Genetics

Modified no. 1

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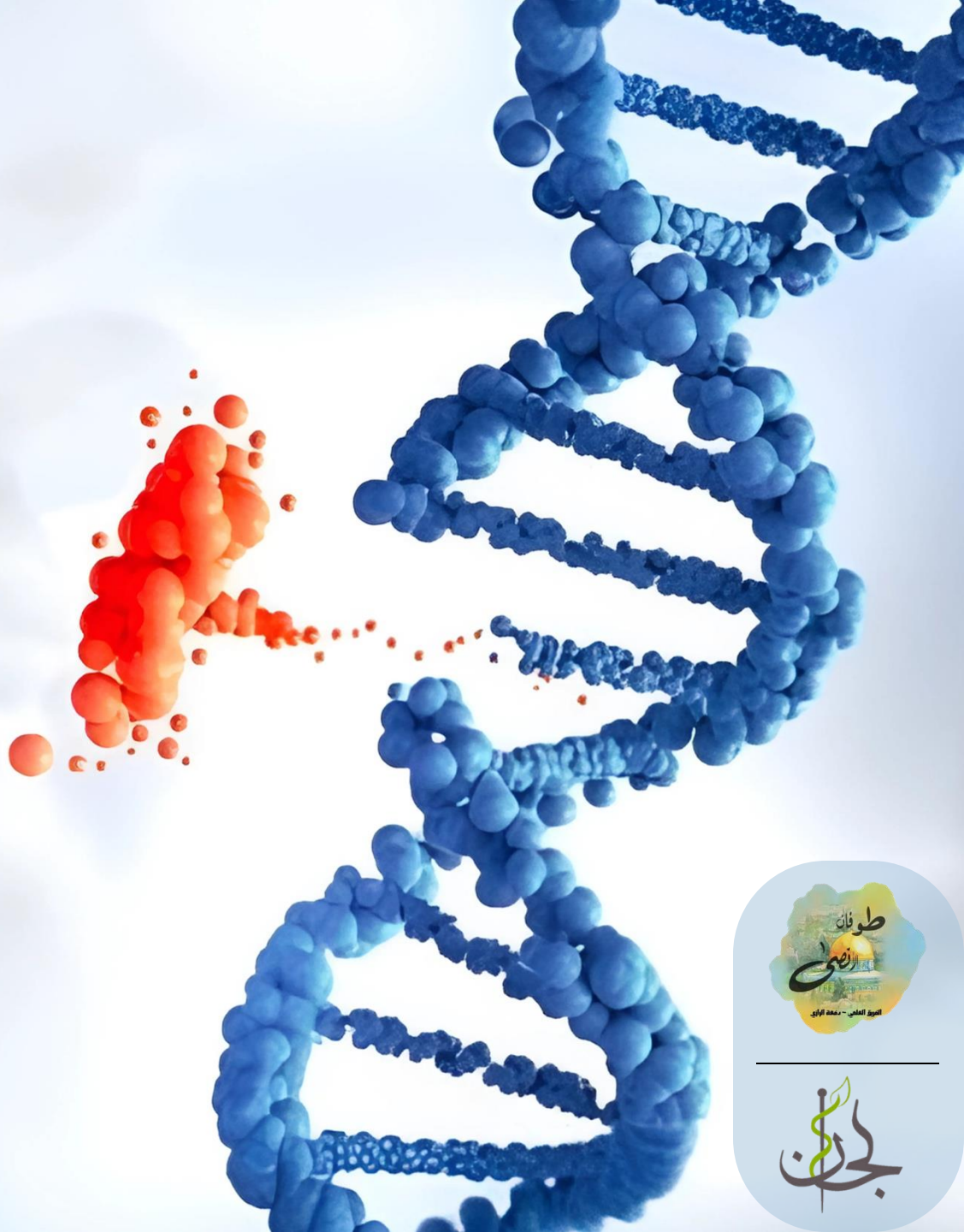

Introduction to Medical Genetics

This is very important because once we talk about genetic disorders later on, we can understand the mechanisms of those diseases and the pathophysiology of them, and how we follow them and diagnose them in the lab & clinically

Color code

- Slides
- Doctor
- Additional info
- Important

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Background

- Medical genetics involves any application of genetics to medical practice.

