Genetics Lecture notes

Dr. Jassim . J. Alnuami

Assistant Ph .D. in Genetics and plant breeding

AL-furat alawst University -Almusaib technical college- Plant production technical Dep.

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Genetics

Introduction:

The science of heredity or genetics is the study of two contradictory aspects of nature : heredity and variation. The process of transmission of characters from one generation to next, either by gametes–sperms and ova–in sexual reproduction or by the asexual reproductive bodies in asexual reproduction, is called **inheritance** or **heredity**.

Heredity is the cause of similarities between individuals. This is the reason that brothers and sisters with the same parents resemble each other and with their parents. **Variation** is the cause of differences between individuals. This is the reason that brothers and sisters who do resemble each other are still unique individuals. Thus, we have no trouble in recognizing the differences between sisters, for example, and even 'identical' twins are recognized as distinctive individuals by their parents and close friends. The science of genetics attempts to explain the mechanism and the basis for both similarities and differences between related individuals. It also tries to explain the phenomenon of evolution and cytodifferentiation.

The heredity and variations play an important role in the formation of new species (speciation). The biological science which deals with the mechanism of heredity and causes of variations in living beings (viruses, bacteria, plants and animals) is known as **genetics**.

The word **genetics** was derived from the(Greek root *genno* which means to give birth or to grow into).is the science of genes ,heredity (is the transfer of characters from parents to offspring),and the variation of organisms .It includes many branches ,but the most important ones for medical students are :

1- Cytogenetic: is the study of heredity at the cellular level through cytological techniques and chromosomal preparation.

2- Medical genetic : is the study genetic causes clinical disease.

3- Molecular genetic : is deal with micro molecular and macromolecular level.

The genetic information of organisms is contained within chemical structure of DNA molecules. Individually inheritance traits, corresponding to regions in the DNA sequence, are called genes. Genes encode the information necessary for synthesizing proteins complex molecules generally responsible for enzymatic reactions , synthesis , communication and structure within a cell.

Augustinian Monk **Gregor Mendel** was the first investigator who laid the foundation of our modern concept of the particulate theory. He could understand the heredity problems

more clearly than anyone in the past, because his approach was simple, logical and scientific. By his famous experiments on pea plant he concluded that the inheritance is
governed by certain factors which occur in the cells of each parent. He thought that each parent has two such factors, while their sex cells (sperm or pollen and ovum or egg)
have only one factor. However, he failed to explain the exact process by which these factors pass on the sex cells. This work published in 1865 and 1866 which was re-discovered in 1900, and were initially very controversial . When they were integrated with the chromosome theory of inheritance by Thomas hunt Morgan in 1915, they become the core of classical genetics.
Like other sciences, the science of genetics has its **specific terminology** .
Allele (Allelomorph). One of two or more forms that can exist at a single gene locus, distinguished by their differing effects on the phenotype. Alleles are genes controlling the
same characteristic (*e.g.* hair colour) but producing different effects (*e.g*. black or red), and occupying corresponding positions on homologous chromosomes.
Dominance. A phenomenon in which one member of a pair of allelic genes expresses itself as a whole (complete dominance) or in part (incomplete dominance).
Dominant allele. An allele that expresses its phenotypic effect even when heterozygous with a recessive allele; thus if *A* is dominant over *a*; then *AA* and *Aa* have the same phenotype.
Dominant phenotype. The phenotype of genotype containing the dominant allele; the parental phenotype that is expressed in a heterozygote.
Dominant trait. When out of two contrasting characters or traits only one expresses or appears in a generation. That trait is known as dominant trait, *e.g*., in pea, round character of seed is dominant over wrinkled character of seed
Gamete. A sex cell having haploid set of chromosomes and arising due to meiotic cell division of diploid germ cell is known as gamete. The male gamete is known as pollen or sperm and female gamete is known as ovum or egg.
Gene. The fundamental physical and functional unit of heredity, which carries information from one generation to the next; a segment of DNA,

composed of a transcribed region and a regulatory sequence, that makes possible transcription.

Genome. A complete set of chromosomes, or of chromosomal genes, inherited as a unit from one parent, or the entire genotype of a cell orindividual.

Genotype. The genetic makeup or constitution of an individual, with reference to the traits under consideration, usually expressed by a symbol, *e.g.,* +, DD (tall), *dd* (short), etc.

Heterozygote (Heterozygous). An individual containing both dominant and recessive genes or traits or characters of a allelic pair is known as heterozygous or hybrid.

Homozygote (Homozygous). The organism having two similar genes for a particular character in a homologous pair of chromosomes is known as homozygous or genetically 'pure' for that particular character.

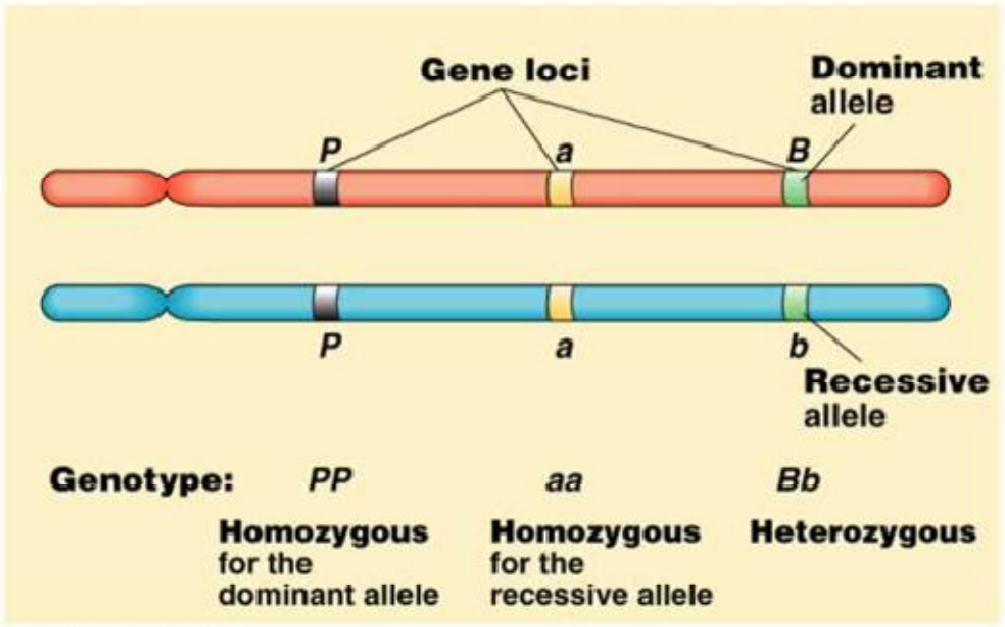
Hybrid. (i) A heterozygote. (2) A progeny individual from any cross involving parents of differing genotypes.

Zygote. The cell formed by the fusion of an egg and a sperm; the unique diploid cell that will divide mitotically to create a differentiated diploid organism.

classical method of symbolization

the dominant character is expressed in capital letter as the tall character is represented by 'T' and the recessive character is represented by 't'. Now homozygous tall plant will contain the genotype 'TT' and likewise a homozygous dwarf plant will have the genotype "tt". Because the sperm or ova contains only one chromosome of a homologous pair, therefore, it contains only single gene, *e.g.,* T or t. A heterozygous has both dominant and recessive characters,therefore, its genotype can be expressed by 'Tt' letters.

Recently, was **modified classical method of symbolization**, add the genetic symbol corresponds to the first letter in the name of the abnormal, recessive or mutant trait. For example, in man the recessive trait of albino is represented by letter 'a' while the normal trait is represented by capital letter 'A'.



Variation in Dominance Relation

Some cases the phenotypes of heterozygotes are found to be different from either of the homozygotes :

1. Incomplete Dominance

Sometimes in a heterozygote dominant allele does not completely mask the phenotypic expression of the recessive allele and there occurs an intermediate phenotype
in the heterozygote. This is called **incomplete dominance**.

Examples. 1. When a red flowered pea plant (RR) is crossed with white flowered pea plant (rr) then the F1 hybrid pea plants are found to have pink flowers. It shows that gene for red colour could not completely dominate the gene for **white** colour as shown in the figure
. In such a case, F2 phenotypic ratio and genotypic ratio are the same, as follows :

F2 phenotypic ratio = 1 Red : 2 Pink : 1 White

F2 genotypic ratio = 1 RR : 2 Rr : 1 rr

2. Codominance

Sometimes both alleles of a gene in a heterozygote lack the dominant and recessive relationship, *i.e.,* each allele is capable of some degree of phenotypic expression. In a sense,
codominance is no dominance at all, the heterozygote showing the phenotypes of both homozygotes. Hence, heterozygote genotype gives rise to a phenotype distinctly different from either of the homozygous genotypes.

Ex. The alleles governing the **ABO blood group** system in humans are codominants and may Blood groups actually represent is a pattern of inheritance in which both alleles of a gene are fully expressed. A person with AB blood has both A and B antigens on their red blood cells. With codominance, both alleles produce an effective product.

Deviation from mendel's dihybrid phenotypic ratio

The Mendelian dihybrid phenotypic ratio of 9 : 3 : 3 : 1 is obtained only when the alleles at both gene loci display dominant and recessive relationship. If one or both gene loci have incompletely dominant alleles, or codominant alleles or lethal alleles, the dihybrid ratio becomes modified variously, such as follows :

Ex 1.- 3 : 6 : 3 : 1 : 2 : 1 Ratio

Ex 2.- 1 : 2 : 1 : 2 : 4 : 2 : 1 : 2 : 1 Ratio

Genetic Interaction (Epistasis)

A gene or locus which suppressed or masked the action of a gene at another locus was termed **epistatic gene.**

Difference Between Dominance and Epistasis

The phenomenon of dominance involves **intra-allelic** gene suppression, or , while the phenomenon of epistasis involves **inter-allelic** gene suppression or the masking effect which . The classical phenotypic ratio of 9 : 3 : 3 : 1 observed in the progeny of dihybrid parents becomes modified by epistasis into ratios which are various combinations of the 9: 3 : 3 : 1 groupings.

