Ministry of Higher Education and Scientific Research
University of Baghdad
College of Science
Department of Biology

Theoretical Genetics
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المرحلة الأولى ـ الدراستين الصباحية والمسائية

الفصل الدراسي الثاني

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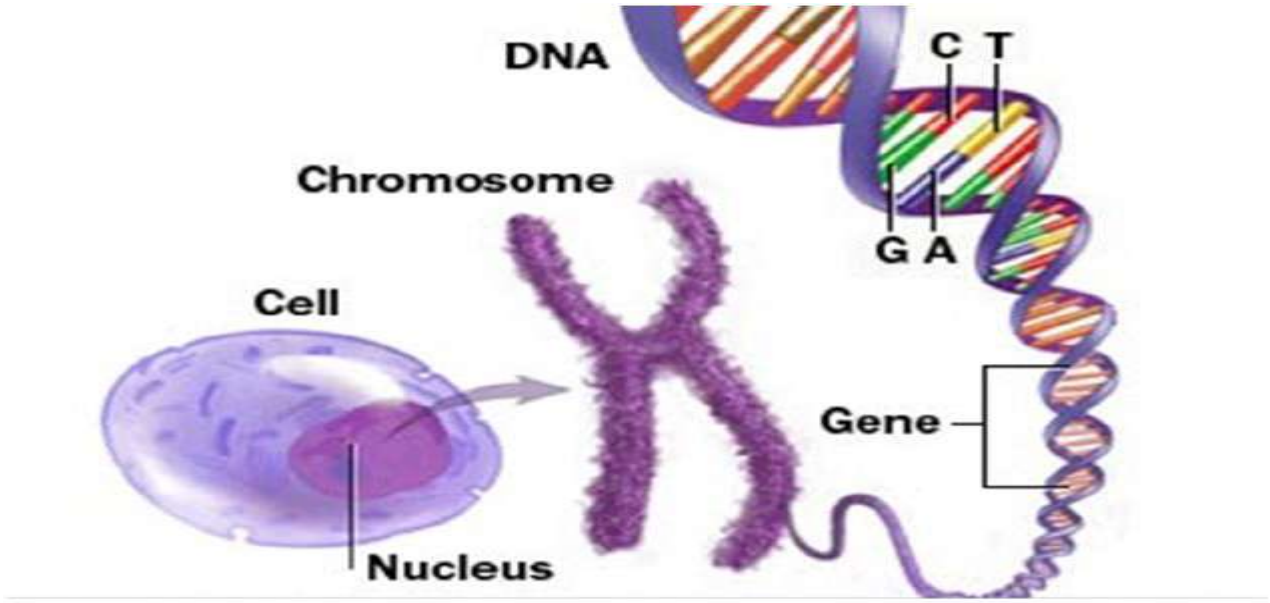


Lecture1: Genetic material

Genetics/ **Heredity**: describes how traits are passed from parents to their children. The **traits** are expressed by **genes,** which are small sections of DNA that are coded for specific traits. **Genes** are found on **chromosomes (**chromosome theory of inheritance**).**

Reasons for Studying Genetics

1. Genetics is relevant to **all fields** of medicine and biological disciplines, biochemistry, physiology, psychology, ecology, and other fields of the sciences.
2. **Understanding** and **control** of **genetic diseases** and in **agriculture**.
3. Explain how the **molecules of life** interact and produce living organisms.
4. **How the genetic information is** transmitted from one cell to its descendent cells, and from one generation to the next.
5. Genetic information **allows** organisms to convert atmospheric oxygen and **ingested** food into **energy production**.
6. Genetic information **regulates** the synthesis and transport of biologically important molecules **protects** against unwarranted **invaders**, such as bacteria, fungi, and viruses by the immune defense system.
7. Genetic information maintains the shape and mobility of bones, muscles, and skin.
8. **Genetically determined** functions of the **sensory organs** enable us to **see**, to **hear**, to **taste**, to **feel heat**, **cold**, and pain, to communicate by **speech**, to support brain function with the ability to learn from experience
9. **Reproduction** and **detoxification** of exogenous molecules likewise are under genetic control.

1. Genetics Progressed from Mendel to DNA in Less Than a Century :

The true **starting point** of our understanding of genetics began in a monastery garden in central Europe in the 1860s, where Gregor Mendel, conducted a **decade-**

long series of experiments using **pea plants**. He applied **quantitative data analysis** to his results and showed that traits are passed from parents to offspring in predictable ways. He further concluded that each trait in the plant is controlled by a pair of genes and that during gamete formation (the formation of egg cells and sperm) members of a gene pair separate from each other. His work forms the **foundation for genetics**, which is defined as the branch of biology concerned with the study of heredity and variation.

2. Discovery of the Double Helix Launched the Era of Molecular Genetics:

Once it was accepted that DNA carries genetic information, efforts were focused on **deciphering** the structure of the DNA molecule and the mechanism by which information stored in it is expressed to produce an observable trait, called the **phenotype**. In the years after this was accomplished, researchers learned how to isolate and make copies of specific regions of DNA molecules, opening the way for the era of **recombinant DNA technology**.

- The first **Nobel Prize** awarded for such work was given to **Thomas Morgan in 1933** for his research on the chromosome theory of inheritance. That award was followed by many others, including prizes for the discovery of genetic recombination, the relationship **between genes and proteins**, the **structure of DNA**, and the **genetic code**.

Some terms in genetics:

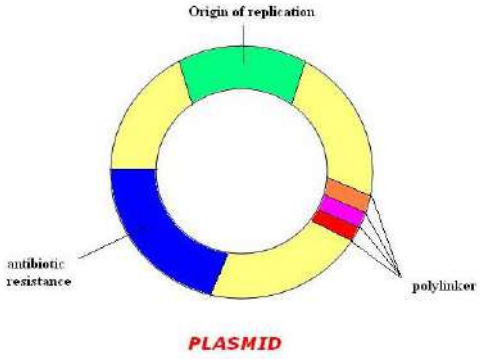
1. **Genomics/ genome:** is a study of the genomes of organisms. It main task is to determine the entire sequence of DNA. Knowledge of the DNA sequence has become an important part of biological research and other research disciplines including **medicine**, **biotechnology**, etc.

2. **Cloning**: the process of making a genetic copy of gene or an individual. Example for this process (Dolly **the sheep).**
3. **Human Genome Project**: Collective name for several projects begun in 1986 to create an ordered set of DNA segments from known chromosomal locations, develop new computational methods for analyzing **genetic map** and **DNA sequence data**, and develop new techniques and instruments for detecting and analyzing DNA.
4. **Genetic recombination**: is the production of offspring with combinations of traits that differ from those found in either parent. In eukaryotes, **genetic recombination** during meiosis (crossing over) can lead to **a novel** set of **genetic** information that can be passed on from the parents to the offspring.
5. **Recombinant DNA**: combining the genetic material from two different sources by means of **genetic engineering**. Recombinant DNA can be used to change the **genetic makeup** of a cell, as in adding a gene to make bacteria cell produce insulin.
6. **Gene expression: is** the process by which **information from a gene** is used in the synthesis of a functional gene product (often **proteins**).

7. **Junk DNA:** Refers to regions of DNA that are **noncoding**. Some of this noncoding DNA is used to produce non-coding RNA components such as **transfer RNA**, **regulatory RNA and ribosomal RNA**. However, other DNA regions are not transcribed into proteins, nor are they used to produce RNA molecules and their function is unknown.

   In the **human** genome for example, almost all (**98%**) of the DNA is noncoding, while in **bacteria**, only (**2%)** of the genetic material does not code for anything.

8. **Plasmid:** is a small DNA molecule within a cell that is physically separated from a chromosomal DNA and can replicate independently. They are most commonly **found in bacteria** as small circular, double stranded DNA molecules.

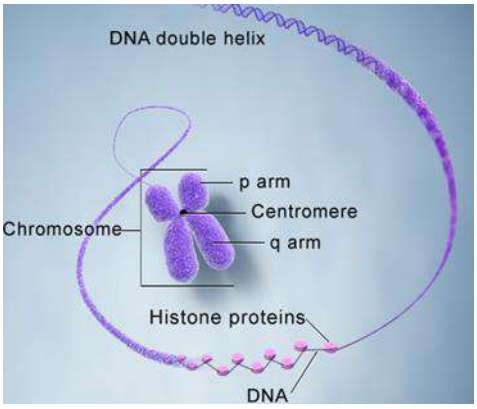


9. **Chromosomes:**

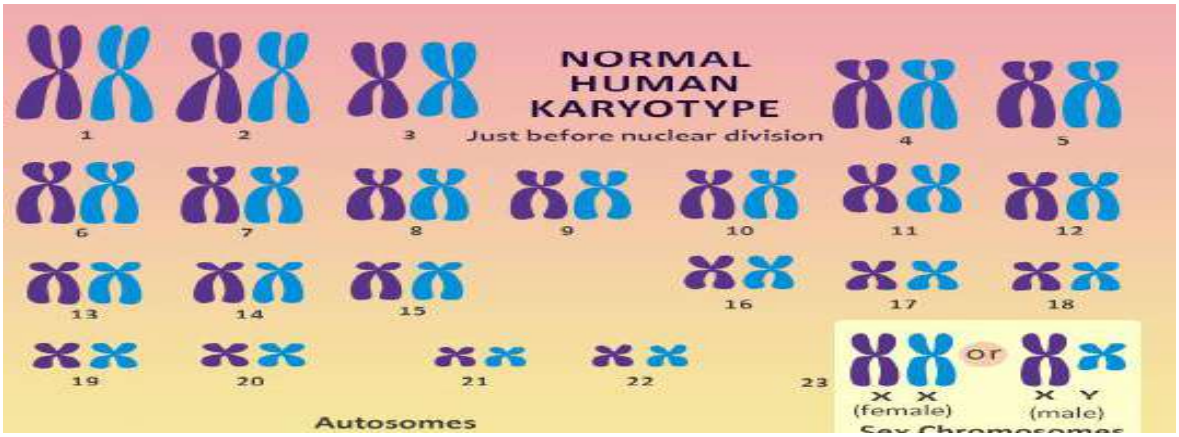
The microscopic **threadlike** part of the cell that carries heredity information in the form of genes. The structure and location of chromosomes are among the chief differences between viruses, prokaryotes, and eukaryotes. Among organisms with **prokaryoti**c cell (i.e., bacteria, and blue-green algae, chromosomes consist entirely of DNA.

The chromosome of **eukaryotic cell** consists primarily of DNA attached to protein core. Every eukaryotic species has a **characteristic number** of **chromosomes**(a human somatic cell has **46** chromosome). In the nucleus of each cell, DNA molecule is **packaged** into thread-like structures called chromosomes, each chromosome is made up of **DNA** tightly coiled many times around proteins called **histones** that support its structure.

Individual chromosomes cannot be seen very clearly in the periods between **cell division**. The structure of chromosomes is called **chromatids** with each chromatid of the pair containing one of the two identical DNA molecules. Each chromosome has a constriction point **called centromere**, which divides the chromosome into two sections, or **arms**. The centromere may occur anywhere along the length of the chromosome. The **short arm** of the chromosome is labeled the" **p arm**" the **long arm** of chromosome is labeled the" **q arm**".



When the sets of chromosomes from a human are lined up according to size it can be seen that they exist in pairs. These are called **homologous pairs** because they are similar in structure. An image of such an arrangement of chromosomes is called the **karyotype**. In humans there are 23 **pairs** of chromosomes. The reason the chromosomes are in pairs is because one set of chromosomes comes from the female parent via the egg and the other set of chromosomes comes from the male parent by way of the sperm.



11.Genes:

A segment of DNA within a chromosome which has a specific genetic function length from several **bps** to several million **bps**. Gene is not the smallest unit of genetic material. Genes are made up of DNA, act as instructions to make molecules called proteins. Genes tell a cell how to make proteins. Genes sometimes affect characteristics in indirect ways.

LEC 2: The genetic material

Types of Nucleic Acids: Nucleic acid as a distinctive class of **macromolecules**. Nucleic acids classified into **deoxyribonucleic acid (DNA)** and **ribonucleic acid (RNA)** that exists both in the nucleus and in the cytoplasm. These nucleic acids are consisting of **Nucleotides**.

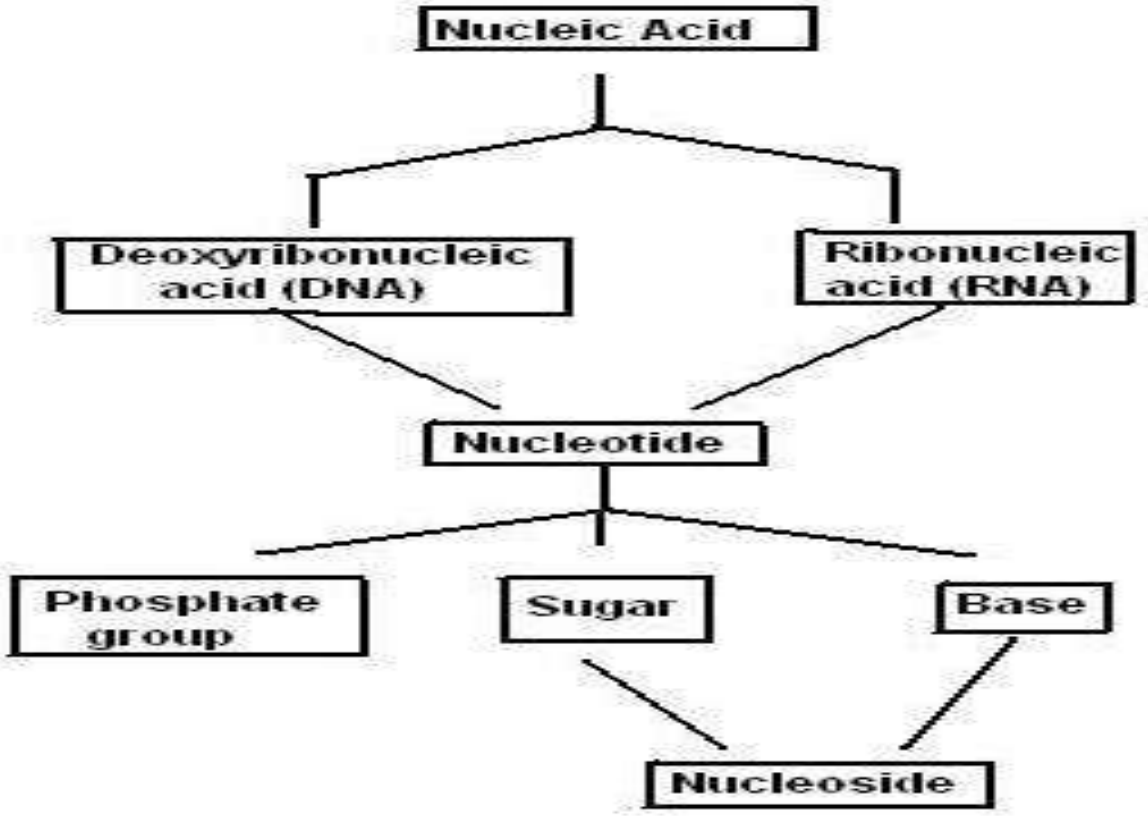


Figure (2): The contents of nucleic acids

- **History proof that DNA is the hereditary material:**

DNA was largely **ignored for decades** after a German chemist, **Friedrich Miescher**, first isolated from the nucleus of cells in 1869. Therafter, new experiments began to suggest that DNA might, in fact, be important. An **important first step** was taken **by Frederick Griffith in 1928** when he demonstrated that a physical trait can be passed from one cell to another. He was working with two strains of the bacterium ***Streptococcus pneumoniae*** identified as **S** and **R**.

- **R strain.** When grown in a petri dish, the R bacteria formed colonies, or clumps of related bacteria, that had well-defined edges and a rough appearance (hence the abbreviation "R"). The R bacteria were nonvirulent, meaning that they did not cause sickness when injected into a mouse.

