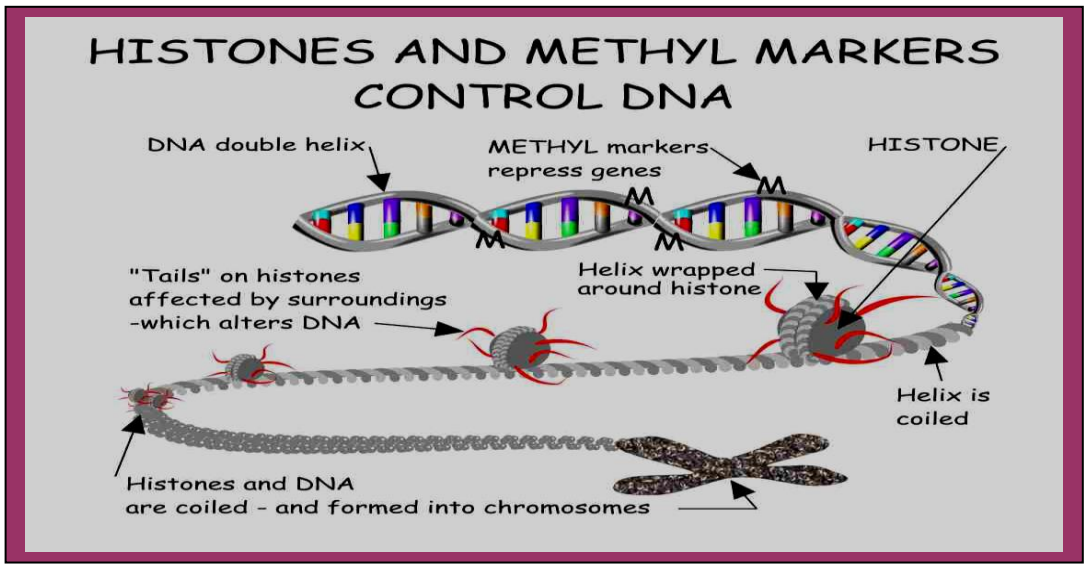
List of dominant X-linked diseases

- Vitamin D resistant rickets: X-linked hypophosphatemia
- Rett syndrome (95% of cases are due to sporadic mutations)
- Most cases of Alport syndrome
- Incontinentia pigmenti
- Giuffrè–Tsukahara syndrome
- Goltz syndrome
- X-linked dominant porphyria
- Fragile X syndrome

Cell cycle and cell division

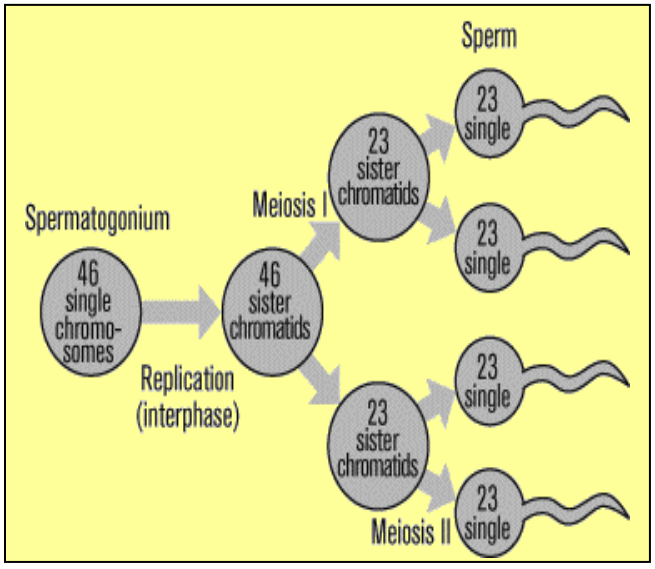
The nucleus is a membrane bound organelle that contains the genetic information in the form of chromatin, highly folded ribbon-like complexes of deoxyribonucleic acid (DNA) and a class of proteins called histones . When a cell divides, chromatin fibers are very highly folded, and become visible in the light microscope as chromosomes. During interphase (between divisions), chromatin is more extended, a form used for expression genetic information.



Cells divide to reproduce organisms, to grow, to replace damaged cells , to transfer genes from cell to cell . During development from stem to fully differentiated , cells in the body alternately divide (mitosis) and appear to be resting (interphase) the sequence of activities exhibited by cell is called cell cycle .

Types of Reproduction

1- Meiosis (sexual) : It is a type of cell division occurs in germ cell of sexually reproducing organisms . Two successive nuclear divisions designated meiosis -1 and meiosis – 2 take place , result in four daughter cells each with half number of chromosomes of parent cells . The specific type of meiosis that forms sperm is called spermatogenesis, while the formation of egg cells, or ova is called oogenesis , fertilization of an egg by sperm occurs in reproductive organs each contain half of the parent cell's chromosomes (fig.)



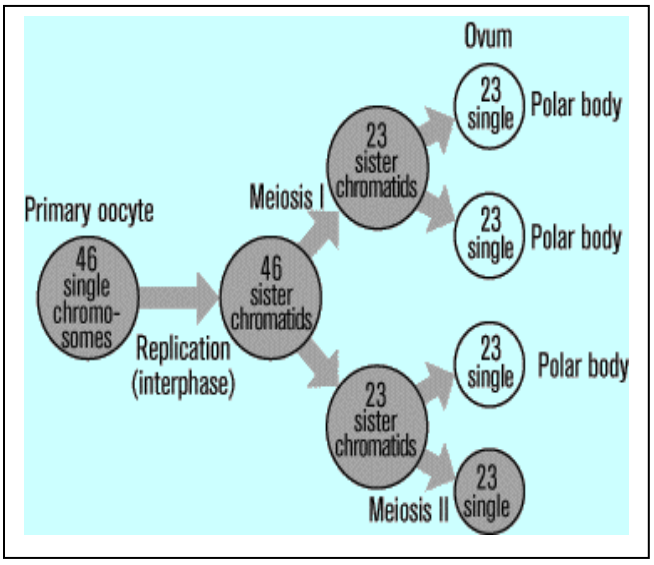


Fig. spermatogonium process **Fig. Oogenesis process**

2- Mitosis (asexual) : is a type of cell division which occurs in somatic cell by which the cell number is multiplied , any cell undergoes mitosis gives rise to 2 identical daughter cells , each daughter cell resembles the mother cell both having the same chromosome number.

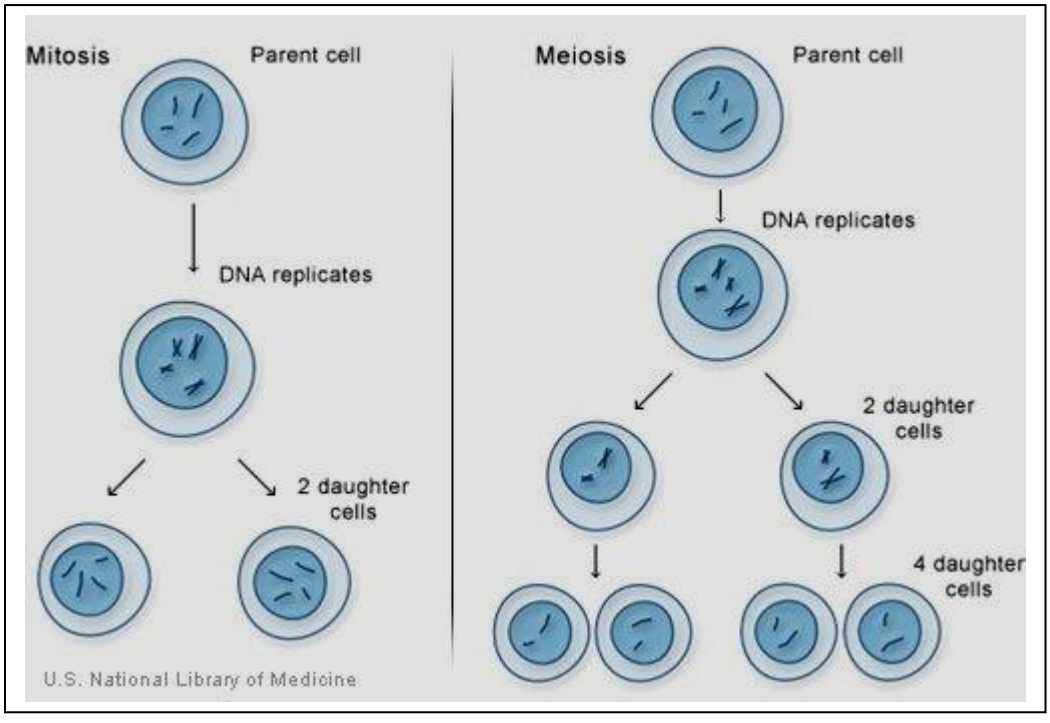


Fig. Mitosis and meiosis

Cell cycle

Cell cycle include four phases namely G1 , S , G2 and mitosis (M- phase) which occur in succession as fellow :

Interphase

Interphase is a period between two successive nuclear divisions, during which the chromosomes are diffuse , nuclear envelope is intact , the cell is most active in transcribing and translating genetic information . If the cell is going to divide, it replicates its DNA during interphase , interphase consists of the G1, S, and G2 phases

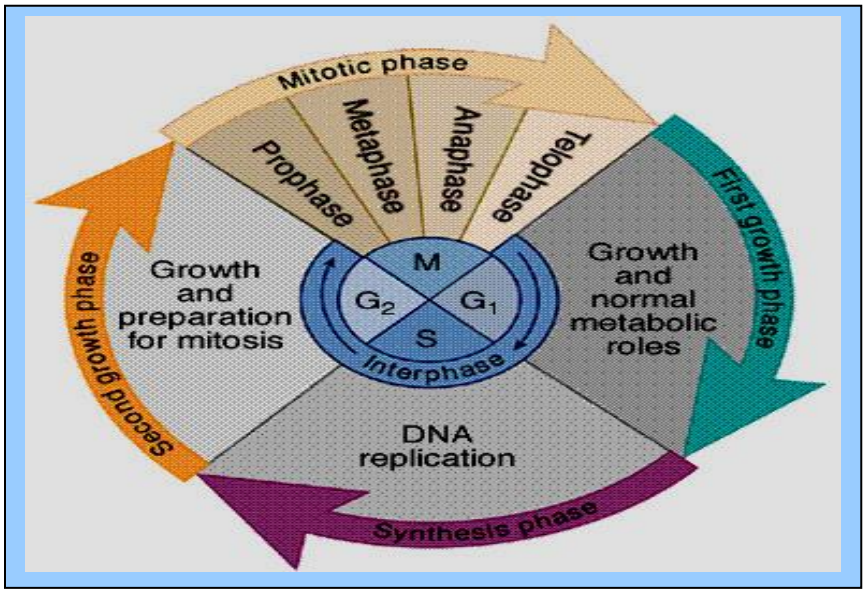


Fig. Cell cycle
(interphase and mitotic phase)

1- First growth phase

It is a period of rapid RNA and protein synthesis , the daughter cells resulting from mitosis usually engaged in metabolism and growth . The genes being coding messages for the production of new protoplasm that lead to increase in cell mass .This stage is devoted to cell growth and chemical preparation for DNA synthesis during G1 phase chromosomes are completely dispersed .

2- Synthesis phase (S)

In the S phase of interphase both DNA and histones synthesis, the nucleus replicates its chromatin. Thus, the amount of DNA doubles. From this point until the centromer divides , each chromosome consist of two chromatids.

3- Second growth phase

After the completion of DNA duplication, cell enters a second growth phase called G2 .It is a period between the end of DNA synthesis and beginning of prophase , In this period all the genes are function fully again and the rate of protein synthesis is high .

The relative lengths of these phases differ in all organisms for example a human cell grown in tissue culture the mitotic cycle is about 18 hr.(G1 :8hr. , S:6hr. , G2 :4hr.) and mitosis (M- phase) consume about one hour the whole cycle is 19hr.