Kinds of epistatic interaction

When in dihybrid crosses, the epistatic interactions occur between two genes, less than

four phenotypes appear in F2. Such bigenic (two gene) epistatic interactions may be of following six types: such as

1. **Dominant Epistasis (12 : 3 : 1)**
2. **Recessive Epistasis (9 : 3 : 4)**

Lethal genes are mutant genes and result in the death of the individual which carries them. Death of the individual occurs either in the prenatal or postnatal period prior to sexual maturity. A **fully** (completely) **dominant lethal allele** kills both in homozygous and heterozygous states. Individuals with a dominant lethal allele die before they can leave progeny. Therefore, the mutant dominant lethal is removed from the population in the same generation in which it arose. **Recessive lethal genes** kill only when they are in a homozygous state and they may be of two kinds :

1. one which has no obvious phenotypic effect in heterozygotes .
2. one which exhibits a distinctive phenotype when heterozygous.

Lethal alleles in human beings. In humans several hereditary diseases have lethal effects.

Few important lethal genes of man are following :

1. Congenital ichthyosis. One of the most typical cases of a recessive lethal gene in man is expressed in congenital ichtyosis. At birth children afflicted with this disease have a crusted leathery skin with deep fissures down to the subcutaneous tissue; the fissures lead to bleeding, infection and death. Congenital ichthyosis occurs only when there occurs homozygous condition for its recessive lethal genes.

2. Infantile amaurotic idiocy. A recessive allele in homozygous condition causes a fatal disease called **infantile amaurotic idiocy** in juvenile stage. Bearers of this genotype begin to lose their eye sight between the age of four to seven years. The complete blindness is followed by mental degeneration and finally death before adolescence.

3. Thalassemia or **Cooley's anaemia** is a haemoglobin disease somewhat similar to sickle cell anaemia. It occurs mostly in children (in India and other countries such as Italy, Greece and Syria) and is nearly 100 per cent fatal (lethal). Thalassemia is controlled by a single gene c which in homozygous condition (cc),
produces the severe Cooley's anaemia or **thalassemia major** and causes death of the patient. The heterozygous condition of this lethal gene (Cc) results in a mild form of the disease called **thalasemia minor** or **microcythemia**

Penetrance

The ability of a given gene or gene combination to be expressed phenotypically to any degree is called **penetrance**. It is of following two kinds :

1. Complete Penetrance

Most dominant and recessive genes in homozygous conditions and many completely dominant genes even in heterozygous conditions give their complete phenotypic expressions. Such genes are called to have **complete penetrance**.

2. Incomplete Penetrance

Some genes in homozygous as well as in heterozygous conditions fail to provide complete (cent per cent) phenotypic expression of them. Such genes are called to have **incomplete penetrance**.

Examples of Incomplete Penetrance

(i) **Polydactyly** in man is thought to be produced by a dominant gene P. The normal condition with five digits on each limb is produced by the recessive genotype (pp). Some heterozygous individuals (Pp) are not polydactylus and, therefore, has a penetrance of less than 70%.

(ii) In man, the tendancy to develop **diabetes mellitus** (a condition in which there is an excess of sugar in the blood) is controlled by certain genes. However, not everyone carrying the genes for diabetes actually develops the condition, for these genes have incomplete penetrance

Effects of environment on penetrance.

The environmental factors and genetical background have some definite effect on the degree of penetrance of a gene. For example, when various twins which carry genes for diabetes mellitus are studied, it is found that the disease appears only in those cases which ate more carbohydrate foods (starch and sugars).

Expressivity

A trait though penetrant, may be quite variable in its phenotypic expressions. The degree of effect produced by a penetrant genotype is called **expressivity**.

Example of expressivity. In man the polydactylous condition may be penetrant in the left hand (6 fingers) and not in the right (5 fingers); or it may be penetrant in the feet and not in the hands.

Effects of environment on expressivity.

The expressivity of a given gene is often influenced by environmental conditions.

Examples of environmental effects on the expressivity of a gene includes such cases as the differences in the severity of symptoms of an inheritable allergy, or the differences in height of identical twins who have been raised in different home (with different diets), or who have had different medical histories (one with a serious childhood disease, the other escaping this disease).

Pleiotropism (pleiotropy)

Up till now we have observed that a specific gene has a specific effect upon a specific phenotypic trait or in other words, each gene (allele) has its relation with a single phenotypic trait, but, this is not the case. A single gene often influences more than one phenotypic trait. However, it may be that one gene may cause evidently well marked expression of some phenotypic trait (**major effect**) then the others with less evident phenotype (**secondary effect**). Most genes have their multiple effects and are called **pleiotropic genes**. The phenomenon of multiple effect (multiple phenotypic expressions) of a single gene is called **pleiotropism**.

Example of Pleiotropism

** In human, the gene for disease **phenylketonuria** has pleiotropic effect and produces various abnormal phenotypic traits, collectively called **syndrome**. For example, the affected individuals secrete excessive quantity of amino acid phenylalanine in their urine, cerebrospinal fluid and blood. They become short stature, mentally deficient, with widely spaced incisors, with pigmented patches on skin, with excessive sweating, and with non-pigmented hairs and eyes.

Quantitative Genetics

(Inheritance of Multiple Genes)

The phenotypic traits of the different organisms may be of two kinds, qualitative and quantitative. The **quali tative traits** are the classical Mendelian traits of **kinds** such as form antigens and antibodies (*e.g.,* blood group types of man) The organisms possessing qualitative traits have distinct (separate) phenotypic classes and are said to exhibit **discontinuous variations**.

The **quantitative traits**, however, are economically important measurable phenotypic traits of **degree** such as height, weight, shape, skin pigmentation, metabolic activity, reproductive rate, behaviour, eye-facet, susceptibility to pathological diseases or intelligence in man; amount of flowers, fruits, seeds, milk, meat or egg. They do not show clear cut differences between individuals and forms a spectrum of phenotypes which blend imperceptively from one type to another to cause **continuous variations**.

The inheritance of polygenes or quantitative traits is called **quantitative inheritance**, **multiple factor inheritance**, **multiple gene inheritance** or **polygenic inheritance**.

Characteristics of multiple genes

Multiple genes for quantitative traits have following characteristics :

1. Each contributing allele in the series of multiple genes produces an equal effect.
2. Effects of each contributing allele are cumulative or additive.
3. There is no dominance, rather, there exist pairs of contributing and non-contributing alleles.
4. There is no epistasis (masking of the phenotypes) among genes at different loci.
5. There is no linkage involved. 5

6. The environmental conditions have considerable effect on the phenotypic expression of poly- genes for the quantitative traits.

Skin Colour in Man:

The classical example of polygenic inheritance was given by **Davenport** (1913). He found that two pairs of genes, A-a and B-b cause the difference in skin
Pigmentation between negro and Caucasian people. These genes were found to affect the character in additive fashion. Thus, a true negro has four dominant
genes, AABB, and a white has four recessive genes aabb. The F1 offspring of mating of
aabb with AABB, are all AaBb and have an intermediate skin colour termed **mulatto**. A mating of two such mulattoes produces a wide variety of skin colour in the offspring,
ranging from skins as dark as the original negro parent to as white as the original white parent. The result of this cross have been shown in Figure .The F2 phenotypicand genotypic ratios have been tabulated in Table .

P1 : AABB × aabb
Negro White
P1 gametes : AB ab
F1 : AaBb
Mulattoes
Intermediate skin colour
Intercross : Aa Bb × AaBb
Mulattoes Mulattoes

♂ / ♀	AB	Ab	aB
AB	AABB Like negro	AABb Darker than mulattoes	AaBB Darker than m
Ab	AABb Darker than mulattoes	AAbb Like mulattoes	AaBb Like mulat
aB	AaBb Darker than mulattoes	AaBb Like mulattoes	aaBB Like mulat
	AaBb	Aabb	aaBb

2. Eye Colour in Man

In human beings, the colour of eye is found to be determined by polygenes. These genes have been suggested to be X-linked . At least 9 classes of eye colour can be recognized in humans. In order of increasing amount of melanin pigmentation, these eye colours can be designated as light blue, medium blue, dark blue, grey, green, hazel, light brown, mediumbrown and dark brown. The number of contributing alleles for these colours have been tabulated in Table 5-4.

Mendel's Model of Heredity

Mendel proposed a simple model. It has become one of the most famous models in the history of science, containing simple assumptions and making clear predictions. The model has five elements:

1. Parents do not transmit physiological traits directly to their offspring. Rather, they transmit discrete information about the traits, what Mendel called "factors." These factors later act in the offspring to produce the trait. In modern terms, we would say that information about the alternative forms of characters that an individual expresses is *encoded* by the factors that it receives from its parents.

2. Each individual receives two factors that may code for the same trait or for two alternative traits for a character. We now know that there are two factors for each character present in each individual because these factors are carried on chromosomes, and each adult individual is *diploid.* When the individual forms gametes (eggs or sperm), they contain only one of each kind of chromosome, the gametes are *haploid.* Therefore, only one factor for each character of the adult organism is contained in the gamete. Which of the two factors ends up in a particular gamete is randomly determined.

3. Not all copies of a factor are identical. In modern terms, the alternative forms of a factor, leading to alternative forms of a character, are called **alleles.** When two haploid gametes containing exactly the same allele of a factor fuse during fertilization to form a zygote, the offspring that develops from that zygote is said to be **homozygous;** when the two haploid gametes contain different alleles, the individual offspring is **heterozygous.**

In modern terminology, Mendel's factors are called **genes.** We now know that each gene is composed of a particular DNA nucleotide sequence The particular location of a gene on a chromosome is referred to as the gene's **locus** (plural, loci).