S strain. S bacteria formed colonies that were rounded and smooth (hence the abbreviation "S"). The smooth appearance was due to a polysaccharide, or sugar-based, coat produced by the bacteria. This coat protected the S bacteria from the mouse immune system, making them virulent (capable of causing disease).

1- Mice injected with live S bacteria developed pneumonia and died.
2- The R bacteria were nonvirulent, meaning that they did not cause sickness when injected into a mouse.
3- injecting mice with heat-killed S bacteria (that is, S bacteria that had been heated to high temperatures, causing the cells to die). Unsurprisingly, the heat-killed S bacteria did not cause disease in mice.
4- when harmless R bacteria were combined with harmless heat-killed S bacteria and injected into a mouse. Not only did the mouse develop pnenumonia and die, but when Griffith took a blood sample from the dead mouse, he found that it contained living S bacteria!

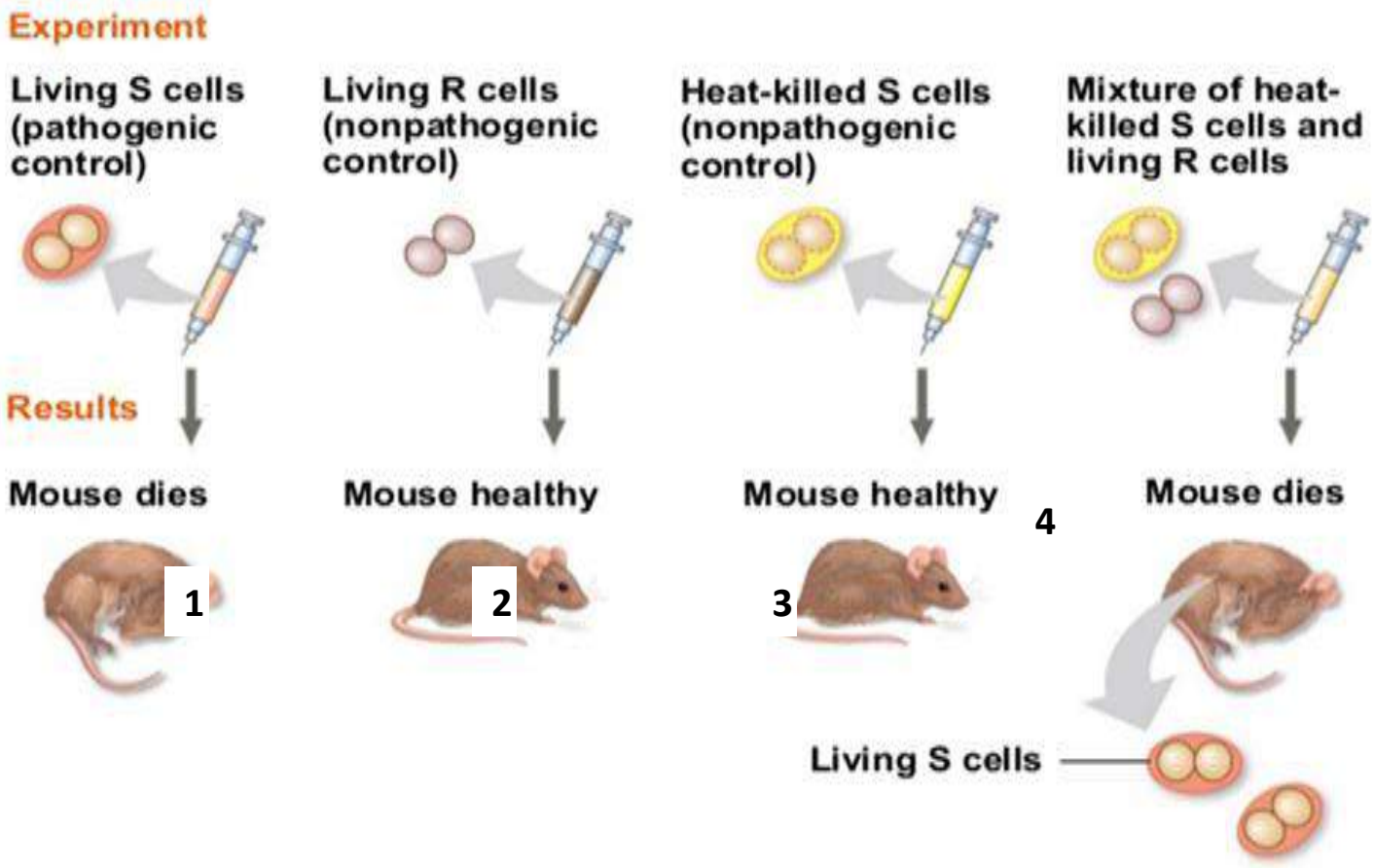
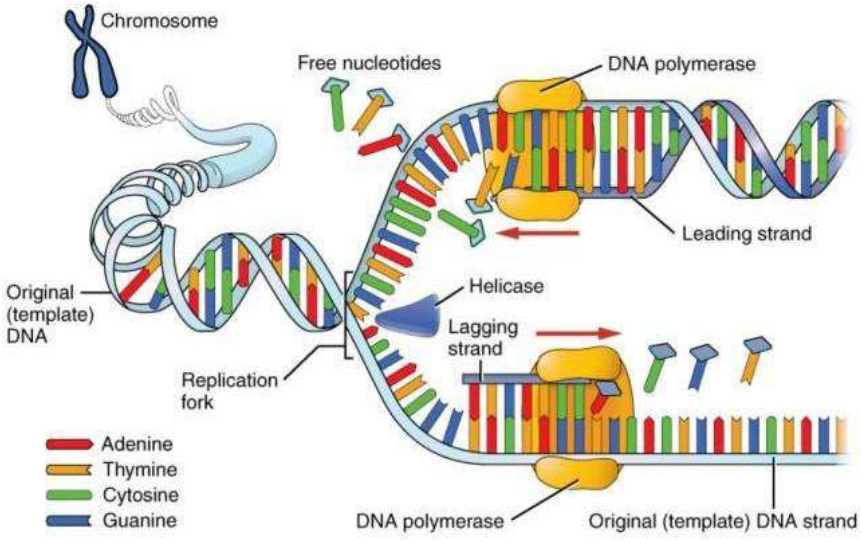


Figure 4: Frederick Griffith experiment (proof that DNA is the carrier of genetic information)

- **How new DNA molecules are made (replication)?**

New DNA molecules are made by **copying**, using old DNA molecules as a template **complementary strand**. Each DNA strand contains the information necessary to reconstruct the other. see **Figure 1 below.**



When a cell needs to copy a DNA molecule, its part of the double helix, breaking the rungs of the ladder in half so that the molecule separates down the middle. New nucleotides, floating free in the cell, can then hook up with complementary nucleotides along each strand. Gradually the unzipping proceeds and the new strands continue to grow until one DNA molecule becomes two identical DNA molecules.

A cell copies its entire DNA in this fashion each time it divides. In the cells of complex organisms such as humans, this process takes an average of 8 hours. Scientists use a similar method to make copies of DNA in the laboratory. They put a piece of DNA in a test tube along with a bunch of free nucleotides, short DNA sequences called **primers**, and some enzymes that help the process along. Given the right conditions of chemistry and temperature, up to a billion DNA molecules, all identical to the original template molecule, may be produced in a matter of hours, and this process known **PCR** (**polymerase chain reaction**).

Lecture 3

Gene Expression: from DNA to phenotype

As noted earlier **nucleotide complementarily** is the basis for gene expression, the chain of events that cause a gene to **produce a phenotype**. This process begins in the nucleus with **transcription**, in which the nucleotide sequence in one strand of DNA is used to construct a complementary RNA sequence (top part of **figure 3**). **Transcription** is a procedure necessary for translation. Once the mRNA created it leaves the nucleus, and protein synthesis, or translation, occurs in the cytoplasm. The coded message in then translated into messenger RNA. The translation occurs on ribosome.

There are three types RNA involved, but only one codes the proteins, mRNA. Once an RNA molecule is produced, it moves to cytoplasm. In protein synthesis, the RNA-called messenger RNA or m RNA –binds to a **ribosome**. The synthesis of proteins under the direction of m RNA is called **translation** (middle part of **figure 3).** Proteins, the end product of many genes, are polymers made up of amino acid monomers. There are 20 different amino acids commonly found in proteins.

How can information contained in m RNA direct the addition of specific amino acids into protein chains as they are synthesized?

The information encoded in mRNA and called the **genetic code** consists of a linear series of nucleotide triplets. Each triplet called a **cordon**, is complementary to the information stored in DNA and specifies the insertion of a specific amino acid into a protein. Protein assembly is accomplished with the aid of adapter molecules called **transfer RNA (tRNA).** Within the ribosome, tRNA recognizes the information encoded in the m RNA codons and carries the proper amino acids for construction of

the protein during translation. This sequence of events, known as the **central dogma** of genetics, occurs with great specify. Using an alphabet of only four letters (A, T, G, and C), genes direct the synthesis of highly specific proteins that collectively serves as the basis for all biological function (**Figure 2**).

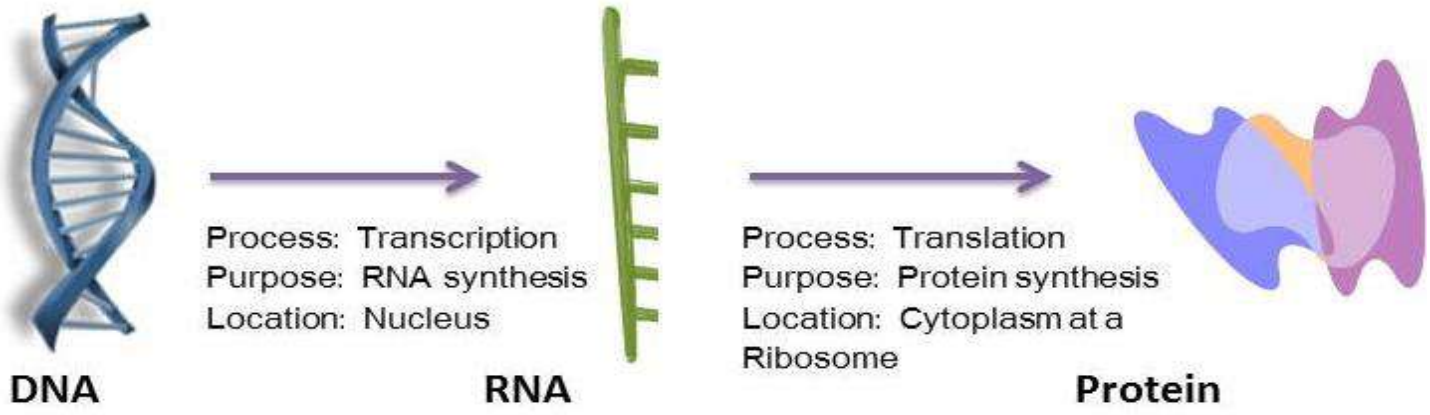


Figure 2: Central dogma: DNA to mRNA to Protein

The genes in DNA encode protein molecules, which are the "workhorses" of the cell, carrying out all the functions necessary for life. For example, enzymes, including those that metabolize nutrients and synthesize new cellular constituents, as well as **DNA polymerases** and other enzymes that make copies of DNA during cell division, are all proteins.

In the simplest sense, expressing a gene means manufacturing its corresponding protein, and this multilayered process has two major steps. **In the first step**, the information in DNA is transferred to a messenger RNA (mRNA) molecule by way of a process called transcription. During transcription, the DNA of a gene serves as a template for complementary base-pairing, and an enzyme called **RNA polymerase II** catalyzes the formation of a pre-mRNA molecule, which is then processed to form mature mRNA **(Figure 3).** The resulting mRNA is a **single-stranded copy** of the gene, which next must be translated into a protein molecule.

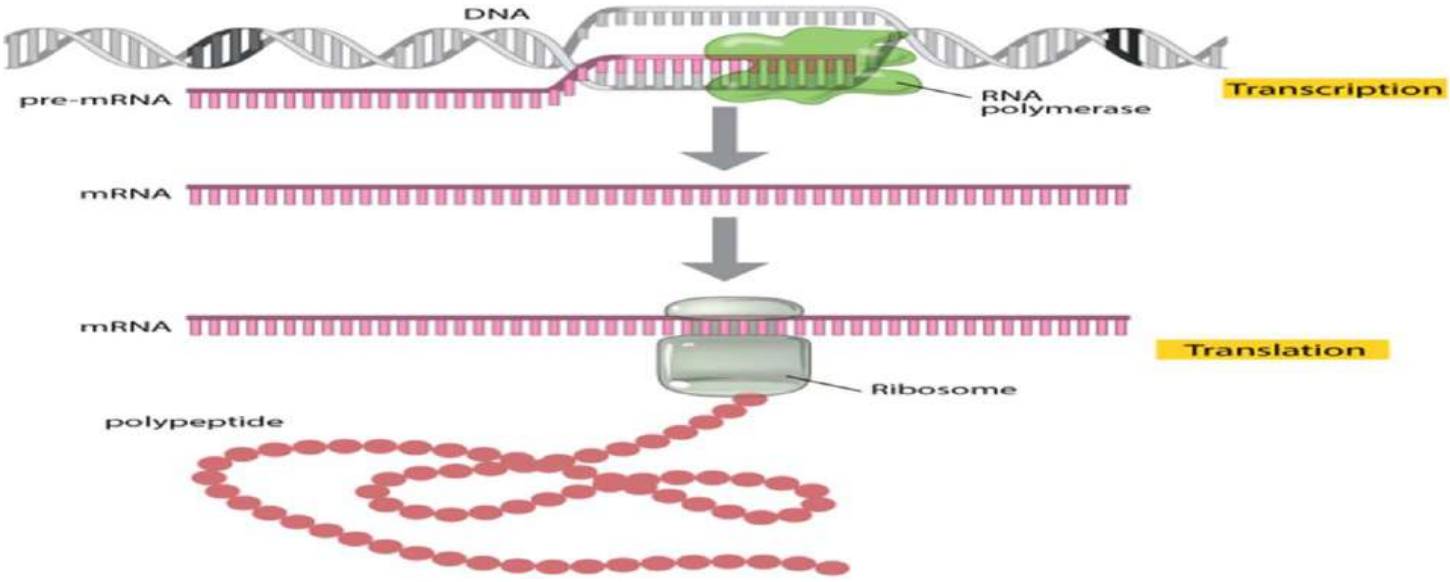


Figure 3: A gene is expressed through the processes of transcription and translation

During translation, which is **the second major step** in gene expression, the mRNA is "**read**" according to the genetic code, which relates the DNA sequence to the amino acid sequence in proteins **(Figure 4).** Each group of **three bases in m**RNA constitutes a codon, and each codon specifies a particular amino acid (hence, it is a triplet code). The mRNA sequence is thus used as a template to assemble—in order—the chain of amino acids that form a protein.

