Genetics

stage II

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MSC. Human molecular genetics

Genetics: is a branch of biology concerned with the study of genes, genetic variation, and heredity in organisms. Human genetics is the scientific study of inherited human variation; Genetics tries to identify which traits are inherited, and explain how these traits are passed from generation to generation. Some traits are part of an organisms' physical appearance; such as a person's eye color, height or weight. Other sorts of traits are not easily seen and include blood types or resistance to diseases. Some traits are inherited through our genes, so tall and thin people tend to have tall and thin children. Other traits come from interactions between our genes and the environment, so a child might inherit the tendency to be tall, but if they are poorly nourished, they will still be short. The way our genes and environment interact to produce a trait can be complicated. For example, the chances of somebody dying of cancer or heart disease seem to depend on both their genes and their lifestyle. This field has been energized in recent years by the Human Genome Project. Modern genetics involves genetic engineering a technique used to manipulate genes and has produced many advances in medicine.

PRINCIPLES OF GENETICS

The site where genes work is the cell; each cell's function within an organism is determined by the genetic information encoded in DNA. In eukaryotes (organisms whose cells contain a nucleus), DNA resides within membrane-bound structures in the cell (nucleus, mitochondria, and chloroplasts in plants). In prokaryotes (one-celled organisms that lack internal membrane- bound structures), DNA floats freely within the cell body. DNA is packaged into structures called chromosomes within a cell, every chromosome in a cell contains many genes, and each gene is located at a particular site, or locus, on the chromosome. Chromosomes usually occur in matched

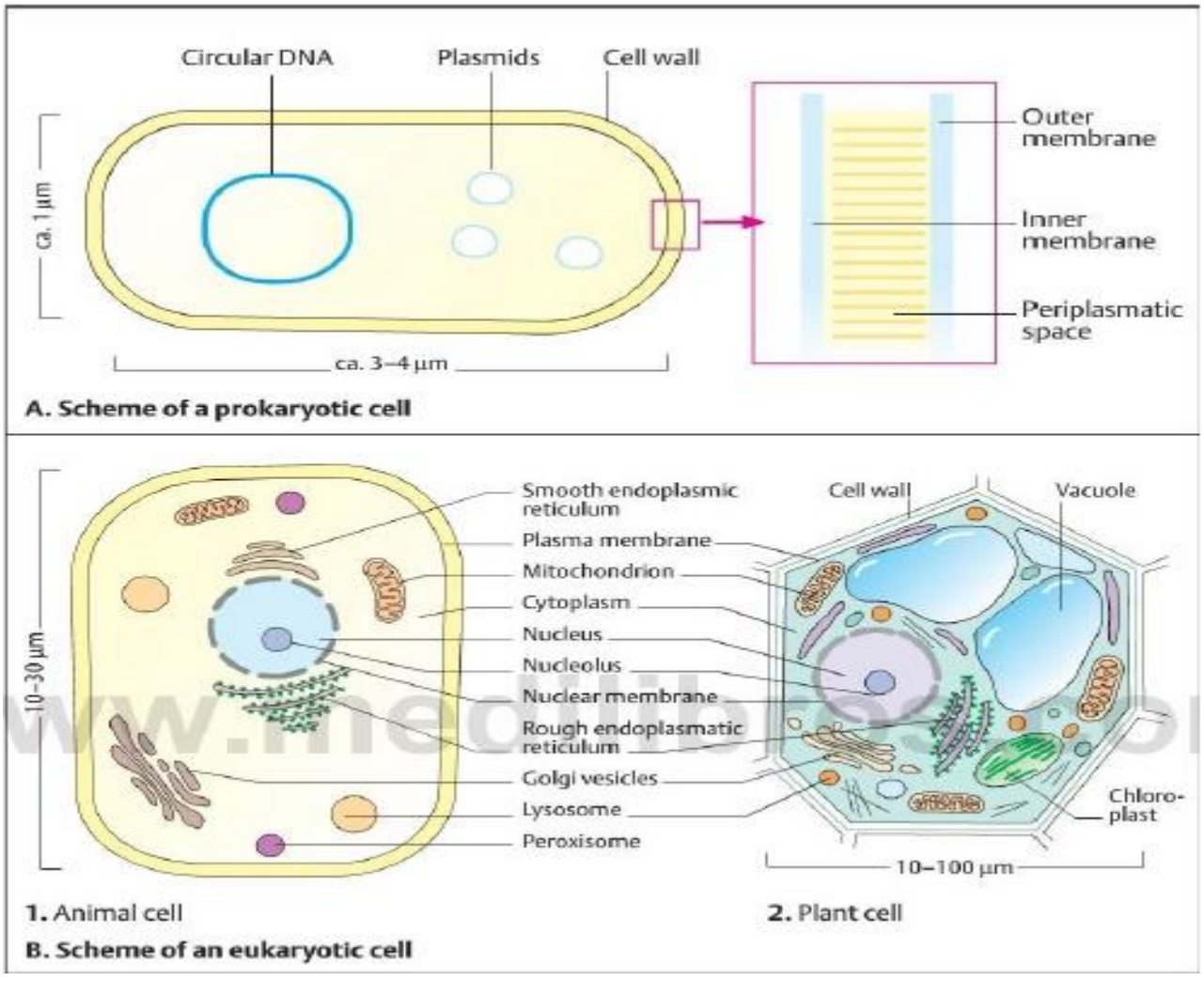
pairs called homologues, the number of homologous chromosomes in the human body contain 23 pairs of chromosomes.

The cell and chromosome behavior

The Cell and its Components :

Cells are the smallest organized structural units of living organisms. Surrounded by a membrane, they are able to carry out a wide variety of functions during a limited life span. Each cell originates from another living cell , Tow basic types of cells exist:

1. **Prokaryotic cells**, which carry their functional information in a circular genome without a nucleus.
2. **Eukaryotic cells**, which contain their genome in individual chromosomes in a nucleus and have a well-organized internal structure.



The chromosome:

A thread-like structure of nucleic acids and protein found in the nucleus of most living cells, carrying genetic information in the form of genes, the DNA molecule is packaged into chromosomes.

In most cells, humans have 22 pairs of these chromosomes plus the two sex chromosomes (XX in females and XY in males) for a total of 46.

- **The X chromosome**. A normal female somatic cell contains two X chromosomes (XX).
- **The Y chromosome.** A normal male somatic cell contains one X chromosome and one Y chromosome (XY).

Chromosomes are not visible in the cell's nucleus not even under a microscope when the cell is not dividing. However, the DNA that makes up chromosomes becomes more tightly packed during cell division and is then **visible under a microscope**. Most of what researchers know about chromosomes was learned by observing chromosomes during cell division.

The structure and location of chromosomes:

The structure and location of chromosomes are among the chief differences between viruses, prokaryotes, and eukaryotes. The nonliving viruses have chromosomes consisting of either DNA (deoxyribonucleic acid) or RNA (ribonucleic acid); this material is very tightly packed into the viral head. Among organisms with prokaryotic cells (i.e., bacteria and blue-green algae), chromosomes consist entirely of DNA. The single chromosome of a prokaryotic cell is not enclosed within a nuclear membrane. Among eukaryotes, the chromosomes are contained in a membrane-bound cell nucleus. The chromosomes of a eukaryotic cell consist primarily of DNA attached to a protein core. They also contain RNA. The remainder of this article pertains to eukaryotic chromosomes.

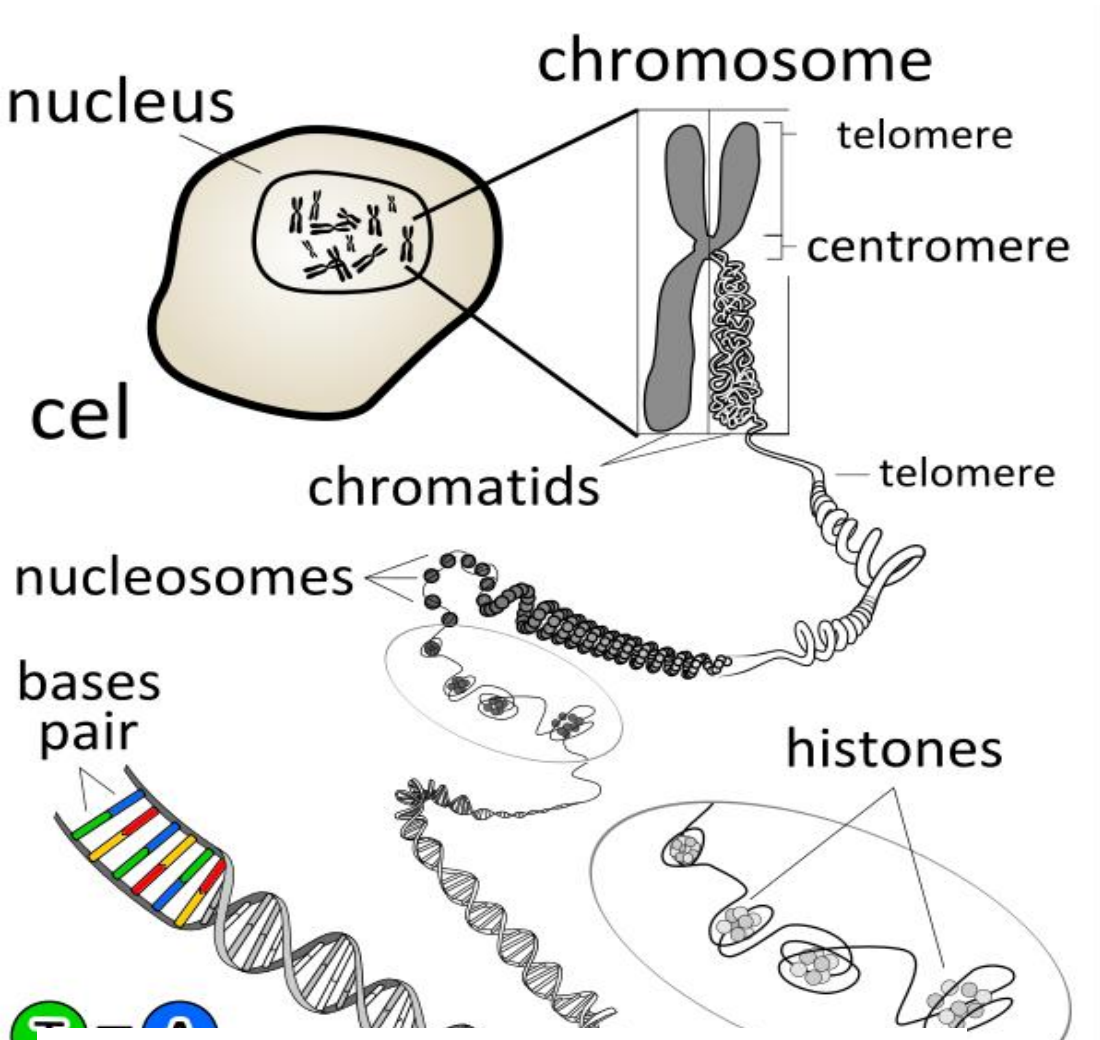
Eukaryotic Chromosome Structure:

Eukaryotic chromosomes consist of a DNA-protein complex that is organized in a compact manner which permits the large amount of DNA to be stored in the nucleus of the cell. The subunit designation of the chromosome is chromatin. The fundamental unit of chromatin is the nucleosome.

- **Chromatin**: the unit of analysis of the chromosome; chromatin reflects the general structure of the chromosome but is not unique to any particular chromosome.
- **Nucleosome**: simplest packaging structure of DNA that is found in all eukaryotic chromosomes; DNA is wrapped around an octamer of small basic proteins called histones; 146 bp is wrapped around the core and the remaining bases link to the next nucleosome; this structure causes negative supercoiling.
- **Histones:** are basic proteins that have an affinity for DNA and are the most abundant proteins associated with DNA. The nucleosome consists of about 200 bp wrapped around a histone octamer that contains **copies** of histone proteins **H2A, H2B, H3 and H4**. These are known as the core histones. The amino acid sequence of these four histones is conserved suggesting a similar function for all.
- **Centromeres** :are those condensed regions within the chromosome that are responsible for the accurate segregation of the replicated chromosome during mitosis and meiosis. When chromosomes are stained they typically show a dark-stained region that is the centromere. During mitosis, the centromere that is shared by the sister chromatids must divide so that the chromatids can migrate to opposite poles of the cell. On the other hand, during the first meiotic division the centromere of sister chromatids must remain intact, whereas during meiosis II they must act as they do during mitosis. Therefore the centromere is an important component of chromosome structure and segregation.

- **Telomeres:** are the region of DNA at the end of the linear eukaryotic chromosome that are required for the replication and stability of the chromosome.

  If two chromosomes were broken in a cell, the end of one could attach to the other and vice versa. What she never observed was the attachment of the broken end to the end of an unbroken chromosome.