Genetics=> every living organism even other than humans has genes, like viruses, animals,etc but here we will focus on human genetics

- It includes

- studies of the inheritance of diseases in families, how genetics/genes move through families
- analyses of the molecular mechanisms through which genes cause disease, and
- the diagnosis and treatment of genetic disease.

- gene therapy- the insertion of normal genes into patients in order to correct genetic disease-is now possible.

- Medical genetics also includes genetic counseling, which involves the communication of informed regarding risks, prognoses, and treatments to patients and their families.

It is very important to follow up on these genetic disorders because some of them can be diagnosed easily, while others are inherited through families or occur by chance. And understanding this is crucial

They contribute to the overall disease burden, particularly in the pediatric population, where defects at birth often indicate an underlying genetic disorder

WHY IS A KNOWLEDGE OF MEDICAL GENETICS IMPORTANT FOR TODAY'S Health CARE- PRACTITIONER?

Chromosome abnormalities can involve an increase, decrease, deletion, or duplication of genetic material, meaning they occur at the chromosomal level. Here are some examples of these abnormalities:

- **Down syndrome**: extra copy of chromosome number 21
- **Klinefelter** (in males): extra X chromosome
- **Trisomy 13** (Patau syndrome)
- **Trisomy 18** (Edward syndrome)
- **Turner syndrome** (in females): one X chromosome is missing

We will discuss this in details at chapter 6 Insha'a Allah 😊

TABLE 1-1 A Partial List of Some Important Genetic Diseases

DISEASE	APPROXIMATE PREVALENCE
Chromosome Abnormalities	
Down syndrome	1/700 to 1/1000
Klinefelter syndrome	1/1000 males
Trisomy 13	1/10,000
Trisomy 18	1/6000
Turner syndrome	1/2500 to 1/10,000 females
Single-Gene Disorders	
Adenomatous polyposis coli	1/6000
Adult polycystic kidney disease	1/1000
α_1-Antitrypsin deficiency	1/2500 to 1/10,000 (whites)*
Cystic fibrosis	1/2000 to 1/4000 (whites)
Duchenne muscular dystrophy	1/3500 males
Familial hypercholesterolemia	1/500
Fragile X syndrome	1/4000 males; 1/8000 females
Hemochromatosis (hereditary)	1/300 whites are homozygotes; approximately 1/1000 to 1/2000 are affected
Hemophilia A	1/5000 to 1/10,000 males
Hereditary nonpolyposis colorectal cancer	Up to 1/200
Huntington disease	1/20,000 (whites)
Marfan syndrome	1/10,000 to 1/20,000
Myotonic dystrophy	1/7000 to 1/20,000 (whites)
Neurofibromatosis type 1	1/3000 to 1/5000
Osteogenesis imperfecta	1/5000 to 1/10,000
Phenylketonuria	1/10,000 to 1/15,000 (whites)
Retinoblastoma	1/20,000
Sickle cell disease	1/400 to 1/600 blacks* in America; up to 1/50 in central Africa
Tay-Sachs disease	
Thalassemia	1/50 to 1/100 (South Asian and circum-Mediterranean populations)

Single-gene disorders result from mutations in genes that produce specific protein products. A change in the coding sequence or regulatory elements of a gene can lead to the production of an abnormal protein (which can be a ligand, hormone, transcription factor, growth factor, or regulatory element)

If this protein is nonfunctional or not produced at all, it can lead to various disorders, such as **hemophilia A** (which results from mutations in hemophilia gene encoding factors 8&9 on the X chromosome) and **thalassemia** (which results from abnormalities in the hemoglobin alpha or beta chain or mutations in alpha or beta globin genes)

Most of these disorders need two copies of the mutated gene to occur, one from the mother and one from the father are required for the condition to manifest in the baby (autosomal recessive)

Some other single-gene disorders are **autosomal dominant**, which means that a single mutated copy is enough for the disease to develop

Single-Gene Disorders

Adenomatous polyposis coli
Adult polycystic kidney disease
α_1-Antitrypsin deficiency
Cystic fibrosis
Duchenne muscular dystrophy
Familial hypercholesterolemia
Fragile X syndrome
Hemochromatosis (hereditary)

Hemophilia A
Hereditary nonpolyposis colorectal cancer
Huntington disease
Marfan syndrome
Myotonic dystrophy
Neurofibromatosis type 1
Osteogenesis imperfecta
Phenylketonuria
Retinoblastoma
Sickle cell disease
Tay-Sachs disease
Thalassemia