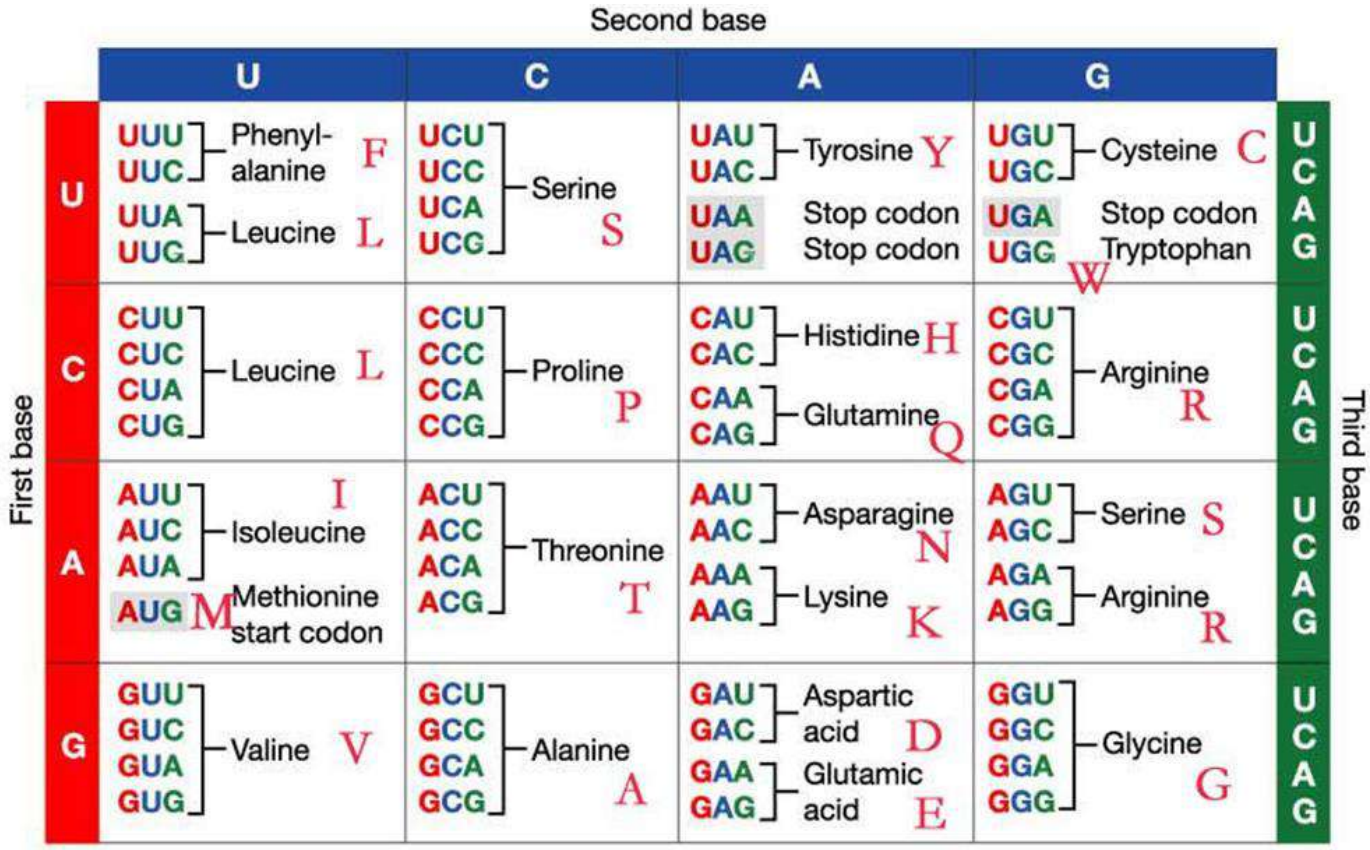


Figure 4: The amino acids specified by each mRNA codon. Multiple codons can code for the same nucleotides.

- **Where Translation Occurs?**

Within all cells, the translation machinery resides within a specialized organelle called the **ribosome**. In eukaryotes, mature mRNA molecules must leave the nucleus and travel to the cytoplasm, where the ribosomes are located. On the other hand, in prokaryotic organisms, ribosomes can attach to mRNA while it is still being transcribed. In this situation, translation begins at the 5' end of the mRNA while the 3' end is still attached to DNA.

Lecture 4: Mutations

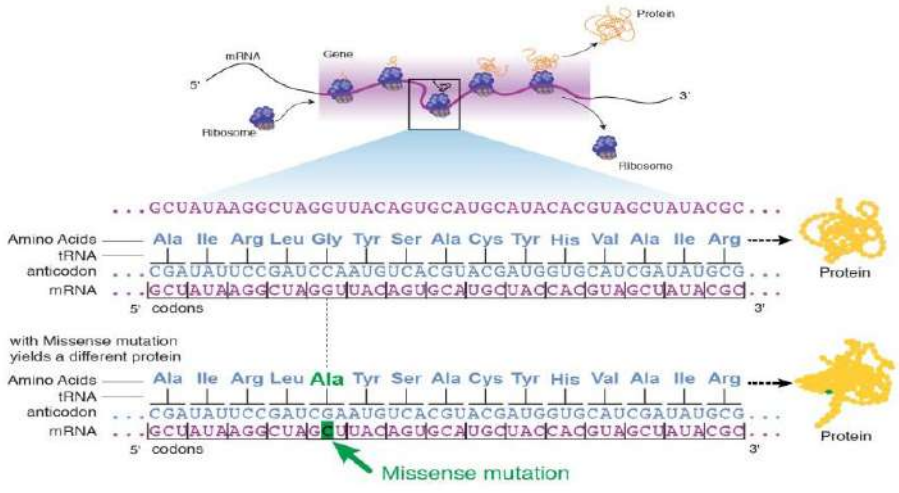
A mutation defines as an **alteration in DNA sequence. Any base-pair change in any part of a DNA molecule can be considered a mutation**. A mutation may comprise a single base-pair **substitution**, a **deletion** or **insertion** of one or more base pairs, or a major alteration in the structure of a chromosome. Mutations may occur within regions of a gene that code for protein or within **noncoding regions of a gene such as introns** and regulatory sequences.

Mutations can occur in **somatic cells** or within **germ cells**. Those that occur in **germ cells are heritable** and are the basis for the transmission of genetic diversity and evolution, as well as genetic diseases. Those that occur **in somatic cells are not transmitted to the next generation** but may lead to altered cellular function or tumors.

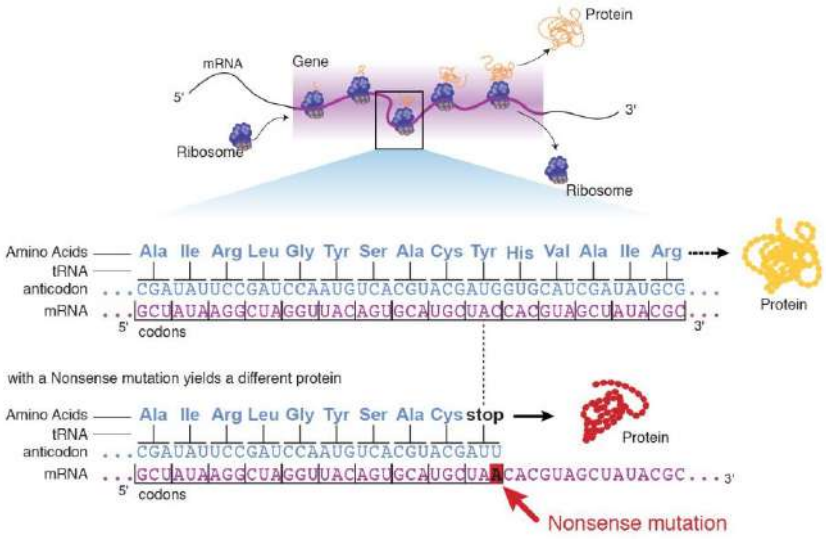
Classification Based on Type of Molecular Change:

Geneticists often classify gene mutations in terms of the nucleotide changes that constitute the mutation. A change of one base pair to another in a DNA molecule is known as a:

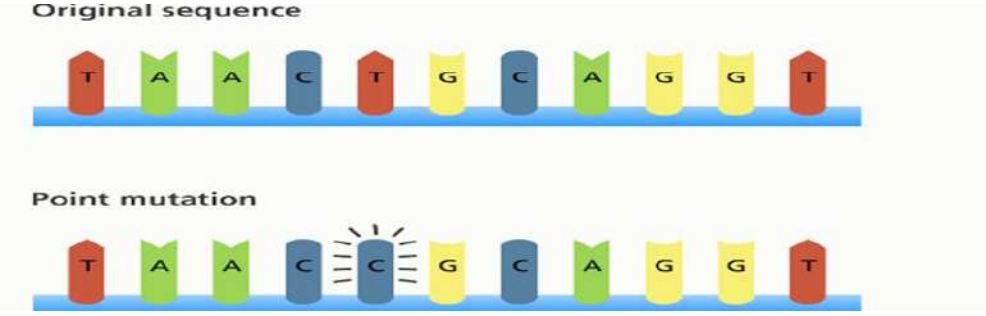
1. **Point mutation**:
   a. **Missense mutation:** A change of one nucleotide of a triplet within a **protein coding portion** of a gene may result in the creation of a new triplet that code for a different amino acid in the protein product.



b. **Nonsense mutation**: A second possible outcome is that the triplet will be changed into a **stop codon UAA**, resulting in the termination of translation of the protein.



c. **Silent mutation**: If the point mutation alters a codon but does not result in a change in the amino acid at that position in the protein (due to degeneracy of the genetic code), For example, ATT, ATC and ATA all correspond to **isoleucine**. If a base substitution were to occur in the codon ATT changing the last nucleotide (T) to a C or an A, everything would remain the same in the resulting protein. The mutation would go undetected, or remain silent **(Figure1).**



(Figure 1): point mutation

2. Insertion:

An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.

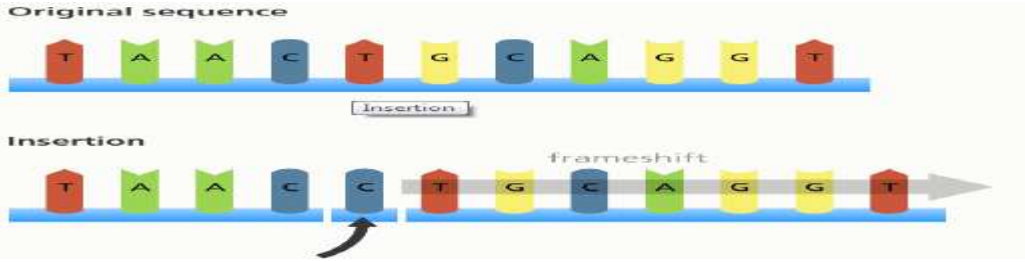
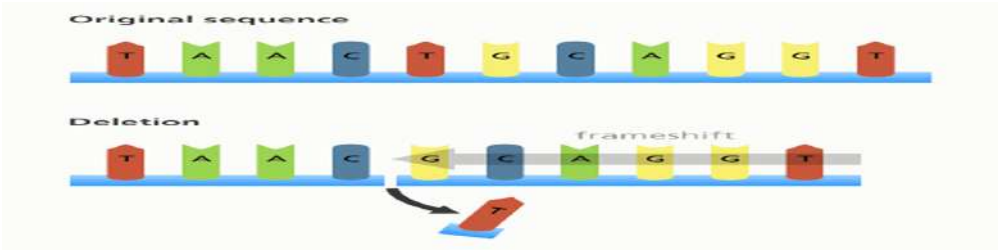
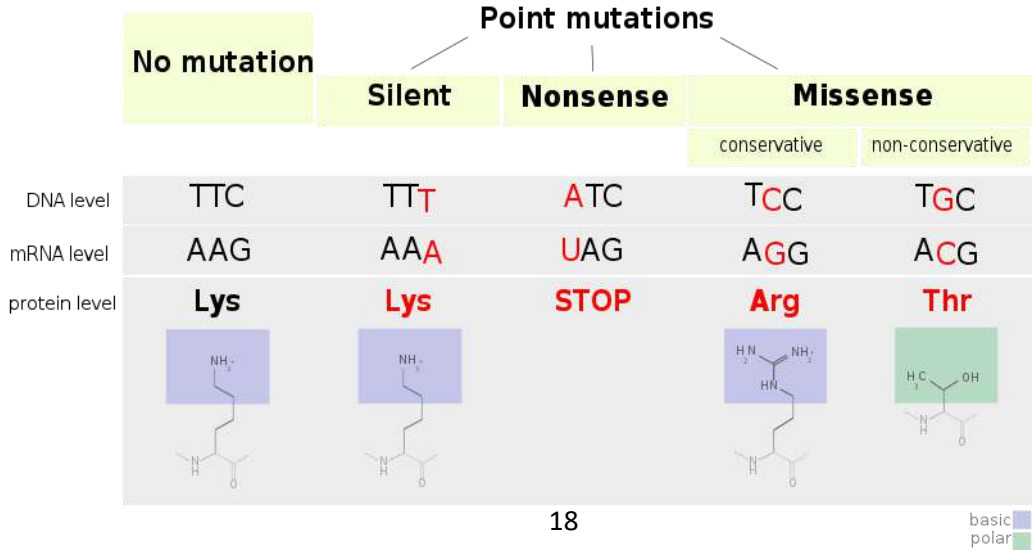


Figure 2 insertion

3. Deletion: A deletion changes the number of **DNA bases by removing a piece of DNA.** Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. **The deleted DNA may alter the function of the resulting protein(s).**





Classification Based on Phenotypic Effects:

Depending on their type and location, mutations can have a **wide range of phenotypic effects**, from none too severe. **A loss of function mutation** is one that reduces or eliminates the function of the gene product. Any type of mutation, from a point mutation to deletion of the entire gene, may lead to a loss of function.

Mutation	Define	Example
Visible mutations	A **gain-of-function mutation** results in a gene product with enhanced or new functions.	change in the amino acid sequence of the protein that confers a new activity
Nutritional mutation	Some mutations give rise to nutritional or biochemical effects. In bacteria and fungi, a typical nutritional mutation results in a loss of ability to synthesize an amino acid or vitamin	In humans, sickle-cell anemia and hemophilia
Behavioral mutations	Do not always affect morphological characters, they affect the function of proteins that can affect the well-being and survival of the affected individual.	The mating behavior of a fruit fly may be impaired if it cannot beat its wings. However, the defect may be in the flight muscles, the nerves leading to them, or the brain
regulatory mutations	Affect the regulation of gene expression.	Substitution, Deletion, and Insertion.

Chromosome mutations or Chromosome aberrations:

Chromosome Mutations: Variation in Number:

The failure of chromosomes to properly separate during meiosis results in variation in the chromosome content of gametes and subsequently in offspring arising from such gametes**.** Variation in chromosome number ranges from the **addition or loss of one or more chromosomes** to the addition of one or more haploid sets of chromosomes are shown in the next table.

Chromosomal numerical changes	Definition
Aneuploidy	gains or losses one or more chromosomes but not a complete set.
Monosomy	loss of a single chromosome from an otherwise diploid genome
Trisomy	gain of one chromosome (see figure 4)
Euploidy	where complete haploid sets of chromosomes are present
Polyploidy	more than two sets are present
Triploid	Organisms with 3 sets of chromosomes & those with 4 sets are **tetraploid**.

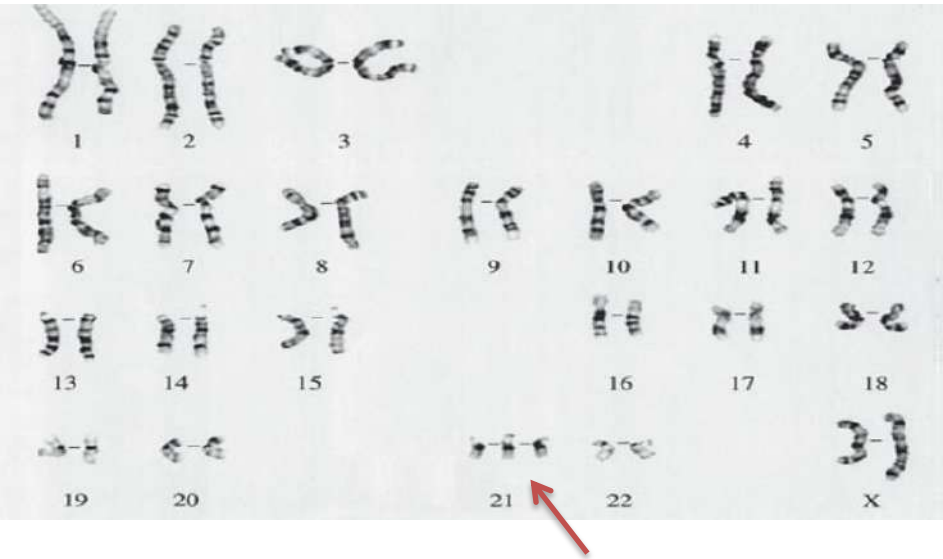


Figure (4): The karyotype and a photograph of a child with Down syndrome (hugging her unaffected sister on the right). In the karyotype, three members of the G-group chromosome 21 are present, creating the 47, 21+ condition.