Cell division

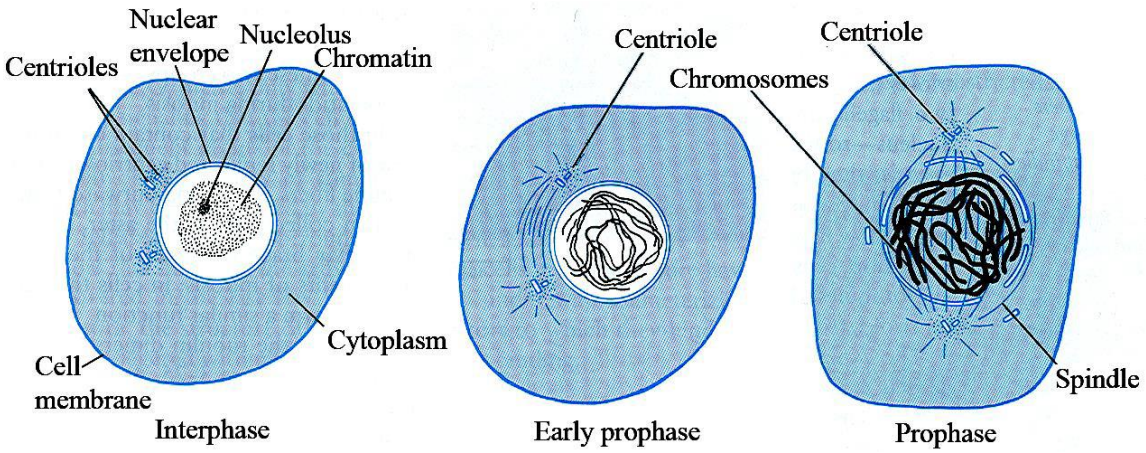
mitosis phase

It occurs during the mitotic phase (M- phase) , it is divided into four phases:

1- Prophase

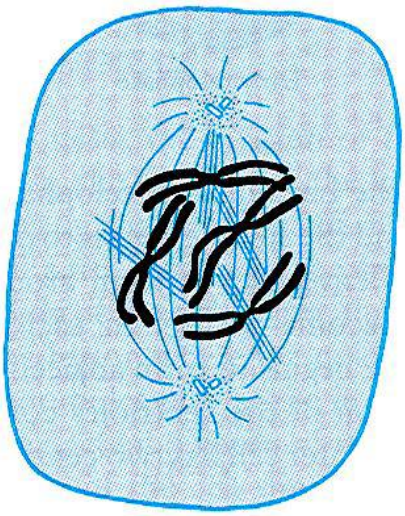
Prophase is the first phase of mitosis ,it begins when chromosomes thread like structure .The nucleoli and nuclear envelope begin to break up and the two centriole pairs move apart. By the end of this phase ,the centriole pairs are at opposite poles of the cell. The centrioles radiate an array of microtubules called asters (little star) between the centrioles ,microtubules form a spindle fibers that extend from pole to pole .The spindle , centrioles and microtubules are collectively called the mitotic spindle or mitotic apparatus.

Spindle : an array of microtubules stretches from pole to pole of a dividing nucleus and pull the chromosomes during mitosis and in both division of meiosis .

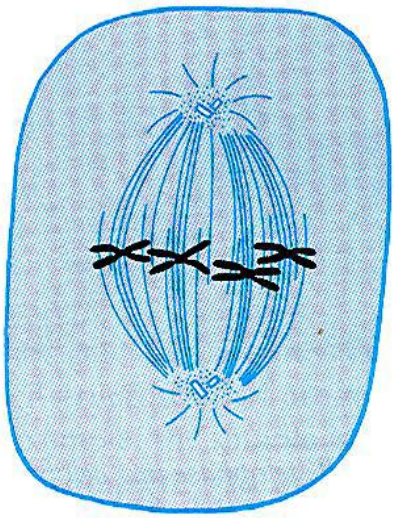


2- Metaphase

At metaphase of a nuclear division, the centromeres of the highly condensed chromosomes are all lying on a plane (equatorial plane) perpendicular to a line connecting the spindle poles. Metaphase ends abruptly as the centromeres divide and anaphase begins.



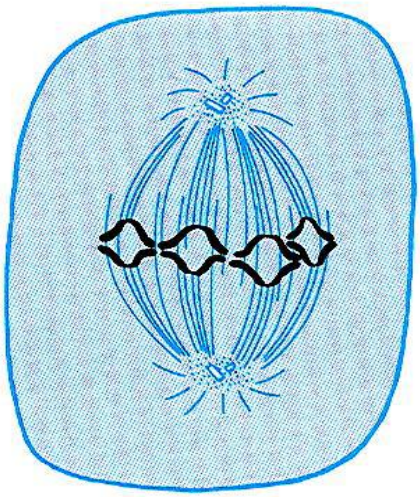
Early metaphase



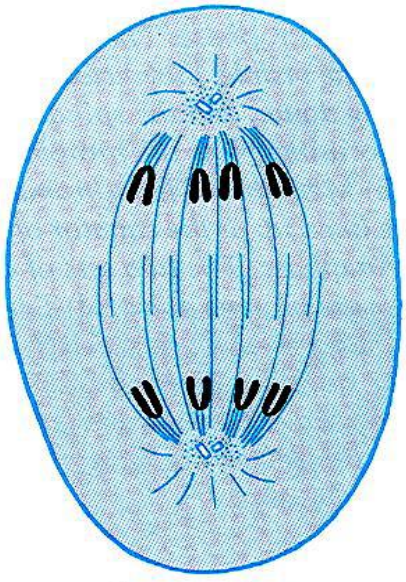
Metaphase

3- Anaphase

During this phase which the shortening of the microtubules in the mitotic spindle pulls each daughter chromosome apart from its copy and toward its respective pole. Anaphase ends when all the daughter chromosomes have moved at the poles of the cell. Each pole now has a complete , identical set of chromosomes .



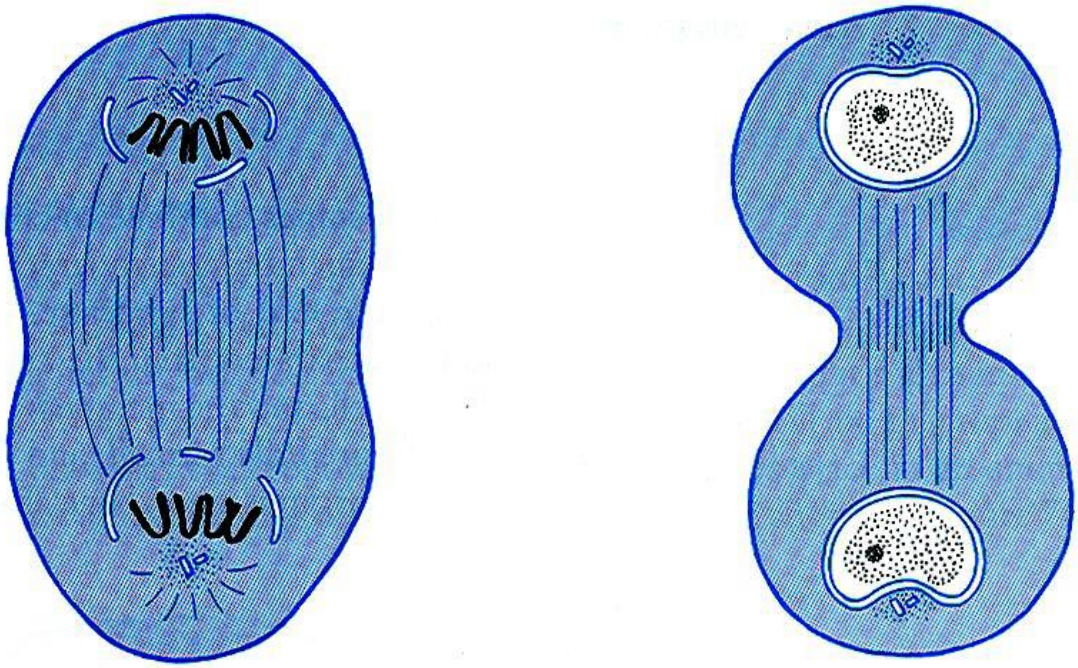
Early anaphase



Late anaphase

4- Telophase

In telophase of mitosis, the chromosomes become diffuse, the spindle breaks down then nuclear envelopes form and nucleoli appear in the daughter nuclei. Telophaes is the final stage of a nuclear division.



Early telophase

Late telophase

Cytokinesis

Division of the cytoplasm is called cytokinesis. In animal cells, cytokinesis often consist of the pinching apart of the two daughter cells by the contraction of a ring of microfilaments.

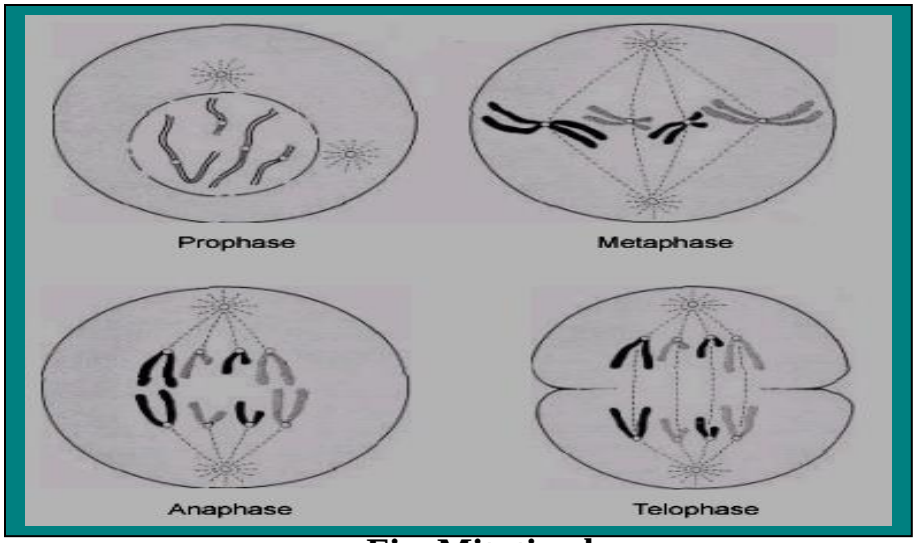


Fig. Mitotic phases

المحاضرة التاسعة / الوراثة النظري

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Genetic Basis of Cancer

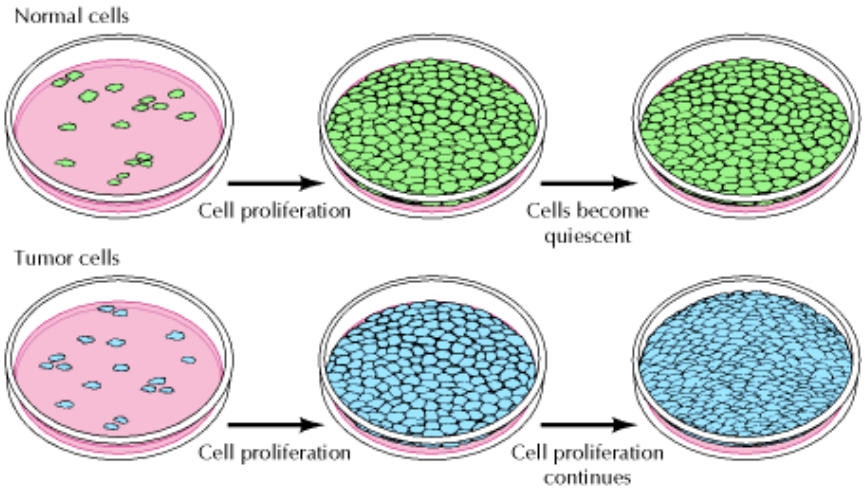
Properties of Cancer cells Cancer cells display abnormalities in the mechanism that regulate **cell proliferation, differentiation and survival**

Targets of genetic damage in carcinogenesis (Normal growth regulatory genes)
1- The growth promoting genes; Protooncogenes Mutant Protooncogenes: Oncogenes Dominant effect
2- The growth inhibiting genes; Tumor-supressor genes Recessive effect

Properties of Cancer cells

- Uncontrolled cell division, Cancer cells are not sensitive to

Density dependent inhibition of cell proliferation



Normal cells proliferate in culture until they reach a finite cell density, at which point they become quiescent. Tumor cells, however, continue to proliferate independent of cell density.

