بسم الله الرحمن الرحيم

BioChemistry

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

MID | Lecture 12

Nucleic Acids

Written by : Raghad Farraj, Shahd Thamer, Lamar Khorma

Reviewed by : Jana Sawafta, Karam Alquiam

Color coding used in the modified:

- *Black: the original slides*
- *Navy Blue: the doctor’s explanation/words*
- *Gray: additional information and explanation*
- *Red: important information*

Structure of nucleic acids

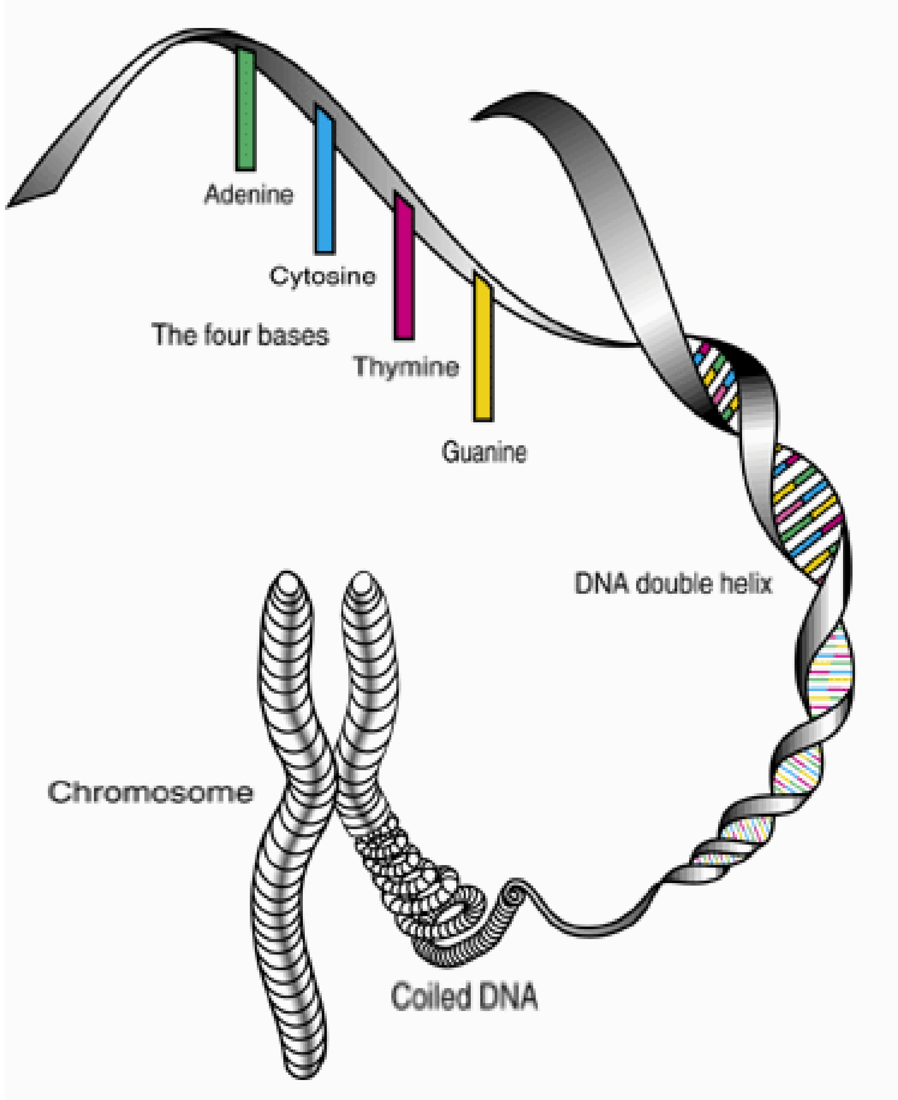
Prof. Mamoun Ahram

https://cdn.wou.edu/chemistry/files/2020/06/best-DNA-animation-ever.mp4?_=1

Nucleic acids

- There are 2 types of nucleic acids:
  - Deoxyribonucleic acid (DNA)
  - Ribonucleic acid (RNA)
- The primary structure of nucleic acids is linear polymers of nucleotides (monomers) bound to each other via phosphodiester bonds.

> A phosphodiester bond = one phosphate group + two ester bonds.
> The phosphate replaces the central atom that would normally be carbon in a regular ester.

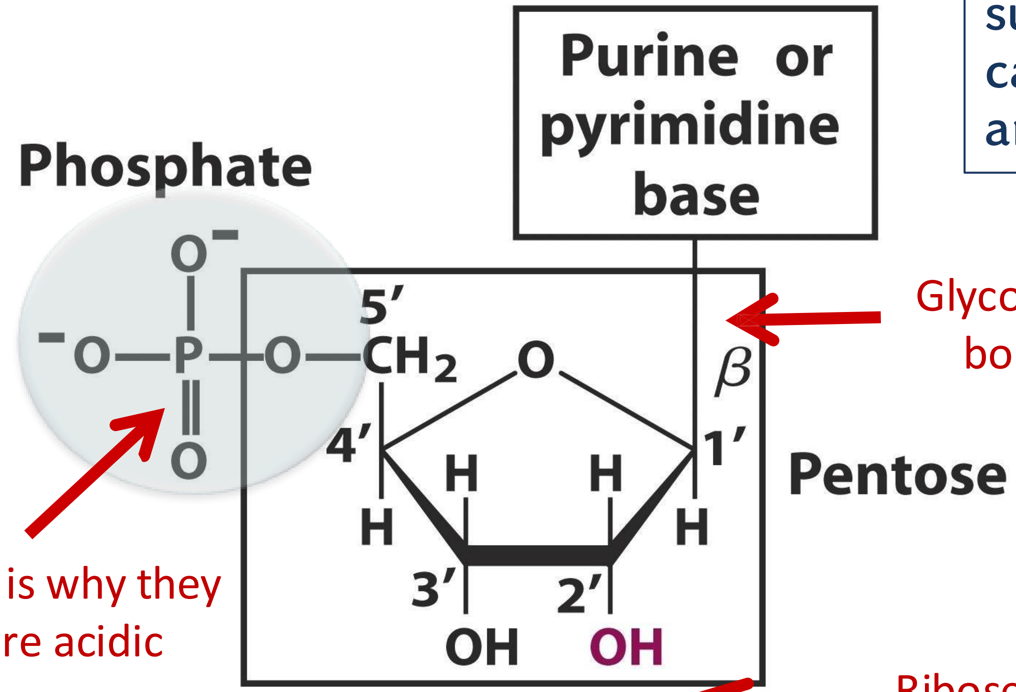


- DNA is coiled and can be associated with proteins forming chromosomes.

> All genetic material in all organisms is organized into chromosomes

Chemical composition and bonds of nucleotides

Nucleotides has a basic structure that has three components:
- A sugar molecule (pentose, a 5 carbon sugar that can be ribose or deoxyribose)
- A phosphate group
- A nitrogenous base



The prime’ on the carbons in the sugar is to differentiate between the carbons that belong to the sugar and the ones that belong to the base

Glycosidic bond

The base is connected to carbon 1 (the anomeric carbon) so its bond is **glycosidic** in the beta orientation

This is why they are acidic

Ribose vs. deoxyribose

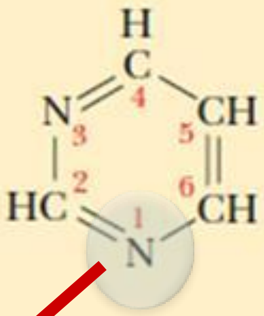
On carbon 5’ is a phosphate group which makes DNA and RNA acidic molecules

This carbon determines if it oxygenated or not

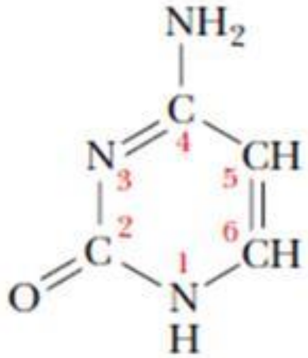
Nitrogenous bases

Nitrogenous bases are classified into two types, depending on the number of rings
One ring (single ring) = pyrimidine
Two rings (double ring) = purine

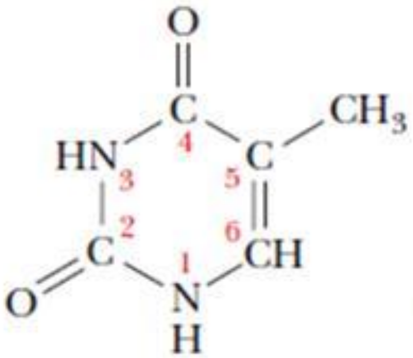
Nitrogen 1 in pyrimidines and nitrogen 9 in purine is what makes the glycosidic bond with the sugar