Variation Occurs in the Composition and Arrangement of Chromosomes:

1. Translocations: Exchanges and transfers are called **translocations,** in which the locations of genes are altered within the genome. Chromosomes can break spontaneously, but **the rate of breakage may increase in cells exposed to chemicals or radiation**. Although the actual ends of chromosomes, known as telomeres, do not readily fuse with newly created ends of "broken" chromosomes or with other **telomeres**, the ends produced at points of breakage are "**sticky**" and can rejoin other broken ends.

A. Deletion Is a Missing Region of a Chromosome:

When a chromosome breaks in one or more places and a portion of it is lost, the missing piece is called a deletion (or a deficiency). The deletion can occur either near one end (i.e. **cri du chat syndrome, figure 6)** or within the interior of the chromosome. If even more genetic information is lost as a result of a deletion, the aberration is often lethal.

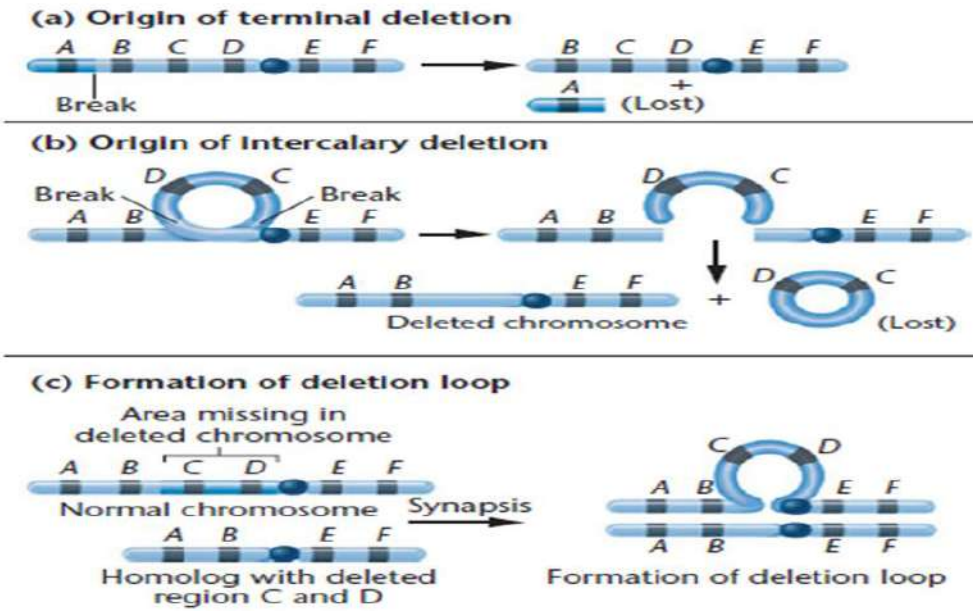


Figure (5): Origins of (a) a terminal and (b) an intercalary deletion. In (c), pairing occurs between a normal chromosome and one with an intercalary deletion by looping out the undeleted portion to form a deletion.

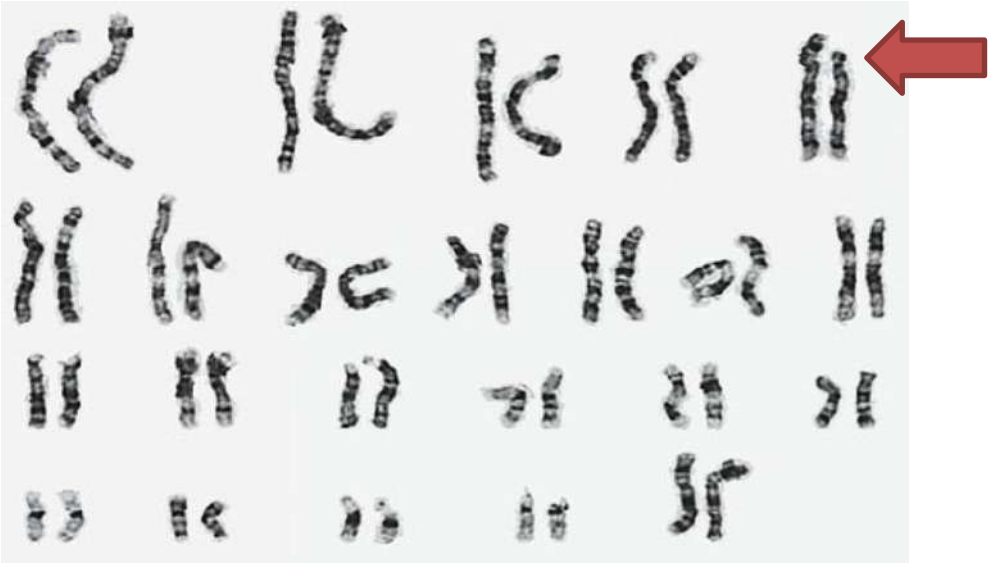
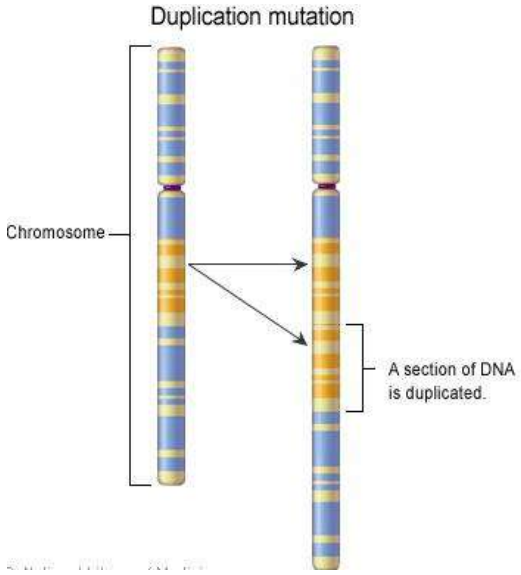


Figure (5): A representative karyotype cri du cat syndrome (46,5p–). In the karyotype, the arrow identifies the absence of a small piece of the short arm of one member of the chromosome 5 homologs

2. Duplication: Is a repeated segment of a chromosome. When any part of the genetic material—a single locus or a large piece of a chromosome—is present more than once in the genome, it is called **duplication**.



3. Inversions:

The inversion, another class of structural variation, is a type of chromosomal aberration in which a segment of a chromosome is turned around 180 degrees within a chromosome. An inversion **does not involve a loss of genetic information but simply rearranges the linear gene sequence**. An inversion requires breaks at two points along the length of the chromosome and subsequent reinsertion of the inverted segment; **Figure (8)**

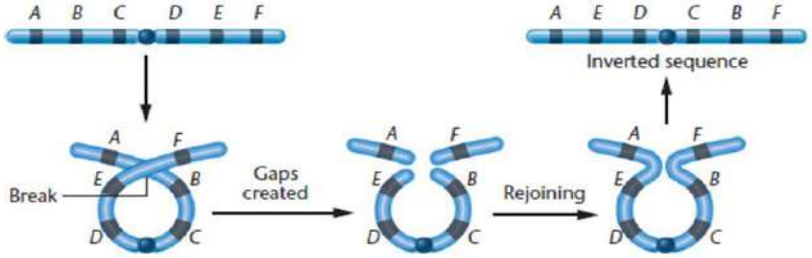


Figure (8): The inversion, another class of structural variation, is a type of chromosomal aberrations

Lecture 5: Mendelian Genetics الوراثة المندلية

Mendel used a model experimental approach to study patterns of inheritance

When Mendel began his studies (1856-1868) of inheritance using *Pisum sativum*, the garden pea, chromosomes and the role and mechanism of meiosis were totally **un**known. Nevertheless, he determined that **discrete** units of inheritance exist and **predicted their behavior** in the formation of gametes. Subsequent investigators, with access to **cytological data**, were able to relate their own observations of chromosome behaviour during meiosis and Mendel's principles of inheritance.

The results of Mendel's experiments went **unappreciated** until the turn of the century, well after his death. However, once Mendel's publications were rediscovered by **geneticists** investigating the function and behavior of chromosomes, the implications of his postulates were immediately apparent. He had discovered the basis for the transmission of hereditary traits!

The monohybrid cross reveals how one trait is transmitted from generation to generation

Mendel's simplest crosses involved **only one pair of contrasting traits**. Each such experiment is called a **monohybrid cross**. When Mendel crossed tall plants with dwarf plants, the resulting F1 generation consisted of only tall plants. When members of the F1 generation were selfed, Mendel observed that 787 of 1064 F2 plants were tall, while 277 of 1064 were dwarf. Note that in this cross (Figure 3–2), the dwarf trait **disappeared in the F1 generation**, only to **reappear in the F2 generation**.

Genetic data are usually **expressed** and **analyzed as ratios**. In this particular example, many identical P1 crosses were made and many F1 plants—all tall—were produced. As noted, of the 1064 F2 offspring, **787** were tall and **277** were dwarf—a ratio of approximately 2.8:1.0, or about **3:1.**

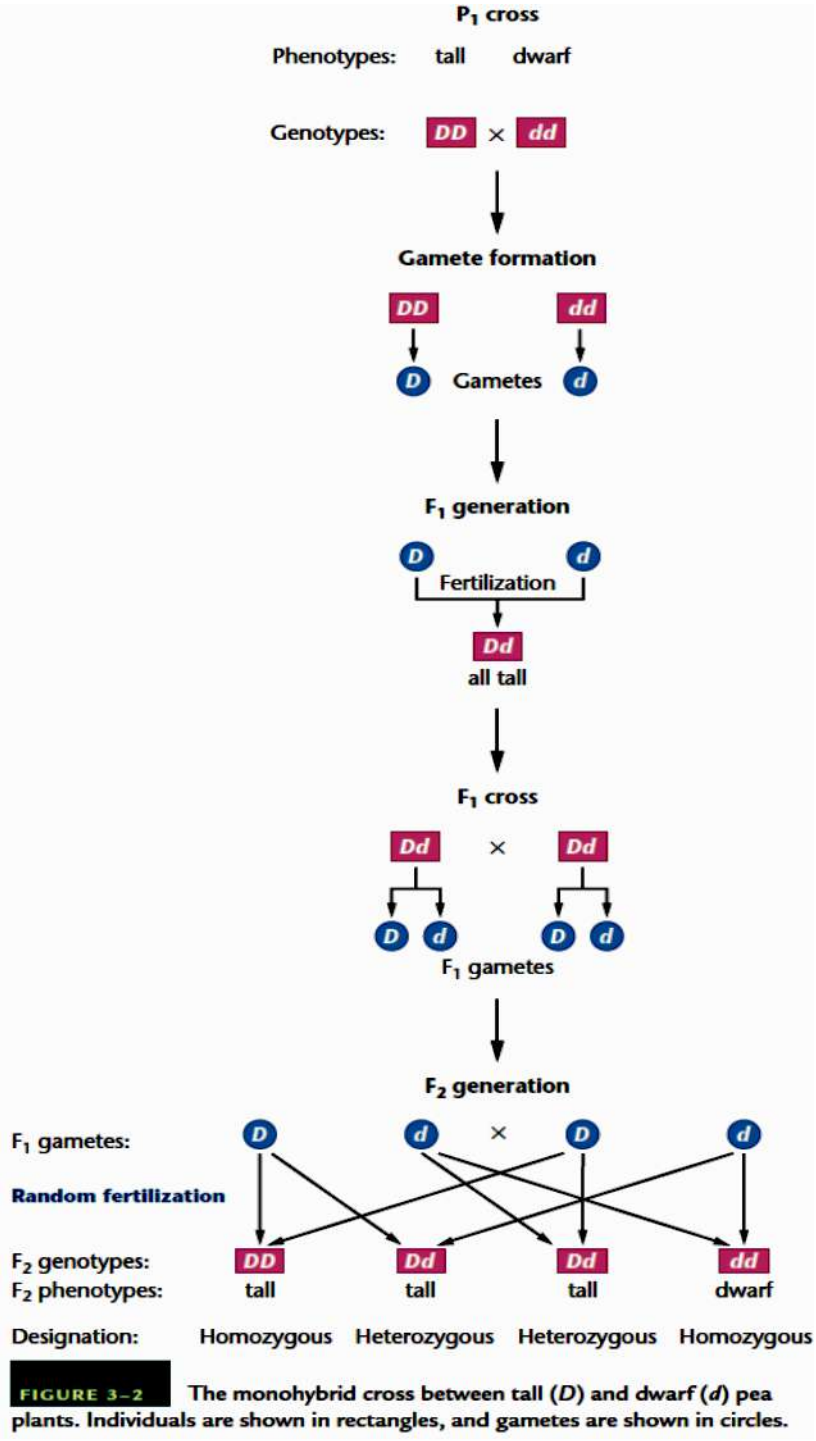
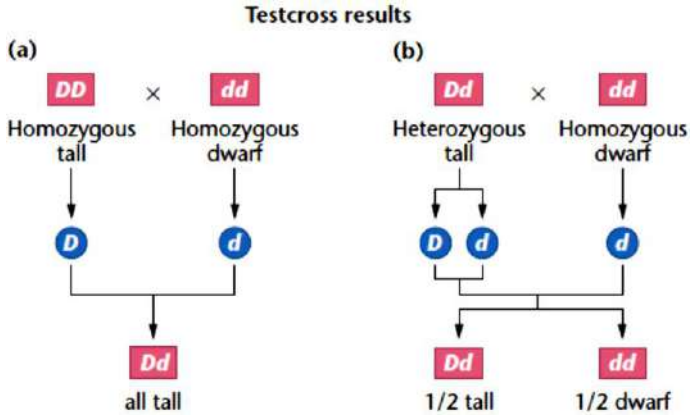


FIGURE 3–2 The monohybrid cross between tall (*D*) and dwarf (*d*) pea plants. Individuals are shown in rectangles, and gametes are shown in circles.

The Testcross: One Character

Tall plants produced in the F2 generation are **predicted** to have either the **DD** or the **Dd** genotype. You might ask if there is a way to **distinguish the genotype**. Mendel devised a rather simple method that is still used today to discover the genotype of plants and animals: the **testcross**. The organism expressing the dominant phenotype

but having an unknown genotype is crossed with a **known homozygous recessive individual**. For example, as shown in Figure (a), if a tall plant of **genotype DD** is test crossed with a dwarf plant, which must have the **dd genotype**, all offspring will be tall phenotypically and Dd genotypically. However, as shown in Figure (b), if a **tall plant is Dd** and is crossed with a **dwarf plant (dd),** then one-half of the offspring will be tall (Dd) and the other half will be dwarf (dd). Therefore, a 1:1 tall/dwarf ratio demonstrates the **heterozygous** nature of the tall plant of unknown genotype.



Mendel's first three postulates

Using the consistent pattern of results in the monohybrid crosses, Mendel **derived** the following **three postulates**, or principles, of inheritance.

1. Unit factors in pairs

Genetic characters are controlled by **unit factors** existing in pairs in individual organisms**.**

In the monohybrid cross involving tall and dwarf stems, a specific unit factor exists for each trait. Each diploid individual receives one **factor** from each parent. Because the **factors** occur in pairs, **three combinations are possible:** two factors for tall stems, two factors for dwarf stems, or one of each factor (see the above example). Every individual possesses one of these three combinations **(DD, Dd, or dd)** which determines stem height.

2. Dominance / Recessiveness السيادة والتنحي

When **two unlike unit factors** responsible for a **single character** are present in a single individual, **one unit factor** is **dominant** to the other, which is said to be **recessive.**

In each **monohybrid cross**, the **trait expressed in the F1** generation is controlled by the dominant unit factor. The trait **not expressed** is controlled by the recessive unit factor. The terms dominant and recessive are also used to designate **traits.** In this case, tall stems are said to be dominant over recessive dwarf stems.

3. Segregation الانعزال

During the formation of gametes, the paired unit factors **separate**, or **segregate**, randomly so that each gamete receives one or the other with equal likelihood.

If an individual contains a pair of like unit factors (e.g., both specific for tall), then all its gametes receive one of that same kind of unit factor (in this case, tall). If an individual contains unlike unit factors (e.g., one for tall and one for dwarf), then each gamete has a 50% probability of receiving either the tall or the dwarf unit factor.