- **Reduced requirements for Growth factors :**

1. some produce GFs; autostimulation autocrine GF production

2. Abnormalities in intracellular signalling pathways i.e.unregulated activity of GF receptors or other proteins (i.e.Ras)

- Cancer cells are **insensitive to contact inhibition**
  1. continue moving after contact with their neighbors.

  2. migrate over adjacent cells, growing multilayered patterns

- **Cancer cells loss anchorage dependence**

1. less adhesive than normal cells

2. less regulated by cell-cel, cell-matrix interactions

3. have spherical shape (changes in cytoskeleton)

- **Secrete proteases** (i.e collagenase)
  1. digest extracellular matrix components i.e.basal lamina
  2. contributes to the ability to invade and metastasize
- **Promote formation of new blood vessels (angiogenesis)**
- **Fail to undergo apoptosis (immortal)**
  1. Normal cells divide 50 times in culture.
  2. Cancer cell divides indefinitely

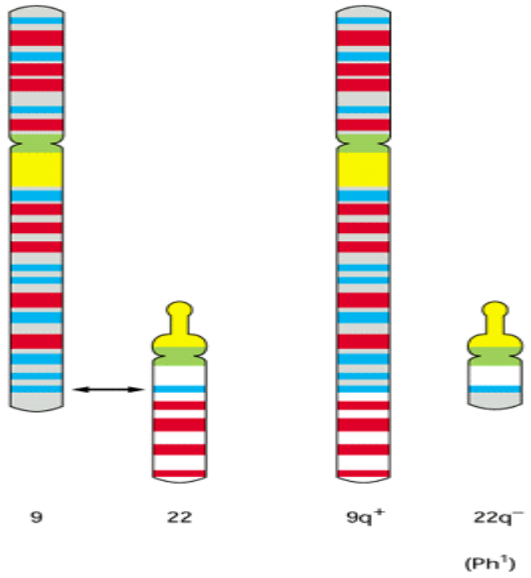
  - **Metastasis**
    1.Enter blood circulation
    2.Migrate to distant regions
    3.Produce secondary tumors
    4.The **DNA repair genes**

Mechanisms which convert a proto-oncogene into an oncogene

1. Changes in the structure of **proto-oncogenes (**point mutation ,translocation, deletion)
2. Abnormal gene product (i.e.Translocation; Philadelphia chromosome (chronic myelogenous leukemia.
3. Activation **by gene amplification.**
4. Normal product is overexpressed (N-myc amplification (700 times increase) in neuroblastoma

5. Oncogene activation by translocation (Philedelphia chromosome in chronic myelogenous leukemia) between Chromosome 9 (abl) and Chromosome 22(bcr) , another example Burkitt lenfoma between Chromosome 8 (c-myc) and Chromosome 14 immunoglobin heavy chain gene

Oncogene activation by chromosome translocation (chronic myelogenous leukemia)



•Philedelphia chromosome

Oncogenes

Growth Factor Genes

□c-sis (PDGF heavy chain) , v-sis mutant astrositoma,osteosarcoma.

(PDGF expression) Autostimulation GF receptors

□erbB ; EGF receptor (Breast carcinoma)

Intracellular signal transduction proteins

□Ras (GTP binding protein) mutant in colon Ca, pancreas Ca

Nuclear Regulatory Proteins

□Myc,Jun,Fos

p53 (Tumor supressor gene)

1- Safety device in G1 check point

2- In the presence of DNA damage p53 increase and stop cell division

3- Allow time to repair DNA

4- Most frequent mutation in human cancers

5- İncrease genetic instability

Retinoblastoma (Rb) gene

1- İnherited childhood eye tumor
2- Rb protein is phosphorylated by cdk4,6/cyclin D
3- Loss of function results in tumor development

Wilms Tumor Gene (WT) (Kidney Tumor)
Transcription factor expressed in Fetal Kidney
Mammary cancer
–BRCA1

–BRCA2

Causes of genetic damage (mutation)
1- **Acquired mutations**
Environmental agents
a-***Carcinogenic chemicals***
Tobacco smoke (cause of 80 to 90 % of lung cancers)

smoking is responsible for ~ 1/3 of all cancer deaths
Aflatoxin (A potent liver carcinogen produced by some molds that contaminate improperly stored grains etc.)
b- ***Radiation***
solar ultraviolet radiation major cause of skin cancer
c- ***Viruses***
Tumor viruses:
Hepatitis B virus; liver cancer)

100 fold increased risk of liver cancer)
□papilloma virus; cervical cancer

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استاذ المادة: م د صابرين هادي
المرحلة : الثالثة
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Chromosome structure, morphology, number and types - Karyotype and Idiogram

A chromosome is a structure that occurs within cells and that contains the cell's genetic material. That genetic material, which determines how an organism develops, is a molecule of deoxyribonucleic acid (DNA). A molecule of DNA is a very long, coiled structure that contains many identifiable subunits known as genes. In prokaryotes, or cells without a nucleus, the chromosome is merely a circle of DNA. In eukaryotes, or cells with a distinct nucleus, chromosomes are much more complex in structure.

Historical background

The terms chromosome and gene were used long before biologists really understood what these structures were. When the Austrian monk and biologist Gregor Mendel (1822–1884) developed the basic ideas of heredity, he assumed that genetic traits were somehow transmitted from parents to offspring in some kind of tiny "package." That package was later given the name "gene." When the term was first suggested, no one had any idea as to what a gene might look like. The term was used simply to convey the idea that traits are transmitted from one generation to the next in certain discrete units.

The term "chromosome" was first suggested in 1888 by the German anatomist Heinrich Wilhelm Gottfried von Waldeyer-Hartz (1836–1921). Waldeyer-Hartz used the term to describe certain structures that form during the process of cell division (reproduction).

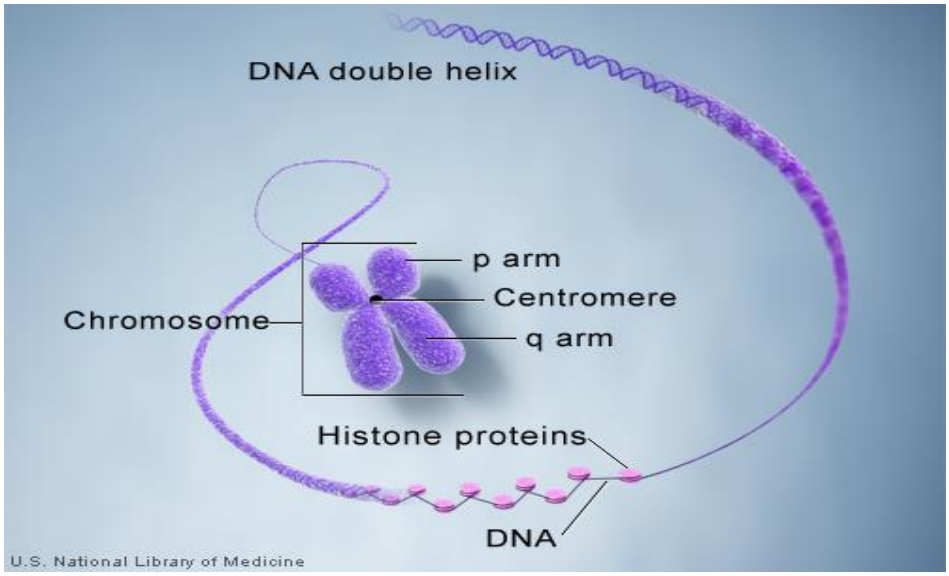
One of the greatest breakthroughs in the history of biology occurred in 1953 when American biologist James Watson and English chemist Francis Crick discovered the chemical structure of a class of compounds known as deoxyribonucleic acids (DNA). The Watson and Crick discovery made it possible to express biological concepts (such as the gene) and structures (such as the chromosome) in concrete chemical terms.

The structure of chromosomes and genes

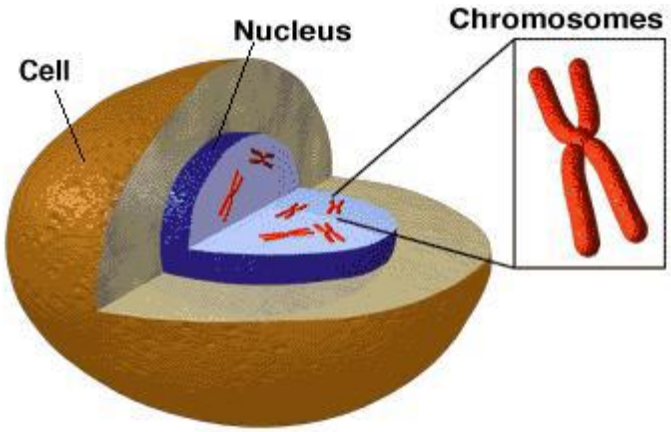
A chromosome is an organized structure of DNA and protein that is found in cells. A chromosome is a single piece of coiled DNA containing many genes, regulatory elements and other nucleotide sequences. Chromosomes also contain DNA-bound proteins, which serve to package the DNA and control its functions. The word *chromosome* comes from the Greek chroma - color and soma - body due to their property of being very strongly stained by particular dyes. Chromosomes vary widely between different organisms. The DNA molecule may be circular or linear, and can be composed of 10,000 to 1,000,000,000 nucleotides in a long chain. Typically eukaryotic cells (cells with nuclei) have large linear chromosomes and prokaryotic cells (cells without defined nuclei) have smaller circular chromosomes, although there are many exceptions to this rule.

Today we know that a chromosome contains a single molecule of DNA along with several kinds of proteins. A molecule of DNA, in turn, consists of thousands and thousands of subunits, known as nucleotides, joined to each other in very long chains. A single molecule of DNA within a chromosome may be as long as 8.5 centimeters (2 meter). To fit within a chromosome, the DNA molecule has to be twisted and folded into a very complex shape.

Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or “arms.” The short arm of the chromosome is labeled the “p arm.” The long arm of the chromosome is labeled the “q arm.” The location of the centromere on each chromosome gives the chromosome its characteristic shape, and can be used to help describe the location of specific genes.



The arrangement of packets of genetic information in a chromosome is as follows:



Furthermore, cells may contain more than one type of chromosome; for example, mitochondria in most eukaryotes and chloroplasts in plants have their own small chromosomes. The following are the different types of chromosomes

Viral Chromosomes

The chromosomes of viruses are called viral chromosomes. They occur singly in a viral species and chemically may contain either DNA or RNA. The DNA containing viral chromosomes may be either of linear shape (e.g., T2, T3, T4, T5, bacteriophages) or circular shape (e.g., most animal viruses and certain bacteriophages). The RNA containing viral chromosomes are composed of a linear, single-stranded RNA molecule and occur in some animal viruses (e.g., poliomyelitis virus, influenza virus, etc.); most plant viruses, (e.g., tobacco mosaic virus, TMV) and some bacteriophages. Both types of viral chromosomes are either tightly packed within the capsids of mature virus particles (virons) or occur freely inside the host cell.

Prokaryotic Chromosomes

The prokaryotes usually consists of a single giant and circular chromosome in each of their nucloids. Each prokaryotic chromosome consists of a single circular, double-stranded DNA molecule; but has no protein and RNA around the DNA molecule like eukaryotes. Different prokaryotic species have different sizes of chromosome.