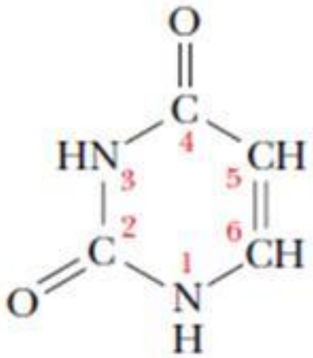
Pyrimidine



Cytosine
(in DNA & RNA)



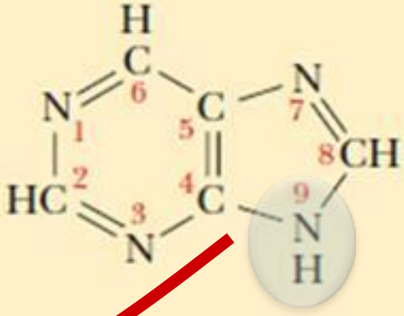
Thymine
(in DNA)



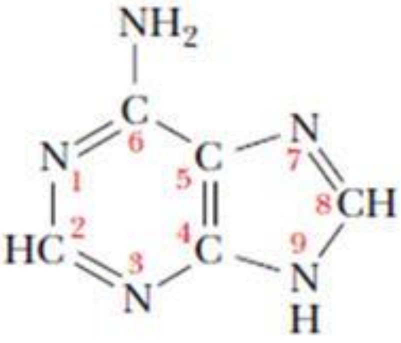
Uracil
(in RNA)

Notice the presence of each base

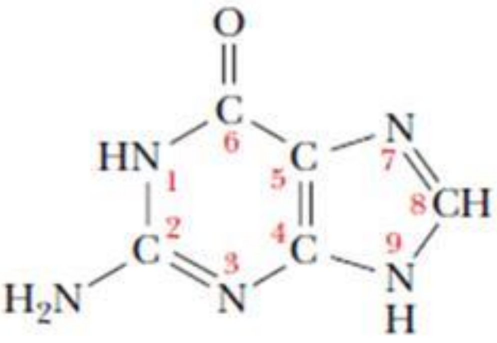
Glycosidic bond



Purine



Adenine
(in DNA & RNA)



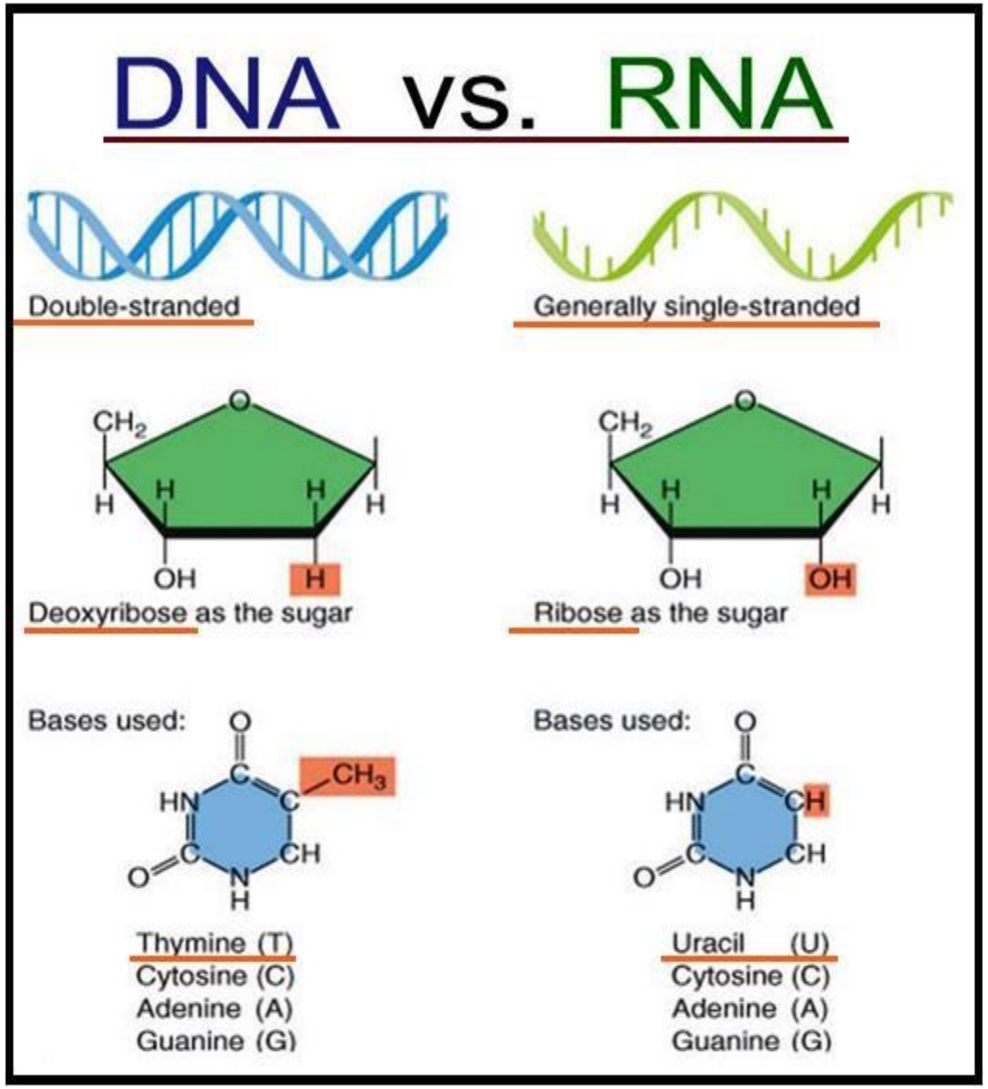
Guanine
(in DNA & RNA)

You don't have to memorize the structure of the bases, but identify them and their abbreviations

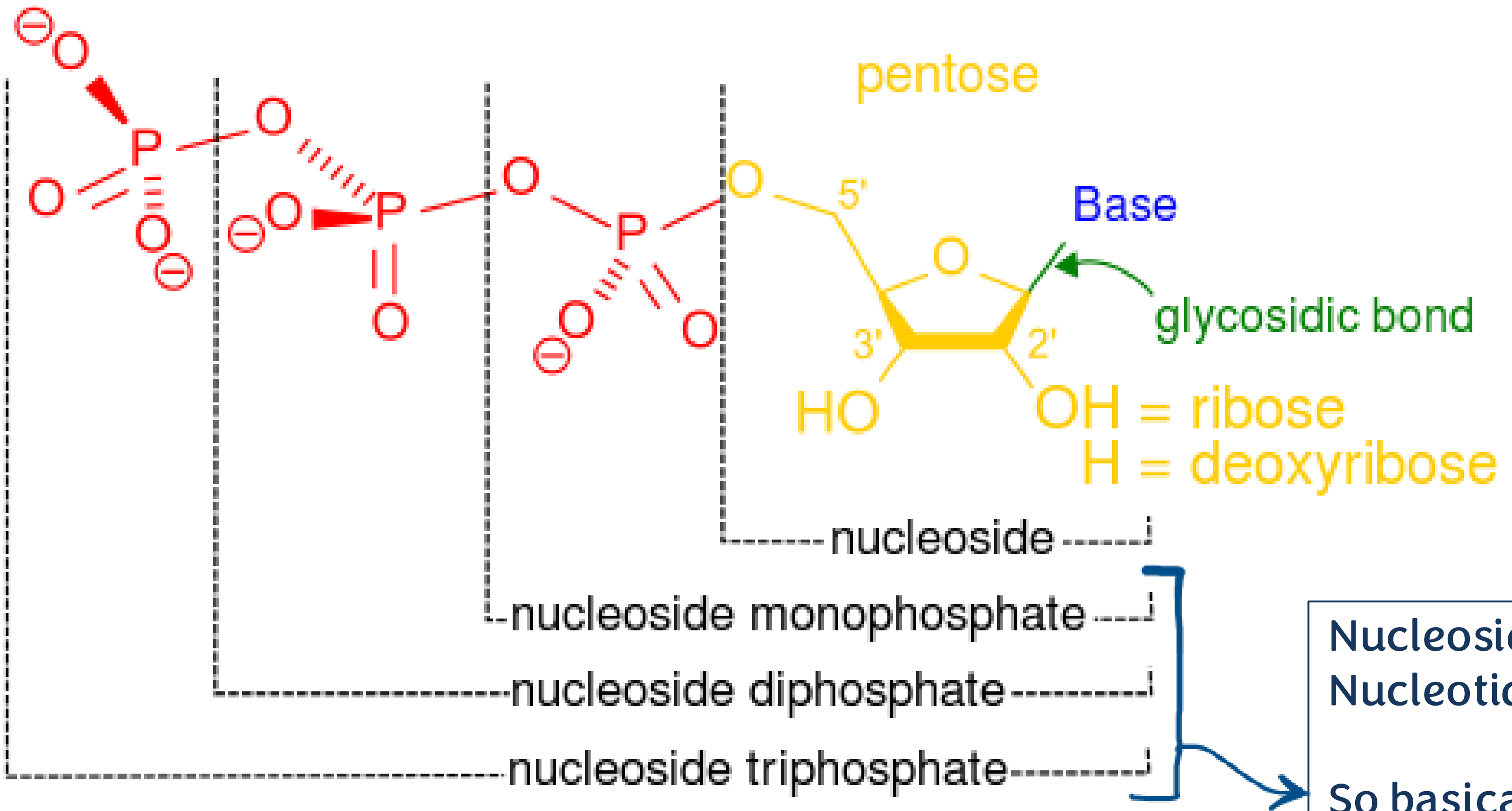
In prokaryotes and eukaryotes (not viruses)