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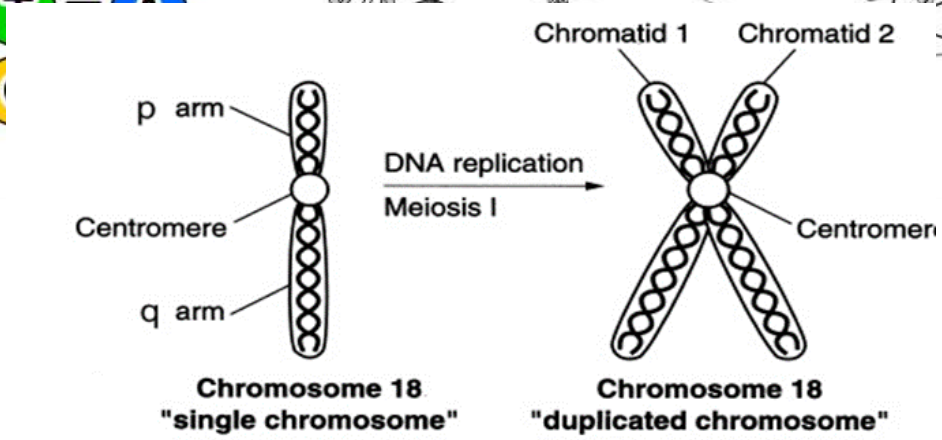


single

chromosome consists of two characteristic regions called **arms (p arm = short arm; q arm = long arm),** which are separated by a centromere. During meiosis I, single chromosomes undergo DNA replication, which essentially duplicates the arms. This forms duplicated chromosomes, which consist of two sister chromatids attached at the centromere.

Cell division:

Cell division is the process by which a parent cell divides into two or more daughter cells. Cell division usually occurs as part of a larger cell cycle. In eukaryotes, there are two distinct types of cell division: a vegetative division, whereby each daughter cell is genetically identical to the parent cell (mitosis), and a reproductive cell division, whereby the number of chromosomes in the daughter cells is reduced by half to produce haploid gametes (meiosis).

Mitosis:

Mitosis is a part of the cell cycle when replicated chromosomes are separated into two new nuclei. In general, mitosis (division of the nucleus) is preceded by the S stage of interphase (during which the DNA is replicated) and is often accompanied or followed by cytokinesis, which divides the cytoplasm, organelles and cell membrane into two new cells containing roughly equal shares of these cellular components.

Phases of mitosis:

- **Interphase :**

  Interphase is divided into three phases: **G_1** (first gap), **S** (synthesis), and **G_2** (second gap). During all three phases, the cell grows by producing proteins and cytoplasmic organelles. However, chromosomes are replicated only during the S phase. Thus, a cell grows (G_1), continues to grow as it duplicates its chromosomes (S), grows more and prepares for mitosis (G_2).

- **Prophase :**
  - Chromosome DNA has been earlier duplicated (S Phase)
  - Chromosomes begin condensing
  - Chromosome pairs (chromatids) held together at centromere
  - Microtubules disassemble
  - Mitotic spindle begins to form
  - Prophase ends when nuclear envelope breaks down
- **Prometaphase :**
  - Microtubules now enter nuclear region
  - Nuclear envelope forms vesicles around mitotic spindle
  - Kinetochores form on centromere attach to some MTs of spindle
  - Prometaphase ends when chromosomes move to metaphase plate
- **Metaphase**
  - Kinetochore MTs align chromosomes in one midpoint plane
  - Metaphase ends when sister kinetochores separate
- **Anaphase**
  - Separation of sister Kinetochores
  - shortening of Kinetochore microtubules pulls chromosome to spindle pole
  - Anaphase ends as nuclear envelope (membrane) begins to reform.

- **Telophase**
  - Chromosomes arrive at spindle poles
  - Kinetochore MTs lost
  - Condensed chromosomes begin expanding
  - Continues through cytokinesis
- **Cytokinesis**
  - Division of cytoplasmic contents

- Contractile ring forms at midpoint under membrane
- Microfilament ring Contracts forming cleavage furrow
- Eventually fully divides cytoplasm

Meiosis:

Meiosis is a type of cell division that reduces the number of chromosomes in the parent cell by half and produces four gamete cells. This process is required to produce egg and sperm cells for sexual reproduction. During reproduction, when the sperm and egg unite to form a single cell, the number of chromosomes is restored in the offspring.

Meiosis begins with a parent cell that is diploid, meaning it has two copies of each chromosome. The parent cell undergoes one round of DNA replication followed by two separate cycles of nuclear division. The process results in four daughter cells that are haploid, which means they contain half the number of chromosomes of the diploid parent cell.

Meiosis I and II

- **Meiosis I** separates the pairs of homologous chromosomes, reduces the cell from diploid to haploid.
- **Meiosis II** separates each chromosome into two chromatids (chromosome behavior in meiosis II is like that of mitosis).

Phases of Meiosis I

- **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 consisting of four chromatids (tetrads).

Pachytene - crossing over between pairs of homologous chromosomes to form chiasmata (form between two nonsister chromatids at points where they have crossed over)

Diplotene - homologous chromosomes begin 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.

- **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 I.** Cellular cytoplasmic division to form two new cells, followed by Meiosis II.

Phases of Meiosis II

- **Prophase II.** Chromosomes begin to condense, nuclear membrane breaks down and spindle forms.

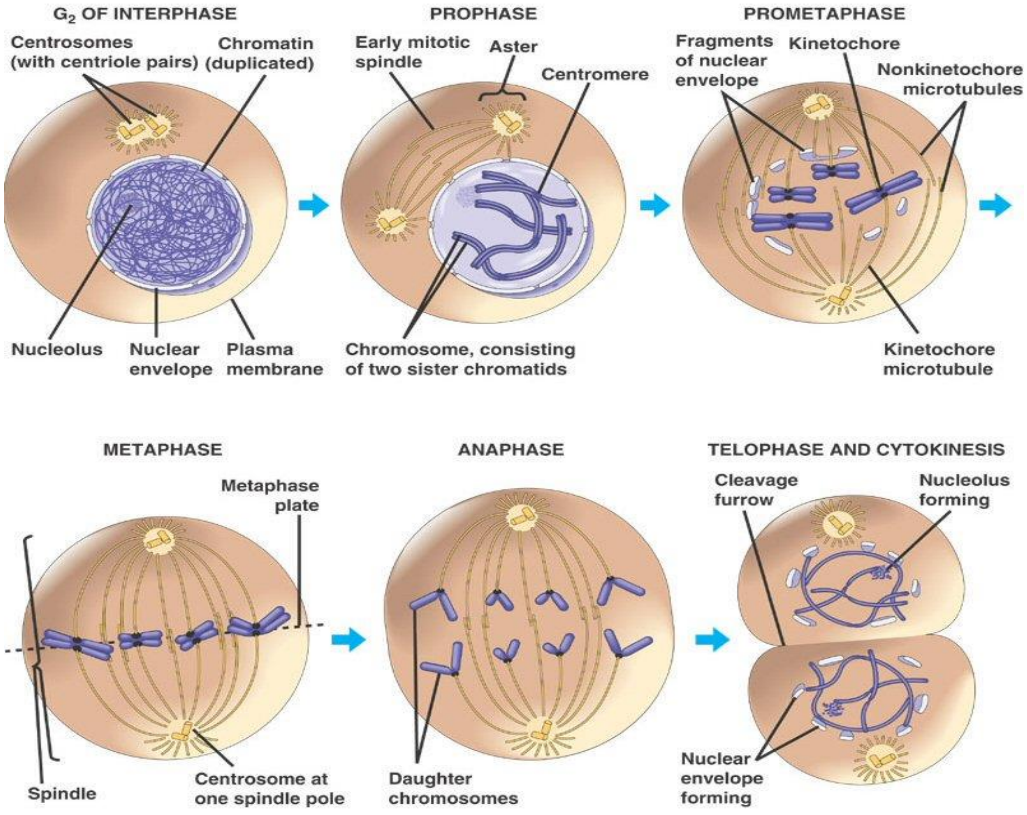
- **Metaphase II.** Spindle fibres attach to chromosomes, chromosomes align in cell centre.
- **Anaphase II.** Chromosomes separate and move to the opposite poles of the cell.
- **Telophase II.** Chromosomes reach spindle pole ends and the nuclear membrane reforms.
- **Cytokinesis .**Cellularr cytoplasmic division to form new cells.

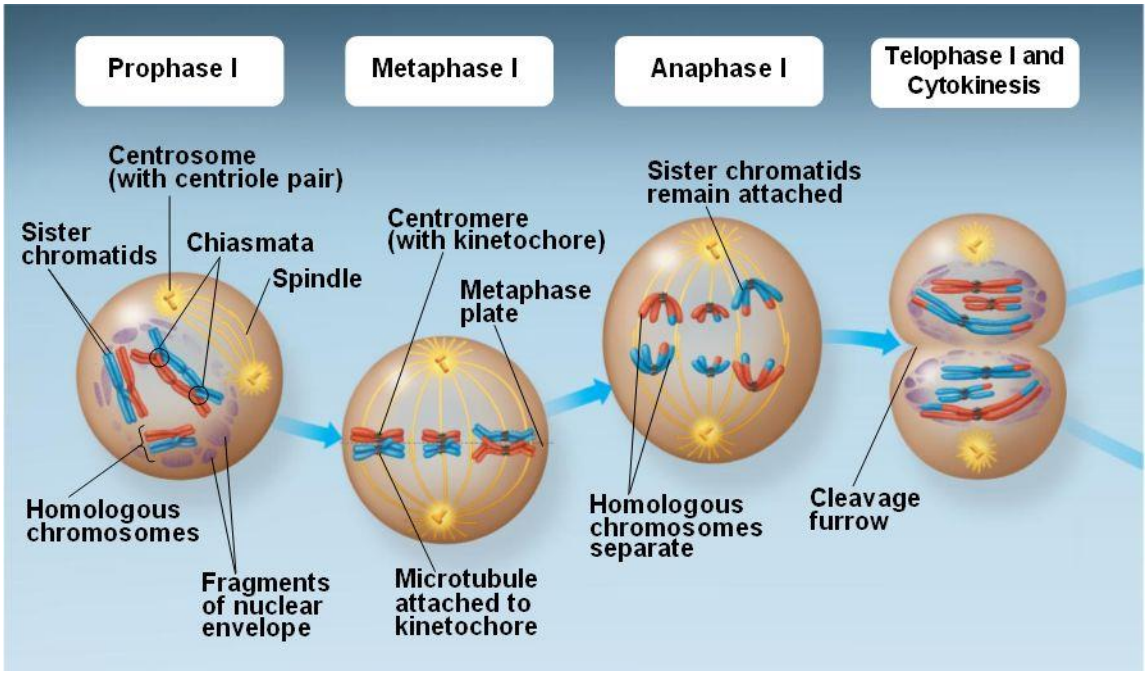
Differences

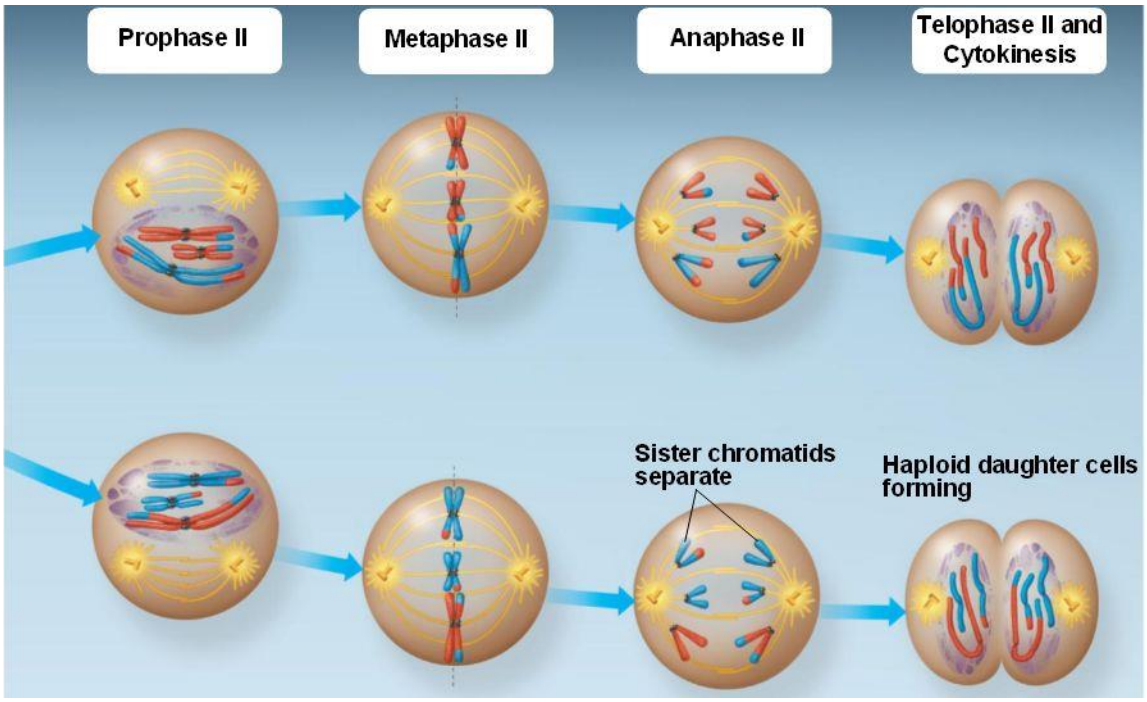
- **Mitosis**
- Involves one cell division?
- Results in two daughter cells
- Results in diploid? daughter cells? (chromosome? number remains the same as parent cell)
- Daughter cells are genetically identical
- Occurs in all organisms except viruses
- Creates all body cells (somatic?) apart from the germ cells? (eggs and sperm)
- Prophase is much shorter
- No recombination/crossing over occurs in prophase.
- In metaphase individual chromosomes (pairs of chromatids) line up along the equator.
- During anaphase the sister chromatids are separated to opposite poles.