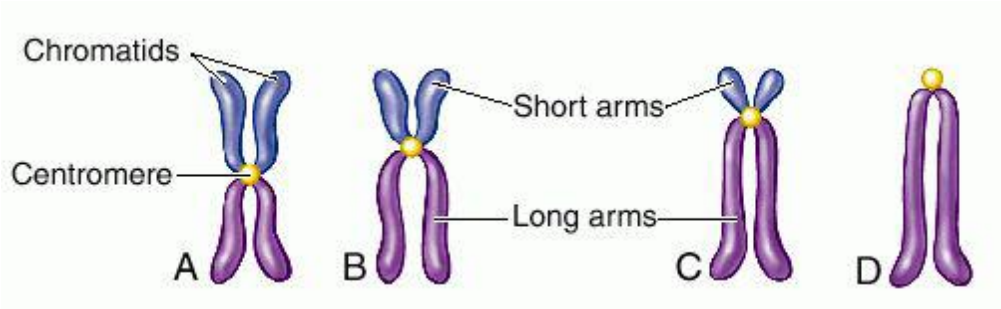
Eukaryotic Chromosomes

The eukaryotic chromosomes differ from the prokaryotic chromosomes in morphology, chemical composition and molecular structure. The eukaryotes (plants and animals) usually contain much more genetic informations than the viruses and prokaryotes, therefore, contain a great amount of genetic material, DNA molecule which here may not occur as a single unit, but, as many units called chromosomes. Different species of eukaryotes have different but always constant and characteristic number of chromosomes. In eukaryotes, nuclear chromosomes are packaged by proteins into a condensed structure called chromatin. This allows the very long DNA molecules to fit into the cell nucleus. The shape of the eukaryotic chromosomes is changeable from phase to phase in the continuous process of the cell growth and cell division. Chromosomes are the essential unit for cellular division and must be replicated, divided, and passed successfully to their daughter cells so as to ensure the genetic diversity and survival of their progeny. They are thin, coiled, elastic, contractile thread-like structures during the interphase (when no division of cell occurs) and are called chromatin threads which under low magnification look like a

compact stainable mass, often called as chromatin substance or material. During metaphase stage of mitosis and prophase of meiosis, these chromatin threads become highly coiled and folded to form compact and individually distinct ribbon-shaped chromosomes. These chromosomes contain a clear zone called kinetochore or centromere along their length. Eukaryotes (cells with nuclei such as plants, yeast, and animals) possess multiple large linear chromosomes contained in the cell's nucleus. Each chromosome has one centromere, with one or two arms projecting from the centromere, although, under most circumstances, these arms are not visible as such. In addition, most eukaryotes have a small circular mitochondrial genome, and some eukaryotes may have additional small circular or linear cytoplasmic chromosomes.

The number and position of centromeres is variable, but is definite in a specific chromosome of all the cells and in all the individuals of the same species. The centromere has small granules or spherules and divides the chromosomes into two or more equal or unequal chromosomal arms.

According to the position of the centromere, the eukaryotic chromosomes may be rod-shaped (telocentric and acrocentric), J-shaped (submetacentric) and V-shaped (metacentric) During the cell divisions the microtubules of the spindle are get attached with the chromosomal centromeres and move them towards the opposite poles of cell. Beside centromere, the chromosomes may bear terminal unipolar segments called telomeres. Certain chromosomes contain an additional specialized segment, the nucleolus organizer, which is associated with the nucleolus.



Position of the centromere in *(A)* metacentric; *(B)* submetacentric; *(C)* acrocentric; and *(D)* telocentric chromosomes

In the nuclear chromosomes of eukaryotes, the uncondensed DNA exists in a semi-ordered structure, where it is wrapped around histones (structural proteins), forming a composite material called chromatin. Chromatin is the complex of DNA and protein found in the eukaryotic nucleus which packages chromosomes. The structure of chromatin varies significantly between different stages of the cell cycle, according to the requirements of the DNA.

Interphase chromatin

During interphase (the period of the cell cycle where the cell is not dividing), two types of chromatin can be distinguished. The density of the chromatin that makes up each chromosome (that is, how tightly it is packed) varies along the length of the chromosome.

dense regions are called heterochromatin

less dense regions are called euchromatin .

- Euchromatin, which consists of DNA that is active, e.g., being expressed as protein.
- Heterochromatin, which consists of mostly inactive DNA. It seems to serve structural purposes during the chromosomal stages. Heterochromatin can be further distinguished into two types:
  - Constitutive heterochromatin, which is never expressed. It is located around the centromere and usually contains repetitive sequences.
  - Facultative heterochromatin, which is sometimes expressed.

Diploids and Haploids

In contrast to prokaryotes, most eukaryote are diploids, i.e., each somatic cell of them contains one set of chromosomes inherited from the maternal (female) parent and a comparable set of chromosomes (called homologous chromosomes) from the paternal (male) parent. The number of chromosomes in a dual set of a diploid somatic cell is called the diploid number (2n). The sex cells (sperms and ova) of a diploid eukaryote cell contain half the number of chromosomal sets found in the somatic cells and are known as haploid (n) cells. A haploid set of chromosome is also called genome.

Chemical Structure of Chromosomes

Chemically, the eukaryotic chromosomes are composed of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), histone and non-histone proteins and certain metallic ions. The histone proteins have basic properties and have significant role in controlling or regulating the functions of chromosomal DNA. The non-histone proteins are mostly acidic and have been considered more important than histones as regulatory molecules. Some non-histone proteins also have enzymatic activities. The most important enzymatic proteins of chromosomes are phosphoproteins, DNA polymerase, RNA-polymerase, DPN-pyropbosphorylase, and nucleoside triphosphatase. The metal ions as Ca+ and Mg+ are supposed to maintain the oragnization of chromosomes intact.

Material of Chromosomes

The chromatin material of the eukaryotic chromosomes according to its percentage of DNA, RNA and proteins and consequently due to its, staining property has been classified into following by classical cytologists:

1. Euchromatin

The euchromatin is the extended form of chromatin and it forms the major, portion of chromosomes. The euchromatin has special affinity for basic stains and is genetically active because its component DNA molecule synthesizes RNA molecules only in the extended form of chromatin.

2. Heterochromatin

The heterochromatin is a condensed intercoiled state of chromatin, containing two to three times more DNA than euchromatin. However, it is genetically inert as it does not direct synthesize RNA (i.e., transcription) and protein and is often replicated at a different time from the rest of the DNA.

Recent molecular biological studies have identified three kinds of heterochromatins, namely constitutive, facultative and condensed heterochromatin. The constitutive heterochromatin is present at all times and in the nuclei of virtually all the cells of an organism. The facultative heterochromatin reflect the existence of a regulatory device designed to adjust the "dosages" of certain genes in the nucleus.
The condensed heterochromatin is deeply staining tightly coiled chromatin which does not resemble with two other kinds of chromatin, has some specific role in gene regulation and is found in many interphase nuclei.

Kinds of Chromosomes

The eukaryotic chromosomes have been classified into autosomes and sex chromosomes. The autosomes have nothing to do with the determination of sex and exceed in number than sex chromosomes. The sex chromosomes determine the sex of their bearer. They are usually two in number and are usually of two kinds: X chromosomes and Y chromosomes.

Genetic Significance of Chromosomes

The chromosomes are considered as the organs of heredity because of following reasons: (i) They form the only link between two generations.

(ii) A diploid chromosome set consists of two morphologically similar (except the X and Y sex chromosomes) sets, one is derived from the mother and another from the father at fertilization.
(iii) The genetic material, DNA or RNA is localized in the chromosome and its contents are relatively constant from one generation to the next.
(iv) The chromosomes maintain and replicate the genetic informations contained in their DNA molecule and this information is transcribed at the right time in proper

sequence into the specific types of RNA molecules which directs the synthesis of different types of proteins to form a body form like the parents.

KARYOTYPE

A karyotype is the characteristic chromosome complement of a eukaryote species. The preparation and study of karyotypes is part of cytogenetics. The basic number of chromosomes in the somatic cells of an individual or a species is called the somatic number and is designated 2n. Thus, in humans 2n=46. In the germ-line (the sex cells) the chromosome number is n (humans: n=23). So, in normal diploid organisms, autosomal chromosomes are present in two copies. There may, or may not, be sex chromosomes. Polyploid cells have multiple copies of chromosomes and haploid cells have single copies. The study of whole sets of chromosomes is sometimes known as karyology. The chromosomes are depicted (by rearranging a microphotograph) in a standard format known as a karyogram or idiogram: in pairs, ordered by size and position of centromere for chromosomes of the same size. Karyotypes can be used for many purposes; such as, to study

chromosomal aberrations, cellular function, taxonomic relationships, and to gather information about past evolutionary events.

Idiogram

Staining

The study of karyotypes is made possible by staining. Usually, a suitable dye is applied after cells have been arrested during cell division by a solution of colchicine. For humans, white blood cells are used most frequently because they are easily induced to divide and grow in tissue culture. Sometimes observations may be made on non-dividing (interphase) cells. The sex of an unborn fetus can be determined by observation of interphase cells (see amniotic centesis and Barr body).

Most (but not all) species have a standard karyotype. The normal human karyotypes contain 22 pairs of autosomal chromosomes and one pair of sex chromosomes. Normal karyotypes for females contain two X chromosomes and are denoted 46, XX; males have both an X and a Y chromosome denoted 46,XY. Any variation from the standard karyotype may lead to developmental abnormalities.

Six different characteristics of karyotypes are usually observed and compared:

1. differences in absolute sizes of chromosomes. Chromosomes can vary in absolute size by as much as twenty-fold between genera of the same family: *Lotus tenuis* and

Vicia faba (legumes), both have six pairs of chromosomes (n=6) yet *V. faba* chromosomes are many times larger. This feature probably reflects different amounts of DNA duplication.

2. differences in the position of centromeres. This is brought about by translocations.

3. differences in relative size of chromosomes can only be caused by segmental interchange of unequal lengths.

4. differences in basic number of chromosomes may occur due to successive unequal translocations which finally remove all the essential genetic material from a chromosome, permitting its loss without penalty to the organism (the dislocation hypothesis). Humans have one pair fewer chromosomes than the great apes, but the genes have been mostly translocated (added) to other chromosomes.

5. differences in number and position of satellites, which (when they occur) are small bodies attached to a chromosome by a thin thread.

6. differences in degree and distribution of heterochromatic regions. Heterochromatin stains darker than euchromatin, indicating tighter packing, and mainly consists of genetically inactive repetitive DNA sequences.

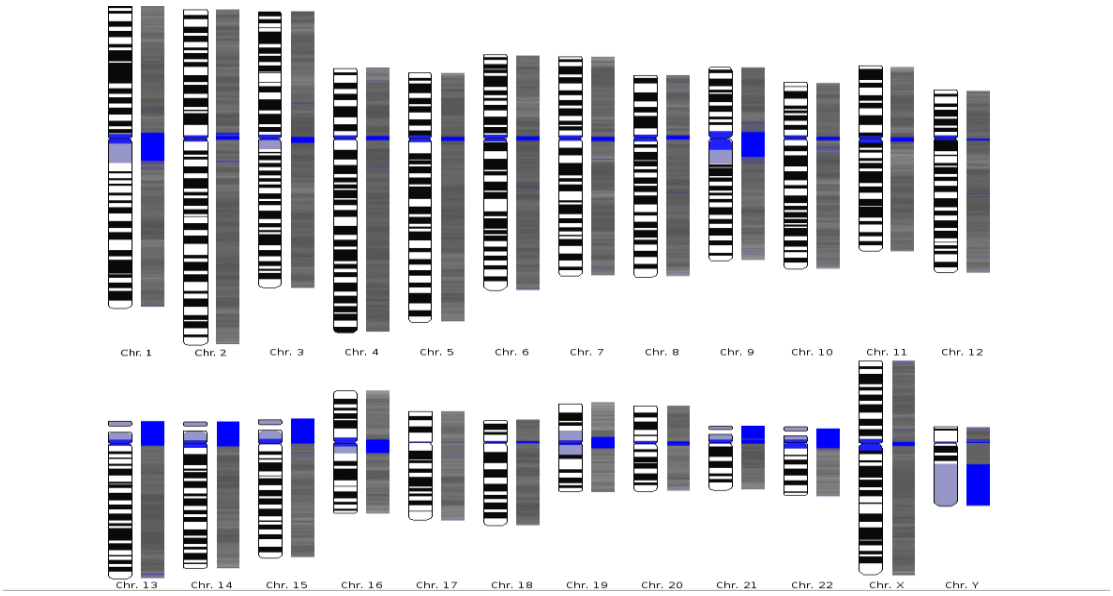
A full account of a karyotype may therefore include the number, type, shape and banding of the chromosomes, as well as other cytogenetic information.