Usually DNA is double-stranded and RNA is single stranded, but there are exceptions in viruses

Usually advanced organisms, bacteria, and all the way up have double stranded DNA



Nucleotides vs. Nucleosides



Nucleoside = Sugar + Base
Nucleotide = Sugar + Base + Phosphate(s)

So basically, all of these are other names for nucleotides, but we use them to be specific

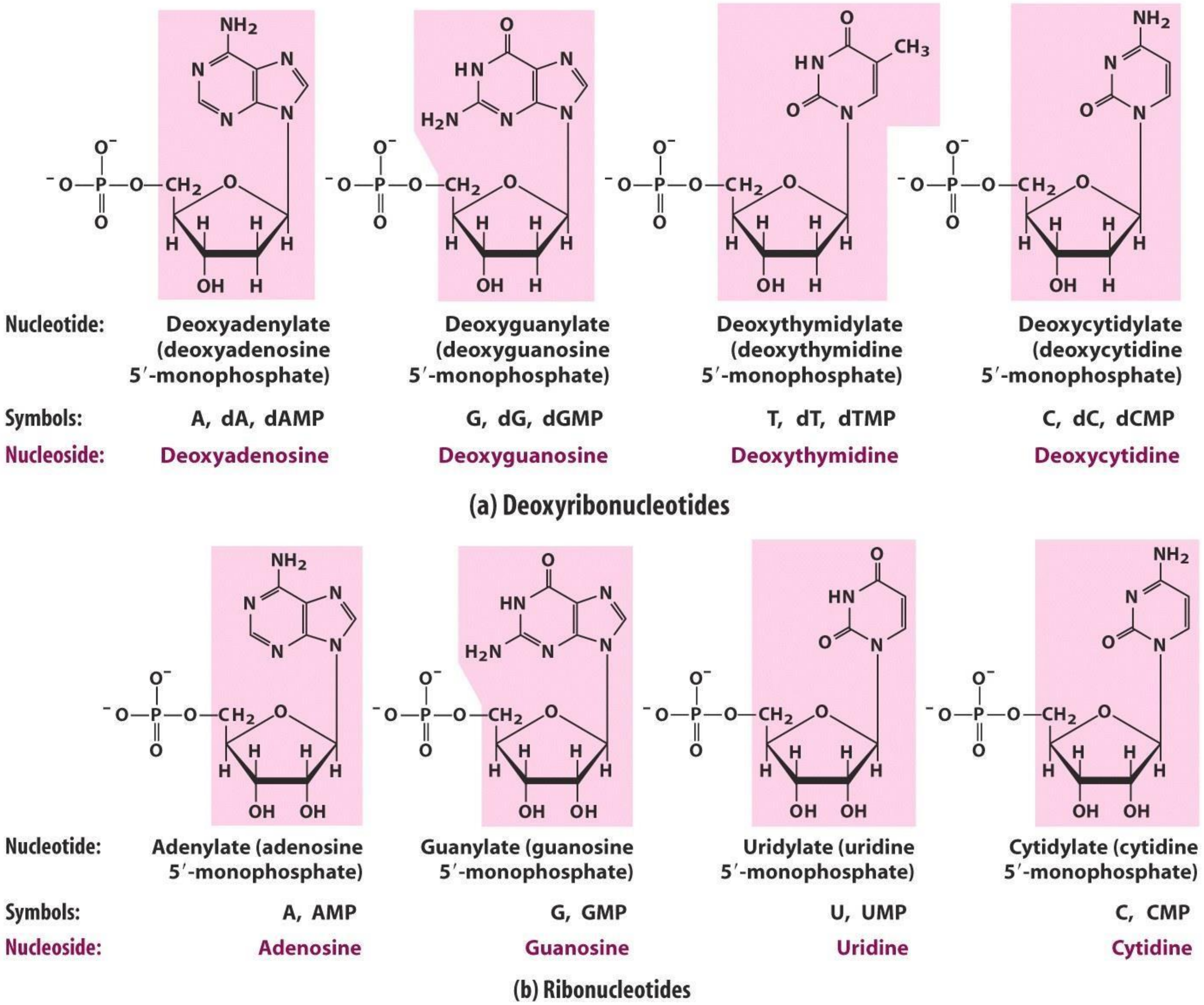
Nucleotides vs. Nucleosides

Naming is important!!

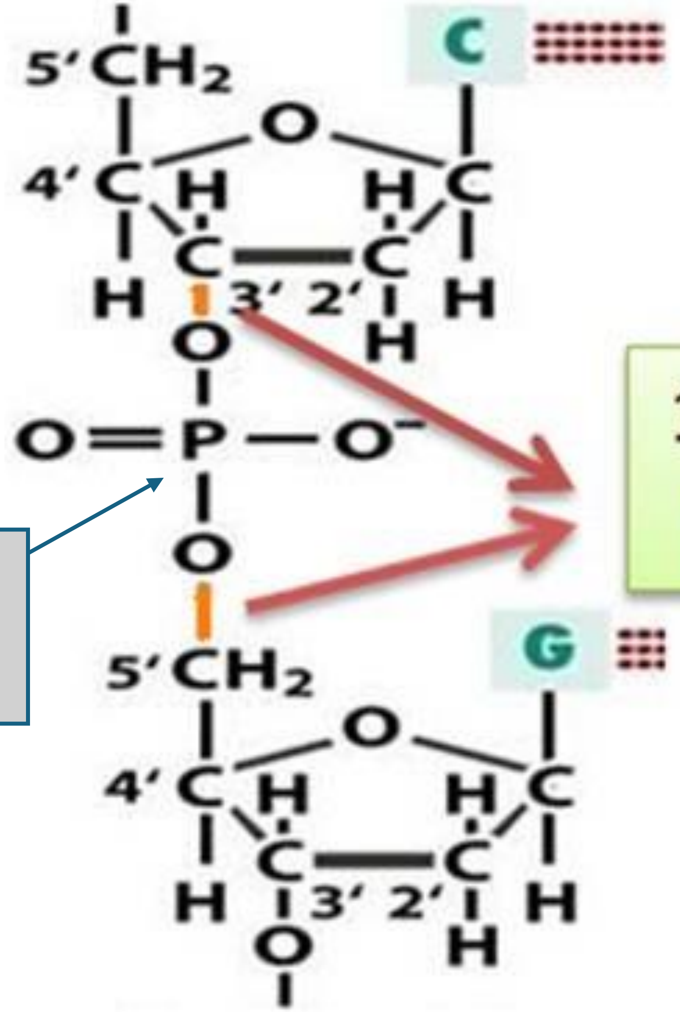
In order to name you follow the following

1. Is it a ribose or a deoxyribose? (to determine if it belongs to a DNA or RNA)
2. Does it have a phosphate? (to determine if it's a nucleotide and what kind)
3. Is the base a purine or pyrimidine?
4. What base is connected to the sugar? (The doctor said it's not important to determine this specifically)

The base itself is adenine.
The nucleoside of it is adenosine.
The nucleotide is adenosine monophosphate or adenylate



Formation of a nucleic acid polymer



1^{st} and 2^{nd} ester linkage (phosphodiester bond)