- **Meiosis**
- Involves two successive cell divisions
- Results in four daughter cells

- Results in haploid[?] daughter cells (chromosome number is halved from the parent cell)
- Daughter cells are genetically different
- Occurs only in animals, plants and fungi
- Creates germ cells (eggs and sperm) only
- Prophase I takes much longer
- Involves recombination/crossing over of chromosomes in prophase I
- In metaphase I pairs of chromosomes line up along the equator.
- During anaphase I the sister chromatids move together to the same pole.
- During anaphase II the sister chromatids are separated to opposite poles.




Prophase I
Metaphase I
Anaphase I
Telophase I and Cytokinesis
Centrosome (with centriole pair)
Sister chromatids
Chiasmata
Spindle
Homologous chromosomes
Fragments of nuclear envelope
Centromere (with kinetochore)
Metaphase plate
Microtubule attached to kinetochore
Sister chromatids remain attached
Homologous chromosomes separate
Cleavage furrow


Prophase II
Metaphase II
Anaphase II
Telophase II and Cytokinesis
Sister chromatids separate
Haploid daughter cells forming

Mendelian inheritance and its modification

- **Gregor Mendel and the Laws of Inheritance.**

Mendelian inheritance (or Mendelian genetics or Mendelism) is a set of primary tenets relating to the transmission of hereditary characteristics from parent organisms to their children; it underlies much of genetics. The tenets were initially derived from the work of Gregor Mendel published in 1865 and 1866, which was "re-discovered" in 1900; they were initially very controversial, but they soon became the core of classical genetics.

The laws of inheritance were derived by Gregor Mendel, conducting hybridization experiments in garden peas (Pisum sativum). Between 1856 and 1863, he cultivated and tested some 28,000-pea plants. From these experiments, he deduced two generalizations that later became known as Mendel's Laws of Heredity or Mendelian inheritance. He described these laws in a two part paper, "Experiments on Plant Hybridization", which was published in 1866.

Genetic Terms.

Pedigree .family relationships chart.

Heredity .parents passing on genes to offspring.

Gene .segment of DNA that controls an organism's traits.

Dominant .the genetic allele that masks the other if both are present. The uppercase allele.

Recessive .the genetic allele that is masked by the other if both are present. Its trait is only observed if homozygous. The lowercase allele.

Pure .contains only one characteristic of a trait. Homozygous.

Hybrid .containg two different alleles of a trait (ex. Aa or Mm); heterozygous.

Allele .the different possible forms of a gene.

Genotype .genetic makeup, all of an organism's genes.

Phenotype .appearance, or physical characteristics.

Heterozygous .having different allels, hybrid.

Homozygous .having the same alleles, pure .

Inheritance .genes passed on from parent to offspring.

Codominance .2 alleles are fully expressed.

incomplete dominance .2 alleles that share expression.

polygenic inheritance .controlled by several genes at once.

sex-linked genes .determined by a gene located on the sex chromosome (the X or Y chromosome).

P1 .parent generation .

F1 .Filial generation, parent's offspring, this generation is the used to fertilize itself.

F2 .filial generation, the offspring resulting from the F1 fertilizing itself.

Mendel's Laws are as follows:

1. The Law of Dominance

2. The Law of Segregation

3. The Law of Independent Assortment

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 also 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**.[5]

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, dominance has to do with the expression of the genotype and not its transmission. The upper case letters are used to represent dominant alleles whereas the lowercase letters are used to represent recessive alleles.

1. The Law of Dominance.

In a cross of parents that are pure for contrasting traits, only one form of the trait will appear in the next generation. Offspring that are hybrid for a trait will have only the dominant trait in the phenotype.

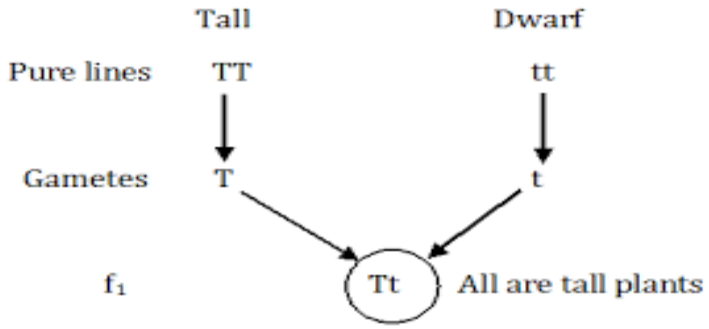
When he crossed **pure tall plants** with pure short plants, all the new pea plants (referred to as the **F1 generation) were tall**. Similarly, **crossing pure yellow seeded** pea plants and pure green seeded pea plants produced an **F1 generation of all yellow** seeded pea plants. The same was true for other pea traits.

Parent Pea Plants	F1 Pea Plants
tall stem x short stem	all tall stems
yellow seeds x green seeds	all yellow seeds
green pea pods x yellow pea pods	all green pea pods
round seeds x wrinkled seeds	all round seeds
axial flowers x terminal flowers	all axial flowers

Three possible genotypes for pea plant.

Genotype Symbol	Genotype Vocab	Phenotype
TT	homozygous DOMINANT or pure tall	tall
Tt	heterozygous or hybrid	tall
tt	homozygous RECESSIVE or pure short	short

Example :

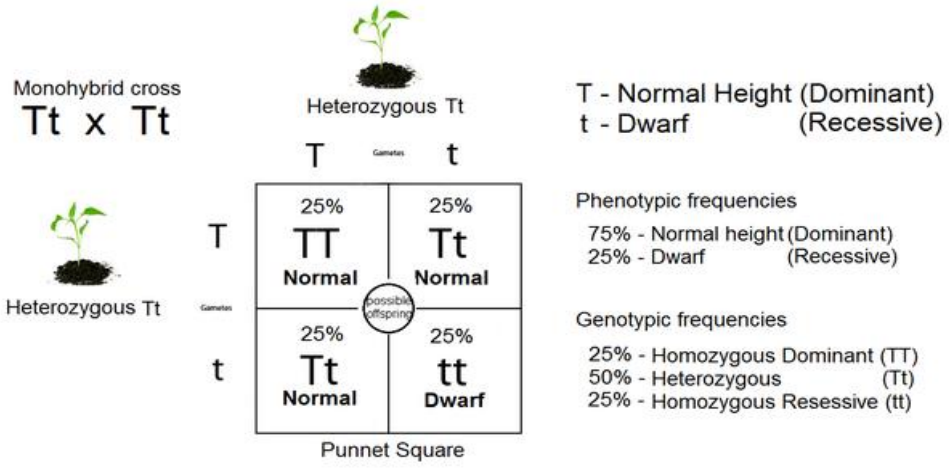


2. The Law of Segregation.

Every individual organism contains two alleles for each trait, during the formation of gametes (eggs or sperm), the two alleles responsible for a trait separate from each other. Alleles for a trait are then "recombined" at fertilization, producing the genotype for the traits of the offspring.

Parent Pea Plants (Two Members of F1 Generation)		**Offspring (F2 Generation)**	
Genotypes: **Tt x Tt**	Phenotypes: tall x tall	Genotypes: 25% TT 50% Tt 25% tt	Phenotypes: 75% tall 25% short

Example:



3. The Law of Independent Assortment.

Alleles for different traits are independently *distributed to individual gametes & offspring* (*from parents to offspring).*

For example

Height (tall or short), **seed shape** (round or wrinkled), **pod color** (green or yellow), etc. Mendel noticed during all his work that the height of the plant and the shape of the seeds and the color of the pods had no impact on one another. In other words, being tall didn't automatically mean the plants had to have green pods, nor did green pods have to be filled only with wrinkled seeds, the different traits seem to be inherited Independent.

The genotypes of our parent pea plants will be:

RrGg x RrGg

where

"R" = dominant allele for round seeds

"r" = recessive allele for wrinkled seeds

"G" = dominant allele for green pods

"g" = recessive allele for yellow pods

Notice that we are dealing with two different traits: **(1) seed texture (round or wrinkled) & (2) pod color (green or yellow).** Notice also that each parent is hybrid for each trait (one dominant & one recessive allele for each trait).

There are four possible letter combinations: RG, Rg, rG, and rg. These gametes are going "outside" the p-square, above 4 columns & in front of 4 rows. We fill things in just like before --- "letters from the left, letters from the top". When we finish each box gets four letters total (two "are's" & two "gees").

This is what it looks like:

	RG	Rg	rG	rg
RG	RRGG round	RRGg round	RrGG round	RrGg round
Rg	RRGg round	RRgg round	RrGg round	Rrgg round
rG	RrGG round	RrGg round	rrGG wrinkled	rrGr wrinkled
rg	RrGg round	Rrgg round	rrGg wrinkled	rrgg wrinkled

The results from a dihybrid cross are always the same:

- 9/16 boxes (offspring) show dominant phenotype for both traits (round & green),
- 3/16 show dominant phenotype for first trait & recessive for second (round & yellow),
- 3/16 show recessive phenotype for first trait & dominant form for second (wrinkled & green), &
- 1/16 show recessive form of both traits (wrinled & yellow).

Summary:

I would like to summarize Mendel's Laws by listing the cross that illustrates each.

LAW	PARENT CROSS	OFFSPRING
DOMINANCE	**TT x tt** **tall x short**	**100% Tt** **tall**
SEGREGATION	**Tt x Tt** **tall x tall**	**75% tall** **25% short**
INDEPENDENT ASSORTMENT	**RrGg x RrGg** **round & green x round & green**	**9/16 round seeds & green pods** **3/16 round seeds & yellow pods** **3/16 wrinkled seeds & green pods** **1/16 wrinkled seeds & yellow pods**

Pedigree Analysis

A pedigree. Is a family tree or chart made of symbols and lines that represent a patient's genetic family history. The pedigree is a visual tool for documenting biological relationships in families and the presence of diseases. Pedigree analysis is an assessment made by a medical professional about genetic risk in a family.

Pedigree Analysis:

The study of an inherited trait in a group of related individuals to determine the pattern and characteristics of the trait, including its mode of inheritance, age of onset, and phenotypic variability.

A pedigree chart displays a family tree, and shows the members of the family who are affected by a genetic trait.

- Pedigrees provide concise and accurate records of families.
- Pedigrees are helpful in following and diagnosing heritable traits (e.g. diseases and medical conditions) .
- pedigrees are useful in mapping (locating and isolating) genes responsible" for certain traits .

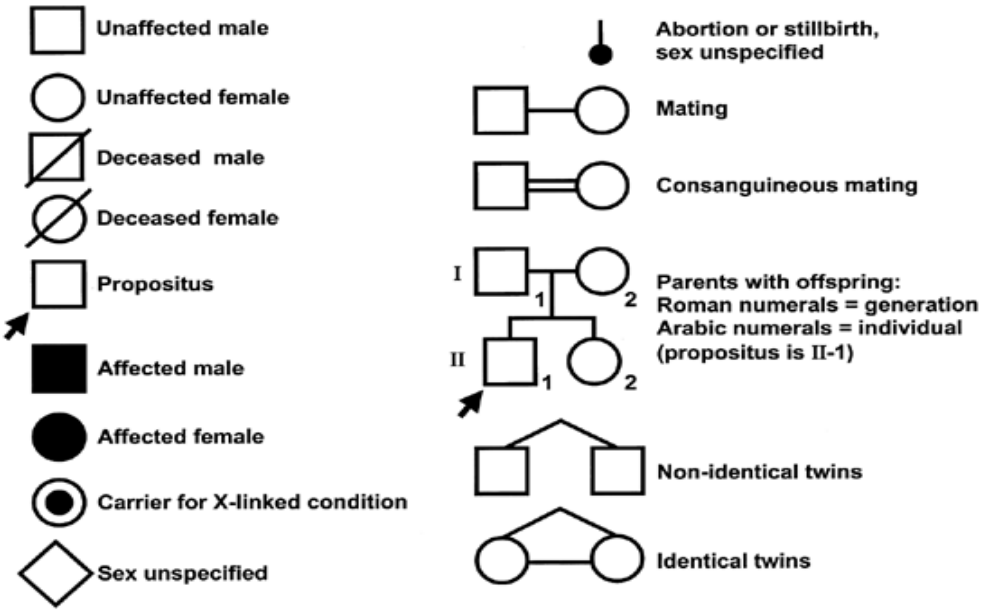
➢ **In humans, pedigree analysis is used to determine individual genotypes and to predict the mode of transmission of single gene traits.**

Goals of Pedigree Analysis:

1. Determine the mode of inheritance: **dominant, recessive, partial dominance, sex linked, autosomal, mitochondrial, maternal effect.**
2. Determine the probability of an affected offspring for a given cross.

Pedigree analysis symbols:

A series of symbols are used to represent different aspects of a pedigree. Below are the principal symbols used when drawing a pedigree.