Variation is often found:

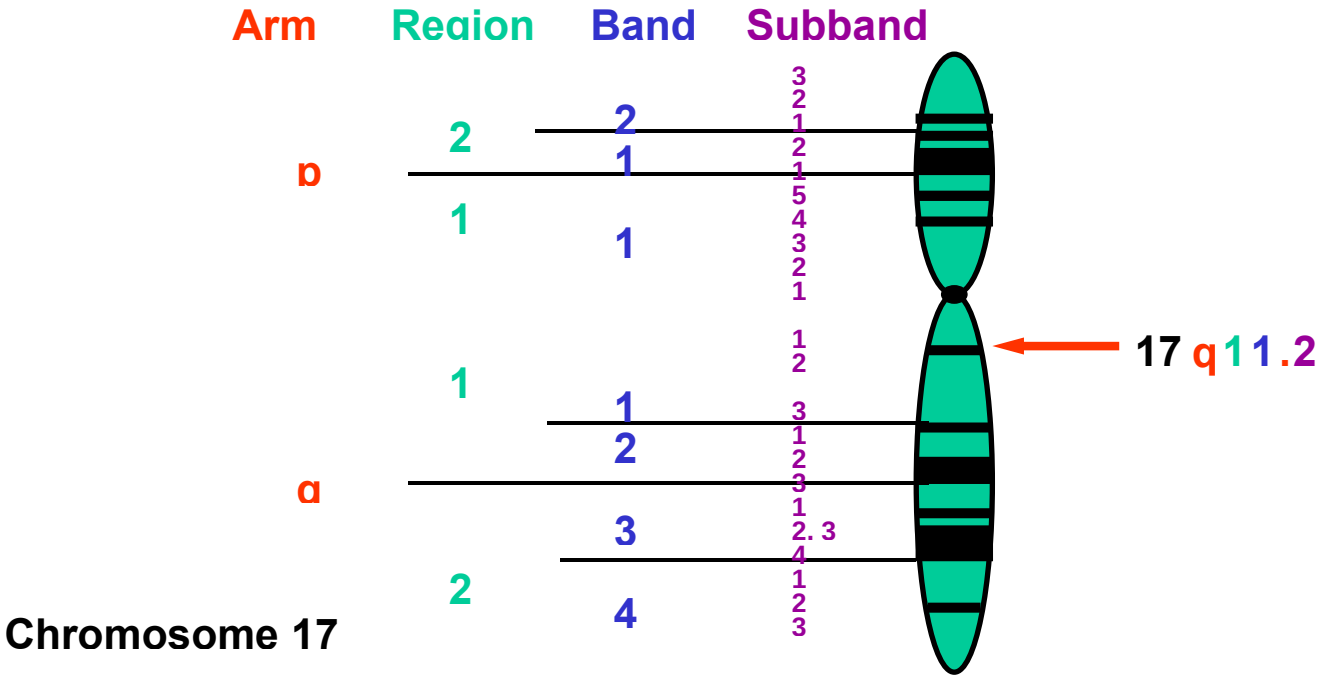
1. between the sexes
2. between the germ-line and soma (between gametes and the rest of the body)
3. between members of a population (chromosome polymorphism)
4. geographical variation between races
5.mosaics or otherwise abnormal individuals

IDEOGRAMS

Ideograms are a schematic representation of chromosomes. They show the relative size of the chromosomes and their banding patterns. A banding pattern appears when a tightly coiled chromosome is stained with specific chemical solutions and then viewed under a microscope. Some parts of the chromosome are stained (G-bands) while others refuse to adopt the dye (R-bands). The resulting alternating stained parts form a characteristic banding pattern which can be used to identify a chromosome. The bands can also be used to describe the location of genes or interspersed elements on a chromosome.



Defining Chromosomal Location



القسم:تقنيات التحليلات المرضية

المادة : الوراثة الطبية نظري

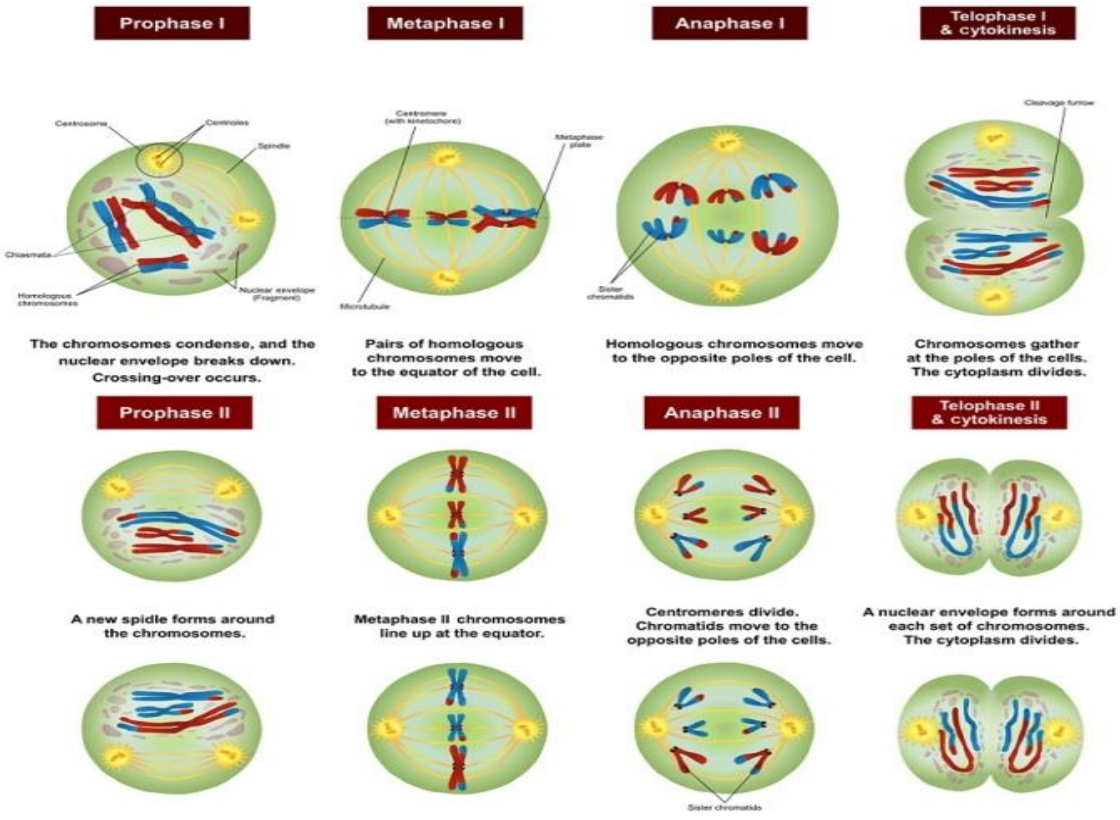
المحاضرة: الثانية

المرحلة : الثالثة

استاذة المادة: م د صابرين هادي

Meiosis

Meiosis is the form of eukaryotic cell division that produces **haploid** sex cells or gametes (which contain a single copy of each chromosome) from **diploid** cells (which contain two copies of each chromosome). The process takes the form of one DNA replication followed by two successive nuclear and cellular divisions (Meiosis I and Meiosis II). As in mitosis, meiosis is preceded by a process of DNA replication that converts each chromosome into two sister chromatids



Prophase I

Prophase I, the first step in meiosis I, is similar to prophase in mitosis in that the chromosomes condense and move towards the middle of the cell. The nuclear envelope degrades, which allows the microtubules originating from the centrioles on either side of the cell to attach to the kinetochores in the centromeres of each

chromosome. Unlike in mitosis, the chromosomes pair with their homologous partner. This can be seen in the red and blue chromosomes that pair together in the diagram. This step does not take place in mitosis.

Metaphase I

In metaphase I of meiosis I, the homologous pairs of chromosomes line up on the metaphase plate, near the center of the cell. This step is referred to as a reductional division. The homologous chromosomes that contain the two different alleles for each gene, are lined up to be separated. As seen in the diagram above, while the chromosomes line up on the metaphase plate with their homologous pair, there is no order upon which side the maternal or paternal chromosomes line up. This process is the molecular reason behind the law of segregation.

The law of segregation tells us that each allele has the same chance at being passed on to offspring. In metaphase I of meiosis, the alleles are separated, allowing for this phenomena to happen. In meiosis II, they will be separated into individual gametes. In mitosis, all the chromosomes line up on their centromeres, and the sister chromatids of each chromosome separate into new cells. The homologous pairs do not pair up in mitosis, and each is split in half to leave the new cells with 2 different alleles for each gene. Even if these alleles are the same allele, they came from a maternal and paternal source. In meiosis, the lining up of homologous chromosomes leaves 2 alleles in the final cells, but they are on sister chromatids and are clones of the same source of DNA.

Also during metaphase I, the homologous chromosomes can swap parts of themselves that are the same parts of the chromosome. This is called crossing-over and is responsible for the other law of genetics, the law of independent assortment. This law states that traits are inherited independently of each other. For traits on different chromosomes, this is certainly true all of the time. For traits on the same chromosome, it makes it possible for the maternal and paternal DNA to recombine, allowing traits to be inherited in an almost infinite number of ways.

Anaphase I

Much like anaphase of mitosis, the chromosomes are now pulled towards the centrioles at each side of the cell. However, the centrosomes holding the sister chromatids together do not dissolve in anaphase I of meiosis, meaning that only homologous chromosomes are separated, not sister chromatids.

Telophase I

In telophase I, the chromosomes are pulled completely apart and new nuclear envelopes form. The plasm membrane is separated by cytokinesis and two new cells are effectively formed.

Results of Meiosis I

Two new cells, each haploid in their DNA, but with 2 copies, are the result of meiosis I. Again, althgough there are 2 alleles for each gene, they are on sister chromatid copies of each other. These are therefore considered haploid cells. These cells take a short rest before entering the second division of meiosis, meiosis II.

Phases of Meiosis II

Prophase II

Prophase II resembles prophase I. The nuclear envelopes disappears and centrioles are formed. Microtubules extend across the cell to connect to the kinetochores of individual chromatids, connected by centromeres. The chromosomes begin to get pulled toward the metaphase plate.

Metaphase II

Now resembling mitosis, the chromosomes line up with their centromeres on the metaphase plate. One sister chromatid is on each side of the metaphase plate. At this stage, the centromeres are still attached by the protein cohesin.

Anaphase II

The sister chromatids separate. They are now called sister chromosomes, and are pulled toward the centrioles. This separation marks the final division of the DNA. Unlike the first division, this division is known as an equational division, because

each cell ends up with the same quantity of chromosomes as when the division started, but with no copies.

Telophase II

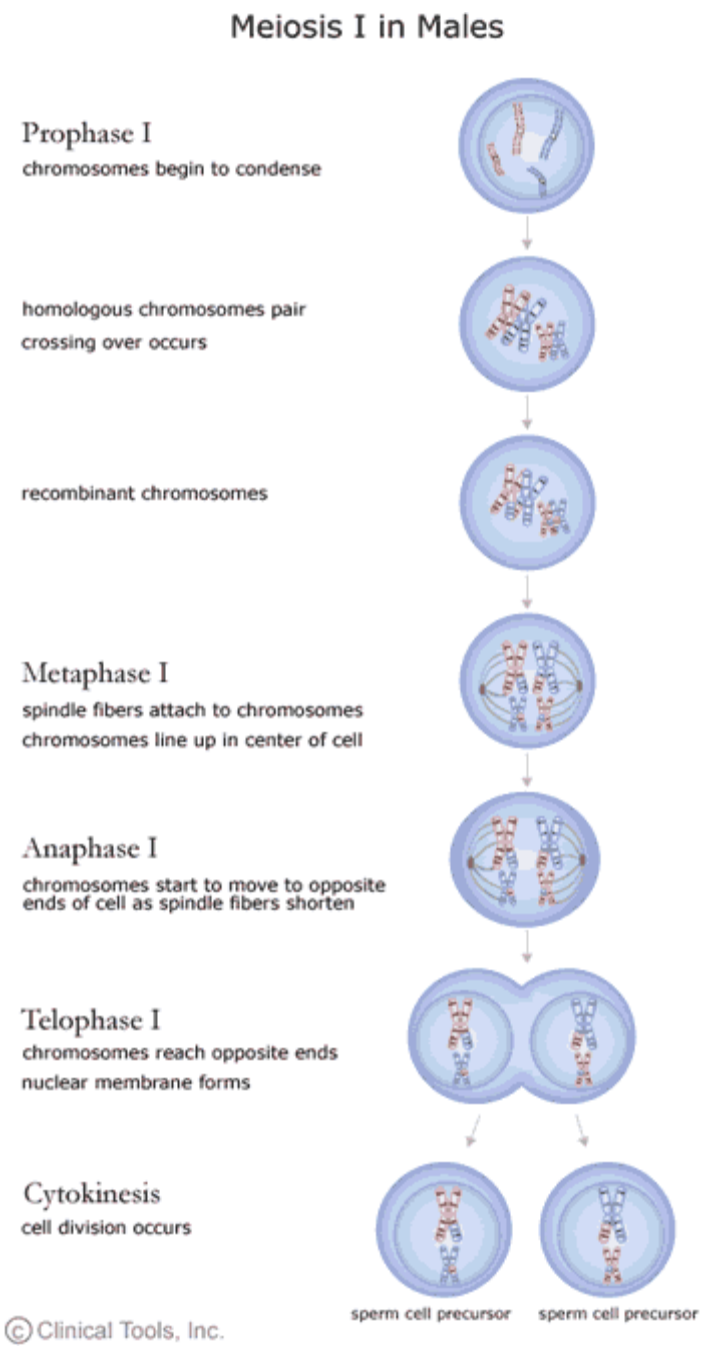
As in the previous telophase I, the cell is now divided in two and the chromosomes are on opposite ends of the cell. Cytokinesis, or plasma division occurs, and new nuclear envelopes are formed around the chromosomes.