So here instead of carbon we have a phosphate

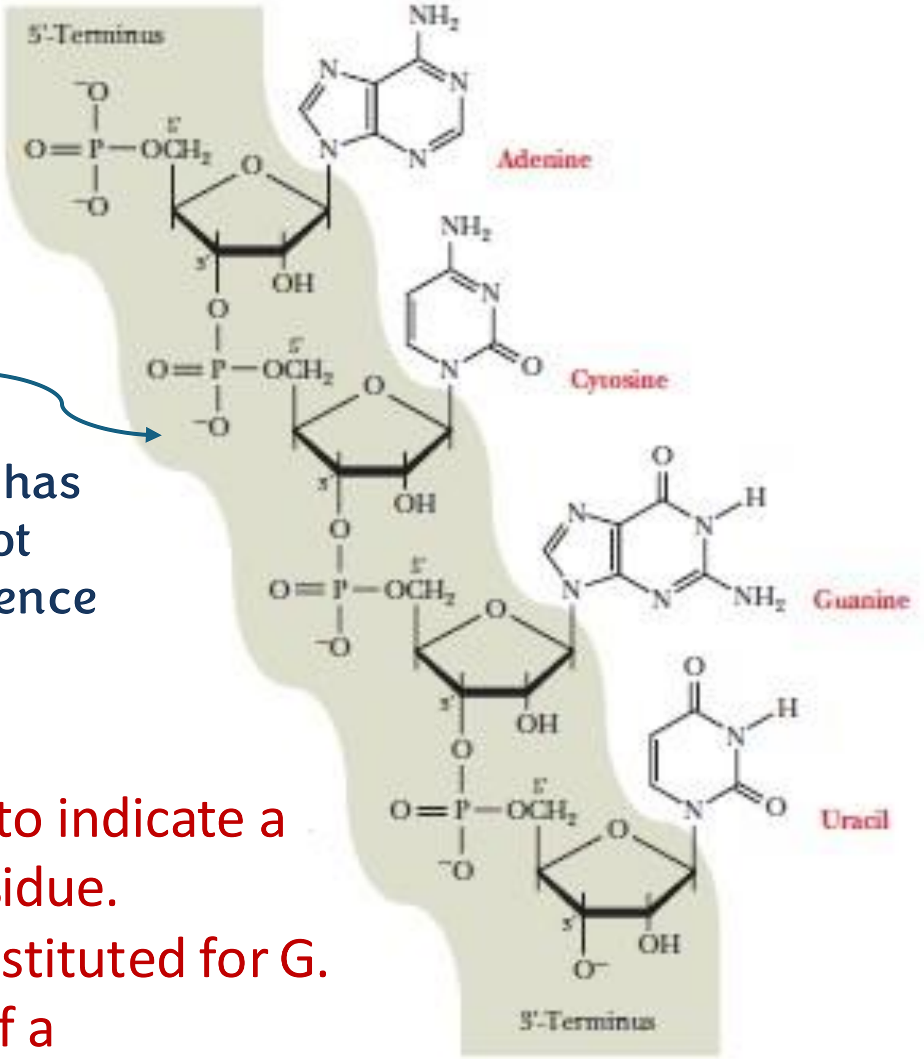
Remember that we add **to** the 3` end and the 5` end stays untouched (stays always free). Elongation:(5`-->3`)

How do we form a nucleic acid polymer?
It is formed by phosphodiester bond.
It is a bond between 3` carbon and the 5` carbon (which has the phosphate group).
So every time we want to elongate the strand we add a 5` to the already existing strand with **free** 3` end.
in other words, we add a nucleotide with the phosphate which will link to the **hydroxyl group on C3** on the linked nucleotide

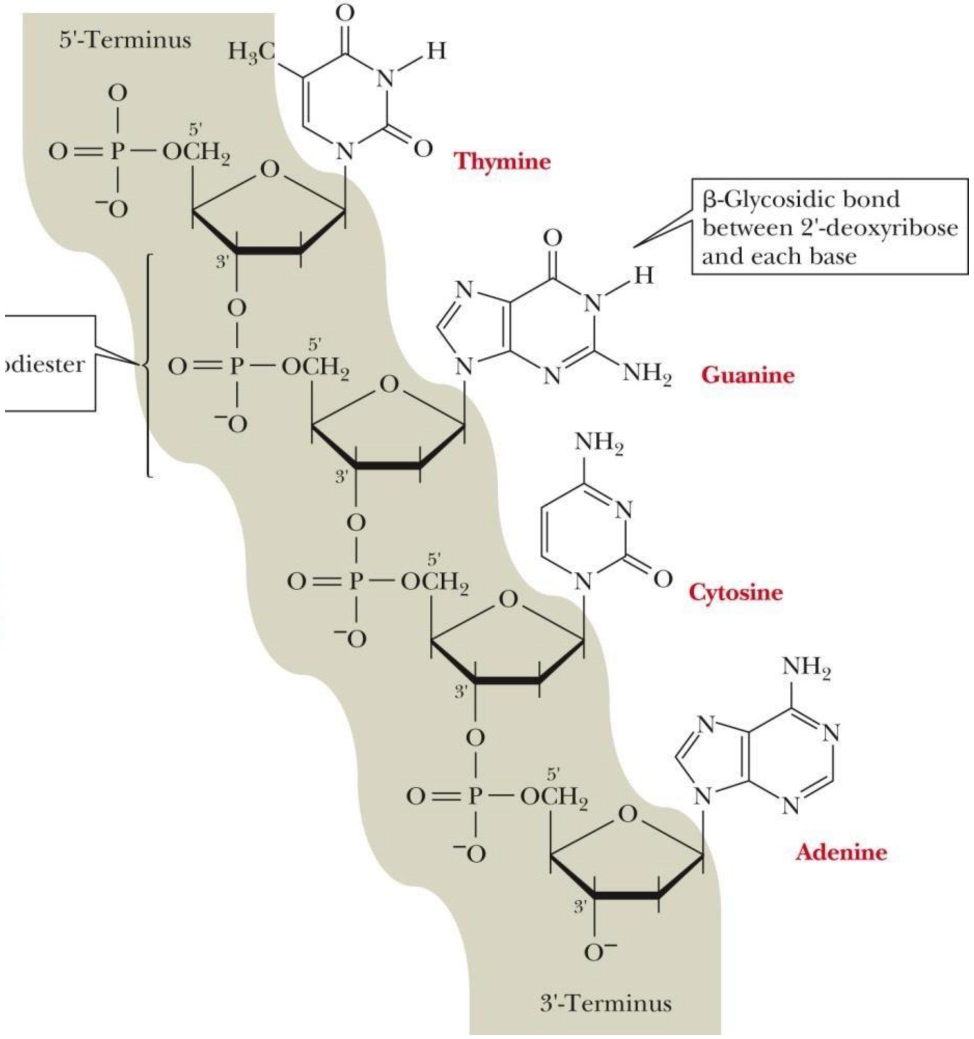
Nucleic acid polymers

This molecule is DNA due to the C2 which lacks OH (deoxy ribose) and it possesses a Thymine.

This is a phosphodiester linkage.



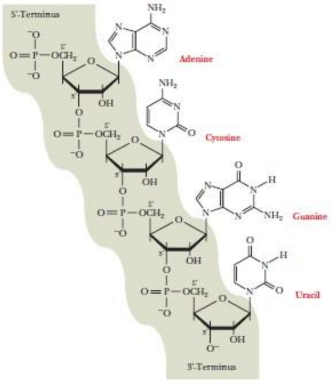
This is RNA from C2 which has OH meaning it's a ribose not deoxyribose, also the existence of uracil indicates that this molecule is RNA.



- A letter d can be added to indicate a deoxyribonucleotide residue.
  - for example, dG is substituted for G.
  - The deoxy analogue of a ribooligonucleotide would be d(GACAT).

Full sequence: 5`ACGU 3`
Abbreviated sequence: ACGU

- Whenever you see DNA or RNA and you get questioned what is the sequence of DNA or RNA you start from the 5`end (terminus) and you end it with the base that exists at the 3` end(terminus).



What is the sequence of this molecule ?

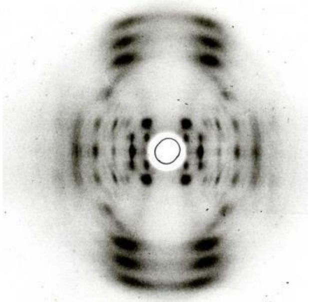
Start from 5'