Inheritance patterns in pedigrees:

•Autosomal dominant

•Autosomal recessive

•X-linked dominant

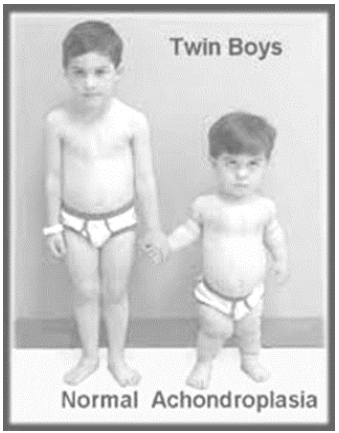
•X-linked recessive

•Y-linked

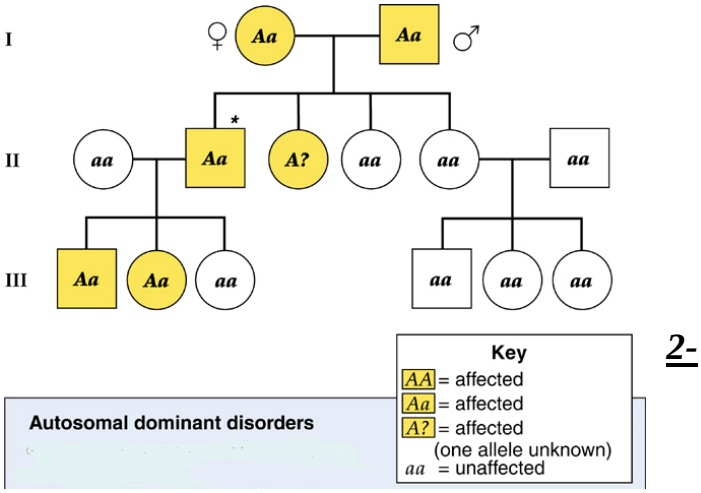
•Mitochondrial inheritance

1- Autosomal dominant Inheritance.

- **Heterozygotes and homozygous dominant** individuals are **affected**.
- Affected offspring have at least **one affected parent**.
- Trait should not **skip** generations (unless penetrance).



- All unaffected individuals are **homozygous** for the **normal recessive allele**.
- An affected person married to a "normal" person should have approximately 50% of the offspring being affected. (Also indicates that the affected individual is heterozygous).
- males and females are equally affected.
- Example as **Marfan syndrome** .An autosomal dominant genetic disorder that affects the skeletal system, cardiovascular system, and eyes.



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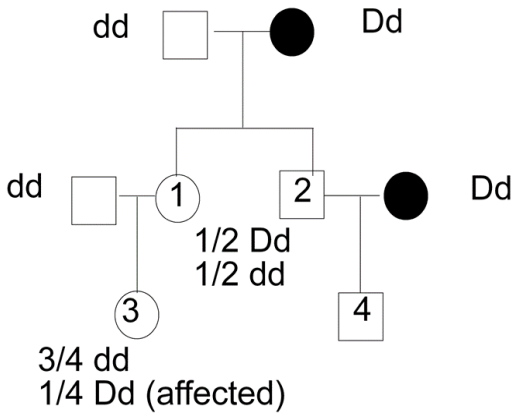
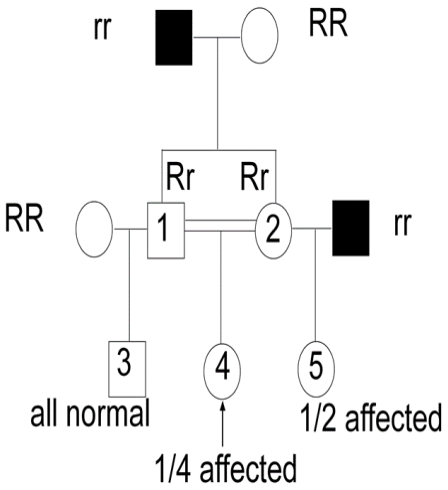


Autosomal Recessive Inheritance.

- Trait often skips generations.
- Males and females are equally affected.
- Affected individual may have unaffected parents.
- All children of two affected individuals are affected.
- The risk of an affected child with heterozygous parents is 25%.



- When a "normal" person is married to an affected individual, all of the children are normal (indicating the normal parent is

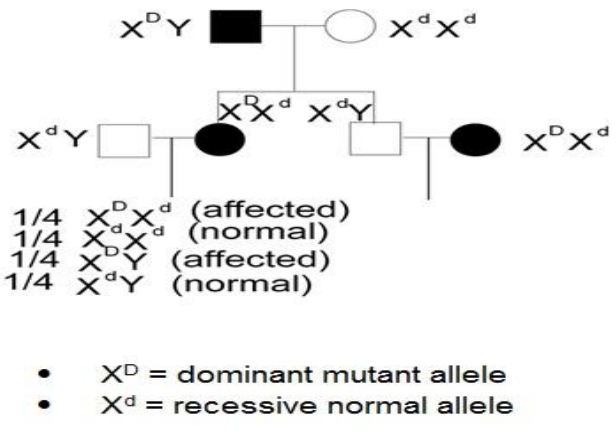
homozygous dominant). **But** If a "normal" person is married to an affected individual and one or more of the **children is affected**, then approximately half of the children should be affected. (**Showing that the "normal" parent is heterozygous**).

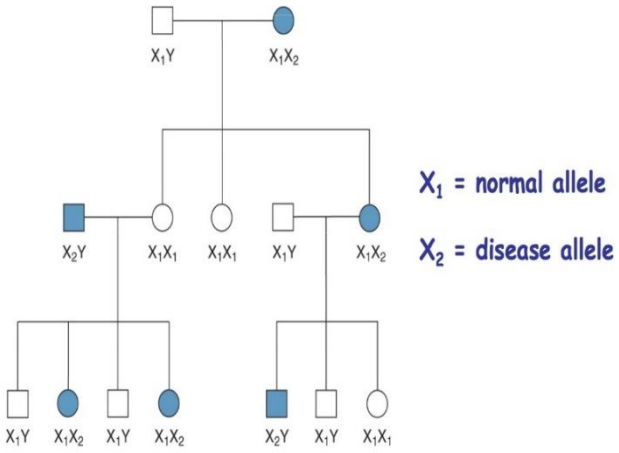
- Examples: cystic fibrosis, galactosemia, albinism, hemophilia, sickle-cell anemia.

3-X (Sex chromosome)-linked dominant Inheritance.

Mothers pass their X's to both sons and daughters ,Fathers pass their X to daughters only.

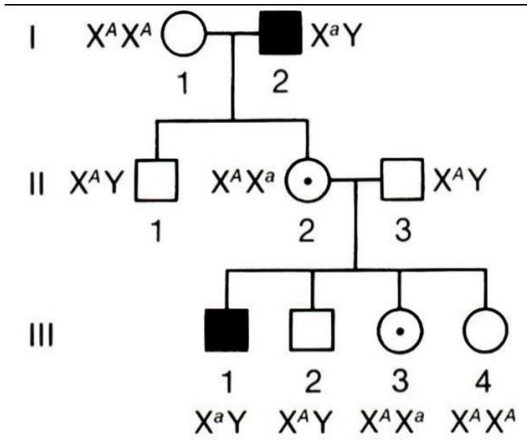
- Trait should not skip generations (unless penetrance).
- Affected males must come from affected mothers.
- Approximately half of the children of an affected female are affected. (Figuring the mother is heterozygous).
- all daughters of an affected male and a normal female are affected.
- For a female child to be affected, the father or the mother must be affected.
- all daughters of an affected male and a normal female are affected.
- females are more likely to be affected than males.
- Examples: fragile X syndrome.





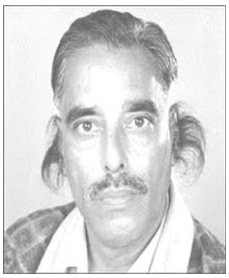
4-X (Sex chromosome)-linked Recessive Inheritance.

Males get their X from their mother fathers pass their X to daughters only.



- Trait is never passed from father to son.
- Males more likely to be affected than females.
- For a female child to be affected, the father must be affected and the mother must be affected or a carrier.
- All of the sons of an affected mother must be affected.
- Approximately half of the sons of carrier females should be affected.
- Example. Hemophilia.

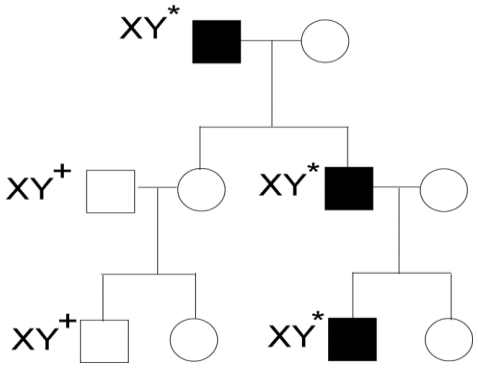
5- Y- (Sex chromosome)- linked Inheritance



Traits on the Y chromosome are only found in males, never in females.

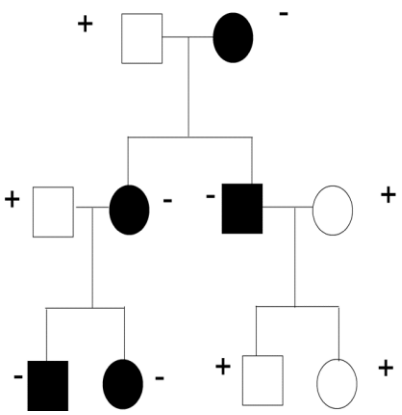
The father's traits are passed to all sons. Dominance is irrelevant: there is only 1 copy of each Y-linked gene (hemizygous).

- Due to an allele on the Y-chromosome.
- Characteristic: when a male is affected, all of his male children are affected.
- Examples: male infertility and hypertrichosis pinnae.



6-Mitochondrial Inheritance:

- Mitochondria (and genetic disorders caused by mutations in mitochondrial genes) are maternally inherited.
- Mitochondria are transmitted from mothers to all their offspring through the cytoplasm of the egg.
- Note that only 1 allele is present in each individual, so **dominance** is not an issue.
- If a male has a mitochondrial trait, none of his offspring inherit it.



Gene Interaction (Non-Mendelian Genetics)

The collaboration of several different genes in the production of one phenotypic character (or related group of characters).

Introduction to Gene Interaction:

Mendelian genetics does not explain all kinds of inheritance for which the phenotypic ratios in some cases are different from Mendelian ratios (3:1 for monohybrid, 9:3:3:1 for di-hybrid in F_2). This is because sometimes a particular allele may be partially or equally dominant to the other or due to existence of more than two alleles or due to lethal alleles.

Gene Interaction Types

- **Allelic gene interaction**

Expression of character is produced by interaction between alleles of a single gene.

- **Non-allelic gene interaction**

Expression of character is produced by interaction between two or more genes.

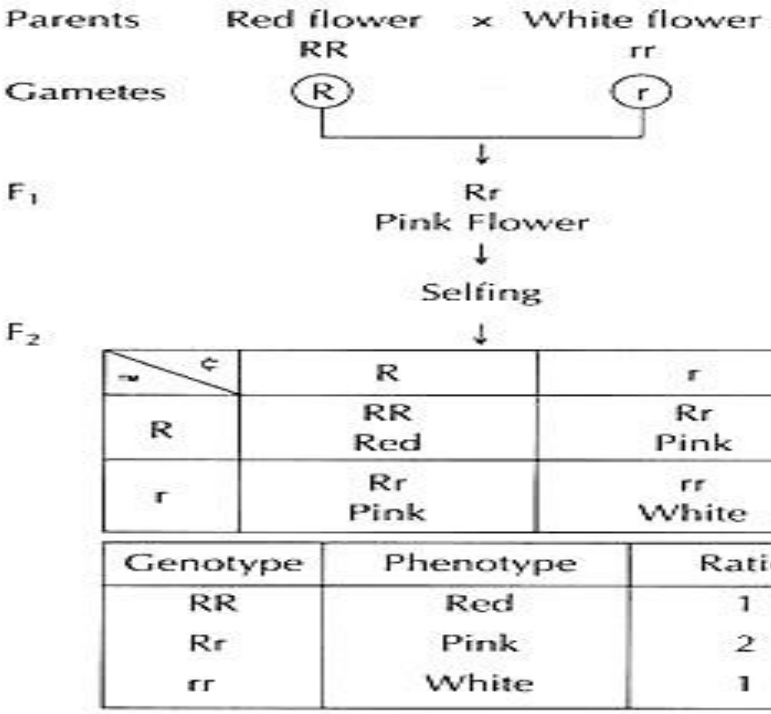
1. **Allelic Gene Interactions types :**

a) Incomplete Dominance or Blending Inheritance (1:2:1):

A dominant allele may not completely suppress other allele, hence a heterozygote is phenotypically distinguishable (intermediate phenotype) from either homozygotes.

Example.

Snapdragon, the cross between pure red-flowered and white-flowered plants yields pink-flowered F_1 hybrid plants (deviation from parental phenotypes), i.e., intermediate of the two parents. When F_1 plants are self-fertilized, the F_2 progeny shows three classes of plants in the ratio 1 red: 2 pink: 1 white instead of 3:1, Therefore, a F1 **di-hybrid** showing incomplete dominance for both the characters will segregate in F2.



♂ \ ♀	R	r
R	RR Red	Rr Pink
r	Rr Pink	rr White

Genotype	Phenotype	Ratio
RR	Red	1
Rr	Pink	2
rr	White	1

Fig. 7.1 : Inheritance of flower colour in snapdragon

b) Co-dominance:

Here both the alleles of a gene express themselves in the heterozygotes. Phenotypes of both the parents appear in F_1 hybrid rather than the intermediate phenotype.

Example.

Only two alleles exist, M and N. Father with N blood group (genotype NN) and mother with M blood group (genotype MM) will have children with MN blood group (genotype MN). Both phenotypes are identifiable in the hybrid. F2 segregates in the ratio 1M blood group: 2 MN blood group: 1 N blood group.

III. Codominance

- When two alleles of a gene specify two distinct, detectable gene products
- MN blood group in humans: L^M, L^N alleles
- MN locus codes for surface glycoprotein on red blood cells; can detect immunochemically.