4. The two alleles, one contributed by the male gamete and one by the female, do not influence each other in any way. In the cells that develop within the new individual,
these alleles remain discrete. They neither blend with nor alter each other. (Mendel referred to them as "uncontaminated.") Thus, when the individual matures and produces its own gametes, the alleles for each gene segregate randomly into these gametes, as described in element 2.
5. The presence of a particular allele does not ensure that the trait encoded by it will be expressed in an individual carrying that allele. In heterozygous individuals, only one allele (the dominant one) is expressed, while the other (recessive) allele is present but unexpressed.
To distinguish between the presence of an allele and its expression, modern geneticists refer to the totality of alleles that an individual contains as the individual's **genotype** and to thephysical appearance of that individual as its **phenotype.** The phenotype of an individual is the observable outward manifestation of its genotype, the result of the functioning of the enzymes and proteins encoded by the genes it carries. In other words, the genotype is the blueprint, and the phenotype is the visible outcome. These five elements, taken together, constitute Mendel's model of the hereditary process. Many traits in humans also exhibit dominant or recessive inheritance, similar to the traits Mendel studied in peas (table 13.1).

When Mendel crossed two contrasting varieties, he found all of the offspring in the first generation exhibited one (dominant) trait, and none exhibited the other (recessive) trait. In the following generation, 25% were pure-breeding for the dominant trait, 50% were hybrid for the two traits and exhibited the dominant trait, and 25% were pure-breeding for the recessive trait.
How Mendel Interpreted His Results
We will assign the symbol *P* to the dominant allele, and the symbol *p* to the recessive allele In this system, the genotype of an individual that is truebreeding for the recessive trait would be designated *pp.* Similarly, the genotype of a true-breeding would be designated *PP,* and a heterozygote would be designated *Pp* (dominant allele first). Using these conventions, and denoting a cross between two strains with ×, we can symbolize Mendel's original cross as *pp* × *PP*.
The F1 **Generation refer to first filial** (*filius* is Latin for "son").
The union of an egg and a sperm from these parents can produce only heterozygous

Pp offspring in the F1 generation. Because the P allele is dominant, all of these F1 individuals are expected to have the same dominant trait . The p allele is present in these 3 heterozygous individuals, but it is not phenotypically expressed. This is the basis for the latency Mendel saw in recessive traits. heterozygous individuals, but it is not phenotypically expressed. This is the basis for the latency Mendel saw in recessive traits

heterozygous individuals, but it is not phenotypically expressed. This is the basis for the latency Mendel saw in recessive traits.

The F2 Generation

When F1 individuals are allowed to self-fertilize, the P and p alleles segregate randomly during gamete formation. Their subsequent union at fertilization to form F2 individuals is also random, not being influenced by which alternative alleles the individual gametes carry. What will the F2 individuals look like? The possibilities may be visualized in a simple diagram called a Punnett square, clearly predicts that the F2 generation should consist of 3/4 dominant trait and 1/4 recessive trait, a phenotypic ratio of 3:1.

Mendel's First Law of Heredity: Segregation

Mendel's first law–the law of segregation is also known as law of purity of gametes. The law states that *the hybrids or heterozygotes of F1 generation have two contrasting characters or allelomorphs of dominant and recessive nature. These alleles though remain together for long time but do not contaminate or mix with each other and separate or segregate at the time of gametogenesis, so that each gamete receives only one allele of a character either dominant or recessive.*

The Testcross

Mendel crossed heterozygous F1 individuals back to the parent homozygous for the recessive trait. He predicted that the dominant and recessive traits would appear in a 1:1 ratio

Alternative 1: unknown individual homozygous
dominant (PP). PP × pp: all offspring have purple flowers (Pp)
Alternative 2: unknown individual heterozygous(Pp).
Pp × pp: 1/2 of offspring have white flowers (pp) and
1/2 have purple flowers (Pp).

Testcrosses can also be used to determine the genotype of an individual when two genes are involved Thus, an F2 individual showing both dominant traits (A_ B_) might have any of the following genotypes: AABB, AaBB, AABb, or AaBb. By crossing dominant-appearing F2 individuals with homozygous recessive individuals (that is, A_ B_ ×aabb).

AABB trait A breeds true trait B breeds true
AaBB _____ trait B breeds true
AABb trait A breeds true _____
AaBb _____ _____

Mendel's Second Law of Heredity: Independent Assortment

To formulate the law of dominance and law of segregation **Mendel** considered **monohybrid** crosses in which single pairs of contrasting characters were considered at a time. But he tried to find out how different characters would behave in relation to each other in their inheritance from generation to generation. For this purpose Mendel crossed two varieties of pea plants which were differing in two pairs of contrasting characters. Because such crosses yielded dihybrids and at a time two pairs of contrasting characters had been considered in them, therefore, these crosses were known as **dihybrid crosses**.

Mendel's discovery is often referred to as **Mendel's Second Law of Heredity,** or the **Law of Independent Assortment.** Genes that assort independently of one another, like the seven genes Mendel studied, usually do so because they are located on different chromosomes, which segregate independently during the meiotic process of gamete formation. A modern restatement of Mendel's Second Law would be that *genes that are located on different chromosomes assort independently during meiosis*

(9:3:3:1 phenotypic ratio))

Multihybrid Cross

The parents which differ in more than two pairs of contrasting characters then the cross between them is known **as polyhybrid** or **multihybrid** cross. The F1 hybrids in these cases are known as polyhybrids or multihybrids. The law of independent assortment is also applicable to these crosses.

Mechanism of Dominance

The chromosomes are specific in number, shape and size to a particular species. A diploid cell has two sets of chromosomes which come from two different parents (male and female) via gametes (sperm and ova). The chromo-somes of similar size and nature often form pairs during meiotic cell division and such identical chromosomes are known as **homologous chromosomes**. Each character of a pair of contrasting characters is represented by an **allele**. (When a gene for a unit character contains two or more alternative forms, they are called **allelomorphs** or **alleles**. All alleles of a gene are produced due to mutation of a wild gene (or normal gene). Thus, homozygous tall pea plant has two identical alleles TT on both gene loci of the homologous chromosomes; likewise, homozygous dwarfDuring the gametogenesis, the homologous chromosomes with TT or tt genes are separated and each chromosome with T or t gene is passed

to the gamete. The gametes of both parents unite during the process of fertilization and produce a new individual containing both tall (T) and dwarf (t) characters. This new individual of first generation (F1) contains two different genes (*i.e.,* alleles) of a contrasting pair of characters, therefore, it is known as **heterozygote** or **hybrid**. Because the hybrids of F1 have tall stems so the character of tallness (T) is considered as **dominant** and because the character for dwarfness could not express itself in F1generation, therefore, it is considered as **recessive**.

P ♂ ♀

TT tt

G T t

F1 Tt (100%) Tall

Example// A human disease known as **cystic fibrosis** is inherited as a recessive trait .A normal couples have affected child .what is the ratio of affected and un affected children.

Pedigree charts

• Pedigree charts show pattern of inheritance within a family.

• Males are designated by squares, females by circles; shaded circles and squares are affected individuals; line between square and circle represents a union; vertical line leads to offspring.

• Generations are numbered in uppercase Roman numerals,I,II,III etc .

• A carrier is a heterozygous individual who has no apparent abnormality but can pass on an allele for a recessively

inherited genetic disorder.

• Autosomal dominant and autosomal recessive alleles have different patterns of inheritance.

Characteristics of autosomal dominant disorders:

• 1) Affected children usually have at least one affected parent.

• 2) Heterozygotes are affected.

• 3) Two affected parents have unafected child.

• 4)Two unaffected parents will not have affected children.

• 5)Affected individuals who mate with un affected individual have 50% affected.

Autosomal Traits

• 1. First determine genotypes of parent (*EE, Ee or ee); this determines gametes produced (E or e).*

• 2. Punnett square provides phenotypic ratio if all sperm are given equal chance to fertilize all eggs.

• a. Two heterozygous parents can produce a 3:1 ratio

b. A heterozygous with homozygous recessive cross produces a 1:1 ratio.

Characteristics of autosomal recessive disorders:

• 1) Most affected children have normal parents since heterozygotes have a normal phenotype.

• 2) Two affected parents always produce an affected child.

• 3) Close relatives who reproduce together are more likely to have affected children.

Some Disorders Are Dominant
• **1. Neurofibromatosis:**

• a. This is an autosomal dominant disorder that affects one in 3,000 people.

• b. Affected individuals have *tan skin spots at birth, which develop into benign* tumors.

• c. Neurofibromas are comprised of nerve cells or other cell types.

• d. Most case symptoms are mild, patients live a normal life; sometimes symptoms are severe:

• 1) skeletal deformities, including a large head;

• 2) eye and ear tumors that can lead to blindness and hearing loss; and

• 3) learning disabilities and hyperactivity.

• e. Gene that codes for neurofibromatosis is huge; includes three smaller *nested genes.*

• 1) It is a tumor-suppressor gene active in controlling cell division.

• 2) When it mutates, a benign tumor results.

2. **Huntington Disease**:
• a. This is also an autosomal dominant disorder that affects one in 20,000 people.

• b. It leads to *progressive degeneration of brain cells, which in turn causes severe muscle spasm, personality disorders, and death in 10 -15 years from onset.*

• c. Most appear normal until they are of middle age and already have had children who might carry the gene; occasionally, first signs of the disease are seen in teenagers or even younger.

• d. The gene for Huntington disease is located on chromosome 4.