Multifactorial diseases

When we say multifactorial, this means that there are both genetic background and environmental background (It helps express the genetic background as a phenotype)

We have adult diseases such as **Alzheimer** disease, **cancer**, **diabetes type 1&2**, **schizophrenia** and **alcoholism**

Also, we have the congenital malformations like **cleft lip and palate**, **congenital heart defects** (the baby is born with openings in heart septa, between ventricles for example)

There are also a few mitochondrial diseases (although not common). It is important to know that mitochondria have their own DNA, which is inherited maternally. These mitochondrial chromosomes contain many genes related to energy production. Therefore, any mutation in the mitochondrial genome can lead to several disorders

Multifactorial Disorders

Congenital Malformations	
Cleft lip with or without cleft palate	1/500 to 1/1000
Club foot (talipes equinovarus)	1/1000
Congenital heart defects	1/200 to 1/500
Neural tube defects (spina bifida, anencephaly)	1/200 to 1/1000
Pyloric stenosis	1/300
Adult Diseases	
Alcoholism	1/10 to 1/20
Alzheimer disease	1/10 (Americans older than 65 years)
Bipolar disorder	1/100 to 1/200
Cancer (all types)	1/3
Diabetes (types 1 and 2)	1/10
Heart disease or stroke	1/3 to 1/5
Schizophrenia	1/100
Mitochondrial Diseases	
Kaerns-Sayre syndrome	Rare
Leber hereditary optic neuropathy (LHON)	Rare
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	Rare
Myoclonic epilepsy and ragged red fiber disease (MERRF)	Rare

*The term "white" refers to individuals of predominantly European descent; the term "black" refers to individuals of predominantly sub-Saharan African descent. These terms are used for convenience; some of the challenges in accurately describing human populations are discussed in Chapter 14.

A BRIEF HISTORY

- Gregor Mendel, an Austrian monk who is usually considered to be the "father" of genetics, advanced the field significantly by

- performing a series of cleverly designed experiments on garden peas.
- He then used the experimental information to formulate a series of fundamental principles of heredity.

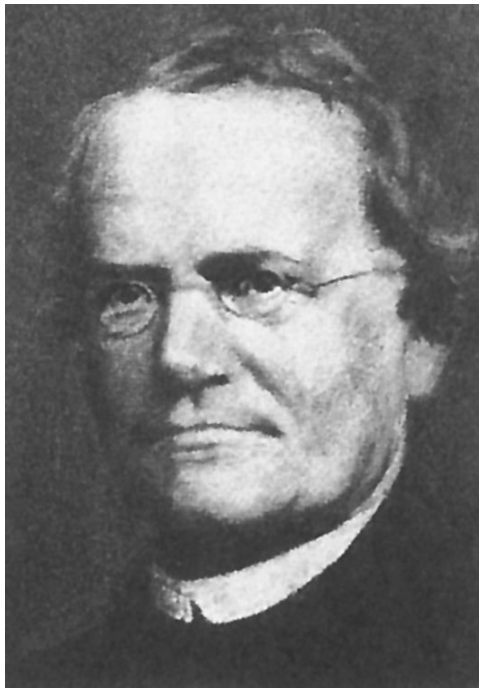

FIG 1-1 Gregor Johann Mendel. (From Raven PH, Johnson GB. *Biology*. 3rd ed. St Louis: Mosby; 1992.)

Unfortunately, his findings we're not published till 1865 in an unpopular journal but they made up the foundation of genetics. 35 years later, Darwin started to give the laws of evolution. Then Galton started to make studies on twins, which are very important in medical genetics, since traits move the same way in identical twins while different genetic composition are there in non-identical twins (This largely helped in studying environmental factors when the genetic factor is constant in identical twins)

History

- Genetics as it is known today is largely the result of research performed during the 20th century.

- Mendel's principles were independently rediscovered in 1900 by three different scientists working in three different countries. Research experiments focused on the interactions of genes mostly in butterflies, mice, and fruit flies (Drosophila), which reemphasized Mendel's principles, established 200 years earlier

- This was also the year in which Landsteiner discovered the ABO blood group.
- In 1902, Archibald Garrod described alkaptonuria as the first "inborn error of metabolism." In biochem we have learned that if there are mutations in the enzymes that control metabolism, there will be accumulation of the metabolites in the cell and these defects are called inborn errors of metabolism

- In 1909, Johannsen coined the term gene to denote the basic unit of heredity.