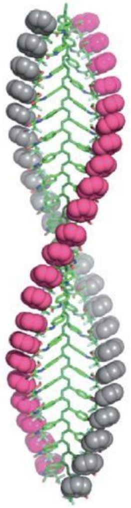
ACGU

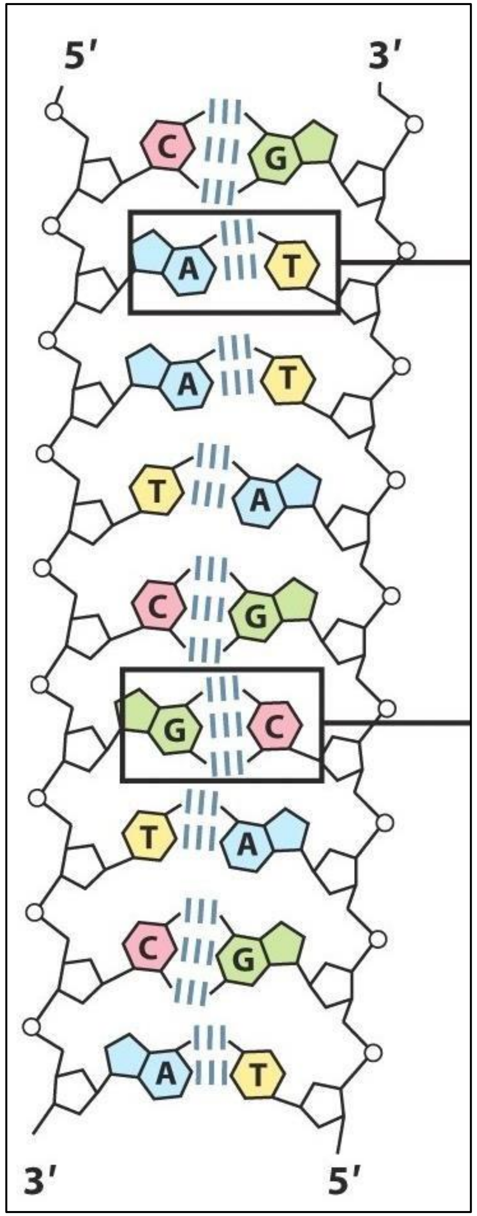
- We notice there is directionality, a direction by which we name nucleic acids. For example when we were naming disaccharides we always start from the left (Lactose=galactose+glucose) -a rule-. And here for nucleic acids we **start from the 5` end at which the sequence of nucleotides starts (order of bases) until we reach 3` end**. For example, you have **"AGCT"** sequence, the *doc doesn't need to tell you* it's **a 5` AGCT 3` sequence but you have to know it by default.**
- Another thing you have to know by default is if you saw Thymine you should already know it's a deoxyribose.

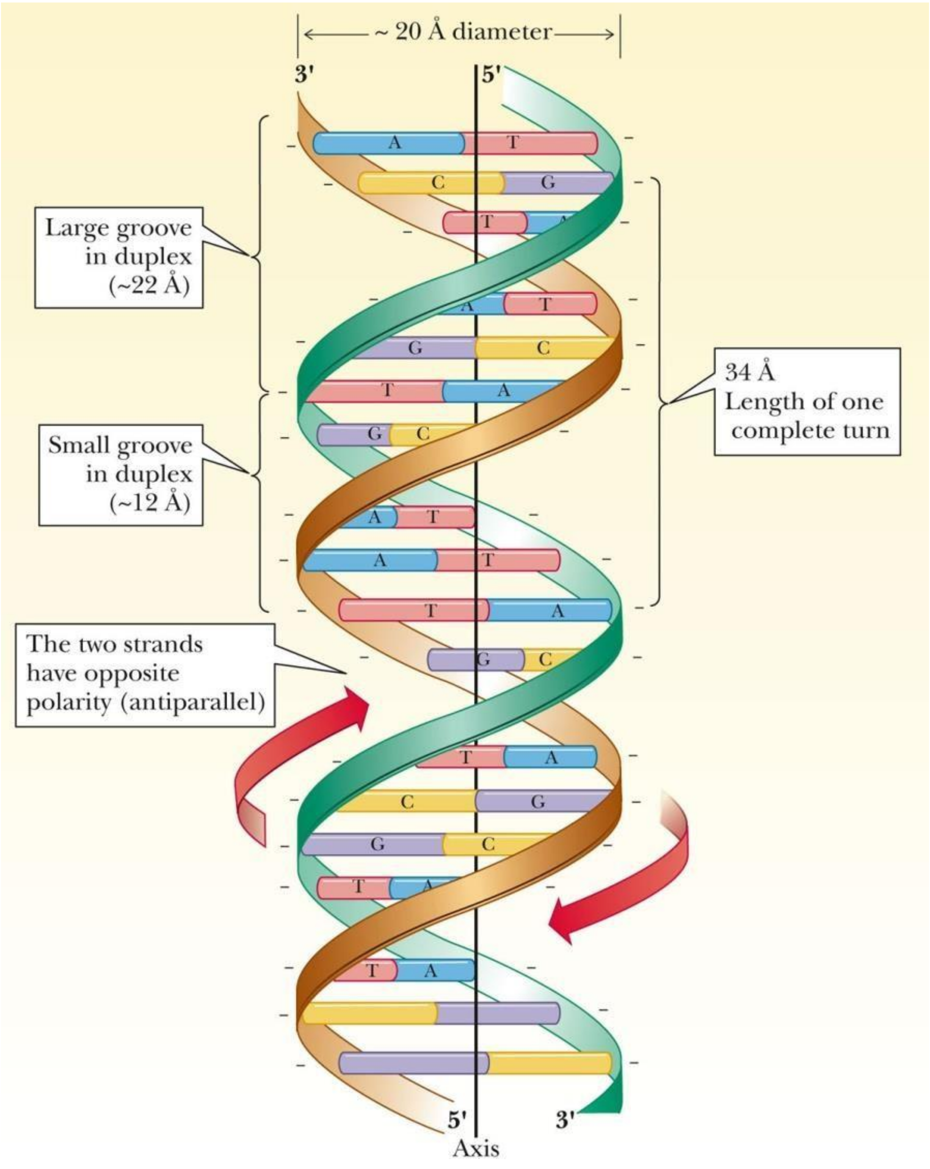
DNA structure

- A double helix
- Specific base-pairing
  - A = T; G = C; Pur = pyr
- Complementary
- Backbone vs. side chains
- Antiparallel
- Stability vs. flexibility
- Groovings



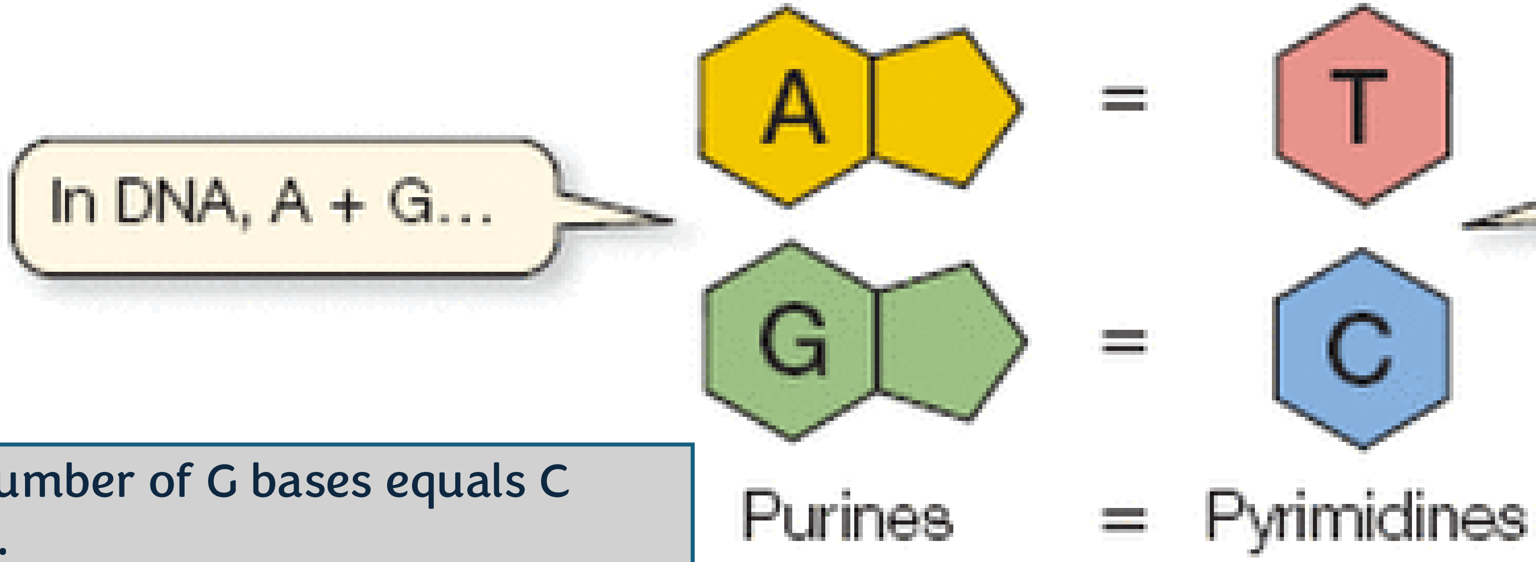






- DNA is a double stranded molecule, meaning its made of two strands. and they intertwine around each other forming a helical structure that's why we name it a double helix.
- Notice its **not** a perfect double helix.
- And the two strands are interconnected to each other (**between bases**) so the bases are embedded inside while the backbone is outside which is the phosphate and the sugar and the branches are the bases (perpendicular on the backbone"make 90 degree angle").
- Between a base from a strand and the other base from the opposite strand there is **hydrogen bond** that stabilizes them and connects them to eachother.