- $L^M L^M$ gives M phenotype
- $L^M L^N$ gives MN phenotype
- $L^N L^N$ gives N phenotype

- $L^M L^N$ X $L^M L^N$ produces 1/4 $L^M L^M$, 1/2 $L^M L^N$, 1/4 $L^N L^N$

c) Over-dominance.

Sometimes the phenotype of F_1 heterozygote is more extreme (vigorous and advantage) than that of either parents.

Example. Sickle cell anemia

Sickle-Cell Anemia:
an example of Overdominance

S=sickle-cell
H=normal

possible offspring

Mom \ Dad	H	S
H	HH	HS
S	HS	SS

Hb
75% Normal
25% Sickle-cell

Malaria
75% Resistant
25% Susceptible

d) Multiple Alleles:

A gene for particular character may have more than two alleles occupying same locus of the chromosome (only two of them present in a diploid organism). These allomorphs make a series of multiple alleles.

Example.

Human ABO blood group system furnishes best example. The gene for antigen may occur in three possible allelic forms – l^A, I^B, i. The allele for the A antigen is co-dominant with the allele I^8 for the B antigen. Both are completely dominant to the allele i which fails to specify any detectable antigenic structure. Therefore, the possible genotypes of the four blood groups are shown in Fig.

Blood Groups	Genotypes
A	I^AI^A, I^Ai
B	I^BI^B, I^Bi
AB	I^AI^B
O	ii

Fig. 7.3: ABO blood groups and their genotypes in human

e) Lethal Factor (2:1):

The genes, which cause the death of the individual carrying it, is called lethal factor.

Balanced lethals are all heterozygous for the lethal genes; both dominant and recessive homozygotes will die.

Recessive lethals are expressed only when they are in homozygous state and the heterozygotes remain unaffected. There are genes that have a dominant phenotypic effect but are recessive lethal, **e.g., gene for yellow coat color in mice.**

But many genes are recessive both in their phenotypic as well as lethal effects, **e.g., gene producing albino seedlings in barley.**

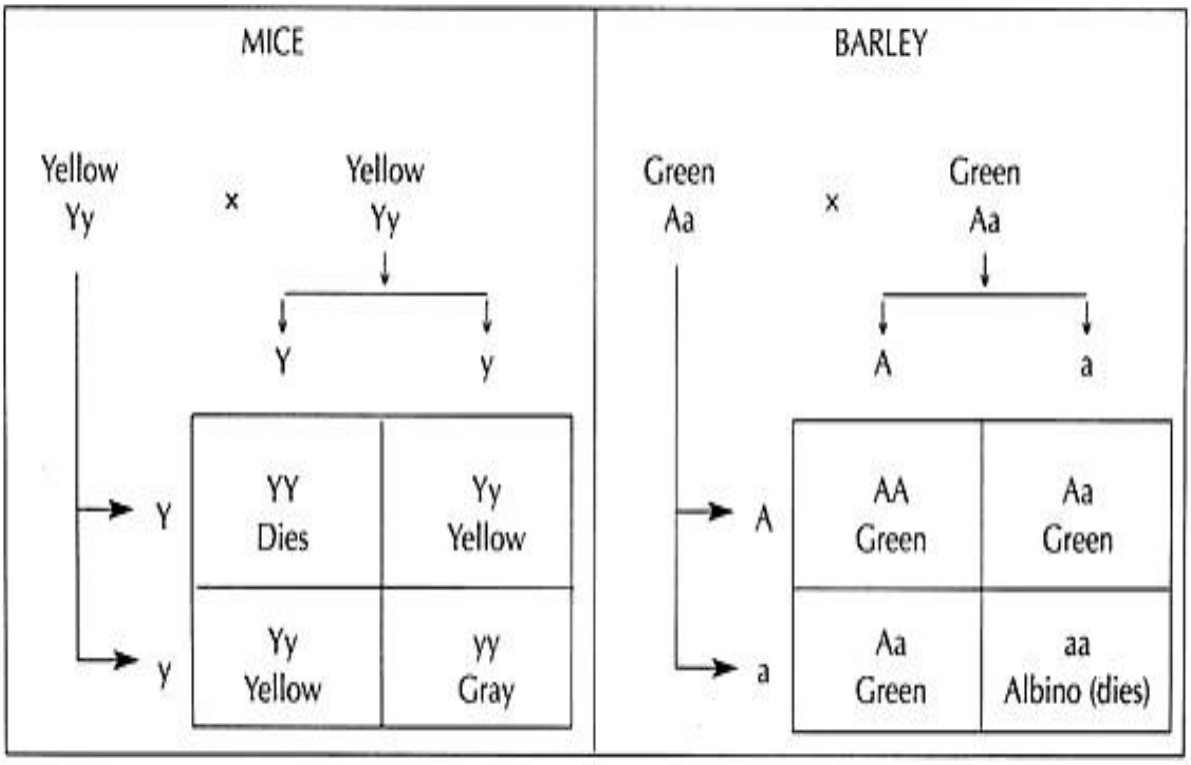


Fig. 7.2: Inheritance of lethal gene in mice and barley

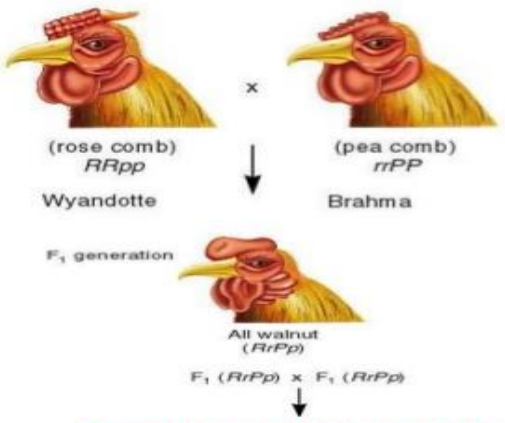
2. Non-allelic gene interaction:

a) Simple Interaction (9:3:3:1):

In this case, two non-allelic gene pairs affect the same character. The dominant allele of each of the two factors produces separate phenotypes when they are alone. When both the dominant alleles are present together, they produce a dis-tinct new phenotype. The absence of both the dominant alleles gives rise to yet another pheno-type.

Example.

The inheritance of **comb types** in fowls is the best example where **R gene** gives rise to **rose comb** and **P gene** gives rise to **pea comb**; both are **dominant over single comb**; the **presence of both the dominant genes** results in **walnut comb** .



F2 Generation

	RP	Rp	rP	rp
RP	RRPP Walnut	RRPp Walnut	RrPP Walnut	RrPp Walnut
Rp	RRPp Walnut	RRpp Rose	RrPp Walnut	Rrpp Rose
rP	RrPP Walnut	RrPp Walnut	rrPP Pea	rrPp Pea
rp	RrPp Walnut	Rrpp Rose	rrPp Pea	rrpp Single

F_2 generation consisted of chickens with four types of combs

9 walnut : 3 rose : 3 pea : 1 single

Bateson and Punnett reasoned that comb morphology is determined by two different genes

b) Complementary Factor (9:7):

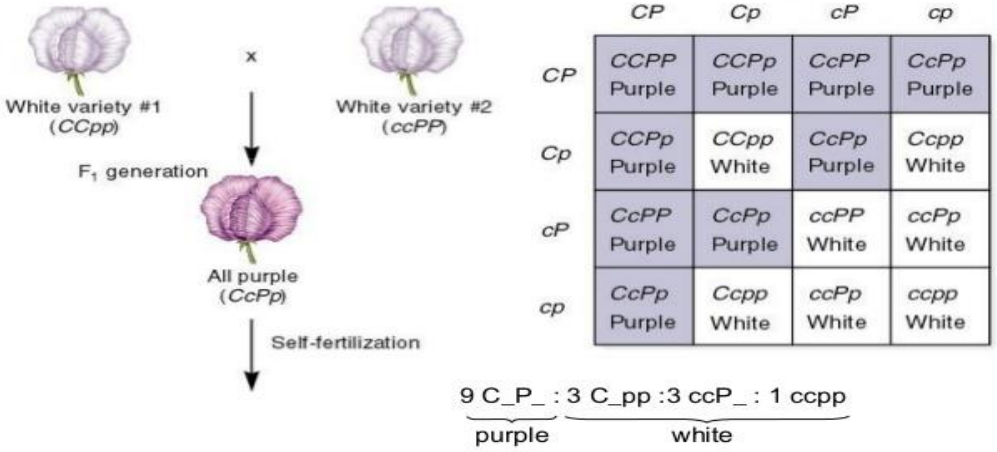
Certain characters are produced by the inter-action between two or more genes occupying different loci inherited from different parents. These genes are complementary to one another, i.e., if present alone they remain unexpressed, only when they are brought together through suitable crossing will express.

Example:

In sweet pea (Lathyrus odoratus), **both the genes C and P** are required to synthesize **anthocyanin pigment** causing **purple colour**. **But absence** of any one cannot produce anthocyanin causing **white flower**. So C and P are complementary to each other for anthocyanin formation.

A Cross Producing a 9:7 ratio

Figure 4.18



c) Epistasis:

When a gene or gene pair masks or prevents the expression of other non-allelic gene, called epistasis. The gene which produces the effect called epistatic gene and the gene whose expression is suppressed called hypostatic gene.

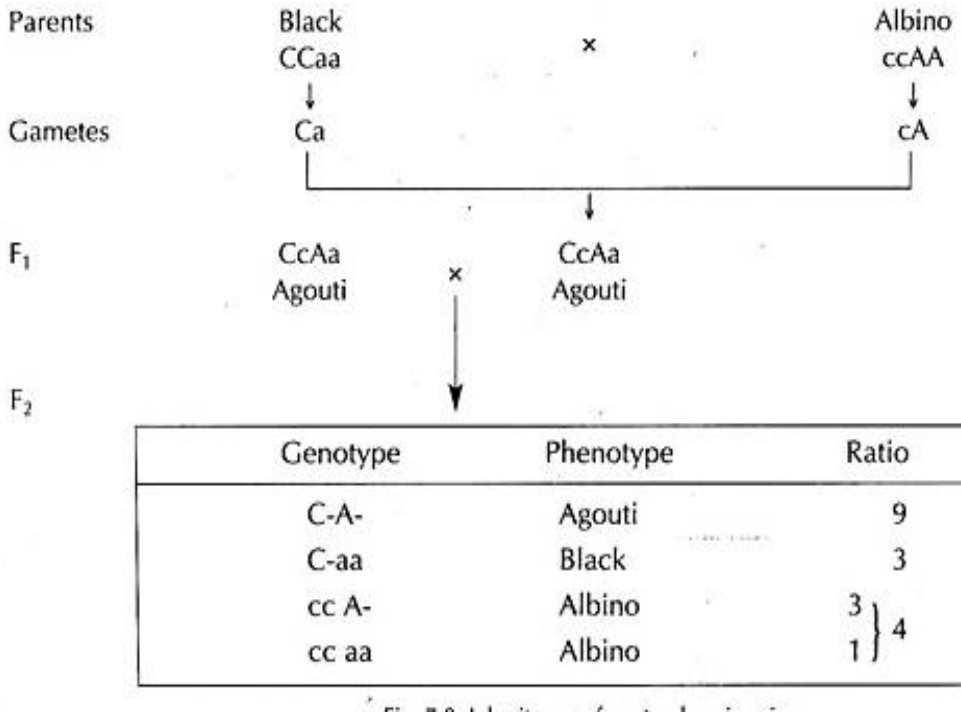
Types of epistasis :

1. **Recessive Epistasis or Supplementary Factor (9:3:4):**

In this case, homozygous recessive condition of a gene determines the phenotype irrespective of the alleles of other gene pairs, i.e., recessive allele hides the effect of the other gene.

Example:

The coat colour of mice is controlled by two pairs of genes. Dominant gene C produces black colour, absence of it causes albino. Gene A produces agouti colour in presence of C, but cannot express in absence of it (with cc) resulting in albino. Thus recessive allele c (cc) is epistatic to dominant allele A.



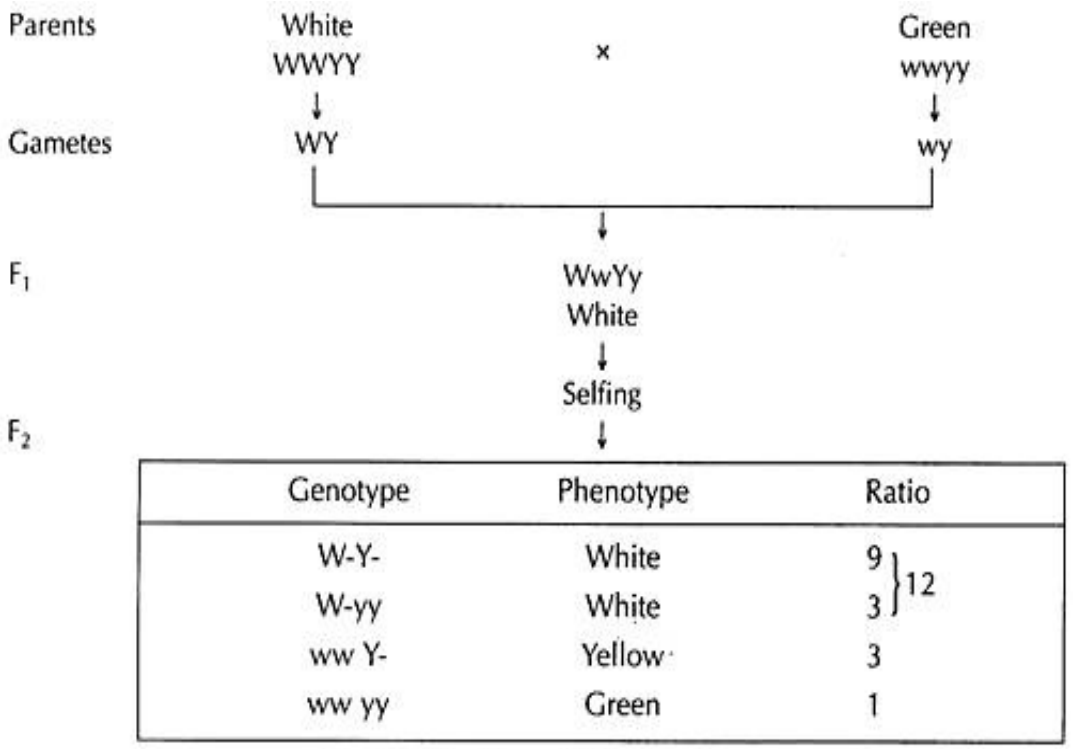
Genotype	Phenotype	Ratio
C-A-	Agouti	9
C-aa	Black	3
cc A-	Albino	3 } 4
cc aa	Albino	1 }

2. Dominant Epistasis (12:3:1):

Sometimes a dominant gene does not allow the expression of other non-allelic gene called dominant epistasis.