- The term **gene**:
- It is one unit that is movable from grandparents to parents to us, and this unit is the smallest physical unit of DNA sequence that is expressed into an mRNA which will be expressed into a protein that has a certain function, and if this protein is not able to achieve its function due to a problem in the previous steps, we will have what we call; **genetic defects**

History

- The next several decades were a period of considerable experimental and theoretical work.

- In 1944, Oswald Avery showed that genes are composed of deoxyribonucleic acid (DNA).

- The most significant achievement of the 1950s was the specification of the physical structure of DNA by James Watson and Francis Crick in 1953.

- The basis for what is now known as molecular genetics (the study of the structure and function of genes at the molecular level) (you've learned about how to polymerize, amplify, sequence them, identify their composition of the different nucleotides and how to discover the mutations in them

History

- Since the early 1920s, it had been thought that humans had 48 chromosomes in each cell. Only in 1956 was the correct number, 46, finally determined.

- The ability to count and identify chromosomes led to a flurry of new findings in cytogenetics, including the discovery in 1959 that Down syndrome is caused by an extra copy of chromosome 21 ”a total of 3 copies” (so they were able to chromosomally diagnose Down syndrome which was discovered 200 years earlier

History

- During the past three decades, thousands of genes have been mapped to specific chromosome locations.

- The Human Genome Project, a large collaborative venture begun in 1990, provided the complete human DNA sequence in the year 2003. Human DNA is 3.2 billion bases in length

- this project was very important to try to unreveal the structure, function, composition of genes in the genome and to discover new genes

- The term **genome** refers to all of the DNA in an organism. So when you isolate your DNA from the cell, this is the genome. It is 99.9% similar between humans, and it is the 0.1% that accounts for the differences in our phenotypes. This small variation is what leads to the expression of genetic diseases, if present in our genome

TYPES OF GENETIC DISEASES

- **Chromosome disorders**, in which entire chromosomes (or large segments of them) are missing, duplicated, or otherwise altered. These disorders include diseases such as Down syndrome and Turner syndrome.

- Disorders in which single genes are altered; these are often termed "mendelian" conditions, or **single-gene disorders**. Well-known examples include cystic fibrosis, sickle cell disease, and hemophilia.

- We have almost 20,000 to 25,000s genes " this estimation had been increased based on the human genome project"

- **Multifactorial disorders,** which result from a combination of multiple genetic and environmental causes. Many birth defects, such as cleft lip and/or cleft palate, as well as many adult disorders, including heart disease and diabetes, belong in this category.

- **Mitochondrial disorders,** a relatively small number of diseases caused by alterations in the small cytoplasmic mitochondrial chromosome.

- The first edition of McKusick's *Mendelian Inheritance in Man*, published in 1966, listed only 1,368 autosomal traits and 119 X-linked traits.

- Today, the online version of McKusick's compendium lists more than 23,000 genes and traits, of which almost 21,000 are autosomal, more than 1200 are X-linked, 59 are Y-linked, and 65 are in the mitochondrial genome. " like identifying that this gene is responsible for this protein or this trait "

- DNA variants responsible for more than 4000 of these traits, most of which are inherited diseases "passed from father to son", have been identified. With continued advances, these numbers are certain to increase.

Causes of diseases could be

a. purely environmental

b. purely genetic like single-gene mutation (examples are on slide 5)

C. Multifactorial has both environmental and genetic background, like adults vascular diseases and some congenital defects, etc (example are on slide 7)

Fig. 1-2. Continuum of disease causation. Some diseases (e.g., cystic fibrosis) are strongly determined by genes, whereas others (e.g., infectious diseases) are strongly determined by environment.

Structure and function of genes and chromosomes

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- **All** genetic diseases involve defects at the level of the cell. For this reason, one must understand basic cell biology to understand genetic disease.