Chargaff's rules

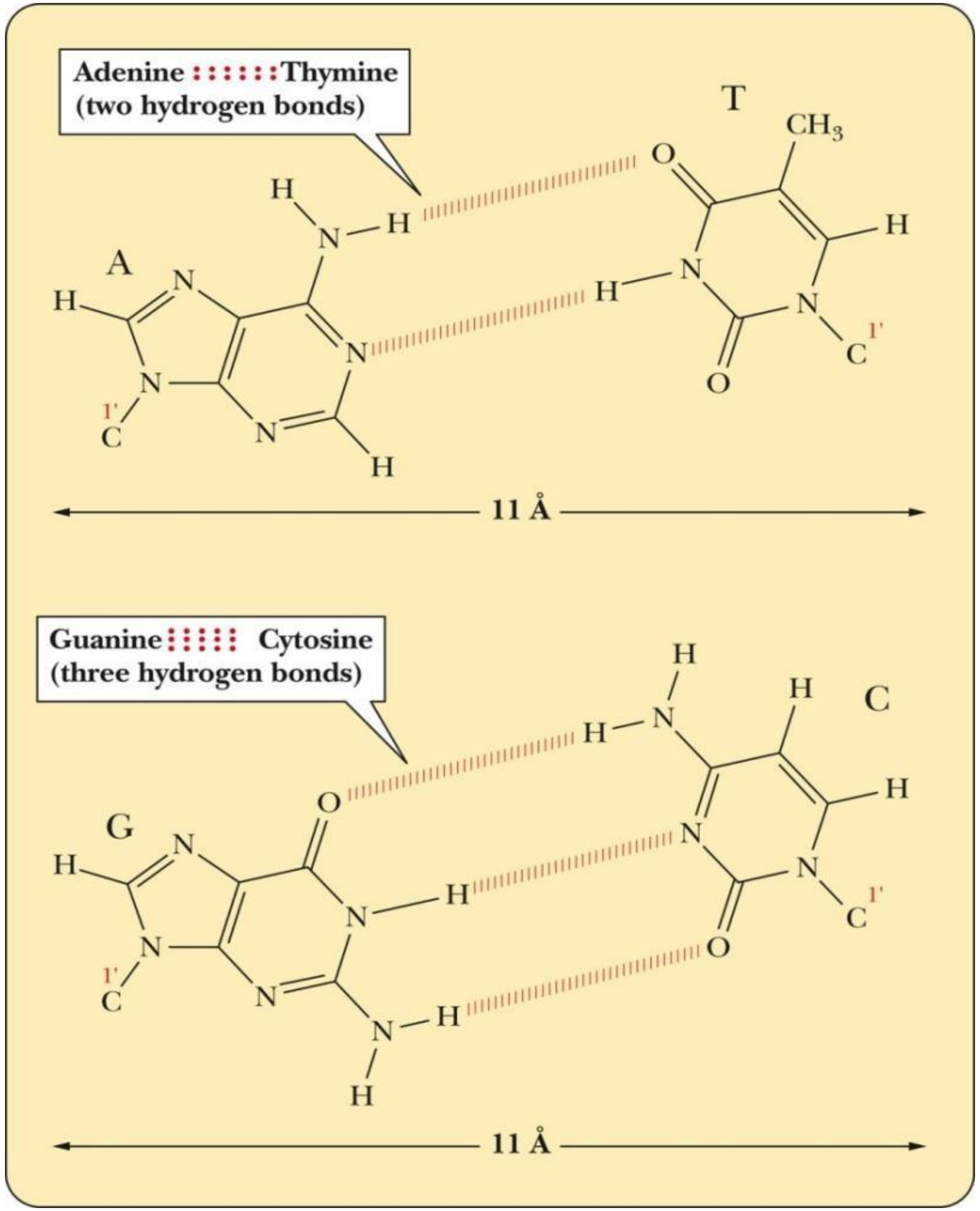


The number of G bases equals C bases.
The number of A bases equals T bases.
The number of purines equals the number of pyrimidines.
so what called "Chargaff's rule".
A+G=T+C

We can can have a dna with a strand that has 99 A bases and 1 G bases while the complimentary strand will have 99 T bases and 1 C base.
Meaning that;
(G+C ≠ T+A)

Base pairing

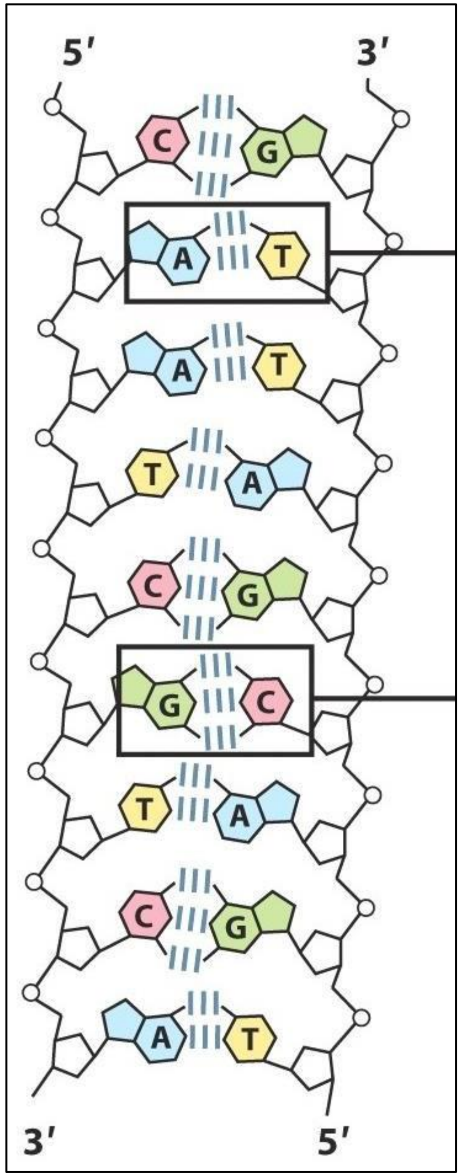
- There is also specific base pairing: A base forms hydrogen bonding with the opposite base and so on.
- This base pairing is not random but rather is specific, for example if we have a G in a strand we should have an A on the opposite strand which is what we mean by specific pairing.
- (A->T) (G->C) in DNA (A->U) (G->C) in RNA.
- Note that between G and C (G from a strand and the C base from the opposite strand) there is **three** hydrogen bonds while between A and T there is **two** hydrogen bonds. (The hydrogen bond stabilizes them and connects them to eachother.)
- This specific pairing enables us to call the DNA strands as complimentary to eachother .