Example:

In summer squash, the fruit colour is governed by two genes. The dominant gene W for white colour, suppresses the expression of the gene Y which controls yellow colour. So yellow colour appears only in absence of W. Thus W is epistatic to Y. In absence of both W and Y, green colour develops.



Genotype	Phenotype	Ratio
W-Y-	White	9 } 12
W-yy	White	3 }
ww Y-	Yellow	3
ww yy	Green	1

Fig. 7.10: Inheritance of fruit colour in summer squash

Pseudoalleles

Is a state in which two or more genes with **similar functions** are **located so close to one another on a chromosome** that they are **genetically linked**. This means that the two or more genes (pseudoalleles) are **nearly always inherited together**. Since the two or more genes have **related functions**, they may appear to act as a **single gene**.

Characteristic of Pseudoalleles:

1. These are closely linked allele within which crossing over occur.
2. They affect the same character.

Examples of Pseudoalleles:

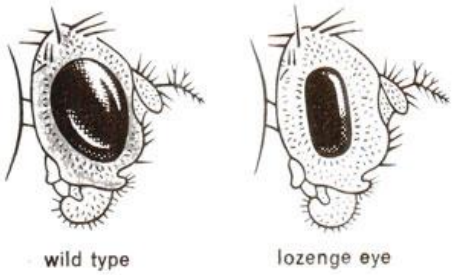
There are several examples of pseudoalleles. The well-known example are **lozenge gene**.

Lozenge Eye in Drosophila:

Lozenge locus in Drosophila. The mutant gene produces eye with glossy smooth surface. Several alleles of lozenge gene were identified and all mapped at one locus. All heterozygotes carrying two different mutants were lozenge in phenotype.

But progeny of such heterozygotes produced wild type recombinants at a frequency much higher than expected spontaneous mutation. This indicated that Iz_1 and Iz_2 were pseudoalleles.

Pseudoalleles have similar phenotypic effects **but can still** be recombined with each other. **The recombination between pseudoalleles is very rare**. Such alleles are considered to be occupying a complex locus divided into sub loci between which recombination can occur.



Iz_1 +/ Iz_2 + Trans-heterozygote (mutant phenotype)

Iz_1Iz_2 /+ + Cis-heterozygote (wild phenotype)

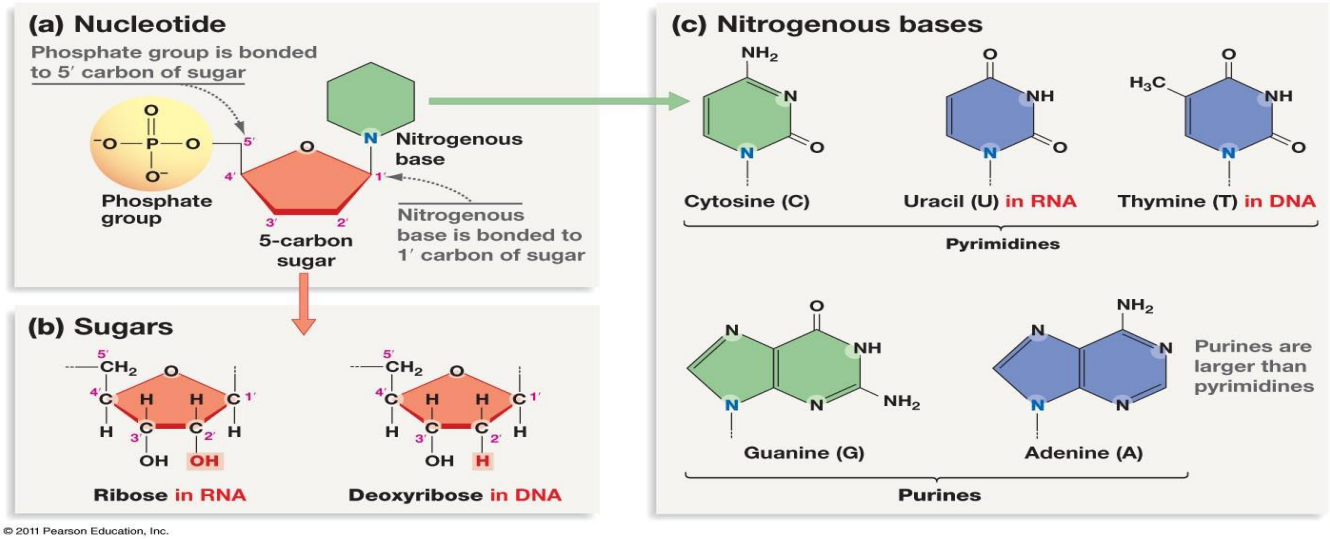
Genetic material

Nucleic acids . Are molecules that allow organisms to transfer genetic information from one generation to the next. There are two types of nucleic acids: deoxyribonucleic acid (better known as **DNA**) and ribonucleic acid (better known as **RNA**).

Nucleic acids are composed of **nucleotide** monomers linked together. Nucleotides contain three parts.

- **A Nitrogenous Base:** There are two kinds of nitrogen-containing bases - purines and pyrimidines. Purines consist of a six-membered and a five-membered nitrogen-containing ring, fused together. Pyridmidines have only a six membered nitrogen-containing ring.
- **A Five-Carbon Sugar**
- **A Phosphate Group**

Nucleotides are linked together to form polynucleotide chains. Nucleotides are joined to one another by covalent bonds between the phosphate of one and the sugar of another. These linkages are called **phosphodiester linkages**. Phosphodiester linkages form the sugar-phosphate backbone of both DNA and RNA.



- Two different kinds of genetic material exist: **deoxyribonucleic acid** (DNA) and **ribonucleic acid** (RNA). Most organisms are made of DNA, but a few **viruses** have RNA as their genetic material. The biological information contained in an organism is encoded in its DNA or RNA sequence. **Prokaryotic** genetic material is organized in a simple circular structure that rests in the **cytoplasm**. Eukaryotic genetic material is more complex and is divided into discrete units called genes. Human genetic material is made up of two distinct components: **the nuclear genome and the mitochondrial genome**. The nuclear genome is divided DNA molecules, each contained in a different **chromosome**. The mitochondrial genome is a circular DNA molecule separate from the nuclear DNA. Although the mitochondrial genome is very small, it codes for some very important proteins.

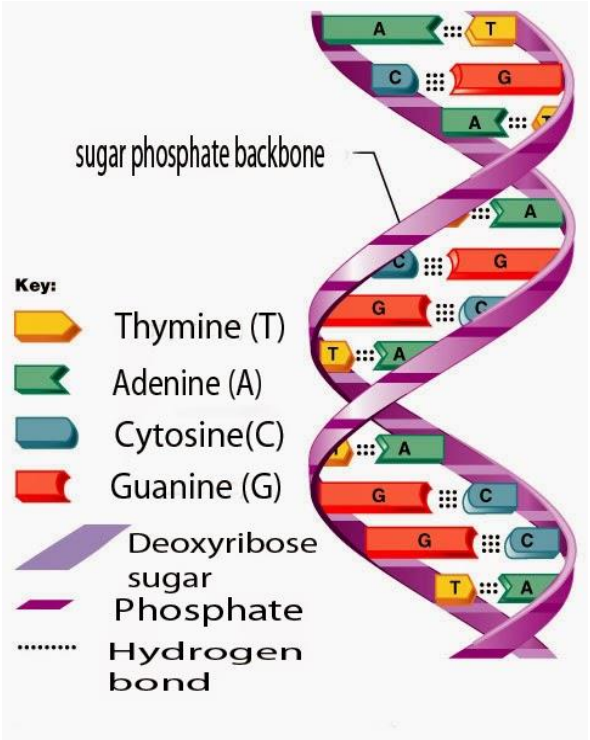
1. DNA

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. Most DNA is located in the **cell nucleus** (where it is called nuclear DNA), but a small amount of DNA can also be **found in the mitochondria** (where it is called mitochondrial DNA or mtDNA).

DNA Structure:

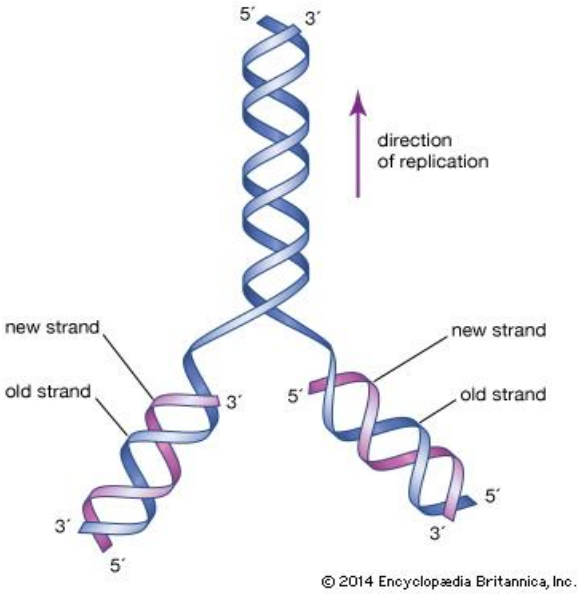
- The information in DNA is stored as a code made up of **four chemical bases**: **adenine (A), guanine (G), cytosine (C), and thymine (T)**. Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people.
- **DNA bases pair up with each other, A with T and C with G, to form units called base pairs.**

- Each base is also **attached to a deoxyribose sugar molecule and a phosphate molecule**. **Together, a base, sugar, and phosphate are called** a **nucleotide**.
- Nucleotides are arranged in two long strands that form a spiral called a **double helix**.(**DNA is a double helix formed by base pairs attached to a sugar-phosphate backbone.**)
- The structure of the double helix is somewhat like a **ladder**, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the **vertical sidepieces of the ladder.**



DNA Replication

The configuration of the DNA molecule is highly stable, allowing it to act as a template for the replication of new DNA molecules, as well as for the production (transcription) of the related RNA (ribonucleic acid) molecule. A segment of DNA that codes for the cell's synthesis of a specific protein is called a gene.



DNA replicates by separating into two single strands, each of which serves as a template for a new strand. The new strands are copied by the same principle of hydrogen-bond pairing between bases that exists in the double helix. **Two new double-stranded**

molecules of DNA are produced, each containing **one of the original strands and one new strand**. This "semiconservative" replication is the key to the stable inheritance of **genetic traits.**

2. **RNA.**

   RNA molecules are single-stranded nucleic acids composed of nucleotides. RNA plays a major role in protein synthesis as it is involved in the transcription, decoding, and translation of the genetic code to produce proteins.

   RNA found in both prokaryotic and eukaryotic cells. In eukaryotic cell RNA found in **cytoplasm as well as in nucleus**. In the cytoplasm it occurs freely as well as in the **ribosomes while in the nucleus it is present in association with chromosomes**. RNA also found in matrix **of mitochondria** and stroma of chloroplast.