Phenotype الطراز المظهري

Phenotype is the physical expression of a trait of the individual. Mendel's unit factors represent units of inheritance called **genes** by modern geneticists. For any given character, such as plant height, the phenotype is determined by alternative forms of a single gene, called **alleles**. For example, the unit factors representing tall and dwarf are alleles determining the height of the pea plant.

The first letter of the recessive trait symbolizes the character in question; in **lowercase** italic, it designates the allele for the recessive trait, and in **uppercase** italic, it designates the allele for the dominant trait. Thus for Mendel's pea plants, we use **d** for the dwarf allele and **D** for the tall allele. When alleles are written in pairs to represent the two unit factors present in any individual (**DD, Dd, or dd**), the resulting symbol is called the **genotype**. The **genotype** designates the **genetic makeup** of an

individual for the trait or traits it describes, whether the individual is **haploid** or **diploid**. By reading the **genotype**, we know the phenotype of the individual: DD and Dd are tall, and dd is dwarf. When both alleles are the same (DD or dd), the individual is **homozygous** for the trait, or a **homozygote**; when the alleles are different (Dd), we use the terms **heterozygous** and **heterozygote**.

Mendel's dihybrid cross generated a unique F2 ratio

As a natural extension of the monohybrid cross, Mendel also designed experiments in which he examined **two characters** simultaneously. Such a cross, involving two pairs of contrasting traits, is a dihybrid cross, or a two-factor cross. For example, if pea plants were having yellow seeds that are round were **bred with** those having green seeds that are wrinkled, the results shown in Figure 3–5 would occur: the F1 offspring would all be yellow and round. It is therefore apparent that yellow is dominant to green and that round is dominant to wrinkled. When the F1 individuals are selfed, approximately 9/16 of the F2 plants express the yellow and round traits, 3/16 express yellow and wrinkled, 3/16 express green and round, and 1/16 express green and wrinkled.

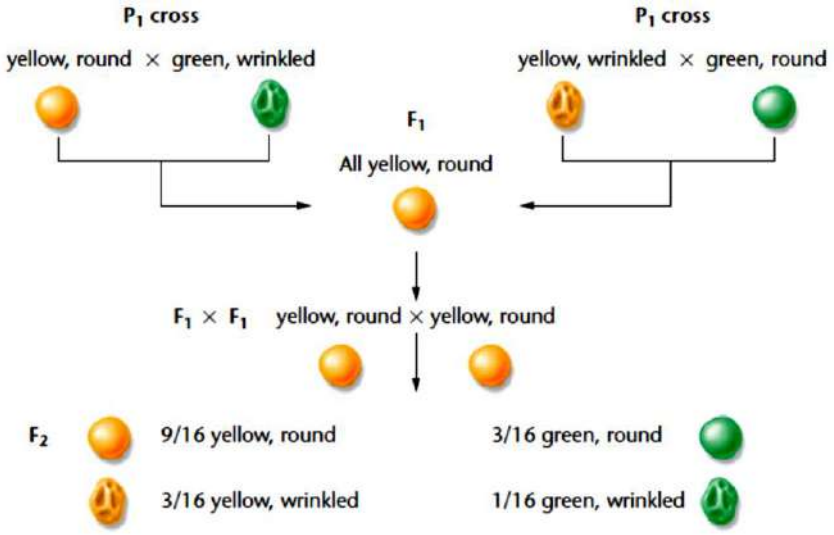


Figure 3-5: F1 and F2 results of Mendel's dihybrid crosses in which the plants on the top left with yellow, round seeds are crossed with plants having green, wrinkled seeds, and the plants on the top right with yellow, wrinkled seeds are crossed with plants having green, round seeds.

Independent assortment قانون التوزيع الحر

During gamete formation, segregating pairs of unit factors assort independently of each other**.**

This postulate stipulates that segregation of any pair of unit factors occurs independently of all others. As a result of random segregation, each gamete receives one member of every pair of unit factors. For one pair, whichever unit factor is received does not influence the outcome of segregation of any other pair. Thus, according to the postulate of independent assortment, all possible combinations of gametes should be formed in equal frequency.

Pedigrees reveal patterns of inheritance of human traits

The traditional way to study inheritance has been to construct a family tree, indicating the presence or absence of the trait in question for each member of each generation. Such a **family tree** is called a **pedigree**. By analyzing a pedigree, we may be able to predict how the trait under study is inherited—for example, is it due to a **dominant** or **recessive** allele? When many pedigrees for the same trait are studied, we can often ascertain the mode of inheritance.

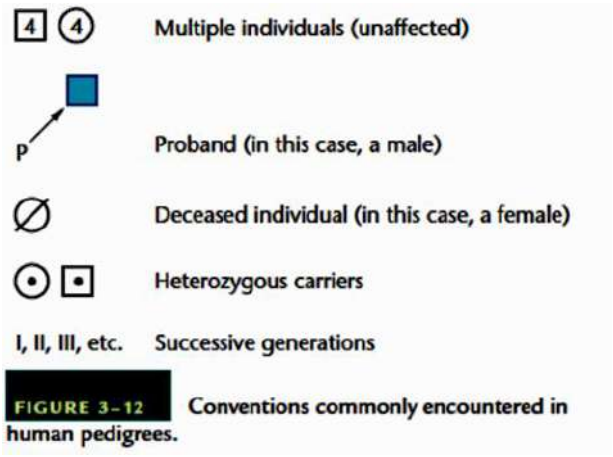
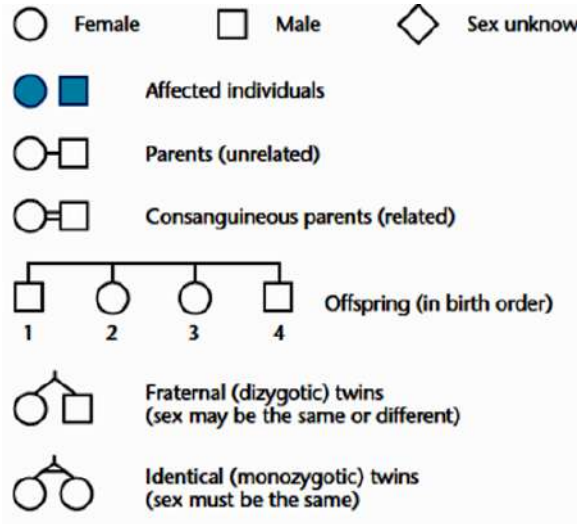
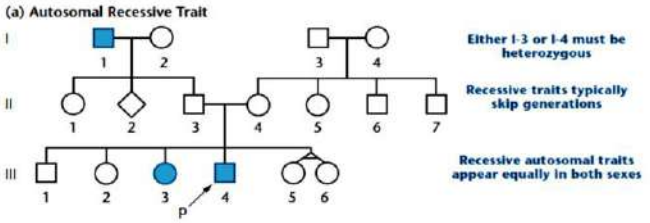


FIGURE 3–12 Conventions commonly encountered in human pedigrees.





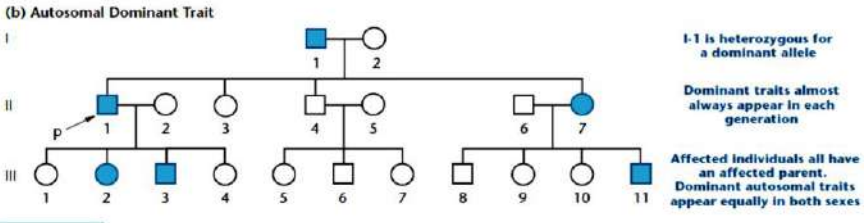


FIGURE 3–13 Representative pedigrees for two characteristics, each followed through three generations.

Lecture 6: Extensions of Mendelian Genetics

Lecture concepts

- Some traits **do not display the clear-cut dominant/recessive** relationship observed by Mendel.
- **Two or more genes** influence the phenotype of a single characteristic.
- Genes are located on the X chromosome, because one of the sexes receives only one copy of that chromosome, eliminating the possibility of heterozygosity.
- Phenotypes are often the combined result of genetics and the environment

Genes are present **on homologous chromosomes** and that these chromosomes **segregate** from each other and **assort independently** from other segregating chromosomes during gamete formation. These two postulates are the basic principles of gene transmission from parent to offspring. Once an offspring has received the total set of genes, it is the **expression of genes** that determines the organism's phenotype. When **gene expression** does not adhere to a simple dominant/recessive mode, or when more than one pair of genes influences the expression of a single character, the classic 3:1 and 9:3:3:1 F2 ratios are usually **modified**.

Alleles alter phenotypes in different ways

To understand the various modes of inheritance, we must first consider the potential function of an allele. An **allele** is an alternative form of a gene. The allele that occurs most frequently in a population, the one that we arbitrarily designate as normal, is called the **wild-type allele**. This is **often**, but **not always**, dominant. **Wild-type alleles** are responsible for the corresponding **wild-type phenotype** and are the standards against which all other mutations occurring at a particular locus are compared.

A mutant allele contains **modified genetic information** and often specifies an altered gene product. The **process of mutation** is the **source of alleles**. For a new

allele to be recognized by observation of an organism, the allele must cause a change in the phenotype. Often, the mutation causes the loss of the specific wild-type function. For example, mutation in gene that may reduce or eliminate the enzyme substrate. Such a mutation is designated as a **Loss-of-function mutation**. If the **loss is complete**, the mutation has resulted in what is called a **null allele**.

Neither allele is Dominant in Incomplete Dominant سيادة ناقصة

Unlike the Mendelian crosses, a cross between parents with **contrasting traits** may sometimes generate offspring with an **intermediate phenotype**. For example, if a **four-o'clock** or a **snapdragon plant** with **red flowers** is crossed with a **white-flowered** plant, the offspring have **pink flowers**. Because some red pigment is produced in the **F1** intermediate-colored plant, **neither the red nor white flower color is dominant.** Such a situation is known as **incomplete, or partial, dominance**.

If the phenotype is **under the control of a single gene and two alleles**, where neither is dominant, the results of the **F1** (**pink**) × **F1** (**pink**) cross can be predicted. The resulting **F2** generation shown in Figure 2-1 confirms the hypothesis that **only one pair of alleles** determines these phenotypes. The **genotypic ratio** (**1:2:1**) of the F2 generation is identical to that of Mendel's monohybrid cross. However, **because neither allele is dominant, the phenotypic ratio is identical to the genotypic ratio (in contrast to the 3:1 phenotypic ratio of a Mendelian monohybrid cross)**.

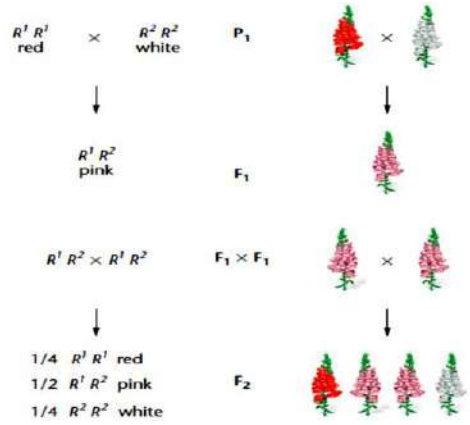


Figure (2-1) :

Incomplete dominance shown in the flower color of snapdragons

In Codominance سيادة مشاركة, the influence of both alleles in a heterozygote is clearly evident

If two alleles of a single gene are responsible for producing **two distinct, detectable gene products**, a situation different from incomplete dominance or dominance/recessiveness arises. In this case, the **joint expression of both alleles in a heterozygote** is called **codominance**. Codominant inheritance is characterized by distinct expression of the gene products of both alleles. This characteristic distinguishes codominance from incomplete dominance, where heterozygotes express an intermediate, blended, phenotype.

Multiple alleles of a gene may exist in a population/ABO

The simplest case of **multiple alleles** occurs when **three alternative alleles** of one gene exist. This situation is illustrated in the inheritance of the ABO blood groups in humans. The ABO system is characterized by the presence of **antigens on the surface of red blood cells**. The A and B antigens are located on chromosome 9. One combination of alleles **(I^A, I^B and i)** in the ABO system exhibits a **codominantmode** of inheritance. In these assignments, the $\mathbf{I^A}$ and $\mathbf{I^B}$ alleles are dominant to the **i** allele, but codominant to each other (Figure 3-2).

Genotype	Antigen	Phenotype
$I^A I^A$	A	A
$I^A i$	A	
$I^B I^B$	B	B
$I^B i$	B	
$I^A I^B$	A, B	AB
$i i$	Neither	O

Lethal Alleles Represent Essential Genes

A genotype (allele combination) that causes death is, by strict definition, lethal. Death from genetic disease can occur at any stage of development or life. **Tay-Sachs disease** is lethal by age 3 or 4yrs, whereas **Huntington disease** may not be lethal until late middle age. In a population and evolutionary sense, a lethal genotype has a more specific meaning—it causes death before the individual can reproduce, which prevents passage of genes to the next generation.

In organisms used in experiments, such as fruit flies, pea plants, or mice, lethal allele combinations remove an expected progeny class following a specific cross. For example, in a cross of **heterozygous flies carrying lethal alleles** in the same gene, **homozygous recessive progeny die as embryos**, leaving only heterozygous and homozygous dominant adult fly offspring. In humans, early-acting lethal alleles cause **spontaneous abortion**. When both parents carry a **recessive lethal allele** for the same gene, each pregnancy has a 25% chance of spontaneously aborting—this is the homozygous recessive class.

Phenotypes are often affected by more than one gene

Soon after Mendel's work was rediscovered, experimentation revealed that in many cases a given phenotype is **affected by more than one gene**. Instead of **single genes controlling** the development of individual parts of a plant or animal body, it soon became clear that phenotypic characters such as **eye color**, **hair color**, or fruit shape can be **influenced by many different genes** and their products. The term **gene interaction** is often used to express the idea that **several genes influence a particular characteristic**. This process illustrates the developmental concept of **epigenesis**, whereby each step of development increases the complexity of the organ or features of interest and is under the control and influence of many genes.

Epistasis

Some of the best examples of **gene interaction** are those showing the phenomenon of **epistasis**, where the expression of one gene pair masks or modifies the effect of another gene pair. Sometimes the genes involved influence the same general phenotypic characteristic in an **antagonistic manner**, which leads to masking. In other cases, however, the genes involved exert their influence on one another in a complementary, **or cooperative, fashion.**

Novel Phenotypes

Other cases of **gene interaction** yield novel, or new, phenotypes in the F2 generation, in addition to producing modified dihybrid ratios. Case 4 in Figure 4–8 depicts the inheritance of fruit shape in the summer squash. When plants with **disc-shaped** fruit (AABB) are crossed with plants **with long fruit (aabb)**, the F1 generation all have disc fruit. However, in the F2 progeny, fruit with a novel shape—sphere—appear, as well as fruit exhibiting the parental phenotypes. In this example of **gene interaction**, both gene pairs influence fruit shape equally. A dominant allele at either locus ensures a sphere-shaped fruit. In the absence of dominant alleles, the fruit is long. However, if both dominant alleles (A and B) are present, the fruit displays a flattened, disc shape.

Summer squash exhibiting various fruit shape phenotypes including disc, long and sphere.

Genetic Background and the Environment May Alter Phenotypic Expression

We assumed that the **genotype** of an organism is always **directly expressed in its phenotype**. For example, pea plants homozygous for the recessive d allele (dd) will always be dwarf. However, the situation is actually much more complex. Most gene products function within the **internal milieu** of the cell, and cells interact with one another in various ways. Furthermore, the organism exists under **diverse environmental influences**. Thus, **gene expression** and the **resultant phenotype** are often modified through the **interaction** between an individual's particular genotype and the external environment.

Penetrance and Expressivity

The **percentage % of individuals** that show at least some degree of expression of a mutant genotype defines the **penetrance of the mutation**. For example, the phenotypic expression of many of the mutant alleles found in Drosophila can overlap with wild-type expression. If 15% of flies with a given mutant genotype show the wild-type appearance, the mutant gene is said to have a penetrance of 85 %.