DNA is complementary

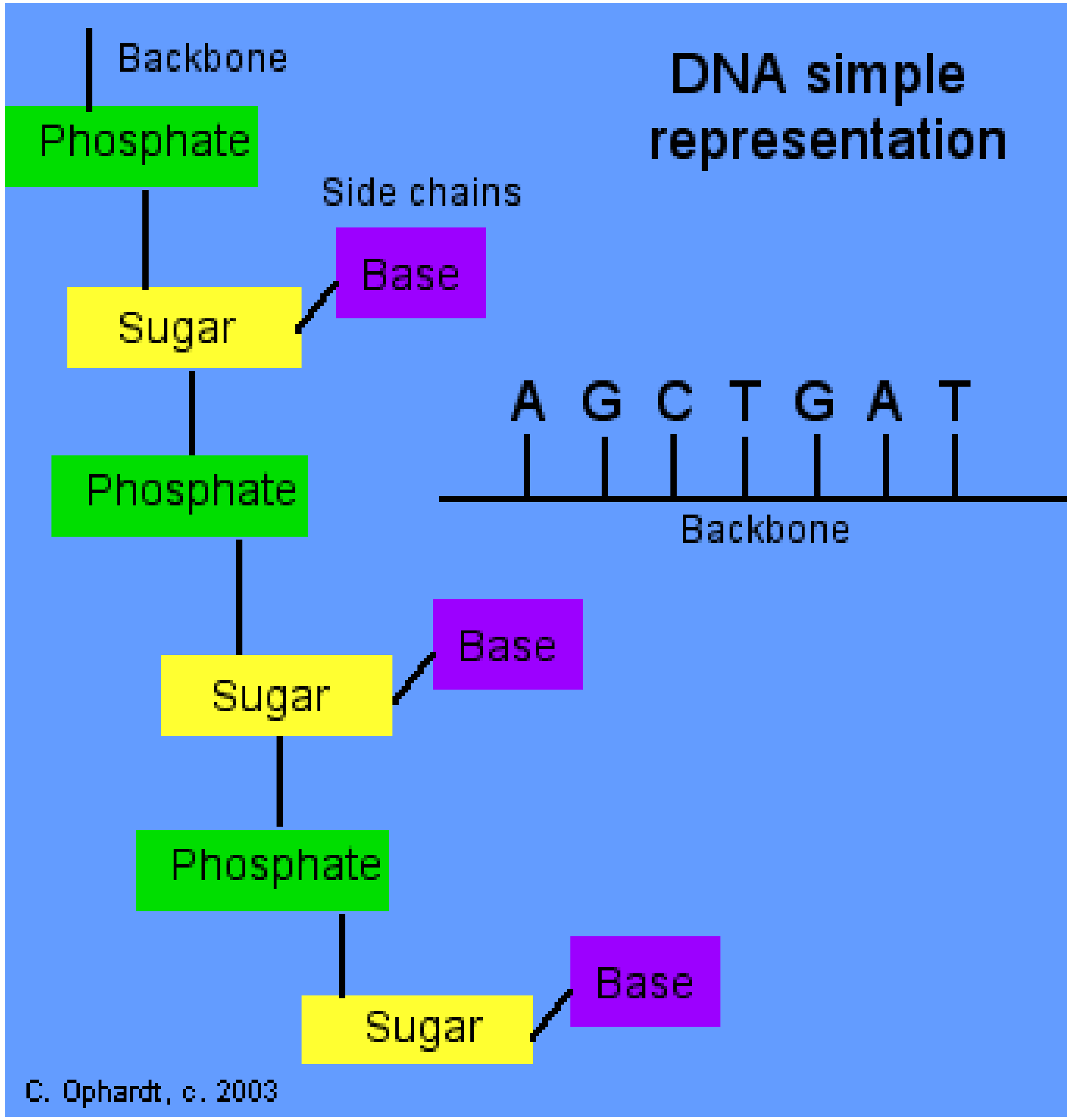
- If I tell you the sequence is

“CAATCGTCA” , I don’t need to tell you what the other strand’s sequence is because you can predict it but it can be tricky because you should start from the 5` end even it the complementary strand (from the bottom in this photo)
So;
The first strand: 5`CAATCGTCA3`
The complementary one : 5’ TGACGATTG 3’
NOTE: you always start from 5` end **UNLESS** the doc asked to start from 3’ to 5’
So the complementary will be 3’ GTTA GCAGT 5’

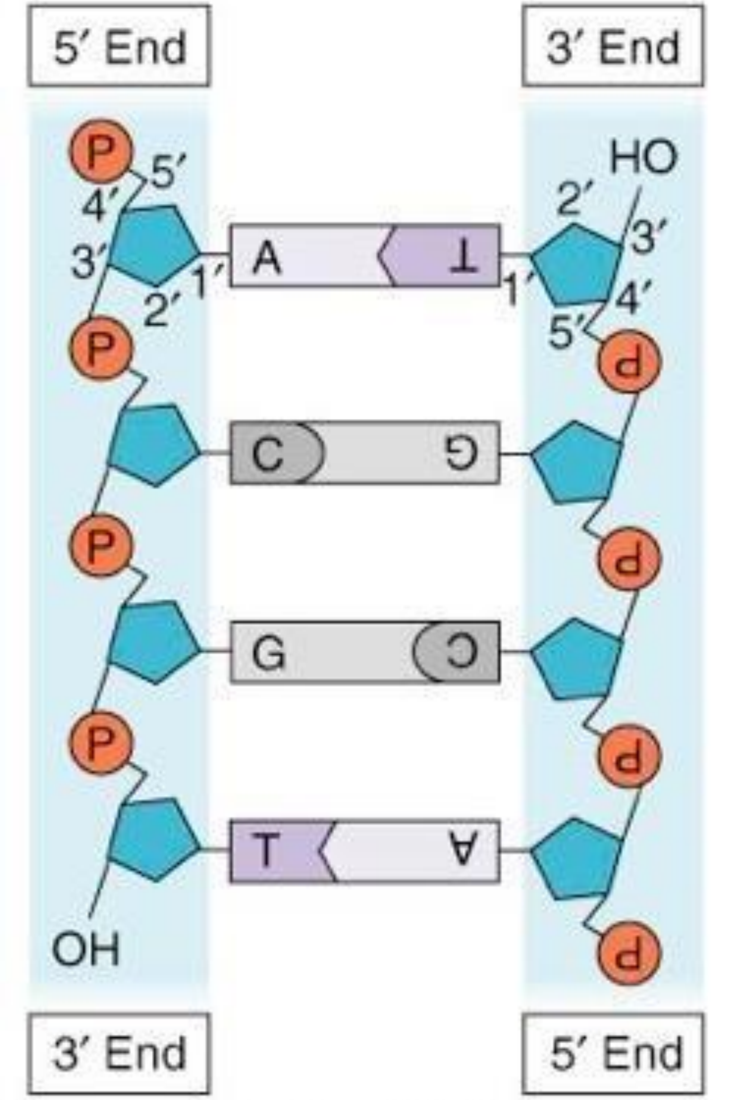


Backbone vs. side chains

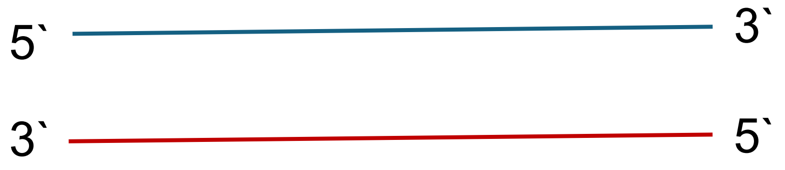
Backbone: phosphate sugar
Branches: bases
(perpendicular to the backbone, oriented inward, embedded)



DNA is anti-parallel



The two DNA strands are **antiparallel**;
5` from strand correlates 3` from the opposite strand.
5`--> 3`
3`--> 5`



Writing the sequence of nucleic acids

You know it's DNA due to the existence of Thymine.

DNA

5' ...A T G G C C T G G A C T T C A... 3'
3' ...T A C C G G A C C T G A A G T... 5'

OR A T G G C C T G G A C T T C A.

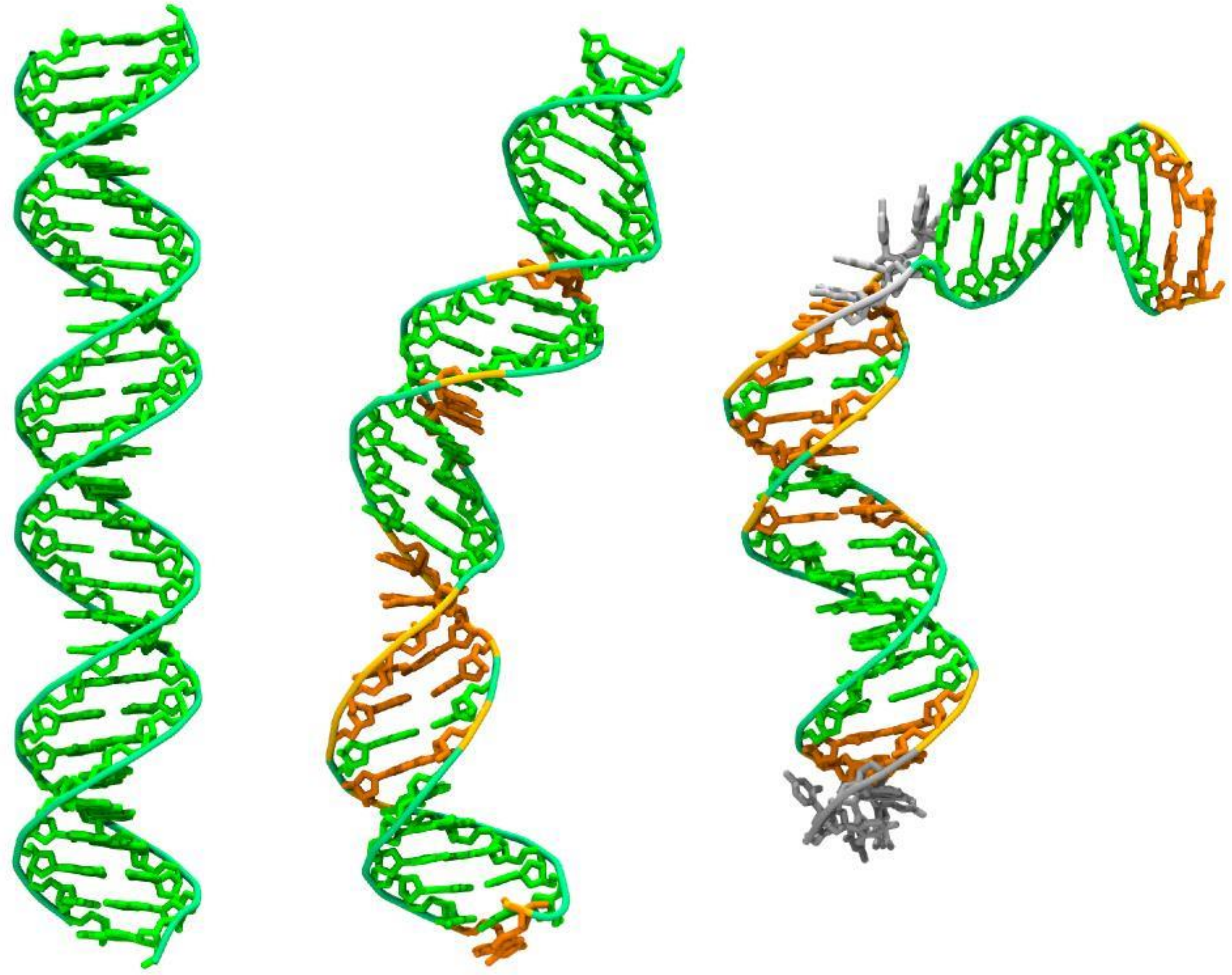
RNA

5' ...A U G G C C U G G A C U U C A... 3'

RNA is single stranded molecule usually.
You can know its RNA because we have Uracil.