• e. Gene contains many repeats of base triplet CAG (cytosine, adenine, guanine); normal persons have 11- 34 copies; affected persons have 42-120 or more copies.

• f. Severity and time of onset of associated disorders depend on number of triplet repeats.

Lecture 6 Dr. jassim .j, alnuami

• ***Sickle-cell disease is a blood disorder controlled by incompletely***

dominant alleles.

• a. *HbAHbA individuals are normal; HbSHbS have sickle-cell disease; HbAHbS have sickle-cell trait.*

• b. With sickle-cell disease, red blood cells are irregular in shape (sickle-shaped)

• rather than biconcave, due to abnormal hemoglobin that the cells contain.

• c. Due to irregular shape, sickle-shaped red blood cells clog vessels and break down; results in poor circulation, anemia, low resistance to infection, hemorrhaging, damage to organs, jaundice, and pain of abdomen and joints.

• d. Persons heterozygous for sickle-cell (*HbAHbS) are usually asymptomatic unless stressed.*

• e. In malaria regions of Africa, infants heterozygous (*HbAHbS) for sickle-cell allele have better chance of surviving; malaria parasite dies as potassium leaks from sickled cells.*

• **Some Disorders Are Recessive**

• **1. Tay-Sachs Disease**

• a. Usually occurs among Jewish people in the U.S. of central and eastern European descent.

• b. Symptoms are not initially apparent; infant's development begins to slow at 4-8 months, neurological and psychomotor difficulties become apparent, child gradually becomes blind and helpless, develops seizures, eventually becomes paralyzed, dies by age of three or fou.

• c. Results from lack of enzyme **hexosaminidase A** (Hex A) and subsequent storage of its substrate, glycosphingolipid, in lysosomes.

• d. Primary sites of storage are cells of the brain; accounts for progressive deterioration.

• e. No treatment or cure; prenatal diagnosis is by amniocentesis and chorionic villi sampling

• 2. **Cystic Fibrosis**

• a. This recessive autosomal disease is most common lethal genetic disease in Caucasians in U.S.

• b. About 1 in 20 Caucasians is a carrier, and about 1 in 2,500 births has this disorder.

• c. Involves production of viscous form of mucus in the lungs and pancreatic ducts.

• 1) Resultant accumulation of mucus in the respiratory tract interferes with gas exchange.

• 2) Digestive enzymes must be mixed with food to supplant the pancreatic juices.

• d. New treatments have raised average life expectancy to 28 years.

• e. Research has demonstrated chloride ions (Cl-) fail to pass plasma membrane proteins.

• f. Since water normally follows Cl- , lack of water in the lungs causes thick mucus.

• g. Cause is *mutated gene on chromosome 7; attempt to insert gene into nasal epithelium has had limited success.*

• 3. **Phenylketonuria (PKU)**

• a. PKU occurs 1 in every 5,000 births; it is *most common inherited disease of nervous system.*

• b. Lack of enzyme needed to metabolize amino acid phenylalanine *results in accumulation of the amino acid in nerve cells of the brain; this impairs nervous system development.*

• c. PKU is caused by

a *mutated gene on chromosome 12*

• d. *Now newborns are routinely tested in hospital for high levels of phenylalanine in the blood.*

• e. If infant has PKU, child is placed on diet low in phenylalanine until brain is fully developed.

Linkage

The genes for different characters may be either situated in the same chromosome or in different chromosomes. When the genes are situated in different chromosomes, the characters they control appear in the next generation either together or apart, depending on the chance alone. They assort independently according to Mendel's law of independent assortment. But if **linkage**.

The phenomenon of linkage has one of the great significance for the living organisms that it reduces the possibility of variability in gametes unless crossing over occurs.

Crosses involving linked genes do not give same results as unlinked genes.

The difference between independent assortment and linkage can be understood by the following two examples :

Example 1. Genes on different chromosomes assort independently giving a 1 : 1 : 1 : 1 test cross ratio which is as follows :

P1 : AA BB × aa bb

P1 gametes : (AB) ↓ (ab)

F1 : Aa Bb

Test cross : Aa Bb × aa bb

Gametes : (AB) (Ab) (aB) (ab) (ab)

F2 : ¼ Aa Bb : ¼ Aa bb : ¼ aa Bb : ¼ aa bb or 1 : 1 : 1 : 1.

Example 2. Linked genes do not assort independently but tend to stay together in the same combination as they were in the parents. In the following figure, the genes to the left of the slash line (/) are on one chromosome and those on the right are on the homologous chromosome.

P1 : AB/AB × ab/ab

P1 gametes : (AB) ↓ (ab)

F1 : AB/ab

Test cross : AB/ab × ab/ab

Gametes : (AB) (ab) (ab)

F2 : ½ AB/ab : ½ ab/ab or 1 : 1.

This type of large deviation of F2 results of example 2 from a 1 : 1 : 1 : 1 ratio in the test cross progeny of dihybrid is an evidence for linkage.

Sex Chromosomes Determine Gender

•1. In most animal species, chromosomes can be categorized as two types:

•a. **Autosomes** are non sex chromosomes that are the same number and kind between sexes.

•b. **Sex chromosomes** differ in number and kind between males and females 2

Figure 1

2. Sex chromosomes in the human female are XX; those of the male are XY.

3. Males produce X-containing and Y-containing gametes; males determine the sex of offspring.

4. Besides genes that determine sex, sex chromosomes carry genes for traits unrelated to sex.

Sex-Linked Inheritance: In XX– XY type organisms, sex-linked genes can be classified into following three types:

A. X-linked. The X-linked type sex-linked inheritance is performed by those genes which are localized in the nonhomologous sections of X-chromosome, and that have no corresponding allele in Y chromosome. The X-linked genes are commonly known as **sex linked genes**.

* X-linked alleles are designated as superscripts to X chromosome.

* Heterozygous females are **carriers;** they do not show the trait but can pass it on. $\mathbf{X^R X_r}$

* Males are never carriers but express the one allele on the X chromosome.

Characteristics of Sex-linked Inheritance

The X-linked genes exhibit following characteristic patterns of inheritance :

1. The differential region of each chromosome (*i.e*., X) contain genes that have no counterparts on the other kind of sex chromosome. These genes, whether dominant or recessive, show their effects in the male phenotype. Genes in the differential regions are called **hemizygous** ("half-zygous") in the males.

2. The X-linked recessive genes are transmitted from P1 male parent (father) to F2 male progeny (grandsons) through its F1 heterozygous females (daughters), which are called **carriers**) .

3. The X-linked recessives can be detected in human pedigrees through the following clues :

(i) The X-linked recessive phenotype is usually found more frequently in the male than in the

female. This is because an affected female can result only when both mother and father bear the X-linked recessive allele (*e.g*., $X^A X^a \times X^a Y$), whereas an affected male can result when only the mother carries the gene. Further, if the recessive X-linked gene is very rare, almost all observed cases will occur in males.

(ii) Usually none of the offspring of an affected male will be affected, 3

but all his daughters will carry the gene in masked heterozygous condcondition, so one half of their sons (*i.e*., grandsons of F1 father) will be affected (Fig.1.)

4. Dominant X-linked genes can be detected in human pedigrees through the following clues :i(a) It is more frequently found in the female than in the male of the species.
(b) The affected males pass the condition on to all of their daughters but to none of their sons (Fig.2.)
(c) Females usually pass the condition (defective phenotype) on to one-half of their sons and daughters (Fig.3.).
d) A X-linked dominant gene fails to be transmitted to any son from a mother which did not exhibit the trait itself.
In humans, X-linked dominant conditions are relatively rare. One example is **hypophosphatemia** (vitamin D-resistant rickets). Another example includes hereditary enamel hypoplasia (**hypoplastic amelogenesis imperfecta**), in which tooth enamel is abnormally thin so that teeth appear small and wear rapidly down to the gums.

Inheritance of X-Linked Recessive Genes in Humans

In human beings more than 150 confirmed or highly probable X-linked traits are known; most of these are recessives. Certain well known examples of X-linked recessive genes in humans are those for red- green colour blindness or **daltonism**, haemophilia and Duchenne's muscular dystrophy.

(1) Colour blindness.

a. Can be X-linked recessive disorder involving mutations of genes coding for green or red-sensitive cone cells, resulting in inability to perceive green or red, respectively.
b. The possible genotypes for color blindness are as follows:
1) $X_B X_B$ = a female who has normal color vision;
2) $X_B X_b$ = a carrier female who has normal color vision;
3) $X_b X_b$ = a female who is color blind;
4) $X_B Y$ = a male who has normal color vision.
5) $X_b Y$ = a male who is color blind.

2) Haemophilia a. About one in 10,000 males is a hemophiliac with impaired ability of blood to clot. 4

b. Hemophilia has two types: Hemophilia A is due to absence of clotting factor IX; Hemophilia B is due to absence of clotting factor VIII.
c. Hemophiliacs bleed externally after an injury and also suffer internal bleeding around joints.
d. Hemorrhages stop with transfusions of
f. Factor VIII is now available as a genetic engineering product.
g. Of Queen Victoria's 26 offspring, 5 grandsons had hemophilia, 4 granddaughters were carriers.

3. **Muscular Dystrophy**

a. Duchenne muscular dystrophy is most common form; characterized by wasting away of muscles, eventually leading to death; it affects one out of every 3,600 male births.
b. X-linked recessive disease involves a mutant gene that fails to produce protein dystrophin.
c. Symptoms (e.g., waddling gait, toe walking, frequent falls, difficulty in rising) soon appear.
d. Muscle weakens until individual is confined to wheelchair; death usually occurs by age 20.
e. Affected males are rarely fathers; the gene passes from carrier mother to carrier daughter.
f. Lack of dystrophin causes calcium ions to leak into muscle cells; this promotes action of an enzyme that dissolves muscle fibers.
g. As body attempts to repair tissue, fibrous tissue forms and cuts off blood supply.
h. Test detects carriers of Duchenne muscular dystrophy; treatments are under research.