Cytogenetics (cellular level)	**Molecular genetics**
at the level of Chromosomes	At the level of DNA
Gain or loss of Chromosomes	single gene mutation
errors occurring during **cell division** can lead to disorders involving entire **chromosomes**.	**Errors** may occur in the **replication** of genetic material or in the **translation** of genes into proteins. These errors commonly produce **single-gene disorders**
The process of cell division (problems in meiosis or mitosis) During Meiosis → non-disjunction could happen , where chromosomes fail to separate properly in anaphase I or II. Leading to gain or loss of a chromosome	**The process** through which genes are replicated and translated into proteins

- Microscopic studies of cells led scientists to suspect that the **nucleus** of the cell contained the important mechanisms of inheritance.

  - **Chromatin** is the loose, granular form of DNA seen in the nucleus during interphase. Under a microscope, it appears as a grey, grainy material because it is loosely coiled and mixed with proteins.

  - **Chromosome** (which means “colored bodies ”, from Greek: chrome: coloured, -somes: bodies) the condensed, tightly coiled form of chromatin, appearing only during cell division (mitosis or meiosis)..

Genes: are transmitted from parent to offspring and are considered to be the basic unit of inheritance. Which are expressed as proteins that perform functional roles in the body

- genes are composed of deoxyribonucleic acid **(DNA**). DNA provides the genetic "blue-print" for all proteins in the body.

- An error (or **mutation**) in one of these genes often leads to a recognizable genetic disease.

There are two types **cells** in our bodies,.

Somatic cell	**Gametes** Sperm and egg cells (oocyte)
contains 23 pairs of different chromosomes -46 chromosome -	contain half the number of chromosomes-23 chromosomes-
Somatic cells, having two of each chromosome, (a copy of each chromosome) are termed **diploid** cells	Human gametes have the **haploid** number of chromosomes, 23.
Mitosis انقسام متساوي Purpose: Cell division for growth, repair, and maintenance. Daughter cells are identical to the parent cell (diploid)	**Meiosis انقسام اختزالي** Purpose: Production of gametes (sperm and egg cells) for sexual reproduction. Each daughter cell has half the number of chromosomes

There are two types **chromosomes** in our cells,.

Autosomes جسدية	**Sex Chromosomes جنسية**
Homologous Means: present as chromosome pairs (one from each parent) that have the same genes	Female → homologous (XX) Male → not homologous (XY)
	Determine the sex of the humans
22 Pairs of Chromosome	1 Pair of chromosomes

Composition and Structure of DNA

- Three basic components: the pentose sugar, **deoxyribose**; a **phosphate** group; and four types of nitrogenous **bases**.

- cytosine and thymine, are single carbon-nitrogen rings called **pyrimidines**
- adenine and guanine, are double carbon- nitrogen rings called **purines**

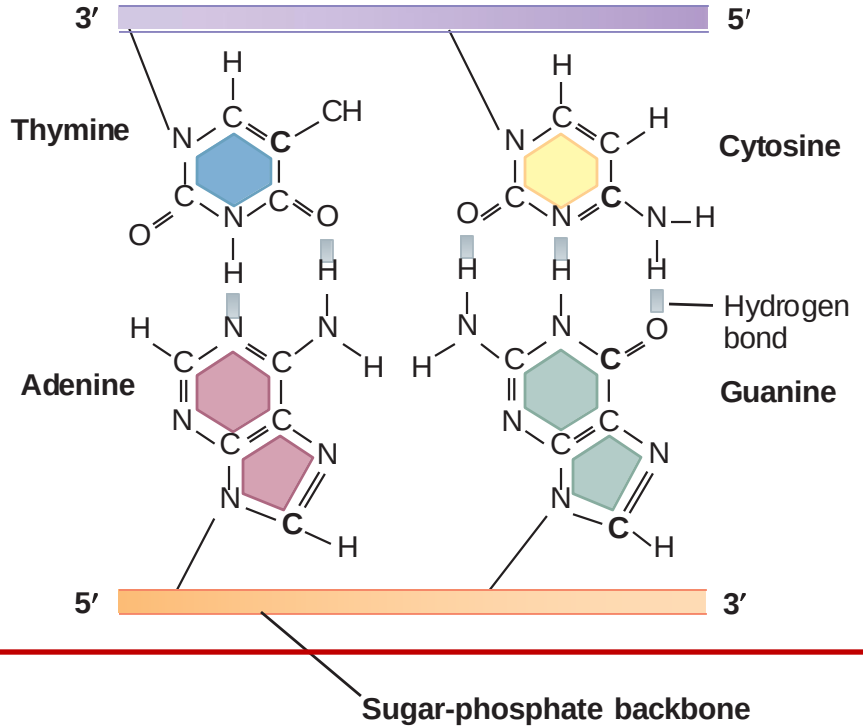

FIG 2-2 Chemical structure of the four bases, which shows hydrogen bonds between base pairs. Three hydrogen bonds are formed between cytosine–guanine pairs, and two bonds are formed between adenine–thymine pairs.