Results of Meiosis II

At the end of meiosis II, there are 4 cells, each haploid, and each with only 1 copy of the genome. These cells can now be developed into gametes, eggs in females and sperm in males.

Meiosis I

Meiosis I separates the pairs of homologous chromosomes.



In Meiosis I a special cell division reduces the cell from diploid to haploid.

Prophase I

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

- **Leptotene**: chromosomes start to condense.
- **Zygotene**: homologous chromosomes become closely associated (synapsis) to form pairs of chromosomes (bivalents) consisting of four chromatids (tetrads).

- **Pachytene**: crossing over between pairs of homologous chromosomes to form chiasmata (sing. chiasma).
- **Diplotene**: homologous chromosomes start to separate but remain attached by chiasmata.
- **Diakinesis**: homologous chromosomes continue to separate, and chiasmata move to the ends of the chromosomes.

Prometaphase I

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

Metaphase I

Homologous pairs of chromosomes (bivalents) arranged as a double row along the metaphase plate. The arrangement of the paired chromosomes with respect to the poles of the spindle apparatus is random along the metaphase plate. (This is a source of genetic variation through random assortment, as the paternal and maternal chromosomes in a homologous pair are similar but not identical. The number of possible arrangements is 2^n, where n is the number of chromosomes in a haploid set. Human beings have 23 different chromosomes, so the number of possible combinations is 2^{23}, which is over 8 million.)

Anaphase I

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

Telophase I

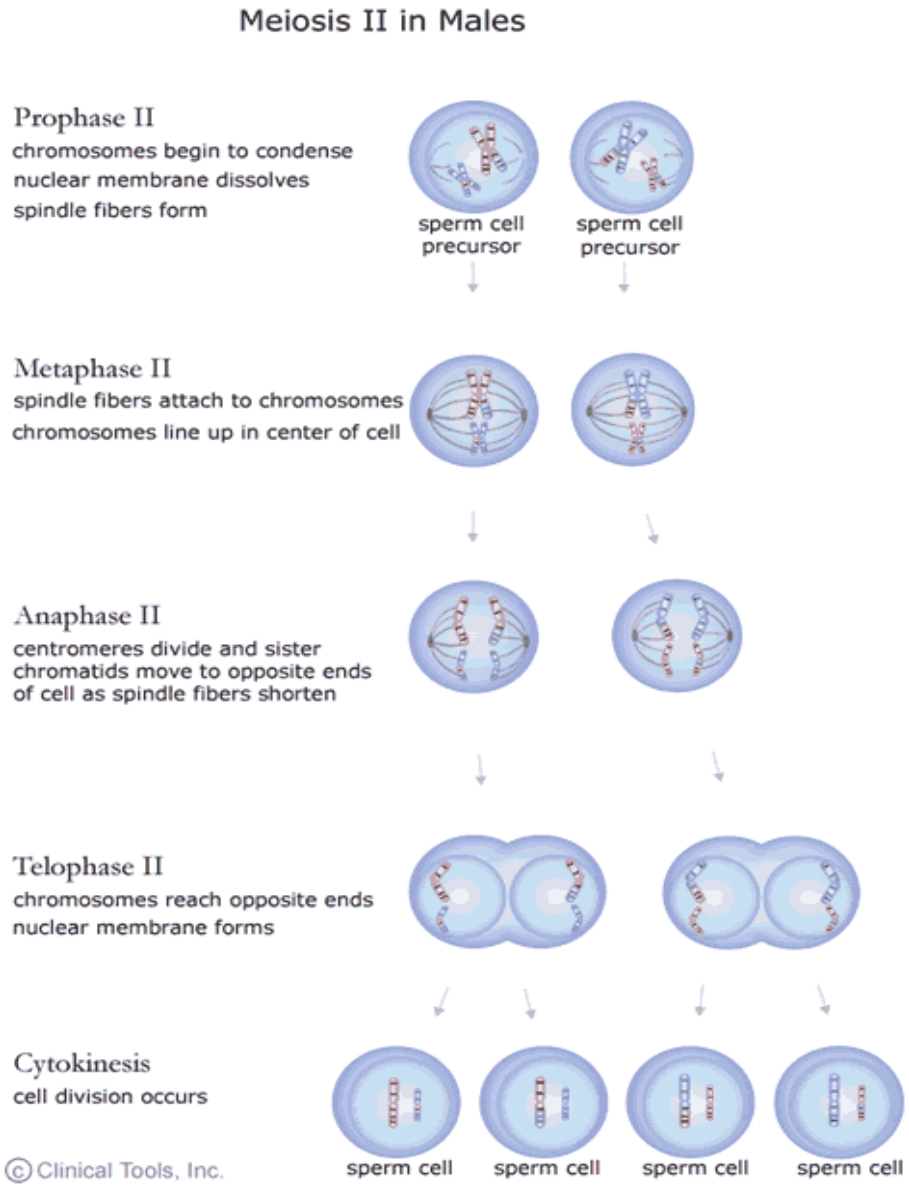
The chromosomes become diffuse and the nuclear membrane reforms.

Cytokinesis

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

Meiosis II

Meiosis II separates each chromosome into two chromatids.

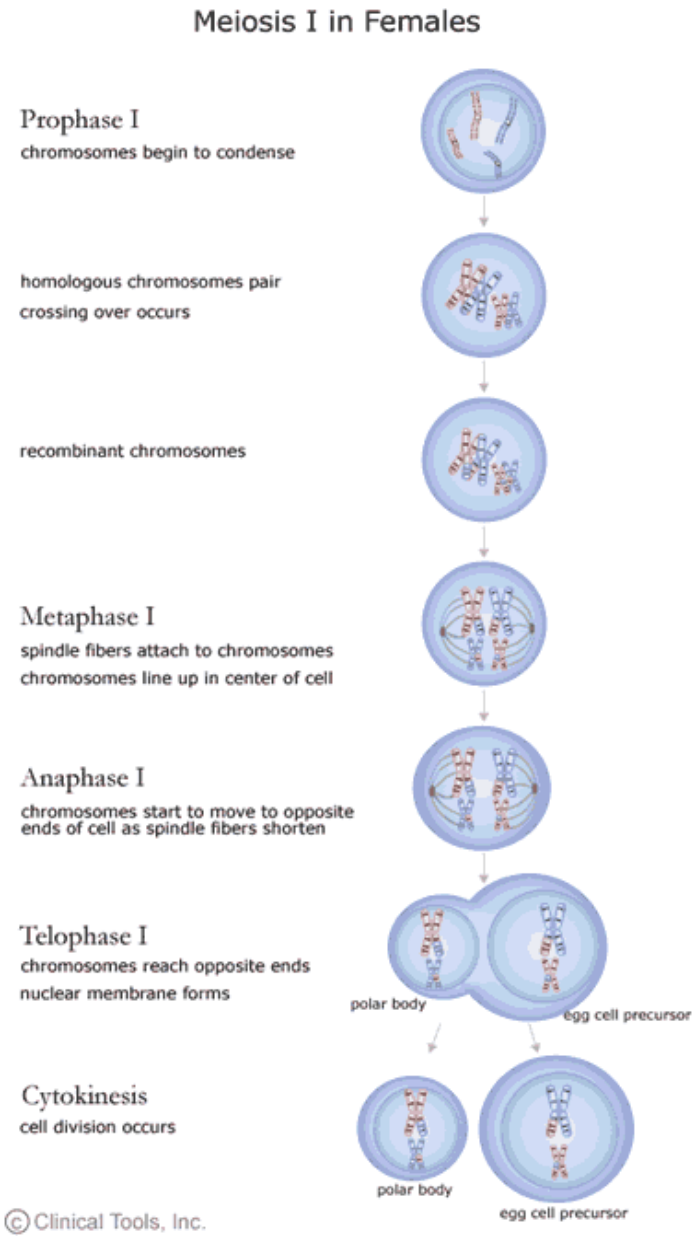


The events of Meiosis II are analogous to those of a mitotic division, although the number of chromosomes involved has been halved.

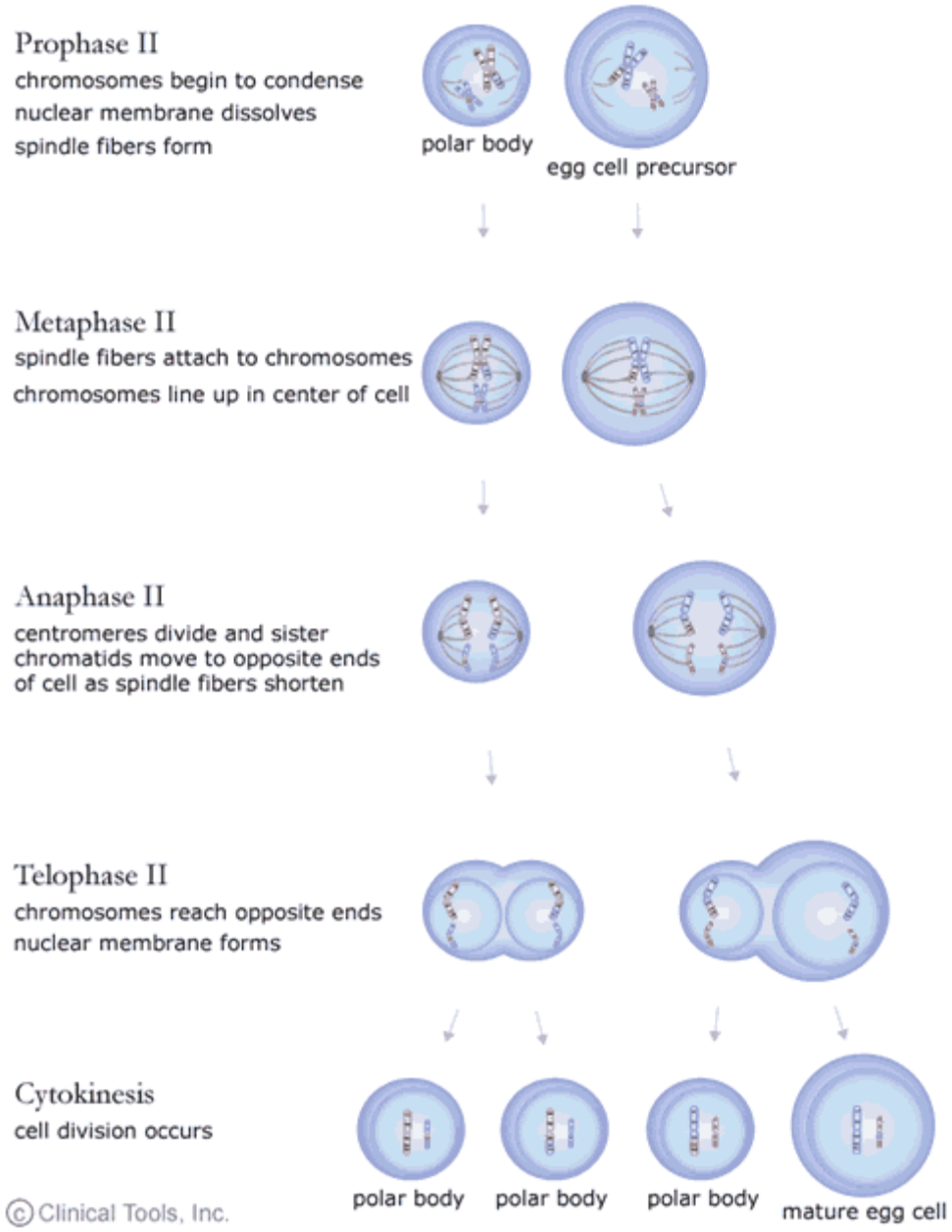
Meiosis generates genetic diversity through:

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

Meiosis in females



Meiosis II in Females



المادة : الوراثة الطبية نظري
استاذ المادة: م د صابرين هادي
المرحلة : الثالثة
المحاضرة الخامسة

Mendelian inheritance is a type of biological inheritance that follows the laws originally proposed by Gregor Mendel in 1865 and 1866 and re-discovered in 1900. These laws were initially controversial. When Mendel's theories were integrated with the Boveri–Sutton chromosome theory of inheritance by Thomas Hunt Morgan in 1915, they became the core of classical genetics. Ronald Fisher combined these ideas with the theory of natural selection in his 1930 book *The Genetical Theory of Natural Selection*, putting evolution onto a mathematical footing and forming the basis for population genetics within the modern evolutionary synthesis.