By contrast**, expressivity** reflects the **range of expression of the mutant genotype**. Flies homozygous for the recessive mutant gene eyeless exhibit phenotypes that range from the **presence of normal eyes** to a **partial reduction in size** to the **complete absence of one or both eyes**.

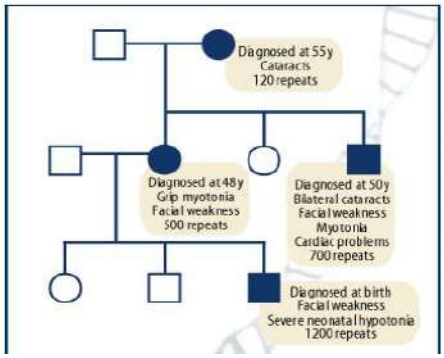
Temperature Effects—An Introduction to Conditional Mutations

Chemical activity depends on the kinetic energy of the reacting substances, which in turn depends on the surrounding temperature. We can thus expect temperature to influence phenotypes. **An example** is seen in the **evening primrose**, which produces **red flowers** when grown at **23°C** and **white flowers** when grown at **18°C**. An even more striking example is seen in **Siamese cats** and **Himalayan rabbits**, which exhibit **dark fur** in certain regions where their body temperature is slightly cooler, particularly the **nose, ears, and paws** (see figures below). In these

cases, it appears that the enzyme normally responsible for pigment production is functional only at the lower temperatures present in the extremities, but it **loses its catalytic** function at the slightly higher temperatures found throughout the rest of the body.

Genetic Anticipation

A phenomenon whereby as a genetic disorder is passed on to the next generation, the symptoms of the genetic disorder b**ecome apparent at an earlier age with each generation**. In most cases, an **increase of severity of symptoms** is also noted.



Genomic (Parental) Imprinting and Gene Silencing

Genomic or parental imprinting is the process of **selective gene silencing** occurs during early development, **impacting on subsequent phenotypic expression**. **DNA methylation (as an epigenetic modification)** is a reasonable mechanism for establishing a **molecular imprint**, since there is evidence that a high level of methylation can inhibit gene activity and that **active genes** (or their regulatory sequences) are often under methylated.

Lecture 7: Sex determination and Sex linkage

Sex determination modes

In many animal species, including humans, the differentiation of the sexes is more evident as **phenotypic dimorphism** of males and females. Dissimilar or **heteromorphic chromosomes**, such as the **XY** pair in mammals, characterize one sex or the other in a wide range of species, resulting in their label as sex chromosomes. Nevertheless, in many species, **genes rather than chromosomes** ultimately serve as the underlying basis of sex determination. Some of these genes are present on sex chromosomes, but others are autosomal.

Protenor Mode: known as the XX/XO mode of sex determination. The presence or absence of the X chromosome in male gametes determines sex. Females are the **homogametic sex** (XX). Males only have one chromosome (X) and are represented by XO - they act as the **heterogametic sex**. Examples include some insects.

Lygaeus Mode: The more common mode of sex determination: XX/XY. There must be the presence of a **Y** chromosome in order to determine the male sex. In humans there is a area, found on the Y chromosome, called the **Sex Determining Region Y**, which **determines maleness.** Individuals that have a Y chromosome will become males independent of the number of X chromosomes.

Although in mammals, etc, the heterogametic sex is male, in birds it is the female sex that is heterogametic and the male that is homogametic.

The **environment affects** sex determination in a number of ways. In **reptiles**, incubation temperature during the critical period of embryonic development can affect the sex of the offspring. This is because the activity of enzymes and inhibitors controlling the production of **steroid hormones** such as **eostrogen** is affected by temperature.

Barr Bodies

Barr body's formation is a genetic mechanism in mammals that compensates for X chromosome dosage disparities. **Barr and Bertram** observed a darkly staining body in interphase nerve cells of female cats that was absent in similar cells of males. In humans, this body can be easily demonstrated in female cells derived from the buccal mucosa (cheek cells), but not in similar male cells (Figure 7–8). This highly condensed structure, about 1mm in diameter, lies against the nuclear envelope of interphase cells. It stains positively in the Feulgen reaction, a cytochemical test for DNA.

Additional X chromosomes lead to Barr bodies being present. These are inactive forms of the X chromosome. **The number of Barr bodies is determined by number of X chromosomes (n) – 1.**

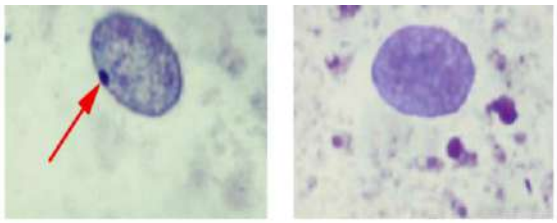


FIGURE 7–8 Photomicrographs comparing cheek epithelial cell nuclei from a male that fails to reveal Barr bodies (right) with a nucleus from a female that demonstrates a Barr body (indicated by the arrow in the left image). This structure, also called a sex chromatin body, represents an inactivated X chromosome.

Human Sex Chromosome Abnormalities			
♀ Genotype (No. Barr bodies)	**Syndrome**	**♂ Genotype (No. Barr bodies)**	**Syndrome**
XX (1)	**normal**	**XY (0)**	**normal**
XO (0)	**Turner**	**XXY (1)**	**Klinefelter**
XXX (2)	**Triple-X**	**XYY (0)**	**XYY**

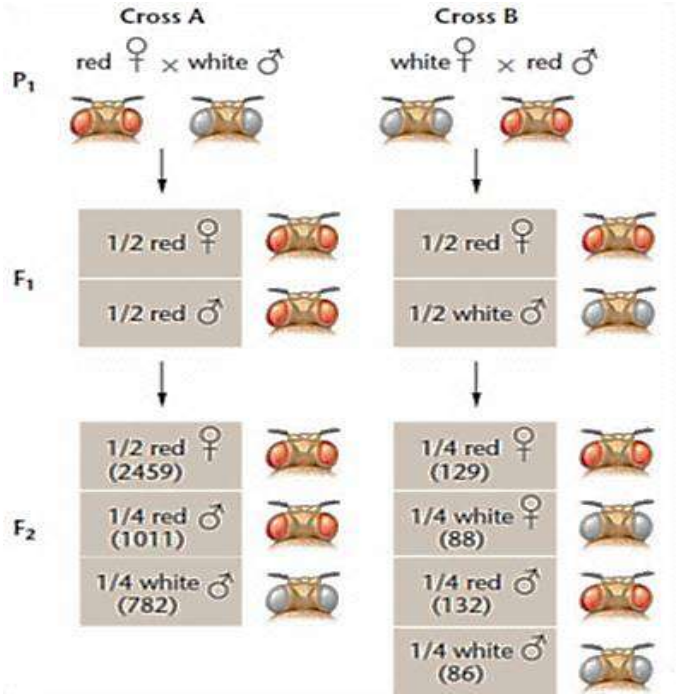
X-Linkage Describes Genes on the X chromosome

In many animals and some plant species, one of the sexes contains a pair of unlike chromosomes that are involved in **sex determination**. In many cases, these are designated as **X** and **Y**. While we now recognize a number of male-specific genes on the human Y chromosome, it lacks copies of most genes present on the X chromosome. As a result, genes present on the X chromosome exhibit patterns of inheritance that are very **different** from those seen with **autosomal genes**. The term **X-linkage** is used to describe these situations. This situation results in **a modification of Mendelian ratios**.

X-Linkage in Drosophila

Morgan's work established that the inheritance pattern of the **white-eye trait** was clearly related to the sex of the parent carrying the mutant allele. Unlike the outcome of the **typical Mendelian monohybrid cross** where F1 and F2 data were similar regardless of **which P1 parent exhibited the recessive mutant trait**, **reciprocal crosses** between white-eyed and **red-eyed** flies did not yield identical results. Morgan's analysis led to the conclusion that the **white locus is present on the X** chromosome rather than on one of the **autosomes**. Both the **gene** and the **trait** are said to be **X-linked**.

Results of **reciprocal crosses** between white-eyed and red-eyed flies are shown in the below figure. The obvious differences in **phenotypic ratios** in both the F1 and F2 generations are dependent on whether or not the P1 white-eyed parent was **male** or **female**.



The F1 and F2 results of T. H. Morgan's reciprocal crosses involving the X-linked white mutation in Drosophila melanogaster. The actual data are shown in parentheses. The photographs show white eye and the brick-red wild-type eye color.

X-Linkage in Humans

In humans, many genes and the respective traits controlled by them are recognized as being linked to the X chromosome (see Table below). These X-linked traits can be easily identified in a pedigree because of the **crisscross pattern** of inheritance.

Human X-Linked Traits

Condition	Characteristics
Color blindness, deutan type	Insensitivity to green light
Color blindness, protan type	Insensitivity to red light
Fabry's disease	Deficiency of galactosidase A; heart and kidney defects, early death
G-6-PD deficiency	Deficiency of glucose-6-phosphate dehydrogenase; severe anemic reaction following intake of primaquines in drugs and certain foods, including fava beans
Hemophilia A	Classic form of clotting deficiency; deficiency of clotting factor VIII
Hemophilia B	Christmas disease; deficiency of clotting factor IX
Hunter syndrome	Mucopolysaccharide storage disease resulting from iduronate sulfatase enzyme deficiency; short stature, claw-like fingers, coarse facial features, slow mental deterioration, and deafness
Ichthyosis	Deficiency of steroid sulfatase enzyme; scaly dry skin, particularly on extremities
Lesch–Nyhan syndrome	Deficiency of hypoxanthine-guanine phosphoribosyltransferase enzyme (HPRT) leading to motor and mental retardation, self-mutilation, and early death
Duchenne muscular dystrophy	Progressive, life-shortening disorder characterized by muscle degeneration and weakness; sometimes associated with mental retardation; deficiency of the protein dystrophin

In Sex-Limited and Sex-Influenced Inheritance, an Individual's Sex Influences the Phenotype

In contrast to **X-linked inheritance**, patterns of gene expression may be **affected** by the sex of an individual even when the genes **are not on** the X chromosome. In numerous examples in different organisms, the sex of the individual plays a determining role in the expression of a phenotype. In some cases, the expression of a specific phenotype is absolutely **limited to one sex**; in others, the sex of an individual **influences the expression** of a phenotype that is not limited to one sex or the other. This distinction differentiates sex limited inheritance from sex-influenced inheritance.

In both types of inheritance, **autosomal genes** are responsible for the existence of contrasting phenotypes, but the expression of these genes is dependent on the **hormone constitution of the individual**. Thus, the **heterozygous genotype** may exhibit one phenotype in males and the contrasting one in females. In domestic fowl, for example, tail and neck plumage is often distinctly different in males and females

(Figure 4–15), demonstrating sex-limited inheritance. Cock feathering is longer, more curved, and pointed, whereas hen feathering is shorter and less curved. Inheritance of these feather phenotypes is controlled by a **single pair of autosomal alleles** whose expression is modified by the individual's sex hormones. As shown in the following chart, hen feathering is due to a dominant allele, **H**, but regardless of the homozygous presence of the recessive h allele, all females remain **hen-feathered**. Only in males does the **hh** genotype result in **cock feathering**.

FIGURE 4–15 Hen feathering (left) and cock feathering (right) in domestic fowl. The hen's feathers are shorter and less curved.

Genotype	Phenotype	
	♀	♂
HH	Hen-feathered	Hen-feathered
Hh	Hen-feathered	Hen-feathered
hh	Hen-feathered	Cock-feathered

FIGURE 4–16 Pattern baldness, a sex-influenced autosomal trait in humans.

Sex influenced inheritance

Genotype	Phenotype	
	♀	♂
BB	Bald	Bald
Bb	Not bald	Bald
bb	Not bald	Not bald

Cases **of sex-influenced inheritance** include pattern **baldness** in humans, **horn** formation in certain breeds of sheep. In such cases, autosomal genes are responsible for the contrasting phenotypes, and while the trait may be displayed by both males and females, the expression of these genes is **dependent on** the hormone constitution of the individual. Thus, the **heterozygous genotype** exhibits one phenotype in one sex and the contrasting one in the other. For example, pattern baldness in humans, where the hair is very thin or absent on the top of the head (Figure 4–16), is inherited.

Females can display pattern baldness, but this phenotype is much more prevalent in males. When females do inherit the BB genotype, the phenotype is less pronounced than in males and is expressed later in life.

Lecture 8: Distribution of Genes in a Population

Population genetics is the scientific study of the **genetic composition of populations**. A principal goal of this science is to estimate **the frequency of alleles at different gene loci** in natural populations (allele frequency, also called gene frequency). From this, conclusions may be drawn about **possible selective influences** that might explain the differences that observed.

Frequency of genotypes in the children of parents with various genotypes

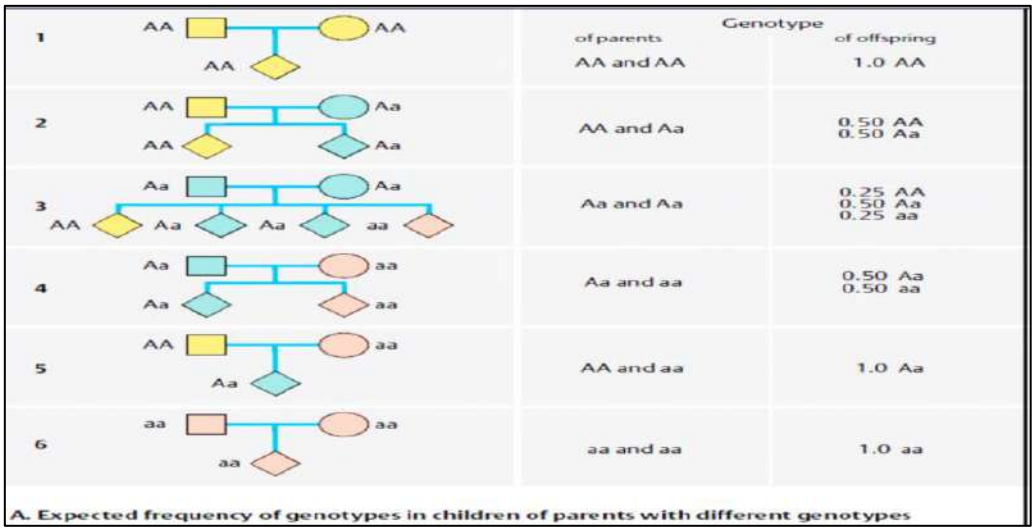
With regard to an allele pair **A** (dominant) and **a** (recessive), **six types** of parental genotype mating's are possible (1-6). Each of these has an expected distribution of genotypes in the offspring according to the **Mendelian laws**, as indicated in the figure A. This pattern will only be observed if all genotypes can participate in mating and are not prohibited by a severe disease. The frequency with which each mating type occurs depends on the frequencies of the alleles in the population.

Allele frequency

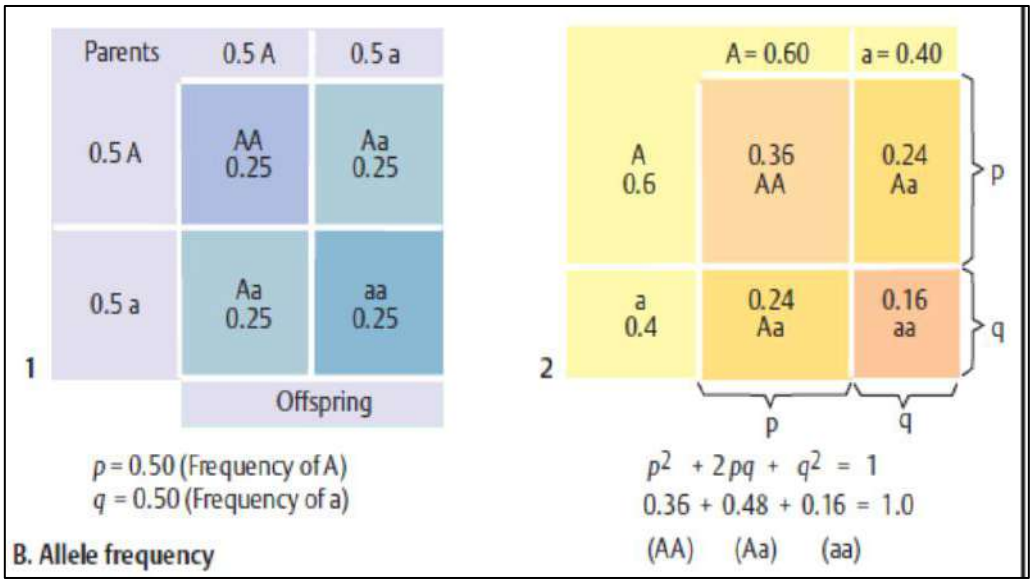
The allele frequency (often called gene frequency) designates the proportion of a given allele at a given locus in a population. If an allele accounts for 20% of all alleles present (at a given locus) in the population, its frequency is 0.20. The allele frequency determines the frequencies of the individual genotypes in a population.