B. Inheritance of y-linked genes

Genes in the non-homologous region of the Y chromosome pass directly from male to male (Fig. In man, the Y-linked or holandric genes such as ichthyosis hystrix gravis hypertrichosis (excessive development of hairs on pinna of ear) are transmitted directly from father to son. Recently, certain other holandric genes have been reported in humans, e.g.,
genes for H-Y antigen, histocompatibility antigen, spermatogenesis, height (stature) and slower maturation of individual.

C. Inheritance of x-y-linked genes Sex-linked lethals

Certain X-linked genes are **lethals,** *i.e*., they cause death of an individual from egg up to sexually mature adult stage.
Ex. The gene for haemophilia is a recessvie **sex-linked lethal,** since it may cause death. Slight scratches, accidental injuries, or even bruises, which would not be serious in normal persons, may result in fatal bleeding for the haemophiliac. Often, internal bleeding (from bruises,

internal lesions and so forth) is more important in producing lethality. By bringing
about death, sex-linked lethals will alter the sex ratio in a progeny.
Duchenne (or progressive pseudohypertrophic) **muscular dystrophy** is another fatal disorder of humans. In it affected individual, though apparently normal in early childhood, 5

exhibits progressive wasting away of the muscules, resulting in confinement to a wheel-chair by about the age of 12 years and death in teen years (in adolescence).
The Y-linked recessive allele responsible for this disorder is a lethal and will change the sex ratio in a given group of offspring over time.

Sex-influenced genes

Sex influenced genes are those whose dominance is influenced by the sex of the bearer. Thus, male and female individuals may be similar for a particular trait but give different phenotypic expressions of the same trait.
Example 1. In man the baldness may occur due to disease, radiation or thyroid defects but in
some families balldness is found to be inherited trait. In such inherited baldness the hairs gradually become thin on head top, leaving ultimately a fringe of hair low on the head and commonly known as **pattern baldness**. The gene B for baldness is found to be dominant in males and recessive in females. In heterozygous condition it expresses itself only in the presence of male hormones (in male sex):

Genotype	**Phenotypes**
	Men	**Women**
BB	Bald	Bald
Bb	Bald	Non-bald
bb	Non-bald	Non-bald

SEX-LIMITED GENES
Sex-limited genes are autosomal genes whose phenotypic expression is determined by the
presence or absence of one of the sex hormones. Their phenotypic effect is limited to one sex or other. In other words, the penetrance of a sex-limited gene in one sex remain zero. The sex-limited genes are mainly responsible for secondary sex characters.
Example .
Beard development in human beings is a sex limited trait as men normally have beards,
whereas women normally do not. Likewise, the genes for male voice, body hair and physique are autosomal in human beings, but they are expressed only in the presence of androgens which are absent in females.
1-Red-green colour blindness in humans is recessive and sex-linked. If a woman heterozygous for colour blindness marries a colour blind man, what is the probability that their first child will be a colourblind daughter ?
2-A married couple, both of whom had normal vision, produced a colour blind son. Examination of cell samples from the son showed the presence of a Barr body. What is the probable genotype of the son with respect to

sex chromosomes and colour blindness ? What is the simplest explanation that will account for this genotype ?

3-. A sex-linked recessive gene in humans produces colourblind men when hemizygous and colour blind women when homozygous. A sex-influenced gene for pattern baldness is dominant in men and recessive in women. A heterozygous bald, colour blind man marries a non-bald woman with normal vision whose father was non-bald and colourblind and whose mother was bald with normal vision. List the phenotypic expectations for their children

Mutation:

The changes in the genome involving chromosome parts, whole chromosomes,
or whole chromosome sets are called **chromosome aberrations** or **chromosome mutations**.
Chromosome mutations are inherited once they occur and are of the following types :

A. Structural changes in chromosomes :

1. Changes in number of genes
(a) Loss : **deletion**: The simplest result of breakage is the loss of a part of a chromosome.

Ex: Human babies missing a portion of the short arm of chromosome 5 (autosome) have a distinctive cat-like cry; hence, the French name "cri du chat" (cry of the cat) syndrome. They are also mentally retarded (IQ below 20), have malformation in the
larynx, moon faces, saddle noses, small mandibles (micrognathia), malformed low-set ears and microcephally (small head).
(b) Addition : **Duplication**: The presence of a part of a chromosome in excess of the

normal Complement.
Ex: In humans, unequal crossing over between homologous chromosomes bearing σ
(sigma) and β (beta) genes for σ and β subunits of adult haemoglobin (HbA), results
in deletions and duplications of these genes, causing anaemia (*i.e.,* one type of thalassemia)

.

2. Changes in gene arrangement :

(a) **inversion** : Inversion involves a rotation of a part of a chromosome or a set of genes by 180 on its own axis . It essentially involves occurrence of *breakage* and *reunion*.

(b) **translocation**. The shifting or transfer of a part of a chromosome or a set of genes to a non-homologous one, is called translocation. There is no addition or loss of genes during translocations, only arearrangement (i.e., change in the sequence and position of a gene).

For example, in humans, patients with chronic leukemia (a kind of cancer). In the bone marrow and in cells derived from it, is present a short chromosome, called the Philadelphia (Ph1) chromosome). Detailed cytological study disclose Ph1 to be a number 22 chromosome that has lost most of the distal part of its longer arm (22 q–). The deleted part of autosome 22 is translocated to one of the larger autosomes (most frequently to the distal end of chromosome 9).

Variation in Chromosome Morphology:

1. **Isochromosomes.** An isochromosome is a chromosome in which both arms are identical.
2. **Ring chromosomes**. Sometimes breaks occur at each end of the chromosome and broken ends are joined to form a ring Chromosome.

2

3. **Robertsonian translocation**. Sometimes whole arm fusions occur in the non-homologous chromosomes Robertsonian translocation is an eucentric reciprocal translocation where the break in one chromosome is near the front of the centromere and the break in the other chromosomes is immediately behind its centromere. The resultant smaller chromosome consists of largely inert heterochromatic material near the centromere; it normally contains no essential genes and tends to become lost. Thus, Robertsonian translocation results in a reduction of the chromosome number.

Euploidy

The term **euploidy** (Gr., *eu* = even or true; *ploid* = unit) designates genomes containing
chromosomes that are multiples of some basic number (*x*). The euploids are those organisms which contain balanced set or sets of chromosomes in any number. The number of chromosomes in a basic set is called the **monoploid number**, *x.* Those euploid types whose number of sets is greater than two are called **polyploid**. Thus, 1*x* is **monoploid**, 2*x* is **diploid**; and the polyploid types are 3*x* (**triploid**), 4*x* (**tetraploid**), 5*x* (**pentaploid**), 6*x* **(hexaploid**) and so on.

Aneuploidy

Changes that involve parts of a chromosome set results in individuals, called aneuploids (Gr.aneu = uneven ; ploid = unit). Aneuploidy can be either due to the loss of one or more chromosomes or due to addition of one or more chromosomes to the complete chromosome set.

B. Changes in number of chromosomes :

1. **Monosomy**

Diploid organisms which are missing one chromosome of a single pair are monosomic with the genomic formula 2n –1.

2. **Nullisomy**

An organism which has lost a chromosome pair is a nullosomic. The nullosomic organism has the genomic formula (2n–2).

3. **Trisomy** :Trisomics are those diploid organisms which have an extra chromosome (2n + 1).Trisomy in humans. In human beings, the following three syndromes have been studied :

A. Down's syndrome (DS) or Trisomy-21. Mongolism:

1. Down syndrome is most common autosomal trisomy, involves chromosome 21**.**
2. Most often, Down syndrome is due to nondisjunction during gametogenesis.
3. In 23% of cases, the sperm had the extra chromosome 21.

4. In 5% of cases, there is translocation where chromosome 21 is attached to chromosome 14.
5. Chances of a woman having a Down syndrome child increase with age.
6. Chorionic villi sampling testing or amniocentesis and karyotyping detects a Down syndrome child. 3

7. Down syndrome child has tendency for ***leukemia, cataracts, faster aging, and mental retardation***

B. Edward's syndrome or Trisomy- 18.

trisomy-18 is found to contain an incidence of about 0.3 per 1000 births. It is character characterized by multiple malformations, primarily low-set ears; small receding lower

jaw; flexed and clenched fingers; cardiac malformations; and various deformaties

of skull, face and feet. Harelip and cleft palate often occurs. Death takes place around 3 to 4 months of age. Like the Down's syndrome, occurrence of Edward's syndrome is too related with maternal age (i.e., 35 to 45 year old mothers have more chance of giving birth to trisomy-18 infant).

C. **Patau syndrome or Trisomy-13**.Its incidence is about 0.2 per 1000 births. Individuals with Patau syndrome appear to be markedly mentally retarded; have sloping forehead, harelip and cleft palate. Polydactyly (both hands and feet) is almost always present; the hands and feet are deformed. Cardiac and various internal defects (of kidney, colon, small intestine) are common. Death usually occurs within hours or days, but the foetus may abort spontaneously.

Kinds of mutation:

1-Classification of Mutation According to Type of Cells

A. Somatic mutations. The mutations occurring in non-reproductive body cells are

known as **somatic mutations**.

B. Gametic mutations. The mutations occurring in gamete cells (*e.g.,* sperms and ova) are called **gametic mutations**. Such mutations are heritable and of immense genetical significance

2-Classification of Mutations According to the Size and Quality 4

A. Point mutation. When heritable alterations occur in a very small segment of DNA molecule, *i.e.,* a single nucleotide or nucleotide pair, The mutations which arise from the insertion or deletion of individual nucleotides and cause the rest of the message downstream of the mutation to be read out of phase, are called **frameshift mutations**. They result in the production of an incorrect, hence, inactive protein, due to which the death of the cell may occur.