Mendel's laws

Mendel discovered that, when he crossed purebred white flower and purple flower pea plants (the parental or P generation), the result was not a blend. Rather than being a mix of the two, the offspring (known as the F_1 generation) was purple-flowered. When Mendel self-fertilized the F_1 generation pea plants, he obtained a purple flower to white flower ratio in the F_2 generation of 3 to 1. The results of this cross are tabulated in the Punnett square to the right.

He then conceived the idea of heredity units, which he called "factors". Mendel found that there are alternative forms of factors—now called genes—that account for variations in inherited characteristics. For example, the gene for flower color in pea plants exists in two forms, one for purple and the other for white. The alternative "forms" are now called alleles. **For each biological trait, an organism inherits two alleles, one from each parent. These alleles may be the same or different. An organism that has two identical alleles for a gene is said to be homozygous for that gene (and is called a homozygote). An organism that has two different alleles for a gene is said be heterozygous for that gene (and is called a heterozygote).**

Mendel hypothesized that allele pairs separate randomly, or segregate, from each other during the production of gametes: egg and sperm. Because allele pairs separate during gamete production, a sperm or egg carries only one allele for each inherited trait. When sperm and egg unite at fertilization, each contributes its allele, restoring the paired condition in the offspring. This is called the **Law of Segregation**. Mendel also found that each pair of alleles segregates independently of the other pairs of alleles during gamete formation. This is known as the **Law of Independent Assortment**.

The genotype of an individual is made up of the many alleles it possesses. An individual's physical appearance, or phenotype, is determined by its alleles as well as by its environment. The presence of an allele does not mean that the trait will be expressed in the individual that possesses it. If the two alleles of an inherited pair differ (the heterozygous condition), then one determines the organism’s appearance and is called the dominant allele; the other has no noticeable effect on the organism’s appearance and is called the recessive allele. Thus, in the example above the dominant purple flower allele will hide the phenotypic effects of the recessive white flower allele. This is known as the **Law of Dominance** but it is not a transmission law: it concerns the expression of the genotype. The upper case letters are used to represent dominant alleles whereas the lowercase letters are used to represent recessive alleles.

Mendel's laws of inheritance

Law	Definition
Law of segregation	During gamete formation, the alleles for each gene segregate from each other so that each gamete carries only one allele for each gene.
Law of independent assortment	Genes for different traits can segregate independently during the formation of gametes.
Law of dominance	Some alleles are dominant while others are recessive; an organism with at least one dominant allele will display the effect of the dominant allele.

In the pea plant example above, the capital "B" represents the dominant allele for purple flowers and lowercase "b" represents the recessive allele for white flowers. Both parental plants were true-breeding, and one parental variety had two alleles for purple flowers (*BB*) while the other had two alleles for white flowers (*bb*). As a result of fertilization, the F_1 hybrids each inherited one allele for purple flowers and one for white. All the F_1 hybrids (*Bb*) had purple flowers, because the dominant *B* allele has its full effect in the heterozygote, while the recessive *b* allele has no effect on flower color. For the F_2 plants, the ratio of plants with purple flowers to those with white flowers (3:1) is called the phenotypic ratio. The genotypic ratio, as seen in the Punnett square, is 1 *BB* : 2 *Bb* : 1 *bb*.

Mutation

A mutation is a permanent change in the sequence of DNA. In order for an observable effect, mutations must occur in gene exons or regulatory elements. Changes in the non-coding regions of DNA (introns and junk DNA) generally do not affect function.

Most mutations are neutral; they either make no change in the expression of any gene, or the changes made do not affect the function of any gene product . .

1- A large percentage of DNA is not part of any gene, and has no known function. Changes in these portions of the DNA do not alter any gene and are thus silent .

2- Because of the wobble concept, the exact identity of the third base of a codon often makes no difference, and if it does, the two amino acids coded for by the old the the new codon are often quite similar in nature, so a change in the DNA of a gene which affects one of these bases will often have no effect on the function of the gene product. This genearlly includes 1/4-1/5 of the bases in the gene. These would be silent or neutral mutations . .

3- Not all portions of a protein are equally important for the function of that protein. Even a mutation which changes an amino acid in the final gene product may not make a difference in the function of the protein, or may alter the precise nature of the function of the gene product without alter the usefulness of that product. These would be neutral mutations .

Causes mutations

Mutations can be caused by external (exogenous) or endogenous (native) factors, or they may be caused by errors in the cellular machinery. Physical or chemical agents that induce mutations in DNA are called

mutagens and are said to be mutagenic.
1-Exogenous factors: environmental factors such as sunlight, radiation, and smoking can cause mutations.

2-Endogenous factors: errors during DNA replication can lead to genetic changes as can toxic by-products of cellular metabolism.

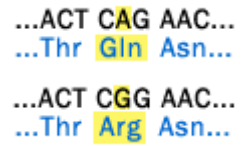
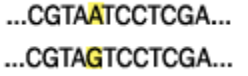
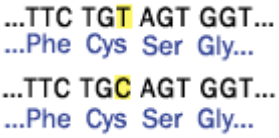
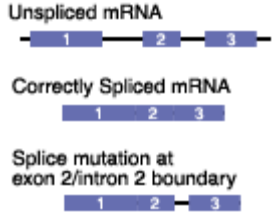
The consequences of mutations

Mutations can be advantageous and lead to an evolutionary advantage of a certain genotype. Mutations can also be deleterious, causing disease, developmental delays, structural abnormalities, or other effects .

Types of Mutations:

There are several classes of mutations described below. The original sequence is shown on the top with the mutated sequence below it

Deletion	Genetic material is removed or deleted. A few bases can be deleted (as shown on the left) or it can be complete or partial loss of a chromosome (shown on right).	...TCGGAATCGC... ...TCGCGC... 
Frameshift	The insertion or deletion of a number of bases that is not a multiple of 3. This alters the reading frame of the gene and frequently results in a premature stop codon and protein truncation.	...ACT TTT CAT AGT... ...Thr Phe His Ser... ...ACT TTT TCA TAG T... ...Thr Phe Ser Stop
Insertion	When genetic material is put into another region of DNA. This may be the insertion of 1 or more bases, or it can be part of one chromosome being inserted into another, non-homologous	...TTGAAAACGCTG... ...TTGAAAAACGCTG...

	chromosome.	
Missense	A change in DNA sequence that changes the codon to a different amino acid. Not all missense mutations are deleterious, some changes can have no effect. Because of the ambiguity of missense mutations, it is often difficult to interpret the consequences of these mutations in causing disease.	
Nonsense	A change in the genetic code that results in the coding for a stop codon rather than an amino acid. The shortened protein is generally non-function or its function is impeded.	
Point	A single base change in DNA sequence. A point mutation may be silent, missense, or nonsense.	
Silent	A change in the genetic sequence that does not change the protein sequence. This can occur because of redundancy in the genetic code where an amino acid may be encoded for by multiple codons.	
Splice Site	A change in the genetic sequence that occurs at the boundary of the exons and introns. The consensus sequences at these boundaries signal where to cut out introns and rejoin exons in the mRNA. A	

	change in these sequences can eliminate splicing at that site which would change the reading frame and protein sequence.	
Translocation	A structural abnormality of chromosomes where genetic material is exchanged between two or more non-homologous chromosomes.	

Mutagen

Mutagen is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level.

Effects of Mutagen

Mutagens can cause changes to the DNA and are therefore genotoxic. They can affect the transcription and replication of the DNA, which in severe cases can lead to cell death. The mutagen produces mutations in the DNA, and deleterious mutation can result in aberrant, impaired or loss of function for a particular gene, and accumulation of mutations may lead to cancer. Mutagens may therefore be also carcinogens. However, some mutagens exert their mutagenic effect through their metabolites, and therefore whether such mutagens actually become carcinogenic may be dependent on the metabolic processes of an organism, and a compound shown to be mutagenic in one organism may not necessarily be carcinogenic in another

Different mutagens act on the DNA differently. Powerful mutagens may result in chromosomal instability, causing chromosomal breakages and

rearrangement of the chromosomes such as translocation, deletion, and inversion. Such mutagens are called clastogens.

Mutagens may also modify the DNA sequence; the changes in nucleic acid sequences by mutations include substitution of nucleotide base-pairs and insertions and deletions of one or more nucleotides in DNA sequences. Although some of these mutations are lethal or cause serious disease, many have minor effects as they do not result in residue changes that have significant effect on the structure and function of the proteins. Many mutations are silent mutations, causing no visible effects at all, either because they occur in non-coding or non-functional sequences, or they do not change the amino-acid sequence due to the redundancy of codons.

Some mutagens can cause aneuploidy and change the number of chromosomes in the cell. They are known as aneuploidogens.

Types of mutagens

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.

1- 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.

2- DNA reactive chemicals

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 are generated by normal cellular processes, for example as a 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 bifunctionalelectophils are mutagenic in mammalian cells and may contribute to the development and/or progression of human cancers (see 15-Hydroxyicosatetraenoic acid). 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 hydrocarbon (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

3- Base analogs

- Base analog, which can substitute for DNA bases during replication and cause transition mutations.

4- 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.

5- 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 VilhelmEllermann 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.

المحاضرة السابعة / الوراثة النظري

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Mitochondria and its DNA

- The cytoplasm of each cell contains several hundred mitochondria. Through the oxidative phosphorylation process (OXPHOS), these essential organelles produce ATP, the energy source used in cellular metabolism.
- Mitochondria have their own distinct DNA called mtDNA, which is comprised of a small double stranded circular molecule. The mtDNA molecule contains only 37 genes. These include genes involved in transcription of DNA into proteins (ribosomal RNA genes) and genes that code for enzymes used in the mitochondria (the complex involved in OXPHOS).
- The mutation rate in mtDNA is ten times higher than in nuclear DNA because mtDNA are subject to damage from reactive oxygen molecules released as a byproduct during OXPHOS. In addition, the mtDNA also lacks the DNA repair mechanisms found in the nucleus.

Heteroplasmy vs. Homoplasmy

- A cell can have some mitochondria that have a mutation in the mtDNA and some that do not. This is termed ***heteroplasmy***.
- ***Homoplasmy*** refers to a cell that has a uniform collection of mtDNA: either completely normal mtDNA or completely mutant mtDNA.
- A unique feature of mtDNA is that, at cell division, the mtDNA replicates and sorts randomly among mitochondria. In turn, the mitochondria sort randomly among daughter cells. Therefore, in cells where heteroplasmy is present, each daughter cell may

receive different proportions of mitochondria carrying normal and mutant mtDNA.