If there was a mismatch during pairing this results in a mutation

The double helix model

- **Watson and Crick's**

→ DNA can be envisioned as a twisted ladder with chemical bonds as its rungs

This model was detected in 1953 describing DNA as a linear double helical molecule, twisted in an antiparallel manner, with the 2 strands oriented in opposite directions: one strand runs 5' to 3', while the complementary strand runs 3' to 5'

The **double-helix model** has made it easier to understand DNA replication in laboratory settings, since hydrogen bonds that connect the two DNA strands are slightly weak bonds and can separate easily, facilitating the replication of specific regions of DNA.

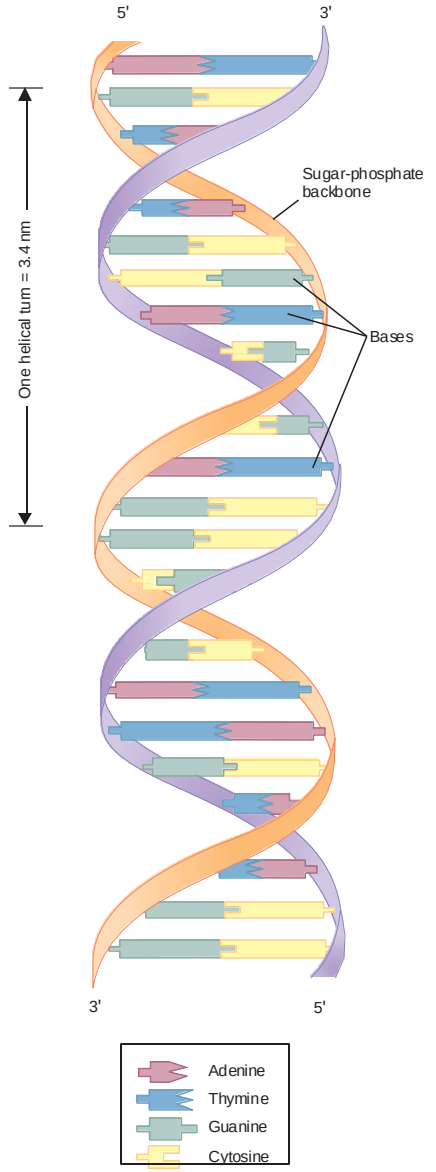

FIG 2-3 The DNA double helix, with sugar-phosphate backbone and nitrogenous bases.

DNA coiling

DNA molecules, which are about 2 meters long and contain 3.2 billion base pairs, must be compacted to fit within the relatively small nucleus, which is only a few micrometers in size. This compaction occurs through a process called DNA packaging.

- The DNA is wound around a histone protein core to form a [1]**nucleosome**
- The nucleosomes form a helical [2]**solenoid**; each turn of the solenoid includes about six nucleosomes.
- The solenoids are organized into [3]**chromatin loops**, which are attached to a protein scaffold.

Ultimately, this organization results in the formation of **chromosomes, allowing the highly condensed DNA to fit inside the nucleus.** Each nucleosome consists of about 140–150 base pairs, while each loop contains approximately 100,000 base pairs.