   RNA Structure:

   RNA stands for ribonucleic acid and like DNA.RNA, nucleotides contain three components:

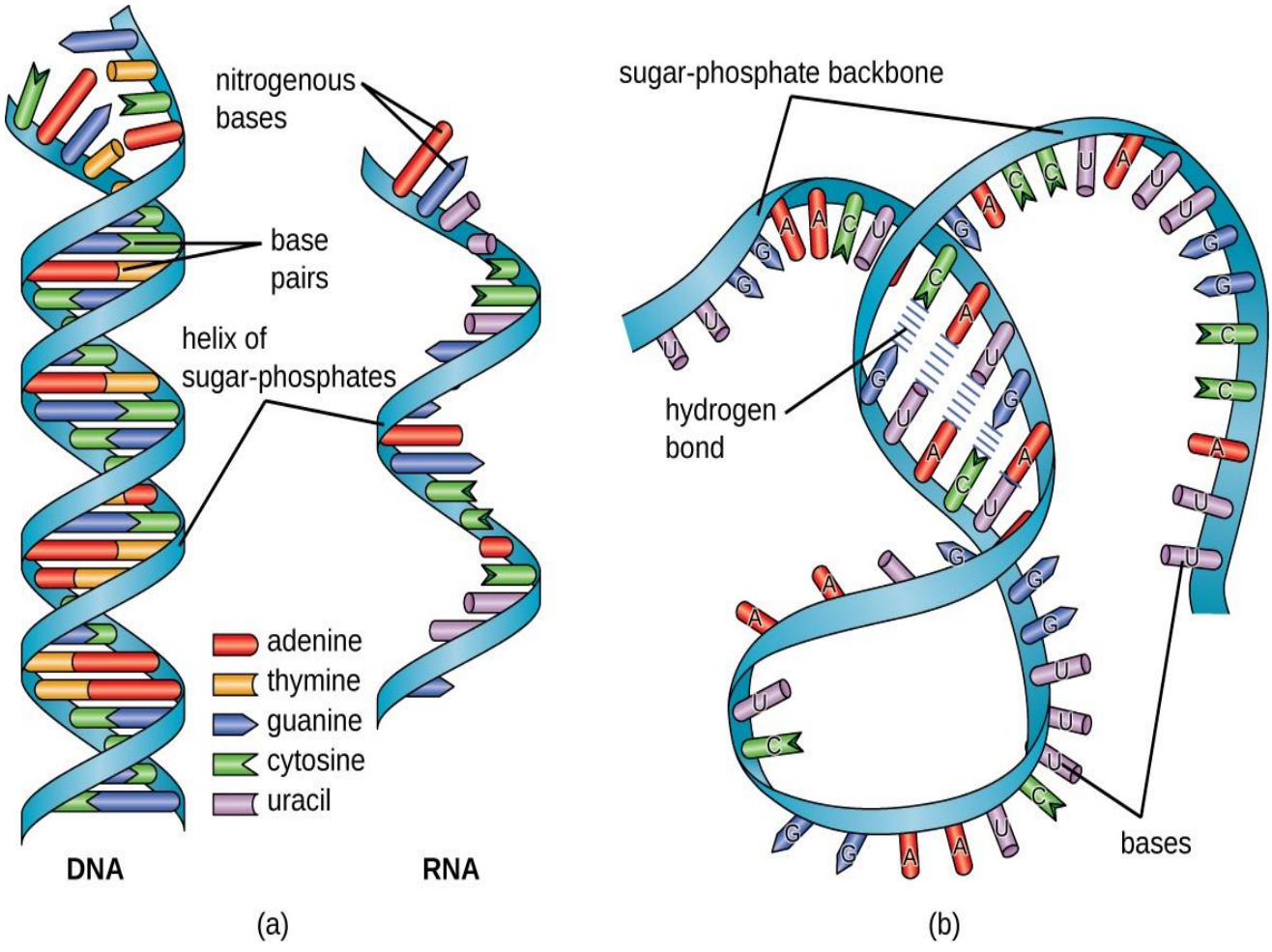
- A Nitrogenous Base
- A Five-Carbon Sugar
- A Phosphate Group

RNA nitrogenous bases include **adenine (A), guanine (G), cytosine (C) and uracil (U)**. The five-carbon (pentose) sugar in RNA **is ribose**. RNA molecules are polymers of nucleotides joined to one another by covalent bonds between the phosphate of one nucleotide and the sugar of another. These linkages are called **phosphodiester linkages**.

Although single-stranded, RNA is not always linear. It has the a**bility to fold into complex three-dimensional shapes** and form hairpin loops. **When this occurs, the**

nitrogenous bases bind to one another. **Adenine pairs with uracil (A-U) and guanine pairs with cytosine (G-C)**. Hairpin loops are commonly observed in RNA molecules such as messenger RNA (mRNA) and transfer RNA (tRNA).

The main job of RNA is to transfer the genetic code need for the creation of proteins from the nucleus to the ribosome. This process prevents the DNA from having to leave the nucleus. This keeps the DNA and genetic code protected from damage. Without RNA, proteins could never be made.



Types of RNA:

RNA molecules are produced in the nucleus of our cells and can also be found in the cytoplasm. The three primary types of RNA molecules are .

(a) Messenger RNA (mRNA):

The mRNA carries the coded information (genetic code) from DNA to ribosomes for synthesis of polypeptides. Hence, it is named messenger RNA. It constitutes about 5-10% of total cellular RNA.

(b) Transfer RNA or (tRNA):

The tRNA is also known as soluble RNA (sRNA) or adaptor RNA. It is the smallest known RNA species that constitute about 10-15 % of the total cellular RNAs. There are at least 20 types of tRNA molecules in every cell, one corresponding to each of the 20 amino acids required for protein synthesis. However, tRNA is always more than 20 and each amino acid is represented by more than one tRNA. Multiple tRNAs representing the same amino acid are called isoaccepting tRNAs. Although tRNAs are less stable in eukaryotes they are more stable in prokaryotes.

(d) Ribosomal RNA (rRNA):

The RNA which is found in ribosomes is called ribosomal RNA. It is most abundant and constitutes about 80% of the total cellular RNA. The rRNA molecule is highly coiled. In combination with proteins, it forms small and large subunits of the ribosomes, hence its name.

Type of RNA	Functions in	Function
Messenger RNA (mRNA) 	Nucleus, migrates to ribosomes in cytoplasm	Carries DNA sequence information to ribosomes
Transfer RNA (tRNA) 	Cytoplasm	Provides linkage between mRNA and amino acids; transfers amino acids to ribosomes
Ribosomal RNA (rRNA) 	Cytoplasm	Structural component of ribosomes

Mutation

Mutation. Is a change in the nucleotide sequence of a gene or a chromosome. Mutations can also be **inherited**, particularly if they have a **positive effect**. The effect of a mutation can **depend on the region in which the sequence** of genetic material has been changed. The simplest and the most harmless are substitutions of a single base pair with another, with no effect on protein sequence. At the other end are insertion or deletion mutations that lead to non-functional gene products. Mutations can also occur on a large scale, with long stretches of DNA (or RNA when it is the genetic material) being inverted, inserted, duplicated, deleted, transposed or translocated.

A mutation could be a loss-of-function or gain-of-function mutation, depending on whether the gene product is inactivated or has enhanced activity. In heterozygotes with two copies of every allele, some mutated gene products can suppress the effect of the wild-type allele. These are called **dominant negative mutations**.

It may be classified into various ways. One of these classifications involves classifying mutations based on the effect on structure:

(1) Small-scale mutations (Gene mutations): affect **one or few** nucleotides of a gene. These are further classified into **substitution mutations**, **insertions**, **inversion,** and **deletions**.

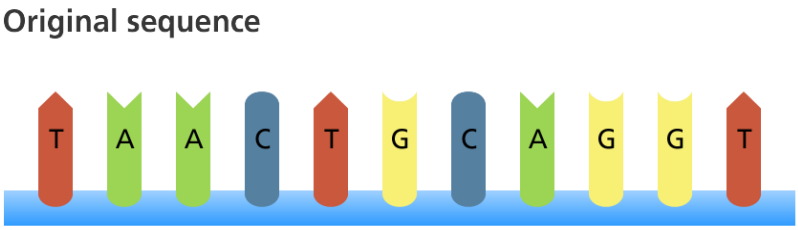
(2) Large-scale mutations (Chromosome mutations): involve a change in the **chromosome**). They are classified further into **amplifications** (or gene duplications), **deletions** of large chromosomal regions, and chromosomal **inversions**.

❖ **A Mutagen.** Anything that causes a mutation (a change in the DNA of a cell). DNA changes caused by mutagens may harm cells and cause certain diseases, such as cancer. Examples of mutagens include **radioactive substances**, x-rays, ultraviolet radiation, and **certain chemicals**.

Classifications of mutation:

A. Small-scale mutations (Gene mutations): affect **one or few** nucleotides of a **gene (Point mutations)**. These are further classified into **substitution mutations, insertions, inversion, and deletions.**

- **Point mutations :** are resulting from a change in **one or a few** nucleotides at a single location in a DNA sequence. **Nucleotides** are the repeating units of a DNA sequence. There are four nucleotides, each with a different nitrogenous base: thymine (T), adenine (A), guanine (G), cytosine (C).
- The **substitution** of a base (e.g. A**T**G becomes A**C**G)
- The **insertion** of a base (e.g. ATG becomes AT**C**G)
- The **deletion** of a base (e.g. A**T**G becomes AG)
- The **inversion** of bases (e.g. A**TG** becomes A**GT**)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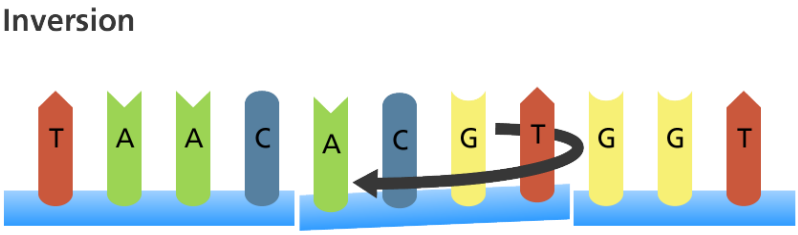
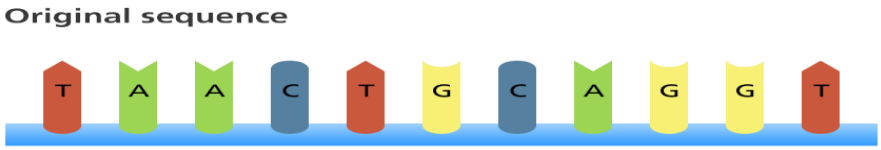
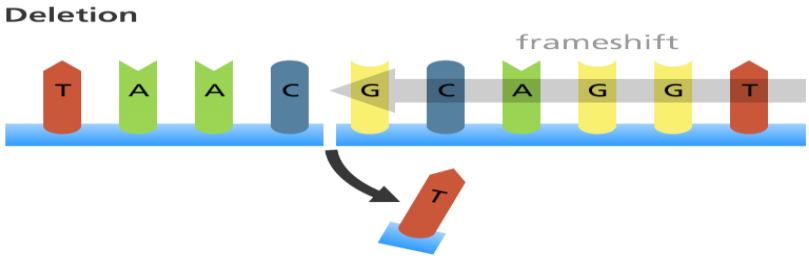
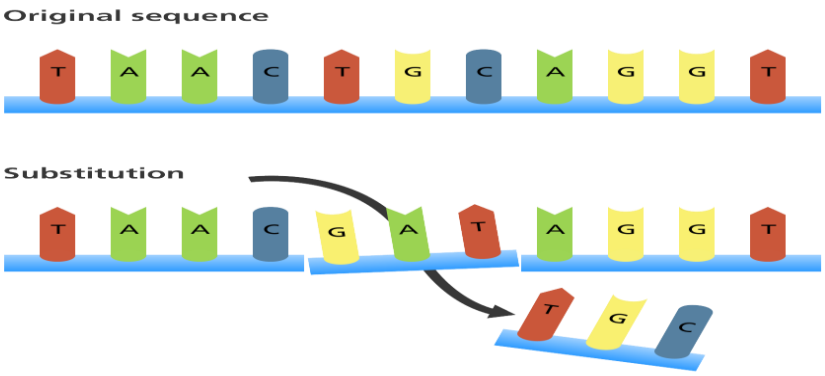
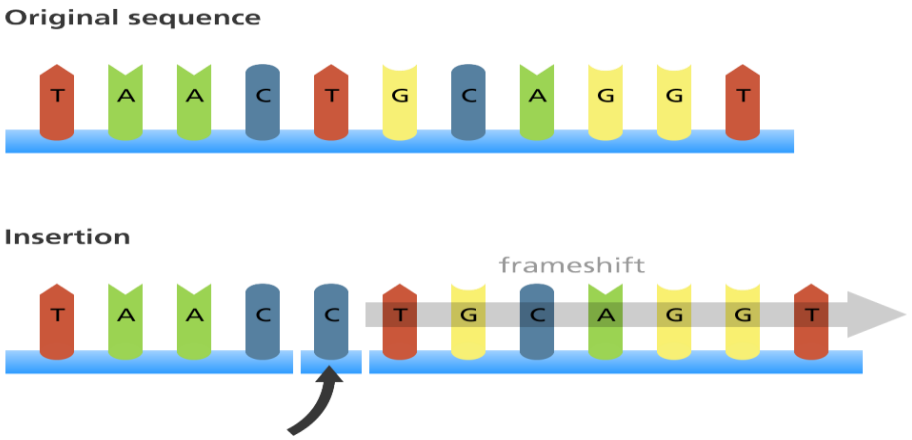

Inversion
T A A C A C G T G G T


Original sequence
T A A C T G C A G G T


Deletion
frameshift
T A A C G C A G G T
T


Original sequence
T A A C T G C A G G T
Substitution
T A A C G A T A G G T
T G C



B. Large-scale mutations :(Chromosome mutations): Changes to the nucleotide sequence in genetic material **can also occur on a large scale, sometimes involving thousands of base pairs and nucleotides**. Involve a **change in the chromosome**.They are classified further into amplifications (or gene **duplications**), **deletions** of large chromosomal regions, **Translocations** and **chromosomal inversions.**

1. Deletion

This type of mutation occurs when a part of the DNA is not duplicated or is lost during DNA replication. The size of this region can either be a mere **nucleotide** or can be large as an entire chromosome.

Disorders Due To Deletion

Common disorders due to deletion mutation in humans are: Cri du chat, Duchenne muscular dystrophy, Di George's syndrome, etc.