For example, for a gene locus with two possible alleles **A** and **a,** three genotypes are possible: **AA**, **Aa**, or **aa**. The frequency of the two alleles together (p the frequency of A and q the frequency of a) is 1.0 (100%). If two alleles **A** and **a** are equally frequent (each 0.5), they have the frequencies of p = 0.5 for the allele A and q = 0.5 for the allele a (1). Thus, the equation p + q = 1 defines the population at this locus. The frequency distribution of the two alleles in a population follows a simple binomial relationship**: (p + q)2 = 1**. Accordingly, the distribution of genotypes in the population corresponds to **p2 +2pq+q2 = 1.0.** The expression **p2** corresponds to the frequency of

the genotype **AA**; the expression 2pq corresponds to the frequency of the heterozygotes **Aa**; and **q2** corresponds to the frequency of the homozygotes **aa**.



A. Expected frequency of genotypes in children of parents with different genotypes



B. Allele frequency

Hardy–Weinberg Equilibrium Principle

The Hardy–Weinberg equilibrium principle states that in certain circumstances (conditions), the frequency of alleles will **remain constant** in a population from one generation to the other. This principle was formulated independently by the English mathematician G. F. Hardy and the German physician W. Weinberg in 1908.

Constant allele frequency

An autosomal recessive allele (here referred to as allele **a**) that leads to a severe disorder in the **homozygous state** remains undetectable in the **heterozygous state** in a

population. Only the homozygotes (aa) can be recognized because of their disease. The frequency of affected individuals (homozygotes aa) depends on the frequency of allele a (corresponding to q). The frequency of the three genotypes is determined by the binomial relationship **(p+q)2 = 1**, where **p** represents the frequency of allele A and **q**, the frequency of allele a (see previous page). The homozygous alleles (aa) eliminated in one generation by illness are replaced by new mutations. This occurs in each generation, and results in equilibrium between elimination due to illness and frequency of the mutation.

Calculating Frequencies for Multiple Alleles in Hardy–Weinberg Populations

We commonly find several alleles of a single gene in a population. The ABO blood group in humans is such an example. Recall that the locus I (isoagglutinin) has three alleles I^A, I^B, and i, yielding six possible genotypic combinations (I^AI^A, I^Bi , ii , I^AI^B, I^Ai , I^Bi). Remember that in this case I^A and I^B are codominant alleles and that both of these are dominant to i. The result is that homozygous I^AI^A and heterozygous I^Ai individuals are phenotypically identical, as are I^BI^B and I^Bi individuals, so we can distinguish only four phenotypic combinations.

By adding another variable to the Hardy–Weinberg equation, we can calculate both the genotype and allele frequencies for the situation involving three alleles. Let p, q, and r represent the frequencies of alleles I^A, I^B, and i, respectively. Note that because there are three alleles:

p + q + r = 1

Under Hardy–Weinberg assumptions, the frequencies of the genotypes are given by **(p + q + r)2 = p2 + q2 + r2 + 2pq + 2pr + 2qr = 1**

If we know the frequencies of blood types for a population, we can then estimate the frequencies for the three alleles of the ABO system. For example, in one population sampled, the following blood-type frequencies are observed: A = 0.53, B =

0.13, O = 0.26. Because the i allele is recessive, the population's frequency of type O blood equals the proportion of the recessive genotype r^2. Thus,

$$r^2 = 0.26$$
$$r = \sqrt{0.26}$$
$$r = 0.51$$

Using r, we can calculate the allele frequencies for the IA and IB alleles. The IA allele is present in two genotypes, I^AI^A and I^Ai. The frequency of the I^AI^A genotype is represented by p^2 and the I^A i genotype by 2pr. Therefore, the combined frequency of type A blood and type O blood is given by

$$p^2 + 2pr + r^2 = 0.53 + 0.26$$

If we factor the left side of the equation and take the sum of the terms on the right

$$(p + r)^2 = 0.79$$
$$p + r = \sqrt{0.79}$$
$$p = 0.89 - r$$
$$p = 0.89 - 0.51 = 0.38$$

Having calculated p and r, the frequencies of allele ^{IA} and allele i, we can now calculate the frequency for the I^B allele:

$$p + q + r = 1$$
$$q = 1 - p - r$$
$$= 1 - 0.38 - 0.51$$
$$= 0.11$$

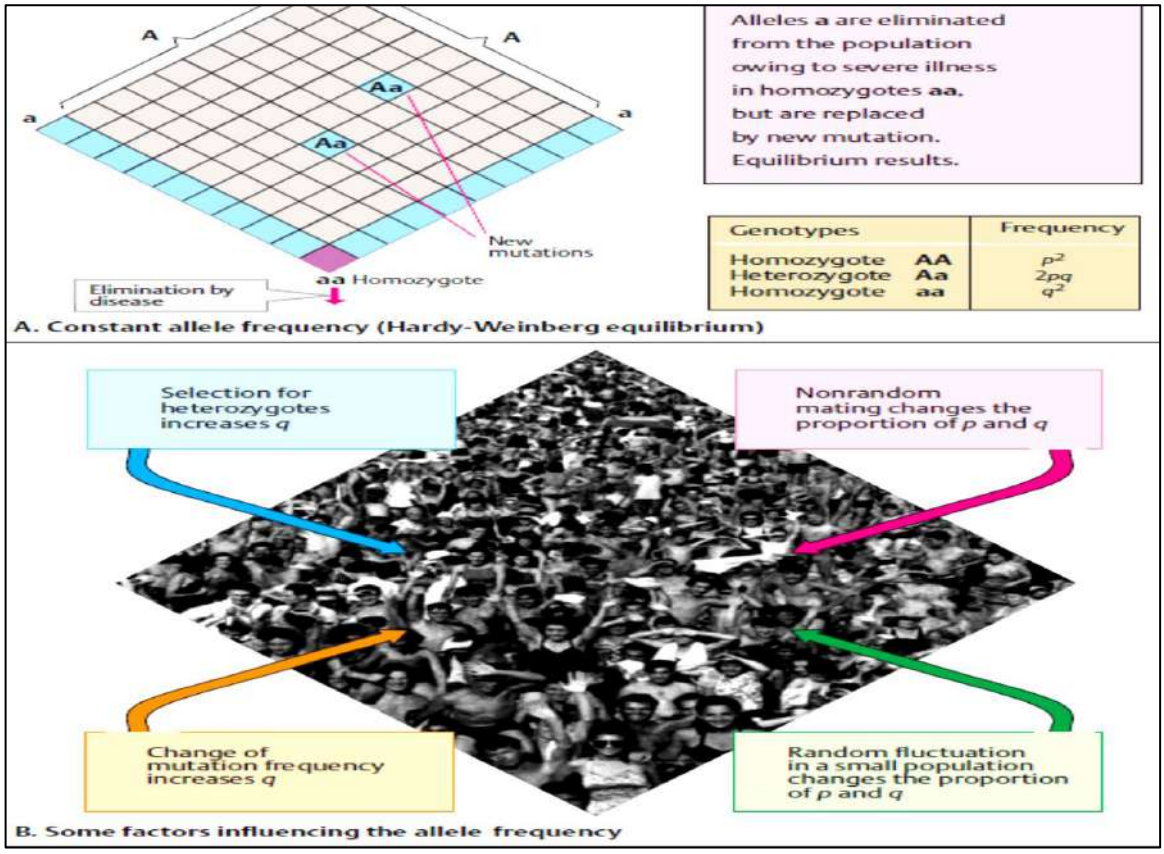
Calculating Genotype Frequencies for Multiple Alleles in a Hardy–Weinberg Population Where the Frequency of Allele I^A = 0.38, Allele I^B = 0.11, and Allele i = 0.51

Genotype	Genotype Frequency	Phenotype	Phenotype Frequency
I^AI^A	$p^2 = (0.38)^2 = 0.14$	A	0.53
I^Ai	$2pr = 2(0.38)(0.51) = 0.39$		
I^BI^B	$q^2 = (0.11)^2 = 0.01$	B	0.12
I^Bi	$2qr = 2(0.11)(0.51) = 0.11$		
I^AI^B	$2pr = 2(0.38)(0.11) = 0.084$	AB	0.08
ii	$r^2 = (0.51)^2 = 0.26$	O	0.26

Some factors influencing the allele frequency

The Hardy–Weinberg equilibrium principle is valid only in certain conditions: 1) it applies only if there is **no selection for one genotype**. Selection for heterozygotes will increase the frequency of the allele with a selective advantage. 2) **Non-random matings:** will change the allele frequency (proportion of p and q). **3)** No

change in the **rate of mutations,** as this will increase the frequency of the allele resulting from mutations. **4)**, Large population size, as it in a small population random fluctuation may change the frequency. This called **genetic drift**.



Consanguinity and inbreeding زواج الاقارب

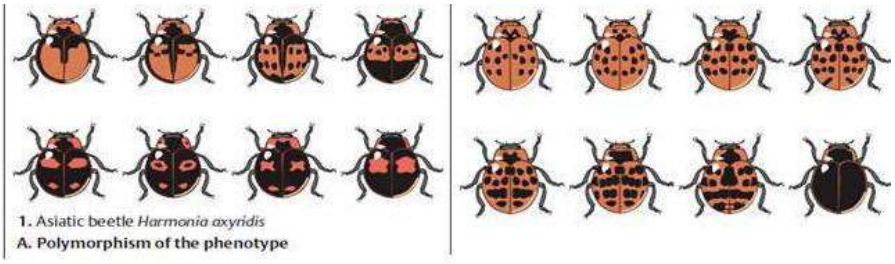
Parental consanguinity refers to parents who have at least one common ancestor (being of the "**same blood**") in the past four generations. Consanguinity increases the chance that an allele will become **homozygous** in a descendant. As both alleles will be identical, this is called **identity by descent** (IBD). For this reason, consanguinityis often observed in very rare autosomal recessive diseases. **Inbreeding** refers to a population in which consanguinity is common. Incest refers to a relationship between first-degree relatives (brother–sister; parent–child).

Polymorphismتعدد الاشكال الوراثية

Genetic polymorphism refers to **genetic variation** as **observed in populations**. Two types of variation are distinguished: **discontinuous** and **continuous**. Two or more common discontinuous variants in a natural population are called a polymorphism. A gene locus is defined as polymorphic if a rare allele has a frequency of 0.01 (1%) or more, corresponding to a heterozygote frequency of 0.02 (2%). An allelic polymorphism often results in **a different phenotype**.

Natural selection refers to the **differential rates** of survival and reproduction. A polymorphism represents an advantage for a population when the resulting genetic variation contributes to individuals having a **better reproductive fitness** in the given environmental conditions.

Polymorphism can be observed at the level of the: **1) whole individual** (phenotype), 2) in variant forms of proteins and blood group substances (**biochemical polymorphism**), 3) in morphological features of chromosomes (chromosomal polymorphism), 4) or at the level of DNA in differences of nucleotides (**DNA polymorphism**).



1. Asiatic beetle *Harmonia axyridis*
A. Polymorphism of the phenotype

Genetic diversity and evolution

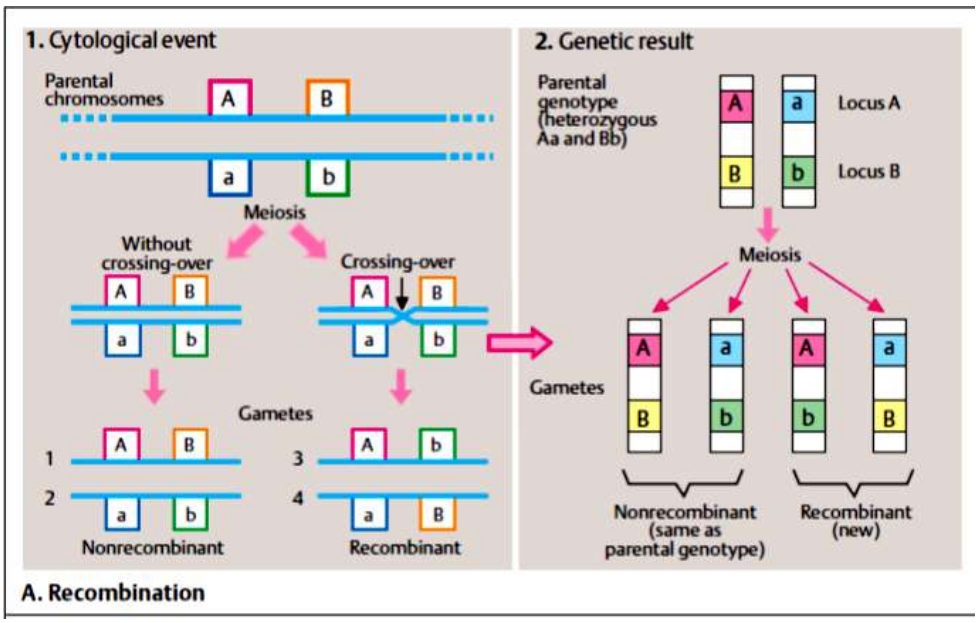
Genetic diversity is **selected** for by **evolution**. A genetically diverse population may have a higher probability of survival in a changing environment than a **homogeneous population**. A genetically diverse population appeared to thrive better than a homogeneous population. At the time, it was interpreted that the population with the **greater genetic diversity** was able to **adjust better** to the environmental conditions than the **homogenous population**.

Linkage and Recombination

Genetic linkage refers to the observation that two or more genes located on the same chromosome are transmitted together. This is in contrast to localization on different chromosomes or on the same chromosome far apart; in this case two genes will be distributed in a 1:1 ratio, independently of each other.