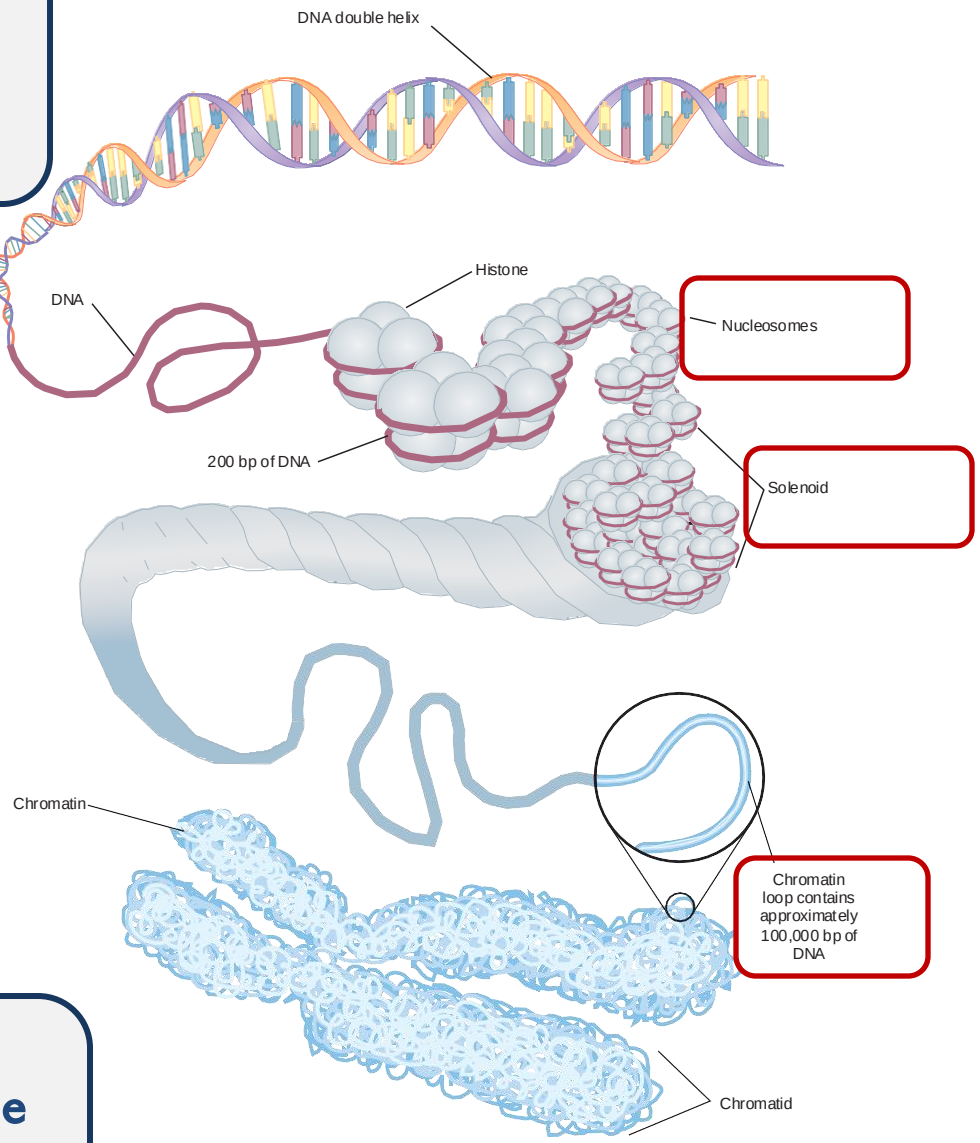

FIG 2-4 Patterns of DNA coiling. DNA is wound around histones to form nucleosomes. These are organized into solenoids, which in turn make up the chromatin loops.

رمضان مبارك🌙

Additional sources:


سُورَةُ البَقَرَة

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

شَهْرُ رَمَضَانَ ٱلَّذِىٓ أُنزِلَ فِيهِ ٱلْقُرْءَانُ هُدًى لِّلنَّاسِ
وَبَيِّنَٰتٍ مِّنَ ٱلْهُدَىٰ وَٱلْفُرْقَانِ ۚ فَمَن شَهِدَ مِنكُمُ
ٱلشَّهْرَ فَلْيَصُمْهُ ۖ وَمَن كَانَ مَرِيضًا أَوْ عَلَىٰ سَفَرٍ فَعِدَّةٌ
مِّنْ أَيَّامٍ أُخَرَ ۗ يُرِيدُ ٱللَّهُ بِكُمُ ٱلْيُسْرَ وَلَا يُرِيدُ بِكُمُ
ٱلْعُسْرَ وَلِتُكْمِلُوا۟ ٱلْعِدَّةَ وَلِتُكَبِّرُوا۟ ٱللَّهَ عَلَىٰ مَا
هَدَىٰكُمْ وَلَعَلَّكُمْ تَشْكُرُونَ ﴿١٨٥﴾

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!