2. Duplication

This type of mutation occurs when an extra copy of a region (or regions) in the DNA is produced. This duplicated region can either be located in its normal location in the chromosome or sometimes be located in other parts of the chromosomes or even in another chromosome.

- This duplication can now supply additional material that has the ability to evolve new functions.

Disorders Due To Duplication

Common disorder due to duplication mutation in humans is: *Charcot-Marie-Tooth disease* type I.

3. inversion

During inversion, a portion in the chromosome is reversed and gets inserted back into the chromosome. Basically, two types of inversion exist: *pericentric* and *paracentric*.

- During a pericentric inversion, the inversion encompasses the **centromere** of the chromosome.
- On the other hand, during a paracentric inversion, it only involves either the short or long arm of the chromosome and the inversion point does not include the centromere.

Disorders Due To Inversion

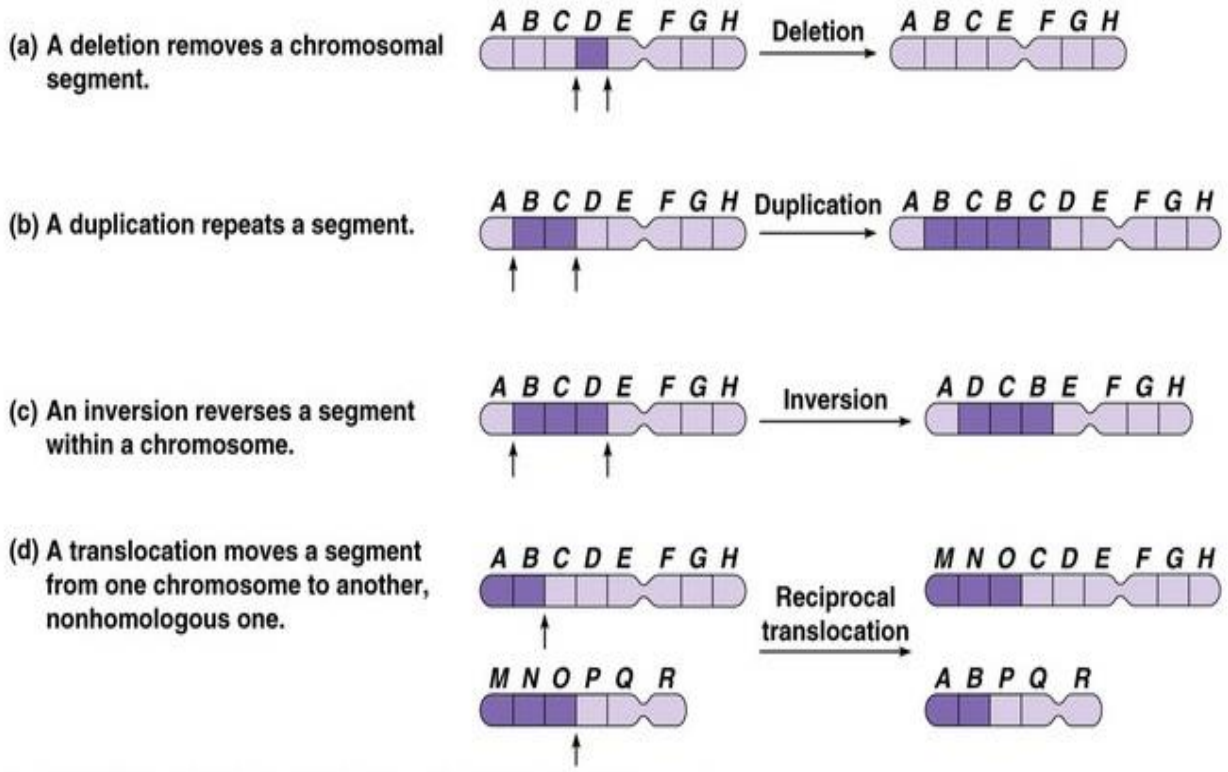
Common disorder due to inversion mutation in humans is *Amniocentensis* during pregnancy.

4. Translocation

Translocation happens when a fragmented chromosome tends to join with a nonhomologous chromosome. This newly-formed segment then detaches from the chromosome and moves to a new position on another chromosome.

Disorders Due To Translocation

Common disorders due to translocation mutation in humans are: XX male syndrome, Down syndrome, Infertility and Cancer.



Sex determination and differentiation

Humans have a total of 46 chromosomes. These include 22 pairs of autosomes, which are the chromosomes that are the same in males and females, and one pair of sex chromosomes, or allosomes, which are different in males and females. Females have two X chromosomes (XX), whereas males have an X and a Y chromosome (XY). An adult female will ovulate around the fourteenth day of her menstrual cycle. Each time a female ovulates, she releases an egg, which contains one X chromosome along with 22 autosomes. An adult male will produce sperm with either an X chromosome or a Y chromosome. Semen, which contains sperm, is released during ejaculation. When an egg and a sperm fuse during reproduction, the chromosome that the sperm carries determines the sex of the child. Sometimes, an individual may receive an abnormal amount of chromosomes, such as in the case of Turner's Syndrome where females have only one functional X chromosome (XO) and the other sex chromosome is either missing or structurally altered. You can learn more about people who are born with reproductive organs and anatomy that does not fit the typical definitions of female or male here.

Human Sex Differentiation

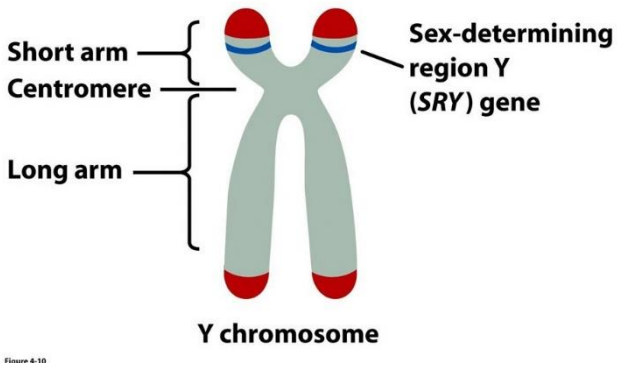
During the process of sex differentiation, a fetus gains characteristics of either a male or a female. Sex differentiation is initiated and controlled by gonadal steroid hormones. These hormones perform organizing functions to permanently differentiate sex organs during development. This process starts before the developing child is even old enough to be considered a fetus, and is instead still an embryo. A developing human is not considered a fetus until the 9th week of development in the uterus, whereas sex differentiation begins during the 6th week of pregnancy.

By the sixth week of development, all embryos have both Wolffian ducts and Müllerian ducts. The Wolffian ducts are embryonic structures that can form the male

internal reproductive system. The Müllerian ducts are embryonic precursor structures to the female internal reproductive system. In this stage, the internal reproductive organ precursors are bipotential, meaning they have the potential to develop into both male and female sex organs given the proper chemical instructions. The way they develop is influenced by hormones, and each fetus will only have one of pair of these ducts by the end of differentiation.

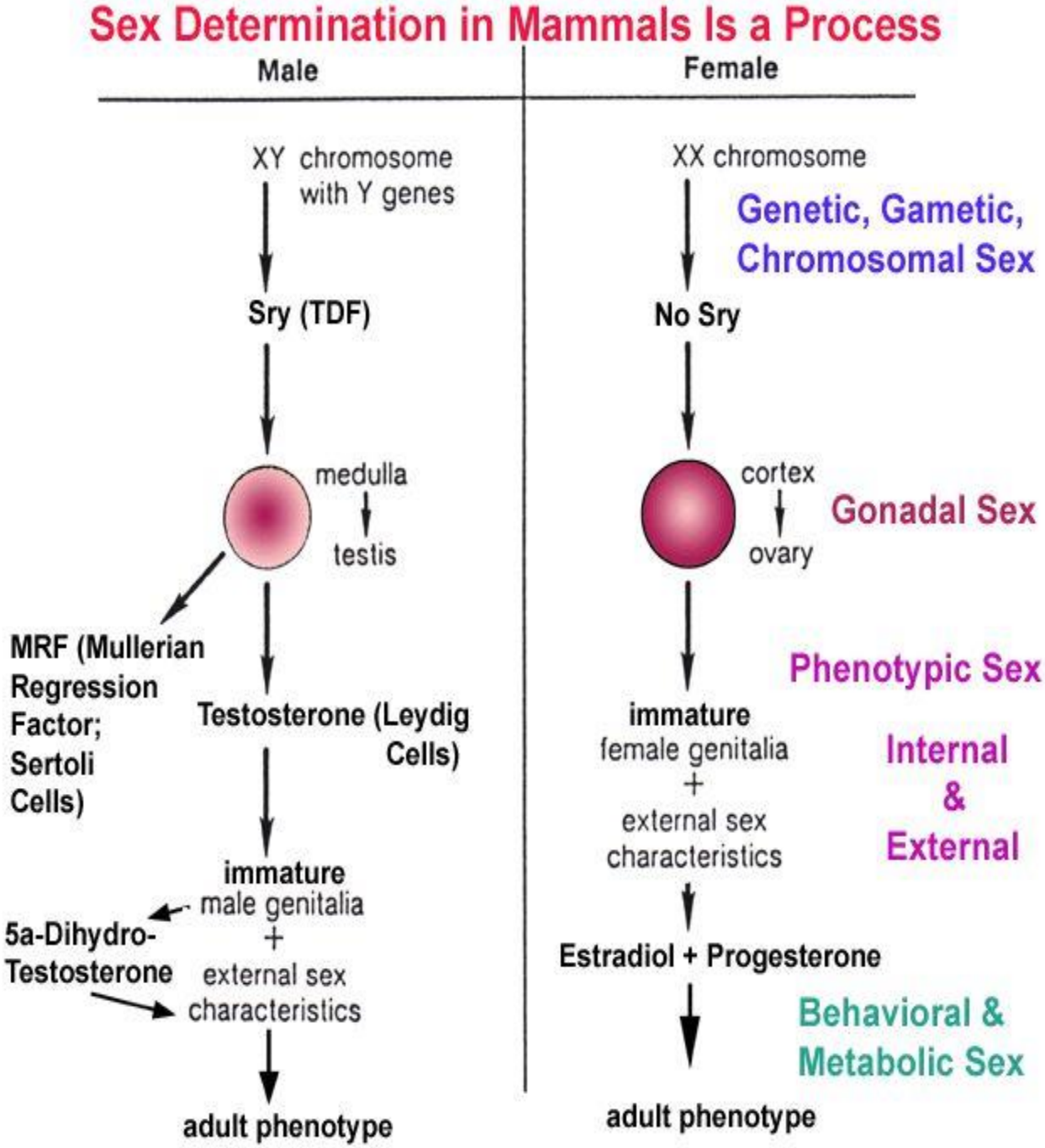
In Males:

For males, the differentiation process is started by the sex determining region Y gene, also known as the SRY-gene (testis – determining factor (TDF) located on the short arm of the Y chromosome) on the Y chromosome. This gene generates the necessary biochemistry inside of a male fetus for him to develop male sex organs. The embryonic gonads secrete a protein called the anti-Müllerian hormone(AMH), which causes the the Müllerian ducts to degenerate. It also causes the Wolffian ducts to develop into the vas deferens and the seminal vesicles. The undifferentiated gonads develop into testes, and other structures such as the prostate gland and the scrotum develop. This illustration shows the location of the SRY-gene on the Y chromosome.



In Females:

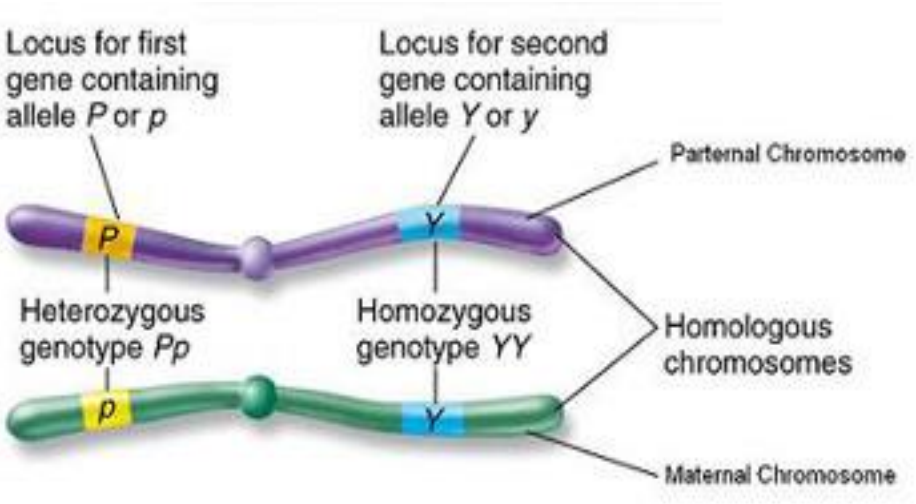
Females have two X chromosomes, so their sexual differentiation is not signaled by the SRY-gene. Instead, the absence of these cues signal their sex organs to develop. The Wolffian ducts degenerate and the Müllerian ducts persist to form the fallopian tubes,



uterus, uterine cervix, and the superior portion of the vagina. The undifferentiated gonads develop into ovaries, and other structures such as the labia and vagina develop.

Genetic selection

Genetic selection is the process by which certain traits become more prevalent in a species than other traits. These traits seen in an organism are due to the genes found on their chromosomes. The genes code for the traits that we are able to observe. Figure 1: Alleles for genes are inherited and come in various forms.



- Some alleles are seen more frequently in a population because there are factors that select those genes.

Types of selection:

1- Natural selection :