3. Substitution mutation. A point mutation in which a nucleotide of a triplet is replaced by another nucleotide.

3. Classification of Mutation According to the Origin

According to the mode of origin, following two kinds of mutations have been recognised :

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

(2) Induced mutations. Besides naturally occurring spontaneous mutations, the mutations can be induced artificially in the living organisms by exposing them to abnormal environment such as radiation, certain physical conditions (*i.e.,* temperature) and chemicals. The substances or agents which induce artificial mutations are called **mutagenes** or **mutagenic agents**.

Human Sex Anomalies

1. **Turner's Syndrome (XO Females).** A female with 44 autosomes and only with one X

chromosome in her body cells exhibits symptoms of Turner's syndrome. Such females are sterile and have short stature, webbed neck, a low hairline on the nape of the neck, broad shield-shaped chest, low intelligence, under developed breasts, poorly developed ovaries, sparse pubic hairs and no axillary hair.

2. **Poly-X Females (XXX Females).** Such females are called super females because they possess an extra X chromosome (44 autosomes+3X chromosomes). Some females may have 4 or 5X chromosomes besides the normal autosomes. All such poly-X females are mentally retarded and sterile showing abnormal sexual development.

3. **Klinefelter's Syndrome (XXY Males).** When an abnormal egg with XX chromosomes is

fertilized by a sperm carrying Y chromosome, a zygote having three sex chromosomes (XXY chromosomes) is formed. The resulting young one is an abnormal sterile male showing the following features : small testicles, mental retardation, longer arms, feeble breasts, higher pitched voice and sparse body hairs.

4. **XYY males.** Presence of an extra Y chromosome in males (XYY) results in their unusual height, mental retardation, severe facial acne during adolescence and criminal bent of mind. Their genitals are affected by developmental abnormalities.
5. **Hermaphroditism**. True hermaphrodites are individuals that possess both ovarian and testicular tissue. The external genitalia are ambiguous, but often more or less masculinized;
secondary sex characters vary from more or less male to more or less female. Ordinarily, true
hermaphrodites are sterile because of rudimentary ovotestes. 5

HUMAN CYTOGENETICS

A successful attempt to count the number of human chromosomes was made in 1912 by

Winiwarter who proposed that human chromosomes are 48 in women and 47 in man; men having one X chromosome and women having two X chromosomes. **Painter**, in 1923, while examining the testicular material of man, observed a heteromorphic pair of sex chromosomes and proposed the XY mechanism of sex determination in man. **Tjio** and **Levan** (1956) cultured somatic cells from fibroblasts of human embryos and counted the human chromosome number as 46. This chromosome number was confirmed by **Ford** and **Hamerton** while working with testicular material in the same year. **Tjio** and

Levan provided greatly improved techniques for chromosome preparations. **Moorhead** *et al.,* (1960) described a simple method of culturing of lymphocytes from human blood.

Karyotyping human chromosomes. For karyotyping of human chromosomes venous blood is taken and blood leucocytes are stimulated to divide (by mitosis) *in vitro* by the addition of

phytohaemagglutinin. Colchicine is added to arrest cell division at metaphase stage. It is further treated with hypotonic saline solution which results in swelling of cells and dispersal and better clarity of chromosomes for counting and morphological study. There after, the material is stained (*e.g.,* with Giemsa technique) to demonstrate the banding patterns of chromosomes. Finally, a suitable metaphase spread is photographed through a high power microscope. The individual chromosomes are cut out from the photograph. The chromosomes are then arranged in an orderly fashion in homologous pairs, to produce a standard arrangement, the karyotype.

To characterize a chromosome in the karyotype, the following parameters are used :

1. Shape of chromosome ;
2. Length of chromosome ;
3. Centromeric index, *i.e.,* this index is expressed in the form of ratio of the short arm length to the total chromosome length : For example, centromeric index in a metacentric chromosome is 0.5.
4. Proportion of the arms,*i.e.,* it is ratio between the long arm and short arm of the chromosome. This ratio is 1 : 1 in a typical metacentric chromosome.

Classification. The human metaphase chromosomes were first of all classified by a conference of cytogeneticists at Denver, Colorado in 1960 and is known as the **Denver**

classification. To follow this classification, each of the 22

pairs of autosomes has been numbered from 1 to 22 according to their decreasing size. **Patau** (1960) divided the human chromosomes into the following seven groups designated A to G :

1. A group : 1 to 3 pairs — Metacentric
2. B group : 4 to 5 pairs — Submetacentric
3. C group : 6 to 12 pairs — Submetacentric
4. D group : 13 to 15 pairs — Acrocentric
5. E group : 16 to 18 pairs — Submetacentric (16 is metacentric)
6. F group : 19 to 20 pairs — Metacentric
7. G group : 21 to 22 pairs — Acrocentric

Group A consists of longest metacentric chromosomes. 6

Group G consists of the shortest acrocentric chromosomes. These chromosomes have satellites
that correspond to nucleolar organizers. Chromosomes of group D also contains satellites. In males,
group G includes a variable Y chromosome which lacks the satellites.
The X chromosome is the member of group C and can be identified by special banding or staining
methods.

BandingTechniques

Recently banding techniques reveals structural
details of chromosomes. The main banding
techniques are identified by letters such as Q, G,
C, R, T, F and N bands:

1. Q banding. It uses fluorescent dyes
(such as quinacrine mustard) and identifies the socalled
Q bands.

2. G banding. It uses Giemsa stain and
identifies the G bands. With G banding three
major types of chromatin can be recognized—
euchromatin, centromeric and intercalary heterochromatin.
The Q and G bands are generally
similar and correspond to intercalary heterochromatin.

3. C banding. It stains specifically centromeric
constitutive heterochromatin.

4. R banding. It gives a pattern that is the
reverse of that of Q and G banding.

5. T banding. It stains telomeres of chromosomes.

Other banding techniques uses the Feulgen
stain (**F bands**) and one selectively stains the
nucleolar organizers (**N bands**) which are localized
in the satellite of chromosomes 13, 14, 15, 21
and 22. G banding has become important tool in
the analysis of mammalian, avian, reptilian and amphibian chromosomes; distinct G bands have not
been found in plant chromosomes.

Q1-

Q2-

Q3-

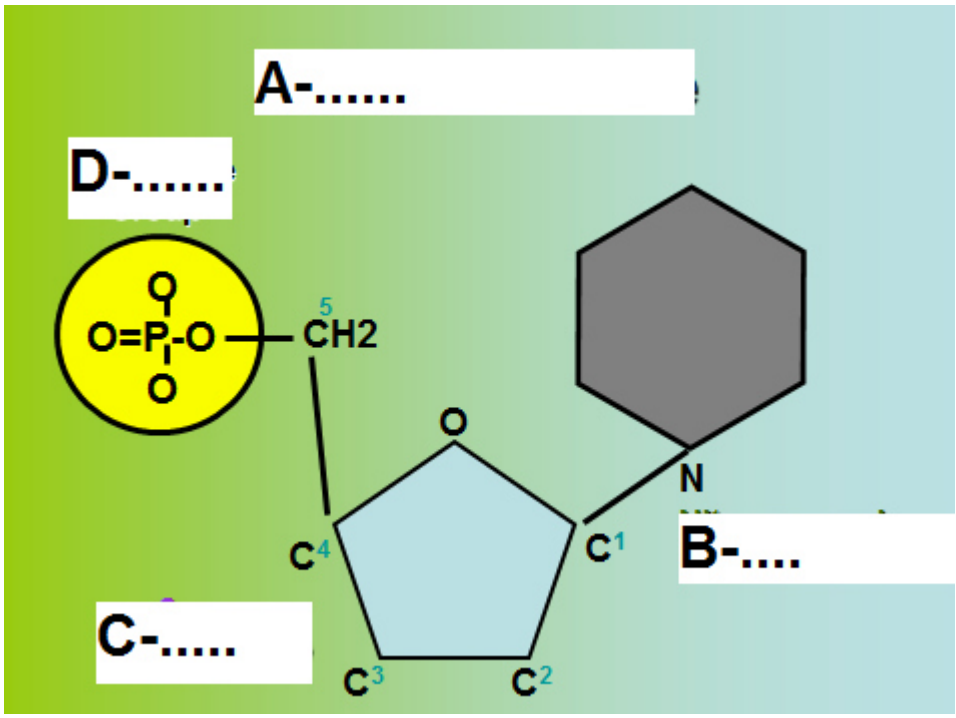
Q4-Complete of the following:

A- Name this structure .
…….

B- ……

C- ……

D- ……



Q5- **C**ircle the correct answer….

A nucleotide triplet codes for

(a) a protein
(b) an enzyme
(c) an amino acid
(d) an organic base

Q6-A -Identify this specimen?----------

B-Give one function of its?----------
--.