Inheritance of Mitochondrial Mutations

- In general, only egg cells contribute mitochondria to offspring. Mutant mtDNA are not typically inherited from a male.
- Thus, mitochondrial mutations exhibit ***maternal inheritance***, or ***mitochondrial inheritance.***
- If a mother is homoplasmic for an mtDNA mutation, then all of the mitochondria she passes to her children will also be homoplasmic for the mutation. In the pedigree illustrated, note that all of an affected female's children are affected, but none of the affected male's children inherited the condition.
- If a mother is heteroplasmic for an mtDNA mutation, then the chance she will pass on the mutation is reduced due to the random assortment of both mtDNA and mitochondria during replication and division. Therefore, the higher the proportion of mutant mtDNA, the higher the chance of passing the mutation, and, therefore, the condition, on to one's offspring.

Mitochondrial Disorders

- Many of the disorders caused by mutations in mtDNA affect tissues that have a high energy demand, such as the central nervous system, the heart, and muscle. Therefore, mitochondrial disorders often involve the neuromuscular system and may include encephalopathy, myopathy, ataxia, retinal degeneration, and loss of function of the external ocular muscles.
- Some examples of conditions caused by mtDNA mutations include LHON (**L**eber's **H**ereditary **O**ptic **N**europathy) and MELAS (**M**itochondrial **E**ncephalomyopathy,**L**actic **A**cidosis, and **S**troke-like episodes).
- Clinical Information on Diseases:
    - LHON
    - MELAS

- Nuclear DNA codes for many of the mitochondrial proteins. Therefore, mutations in nuclear genes can also affect mitochondrial function and cause disease, such as Friedreich's ataxia. While these disorders are inherited in Mendelian patterns (not maternally, like mutations in mitochondrial DNA), they exhibit symptoms similar to the disorders caused by mtDNA mutations.

Symptoms Associated with Systems Affected by Mitochondrial Disorders

- **Central nervous system**
  Encephalopathy
  Stroke-like episodes
  Seizures and dementia
  Psychosis and depression
  Ataxia
  Migraine headaches
- **Eye**
  External ophthalmoplegia
  Ptosis
  Cataract
  Pigmentary retinopathy
  Optic atrophy
- **Hearing**
  Bilateral sensorineural deafness
- **Heart**
  Cardiomyopathy
  Heart block
  Pre-excitation syndrome
- **Renal**
  Renal tubular defects
- **Endocrine**
  Hypoparathyroidism
  Hypothyroidism
  Gonadal failure
- **Intestinal**
  Dysphagia
  Constipation
  Hepatic failure
- **Peripheral nervous system**
  Myopathy
  Axonal sensorimotor neuropathy

LHON (Leber's Hereditary Optic Neuropathy)

- Individuals with LHON experience fast, sudden, painless loss of vision in both eyes in their late teens or early 20s.
- Males are more commonly affected than females; however, women tend to develop the disorder later in life and be more severely affected.
- Some individuals with LHON (usually women) may also have a multiple sclerosis-like condition.

- An estimated 1 in 10,000 individuals carry a LHON mutation. However, due to the reduced penetrance of the condition, 1 in 14,000 adult males have visual loss due to LHON.
- Approximately 95% of patients have one of three common mtDNA mutations; testing is available for these three mutations.
- However, LHON mutations exhibit reduced penetrance: males who carry a mutation have a 40% chance of developing symptoms in their lifetime and women a 10% chance.
- LHON is inherited in a maternal pattern due to the mutations in mtDNA; an individual must be homoplasmic for the LHON mutation, or have a very high percentage of mutated mtDNA, in order to be at risk for developing the condition.

MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes)

- MELAS affects many systems of the body, with typical onset in the first decade of life. The major clinical features, like the name suggests, include:
    - Encephalomyopathy with seizures and/or dementia
    - Mitochondrial myopathy, as seen by lactic acidosis and/or ragged red fibers (RRF) on muscle biopsy
    - Stroke-like episodes, usually before the age of 40
- However, there are a wide range of clinical symptoms in addition to these major three, including diabetes mellitus, cardiomyopathy, migraines, and deafness.
- Approximately 1.6 per 10,000 individuals are affected with MELAS.
- The most common mutation, present in 80% of MELAS patients, is in the mtDNA gene MTTL1. Clinical testing is available for this gene.

المحاضرة السادسة

الوراثة النظري

المرحلة :الثالثة

Patterns of inheritance

Observations of the way traits, or characteristics, are passed from one generation to the next in the form of identifiable phenotypes probably represent the oldest form of genetics. However, the scientific study of patterns of inheritance is conventionally said to have started with the work of the Austrian monk Gregor Mendel in the second half of the nineteenth century.

In diploid organisms each body cell (or 'somatic cell') contains two copies of the genome. So each somatic cell contains two copies of each chromosome, and two copies of each gene. The exceptions to this rule are the **sex chromosomes** that determine sex in a given species. For example, in the XY system that is found in most mammals - including human beings - males have one X chromosome and one Y chromosome (XY) and females have two X chromosomes (XX). The paired chromosomes that are not involved in sex determination are called **autosomes**, to distinguish them from the sex chromosomes. Human beings have 46 chromosomes: 22 pairs of autosomes and one pair of sex chromosomes (X and Y).

The different forms of a gene that are found at a specific point (or locus) along a given chromosome are known as alleles. Diploid organisms have two alleles for each autosomal gene - one inherited from the mother, one inherited from the father.

Mendelian inheritance patterns

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

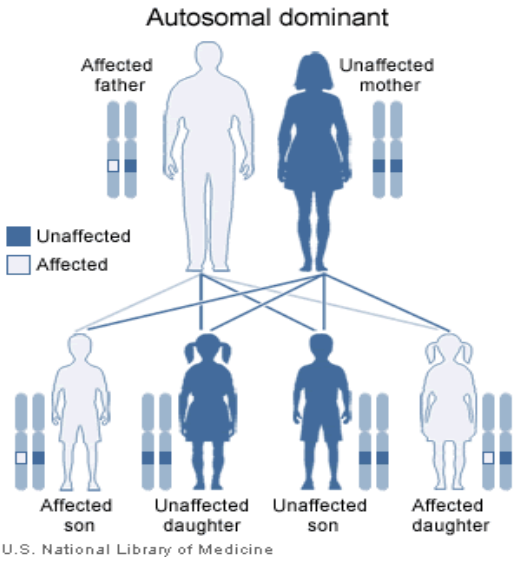
Autosomal dominant

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

Autosomal dominant is one of many ways that a trait or disorder can be passed down through families.

In an autosomal dominant disease, if you get the abnormal gene from only one parent, you can get the disease. Often, one of the parents may also have the disease.

An autosomal gene is a gene located on a numbered chromosome (somatic chromosome) and usually affects males and females in the same way.



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

Sex-linked or X-linked inheritance

In many organisms, the determination of sex involves a pair of chromosomes that differ in length and genetic content - for example, the XY system used in human beings and other mammals.

The X chromosome carries hundreds of genes, and many of these are not connected with the determination of sex. The smaller Y chromosome contains a number of genes responsible for the initiation and maintenance of maleness, but it lacks copies of most of the genes that are found on the X chromosome. As a result, the genes located on the X chromosome display a characteristic pattern of inheritance referred to as **sex-linkage** or **X-linkage**.

An X-linked gene is located on the X or Y chromosome and affects males and females differently

Females (XX) have two copies of each gene on the X chromosome, so they can be heterozygous or homozygous for a given allele. However, males (XY) will express all the alleles present on the single X chromosome that they receive from their mother, and concepts such as 'dominant' or 'recessive' are irrelevant.

A number of medical conditions in humans are associated with genes on the X chromosome, including haemophilia, muscular dystrophy and some forms of colour blindness.

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Types of Genes Involved In Cancer

Cancer is caused by the accumulation of genetic and epigenetic mutations in genes that normally play a role in the regulation of cell proliferation, thus leading to uncontrolled cell growth. Cells acquire mutations in these genes as a result of spontaneous and environmentally-induced DNA damage.

Those cells with mutations that promote a growth and survival advantage over normal cells are selected for through a Darwinian process, leading to the evolution of a tumor. Genes involved in tumorigenesis include those whose products: 1) directly regulate cell proliferation (either promoting or inhibiting), 2) control programmed cell death or apoptosis, and 3) are involved in the repair of damaged DNA. Depending on how they affect each process, these genes can be grouped into two general categories: **tumor suppressor genes** (growth inhibitory) and **proto-oncogenes** (growth promoting).

Mutant alleles of proto-oncogenes are called **oncogenes**. Since mutation in a single allele of a proto-oncogene can lead to cellular transformation, such mutations are considered dominant. In contrast, typically both alleles of a tumor suppressor gene must be altered for transformation to occur. Genes that regulate apoptosis may be dominant, as with proto-oncogenes, or they may behave as tumor suppressor genes. Tumor suppressor genes may be divided into two general groups: **promoters** and **caretakers**.

Promoters are the traditional tumor suppressors, like p53 and RB. Mutation of these genes leads to transformation by directly releasing the brakes on cellular proliferation. **Caretaker genes** are responsible for processes that ensure the integrity of the genome, such as those involved in DNA repair. Although they do not directly control cell proliferation, cells with mutations in these genes are compromised in their ability to repair DNA damage and thus can acquire mutations in other genes,

including proto-oncogenes, tumor suppressor genes and genes that control apoptosis. A disability in DNA repair can predispose cells to widespread mutations in the genome, and thus to neoplastic transformation. Cells with mutations in caretaker genes are therefore said to have a "**mutator phenotype**". The fact that patients with defects in DNA repair are cancer prone provides one of the most striking pieces of evidence that mutations in DNA lie at the heart of the neoplastic process.

Proto-oncogenes are genes that normally help cells grow. When a proto-oncogene mutates (changes) or there are too many copies of it, it becomes a "bad" gene that can become permanently turned on or activated when it is not supposed to be. When this happens, the cell grows out of control, which can lead to cancer. This bad gene is called an oncogene.

II. Tumor Suppressor Genes: Tumor suppressor genes can be defined as genes which encode proteins that normally inhibit the formation of tumors. Their normal function is to inhibit cell proliferation, or act as the "brakes" for the cell cycle. Mutations in tumor suppressor genes contribute to the development of cancer by inactivating that inhibitory function. Mutations of this type are termed **loss-of-function** mutations. As long as the cell contains one functional copy of a given tumor suppressor gene (expressing enough protein to control cell proliferation), that gene can inhibit the formation of tumors. Inactivation of both copies of a tumor suppressor gene is required before their function can be eliminated. Therefore, mutations in tumor suppressor genes are *recessive* at the level of an individual cell. As we will see, the inactivation of tumor suppressor genes plays a major role in cancer.

Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as *apoptosis* or *programmed cell death*). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.

A. Retinoblastoma

Retinoblastoma (RB) is a rare childhood tumor of the eye (see clinical correlate). Most cases (60-70%) are sporadic (as opposed to inherited), occur unilaterally (affecting one eye), and present in children 1-4 years of age. The remaining 30-40% of patients have a hereditary form of

retinoblastoma and thus have inherited a germline cancer predisposing mutation (see below). These children tend to acquire tumors earlier than those with sporadic disease and are more likely to have multiple tumors in one (unilateral) or both (bilateral) eyes. In families with the inherited form of retinoblastoma, the disease shows an autosomal dominant inheritance pattern.

p53: a key tumor suppressor **p53**, located on chromosome 17p13.1, is the single most common target for genetic alteration in human tumors. In fact, more than 50% of human tumors contain mutations in this gene! Thus it is among the most important "brakes" on tumor formation. Homozygous loss of the p53 gene is found in virtually every type of cancer, including carcinomas of the breast, colon, and lung – the three leading causes of cancer deaths. In most cases, the inactivating mutations affecting both p53 alleles are acquired in somatic cells. In some cases, although it is rare, individuals inherit a mutant p53 allele. As with *RB1*, inheritance of one mutant allele predisposes these individuals to develop malignant tumors because only one additional "hit" is needed to inactivate the second, normal, allele. Inactivation of the second p53 allele leads to increased cell proliferation, decreased apoptosis, and tumor development.