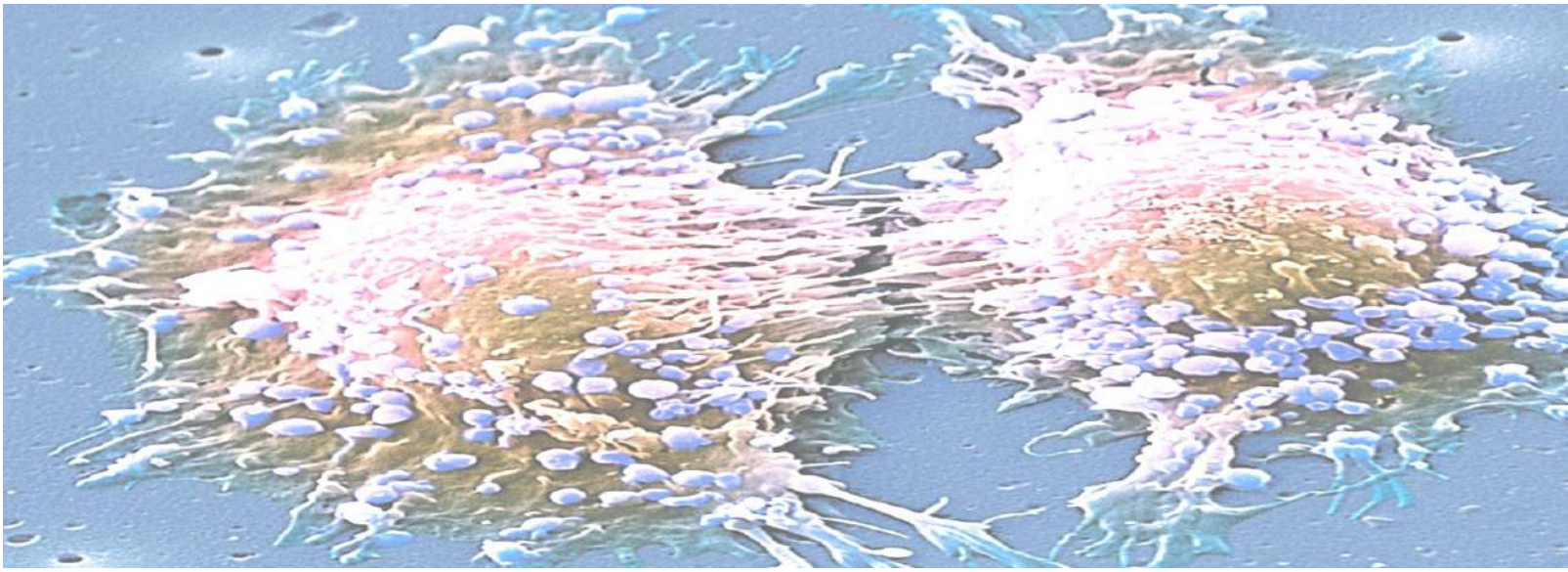
Recombination by crossing-over (see lecture1)

Whether neighboring genes on the same parental chromosome remain together or become separated depends on the cytological events during meiosis. If there is no crossing-over between the two gene loci **A** and **B**, having the respective alleles A, a and B, b, then they remain together on the same chromosome. The gamete chromosomes formed during meiosis in this case **are not recombinant** and correspond to the parental chromosomes. However, if **crossing over** occurs between the two gene loci, then the gametes formed are **recombinant** with reference to these two gene loci. The cytological events (1) are reflected in the genetic result (2). For two neighboring gene loci A and B on the same chromosome, the genetic result is one of two possibilities: not recombinant (gametes correspond to parental genotype) or recombinant (new combination). The two possibilities can be differentiated only when the parental genotype is informative for both gene loci (Aa &Bb).



Lecture 9: Genetic Diseases

Cancer and Regulation of the Cell Cycle



Scanning electron micrograph of two prostate cancer cells in the final stages of cell division (cytokinesis). The cells are still joined by strands of cytoplasm.

Cancer biology

1. Cancer is a group of genetic diseases affecting fundamental aspects of cellular function, including **DNA repair**, **cell-cycle regulation**, **apoptosis**, and **signal transduction**.
2. Most **cancer-causing mutations** occur in somatic cells; only about **1%** of cancers have a hereditary component.
3. Mutations in **cancer-related genes** lead to abnormal proliferation and loss of control over how cells spread and invade surrounding tissues.
4. The development of cancer is a **multistep process** requiring mutations in genes controlling many aspects of **cell proliferation** and **metastasis**.
5. Cancer cells show high levels of **genomic instability**, leading to the accumulation of multiple mutations in cancer-related genes.
6. **Epigenetic effects** such as **DNA methylation** and **histone modifications** may play significant roles in the development of cancers.

7. Mutations in **proto-oncogenes** and **tumor-suppressor** genes contribute to the development of cancers.
8. **Oncogenic viruses** introduce oncogenes into infected cells and stimulate cell proliferation.

Cancer Is a Genetic Disease at the Level of Somatic Cells

Perhaps the most significant development in understanding the causes of cancer is the realization that **cancer is a genetic disease**. **Genomic alterations** that are **associated with cancer** range from 1) single-nucleotide substitutions to 2) large-scale chromosome rearrangements, amplifications, and deletions.

Another important **difference between cancers and other genetic diseases** is that cancers rarely arise from a single mutation in a single gene, but from **the accumulation of mutations** in many genes— as many **as six to twelve**.

Cancer Cells Contain Genetic Defects Affecting Cell-Cycle Regulation

Normal regulation over cell proliferation involves a **large number of gene products** such as cyclin-dependent kinases (CDKs. In cancer cells, **many of the genes that control these function are mutated or aberrantly expressed**, leading to uncontrolled cell proliferation.

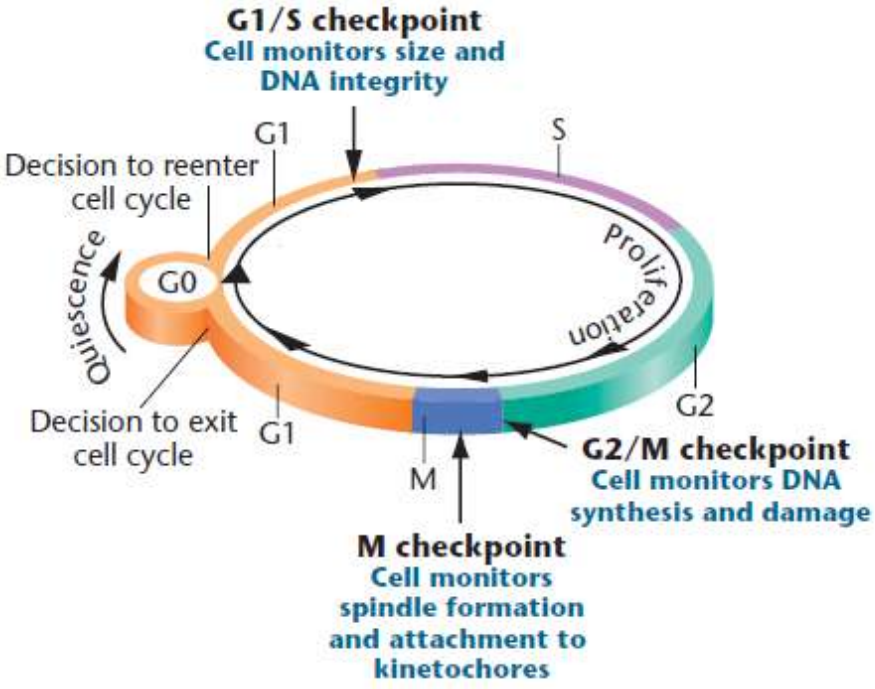


Figure: Checkpoints and proliferation decision points monitor the progress of the cell through the cell cycle

Proto-oncogenes and Tumor-suppressor Genes Are Altered in Cancer Cells

Two general categories of cancer-causing genes are **mutated** or **misexpressed** in cancer cells—the **proto-oncogenes** and the **tumor-suppressor genes**.

Proto-oncogenes encode transcription factors that stimulate expression of other genes, signal transduction molecules that stimulate cell division, and cell-cycle regulators that move the cell through the cell cycle. When a proto-oncogene is mutated or abnormally expressed and contributes to the development of cancer. **Oncogenes confer a dominant cancer phenotype**.

Tumor-suppressor genes are genes whose products **normally regulate cell-cycle checkpoints** or **initiate the process of apoptosis** (such as ***p53*** gene). When tumor suppressor genes are **mutated or inactivated**, cells are unable to respond normally to cell-cycle checkpoints, or are **unable** to undergo programmed cell death if

DNA damage is extensive. This leads to the accumulation of more mutations and the development of cancer.

Environmental Agents Contribute to Human Cancers

Our environment, both natural and human-made, contains abundant carcinogens. These include **chemicals**, **radiation**, **some viruses**, and **chronic infections**. Perhaps the most significant carcinogen in our environment is **tobacco smoke**, which contains at **least 60 chemicals** that **interact with DNA** and **cause mutations**. Epidemiologists estimate that about **30%** of **human cancer deaths** are associated with **cigarette smoking**. Smokers have a 20-fold increased risk of developing lung cancer, which kills more than **one million** people, worldwide, each year.

Diet is often implicated in the development of cancer. Consumption of **red meat** and **animal fat** is associated with some cancers, such as colon, prostate, and breast cancer. **Alcohol** may cause inflammation of the liver and contribute to liver cancer.

Aflatoxin, a component of a **mold** that grows on **peanuts** and **corn**, is one of the most carcinogenic chemicals known. Most chemical carcinogens, such as **nitrosamines**, are components of synthetic substances and are found in some **preserved meats**.A serious cancer risks to specific populations who are exposed to human-made carcinogens such as synthetic **pesticides** or **asbestos**.

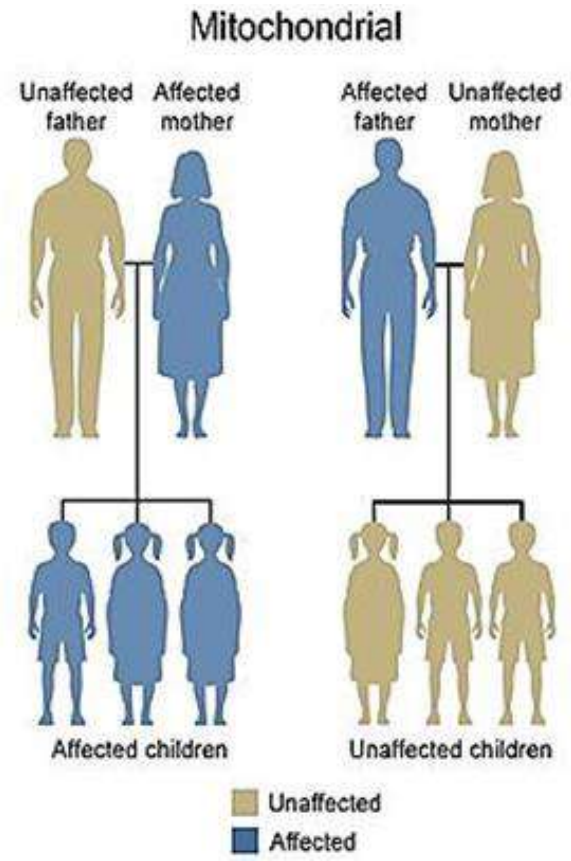
DNA lesions brought about by **natural radiation** (**X rays**, **ultraviolet light**), natural dietary substances, and substances in the external environment contribute the majority of environmentally caused mutations that lead to cancer.

Lecture 10:

Other Genetic diseases

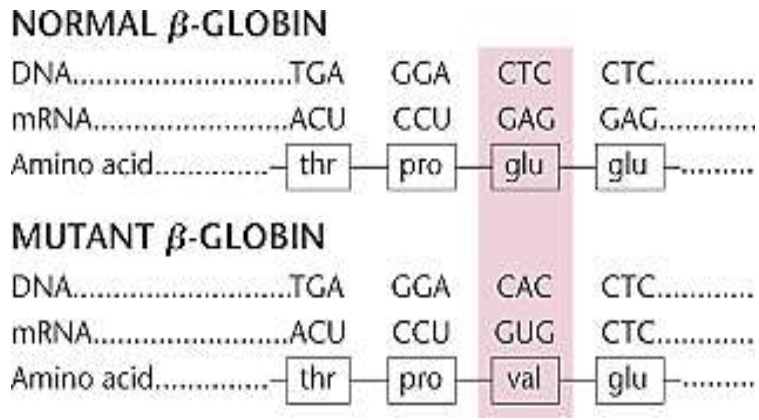
Human mitochondrial diseases

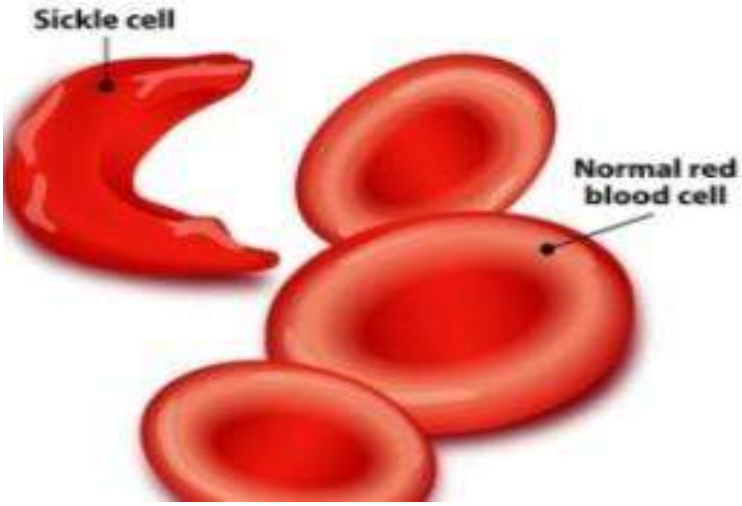
The mitochondrial genome is completely separate from the nuclear genome. In this regard, transcription of mitochondrial DNA (mtDNA) occurs in the mitochondrial matrix, whereas transcription of nuclear DNA occurs in the nucleus. The human mitochondrial genome codes for 37 genes, which make up _93% of the human mitochondrial genome. Mitochondrial mutations are also involved in a number of common human diseases, which include sensorineural deafness. The MELAS mutation is associated with some cases of noninsulin dependent diabetes, Alzheimer disease, Parkinson disease, and hypertrophic cardiomyopathy.



Sickle Cell Anemia فقر الدم المنجلي

Sickle cell anemia is a severe hemolyticanemia associated with many complications. It results from homozygosity for a mutation in the **globin gene**. It is frequent in tropical regions where malaria is endemic. With a frequency of 1 in 500, it is an important cause of morbidity and mortality in these regions.

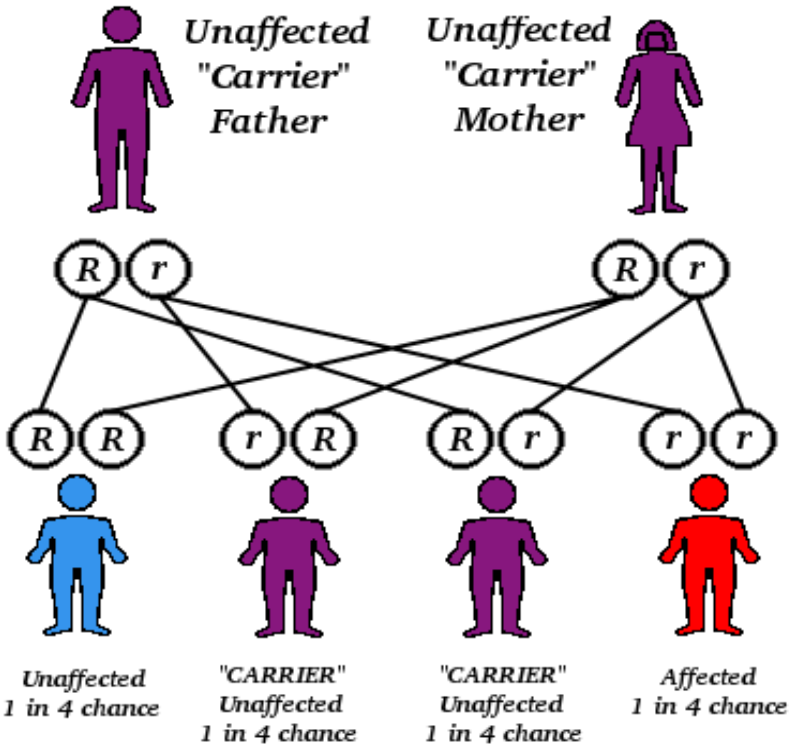




Single Base-Pair Mutations and B-Thalassemia

Caused by any of **a large number of different mutations globulin gene**. β-thalassemia is an inherited autosomal recessive blood disorder resulting from a reduction or absence of hemoglobin. It is the most common single-gene disease in the world, affecting people worldwide, but especially populations in Mediterranean, North African, Middle Eastern, Central Asian, and Southeast Asian countries.

People with β-thalassemia have varying degrees of anemia—from severe to mild—with symptoms including weakness, delayed development, enlarged organs, and often a need for frequent blood transfusions.



Phenylketonuria

inherited human metabolic disorder phenylketonuria (PKU) results in mental retardation and is transmitted as an autosomal recessive disease (see figure below). Afflicted individuals are unable to convert the **amino acid phenylalanine** to the amino acid tyrosine. The reaction is catalyzed by the enzyme phenylalanine hydroxylase, which is inactive in affected individuals and active at a level of about 30 percent in heterozygotes. The enzyme functions in the liver. While the normal blood level of phenylalanine is about 1 mg/100 mL, people with phenylketonuria show a level as high as 50 mg/100 mL.