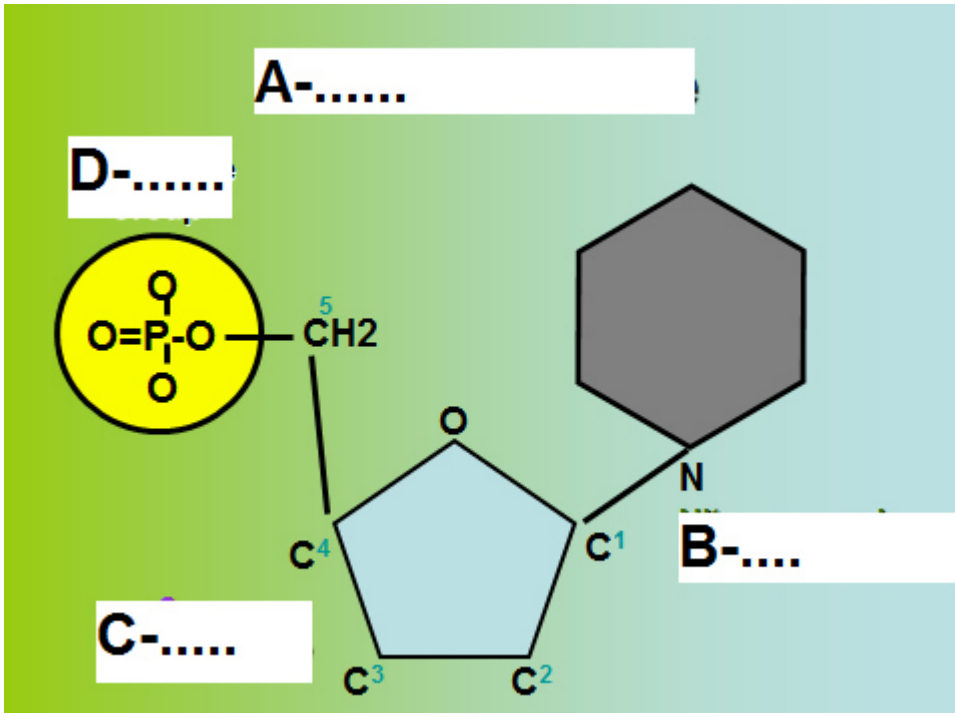
Q7-A -Identify this specimen?----------

B-Give one function of its?----------.

Q8-Draw the prophase and telophase in mitosis.

Sex Determination in Man

In man XX-XY type sex determining mechanism occurs but here the Y chromosome contains potent male sex-determining genes which can almost completely overcome the feminizing action of the rest of the genotype. The conclusive evidences that Y chromosome is a determiner of fertility and sex of male individual came from certain abnormal conditions (called syndromes) which contained aneuploidic sex-chromosomal abnormalities.



For instance, **Turner's syndromes** (XO) are sterile female individuals. Similarly, **Klinefelter's syndromes** (XX Y) are males, despite the presence of two X chromosomes. A person with extra one X and Y chromosome display true **hermaphroditism** having both ovarian and testicular tissues and variable degrees of intersexual development of the genitalia.

Sex differentiation

In human beings sex differentiation occurs in the following steps :

1. Genetic Sex

Normal females ordinarily have two X chromosomes; normal males have one X and one Y. The genes on these sex chromosomes determine femaleness or maleness.

Further, since the X-chromosome carries much more genetic information in striking contrast to Y chromosome, one might wonder how it is that the female can carry a double dose of many vital X-linked genes, whereas the

male has only a single dose of these X-linked genes. Such inequality in fact cannot be tolerated and so female seem to have developed their owntypes of dosage compensation mechanisms.

Dosage Compensation of Genes

Dosage compensation of the genes is done either by **hypoproduction** due to inactivation of one X chromosome in homogametic female sex.

(i) X-chromosome inactivation in mammals. It has been demonstrated that in homogametic XX female individuals, one X chromosome gets characteristically
condensed and inactivated.

Since it becomes inactive in certain part of the life cycle and resumes activity before entering the germ line. The phenomenon of inactivation of X chromosome was confirmed by the observation of the Barr body. It has also been observed in most of the body cells (*e.g.,* skin, oral epithelium and blood cells) of man .

The sex chromatin appears in the interphase nucleus as a small chromocentre, heavily stained
with basic dyes.It can be found in four position:

(i) attached to the nucleus as in nerve cells of certain species;

(ii) attached to the nuclear membrane as in cells of epidermis or of the oral mucosa;

(iii) free in the nucleoplasm as in neurons after electric stimulation,

2

(iv) as a nuclear expansion.

The best known example of nuclear expansion is that of the neutrophil leukocyte of female in which the sex chromatin (Barr body) appears as a small rod called the **drumstick**.

Lyon's hypothesis.

The number of X chromosomes was two or more than two, the number of Barr bodies was one less than the number of X chromosomes (nX-1; *i.e.,* one Barr body in XX females and XXY males; two Barr bodies in XXXY males and XXX metafemales). Thus, in normal female only one active X chromosome is present. Which of the two X chromosomes remains active in female individuals, is determined at the early stages of development.

In other words, the inactivation of X chromosome is a random phenomenon. This fact has been demonstrated in human diseases linked to X chromosome. The **Lesch-Nyhan syndrome**, in which a deficiency of one enzyme of the purine metabolism (*i.e.,* hypoxanthineguanine phosphoribosyl transferase) produces mental retardation and

increased uric acid levels results, from a recessive mutation in the X chromosome. This is shown as follows : if fibroblasts of these patients are cultured *in vitro,* two types of cell clones are obtained. Half the clones contain the enzyme, whereas the other half (in which the X carrying the normal gene is condensed) lack the enzyme.

In the human embryo X chromosome inactivation starts in the late blastocyst about the

16th day of life. Once the inactivation is established, it is irreversibly maintained in somatic

cells, however, in germ cell line reactivation occurs at a specific stage of germ cell development .

The good illustration of X chromosome inactivation is seen with calico cats, where the coat is a mosaic patchwork of black and yellow hair. Black hair is produced by the dominant allele B, and yellow by its recessive allele b. This gene is X-linked, so if one X chromosome contains the dominant allele B and other X chromosome the recessive allele b, random inactivation will allow both coat colours to be expressed. Male calico cats are understandably rare, since it has only one X chromosome. 3

2. Gonadal Sex

In the human embryos until the six weeks the gonads and primordia of the urinogenital tract are identical in males and females. At this stage (time) the gonad has already been invaded by the primary XX or XY cells. At this point, a gene or set of genes, called **testis determining factor** or **TDF**, present in the Y chromosome causes the undifferentiated gonad to differentiate into a testis and the absence of this gene allows the gonad to become an ovary. The development into a testis starts as soon as the gonocytes (*i.e.,* primordial germ cells) from the yolk sac have finished their migration into the gonadal ridge. Gonocytes of the male (XY) migrate deeper into the gonadal blastema forming the medulla and female gonocytes (XX) remain at the periphery, forming a thick cortical layer. Hence, the XX genetic sex is ordinarily associated with **ovarian gonadal sex**, and XY is associated with **testicular gonadal sex**.

Sex determination

In human beings, the presence of Y chromosome determines maleness and its absence determines femaleness. So, males are XY and females are XX in human beings. However, in 1986, certain peculiar cases have been reported which were found to be males with XX chromosomes and females with XY chromosomes. These can be due to any one of the following two reasons : (i) A sex reversal gene SRY located on the Y chromosome leads to XX males and XY females. (ii) Translocation of a small segment of the Y chromosome to an X chromosome in XX males and its deletion from the Y chromosome results in the XY females.

How does the extra X chromosome get 'turned off'? There are set of genes which are found on the X chromosome. This area is known as Xic or the 'X Inactivation Center'. Inside Xic there is a counting duo, two genes Xist and Tsix who have the jobs of kicking off the inactivation of one randomly selected X chromosome.

Both Xist and Tsix produce non coding RNA transcripts. The Tsix RNA transcript is anti sense to the Xist and therefore can bind to the Xist sequence and thus inhibit its action. Before an X chromosome is inactivated both chromosomes will express Xist in low concentrations. Shortly after this one X chromosome will begin to express Tsix in high levels. Because Txis is an inhibitor of Xist expression what follows is a dramatic reduction

Transcription

The synthesis of RNA molecules using DNA strands as the templates so that the genetic information can be transferred from DNA to RNA.

Similarity between replication and transcription:

1- **Both processes use DNA as the template.**

2- **Phosphodiester bonds are formed in both cases.**

3- **Both synthesis directions are from 5´ to 3´.**

Differences between replication and transcription:

transcription	replication	
single strand	**double strands**	**template**
NTP	**dNTP**	**substrate**
no	yes	**primer**
RNA polymerase	**DNA polymerase**	**Enzyme**
ssRNA	**dsDNA**	**product**
A-U, T-A, G-C	**A-T, G-C**	**base pair**

Template and Enzymes:

• The whole genome of DNA needs to be replicated, but only small portion of genome is transcribed in response to the development requirement, physiological need and environmental changes.

1.1 Template

1.1 Template

The template strand is the strand from which the RNA is actually transcribed. It is also termed as antisense strand.
The coding strand is the strand whose base sequence specifies the amino acid sequence of the encoded protein. Therefore, it is also called as sense strand.
-DNA regions that can be transcribed into RNA are called structural genes. The template strand is the strand from which the RNA is actually transcribed. It is also termed as antisense strand. transcription RNA G C A G U A C A U G U C 5' 3'

2-RNA Polymerase:

• The enzyme responsible for the RNA synthesis is DNA-dependent RNA polymerase.
– The prokaryotic RNA polymerase is a multiple-subunit protein of ~480kD.

– Eukaryotic systems have three kinds of RNA polymerases, each of which is a multiple-subunit protein and responsible for transcription of different RNAs.
• Holoenzyme

• The holoenzyme of RNA-pol in *E.coli* consists of 5 different subunits: □2 □ □□ □□.

4- Recognition of Origins

• Each transcriptable region is called operon.

• The promoter is the DNA sequence that RNA-pol can bind. It is the key point for the transcription control.

Promoter 5' 3' 3' 5' regulatory sequences structural geneMolecular biology /

The steps of Transcription:

1- **Initiation phase: RNA-pol recognizes the promoter and starts the transcription.**

2- **Elongation phase: the RNA strand is continuously growing.**

3- Termination phase: the RNA-pol stops synthesis and the nascent RNA is separated from the

DNA template

a. Initiation

• RNA-pol recognizes the TTGACA region, and slides to the TATAAT region, then opens the DNA duplex.

b. Elongation

• The release of the subunit causes the conformational change of the core enzyme. The core enzyme slides on the DNA template toward the 3 end.

Free NTPs are added sequentially to the 3 -OH of the nascent RNA strand (NMP)n + NTP (NMP)n+1 + PPiRNA strandsubstrateelongated RNA strand

c. Termination

• The RNA-pol stops moving on the DNA template. The RNA transcript

falls off from the transcription complex.

Post-Transcriptional :

• Modification

• The nascent RNA, also known as primary transcript, needs to be

modified to become functional tRNAs, rRNAs, and mRNAs.

• The modification is critical to eukaryotic systems.

Modification of hnRNA

• Primary transcripts of mRNA are called as

heteronuclear RNA (hnRNA).

• hnRNA are larger than matured mRNA by

many folds.

• Modification includes

1- **Capping at the 5- end**

2- **Tailing at the 3- end**

3- **mRNA splicing**

OOOHCH2OPOONNHNNONH2AAAAA-
OHOPi5'3'OOHOHH2CNHNNNOH2NOPOOOPOOOPOO5

1 . Capping at the 5- end

m7GpppGp----

• The 5- cap structure is found on hnRNA too. The capping process occurs in nuclei.

• The cap structure of mRNA will be recognized by the cap-binding protein required for translation.

• The capping occurs prior to the splicing.

2 . Poly-A tailing at 3 - end

• There is no poly(dT) sequence on the DNA template. The tailing process dose not depend on

the template.

• The tailing process occurs prior to the splicing.

• The tailing process takes place in the nuclei.

2 . mRNA splicing

The matured mRNAs are much shorter than the DNA templates

Split gene :

The structural genes are composed of coding and non-coding regions that are alternatively separated.

Exon and intron :

Exons are the coding sequences that appear on split genes and primary transcripts, and will be expressed to matured mRNA.

Introns are the non-coding sequences that are transcripted into primary mRNAs, and will be cleaved out in the later splicing process.

Translation

The Central Dogma

DNA RNA Proteins

Transcription Translation

Transcription is the process by which a molecule of DNA is copied into a **complementary strand of RNA**.

This is called **messenger RNA (mRNA)** because it acts as a messenger between DNA and the ribosomes where **protein synthesis is carried out**

Translation is the process of decoding a mRNA molecule into a **polypeptide chain or protein.**

Each combination of 3 nucleotides on mRNA is called a **codon or three-letter code word.**

Each codon specifies a **particular amino acid** that is to be placed in the polypeptide chain (protein).

• A three-letter code is used because there are **20 different amino acids** that are used to make proteins.

• If a **two-letter code** were used there would not be enough codons to select all 20 amino acids.

• That is, there are 4 bases in RNA, so 4_2 (4x 4)=16; **where as 4_3 (4x4x4)=64**.

• Each tRNA molecule has **2 important sites of attachment**.

• One site, called the **anticodon**, binds to the codon on the mRNA molecule.

• The other site attaches to a **particular amino acid**.

During protein synthesis, the anticodon of a tRNA molecule **base pairs** with the appropriate mRNA codon.
• Are made up of 2 subunits, a large one and a smaller one, each subunit

• contains **ribosomal RNA (rRNA) & proteins**.

• Protein synthesis starts when the **two subunits bind to mRNA**.

• The initiator codon AUG binds to the first anticodon of tRNA,

• **signaling the start of a protein.**

• The anticodon of another tRNA binds to the next mRNA codon,

• bringing the **2nd amino acid** to be placed in the protein.

• As each anticodon & codon bind together

• a **peptide bond forms between the two amino acids.**

• The protein chain continues to grow until a **stop codon** reaches the ribosome,
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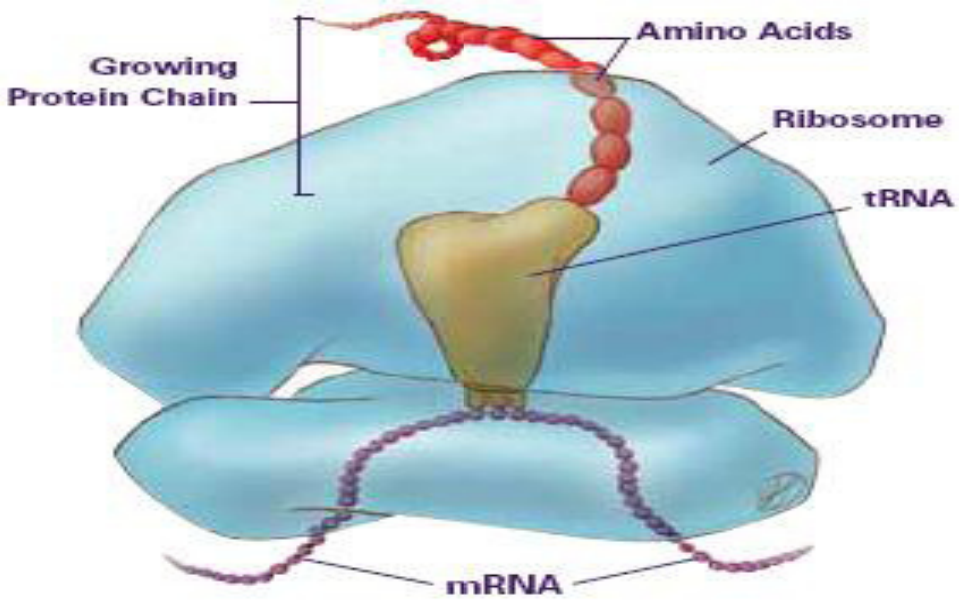
• which results in the release of the new protein and mRNA,

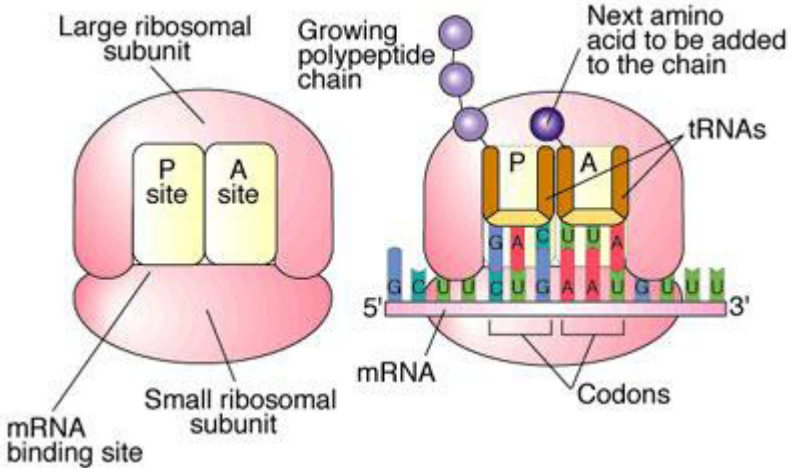
• **completing the process of translation**.

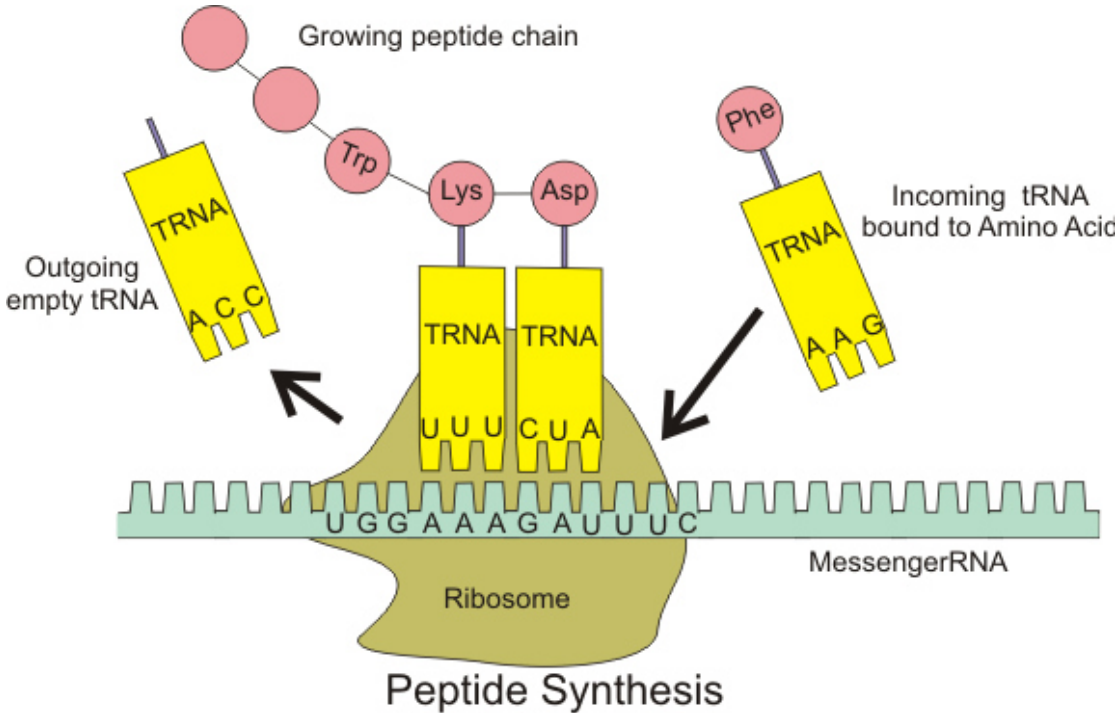
At the tart of each cycle;
• 1-The A (aminoacyl)site on the ribosome is empty.

• 2-the P (peptidyle)site contains a peptidyle-tRNA.

• 3-The E (exit) site contains an uncharged tRNA.







Peptide Synthesis