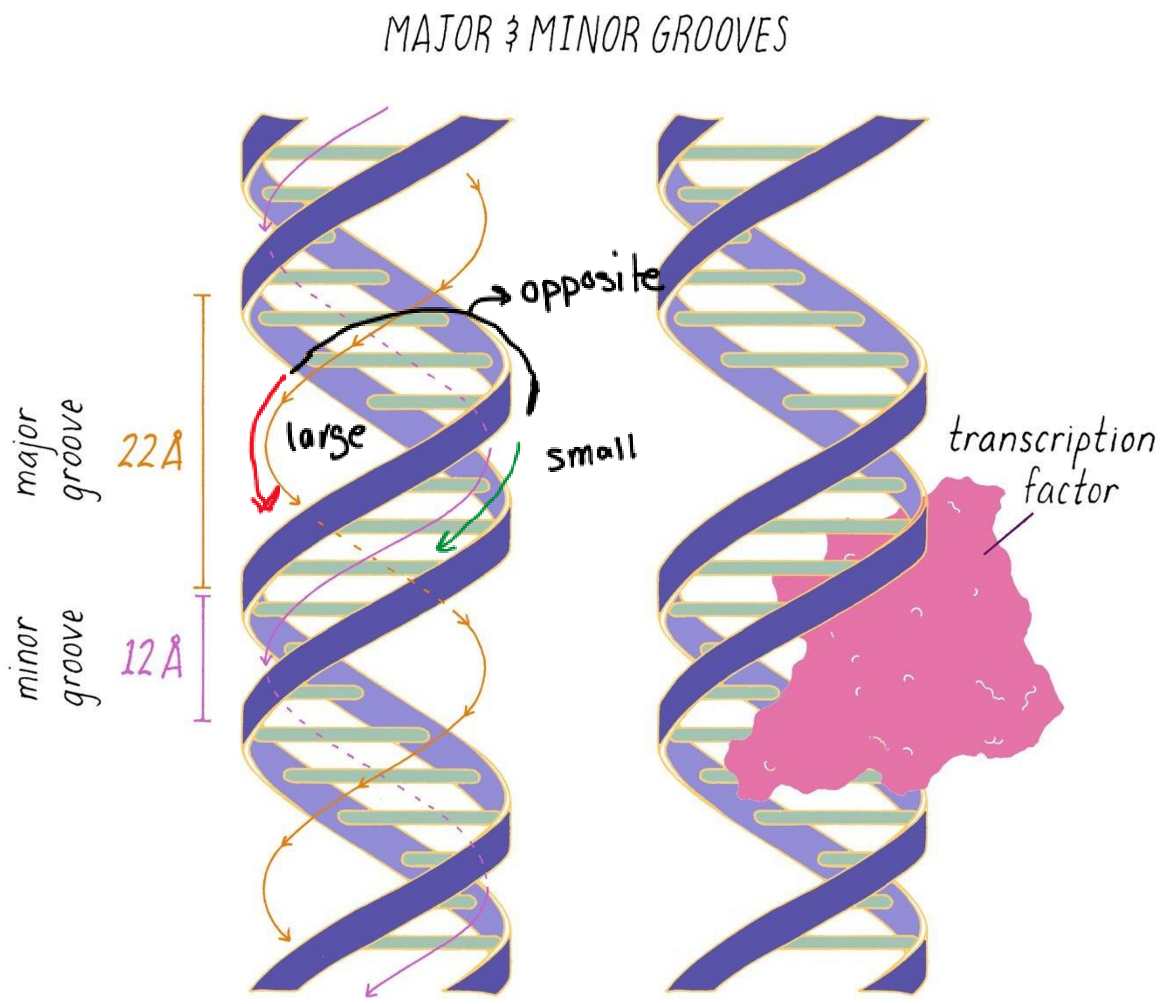
DNA is flexible, yet stable

Like a wire, Dna is stable yet flexible (its hard to tear it off but we can bend it easily).
It should be flexible so that the 2 meters DNA can fit in the nucleus.



DNA grooves

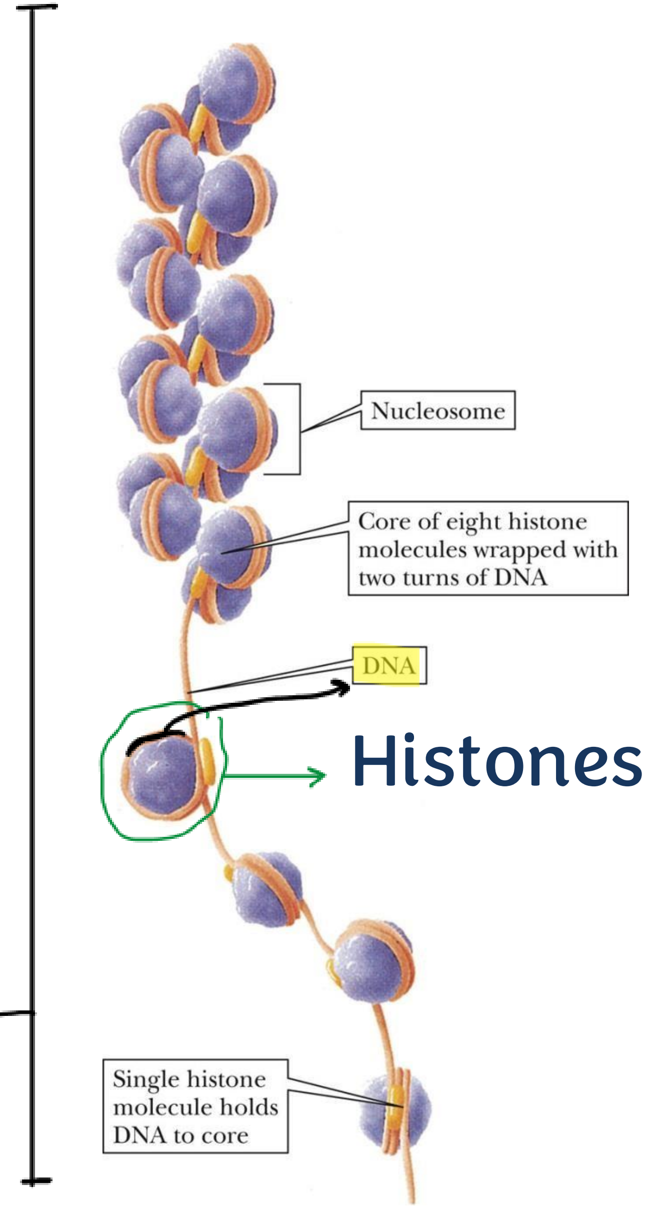
- Because DNA is not a perfect double helical molecule secondary localized structures are formed known as grooves انحناء.
- Note that a large groove lies opposite to a small groove.
- Major grooves (large) and minor grooves(small).
- The importance of the major groove it allows for proteins to bind to DNA, so that the protein can fit in it.



In eukaryotes…

- In eukaryotes, DNA is coiled to package the large DNA in the nucleus
- Eukaryotic DNA is complexed with a number of proteins, principally histones, which package DNA.
- Chromatin = DNA molecule + proteins (**Histones**).
- The basic structural unit of chromatin is known as a nucleosome.

Chromatin



- In eukaryotic cells, DNA is extensively coiled so that it can be packaged inside the nucleus. To achieve this packaging, DNA binds to histone proteins (histones). DNA wraps around these histone proteins, allowing it to become highly condensed and organized so that the entire genome can fit within the nucleus.

- When *DNA binds to histone* proteins, it forms a structure known as **chromatin**. In this structure, DNA is wrapped around histone proteins, forming repeating bead-like units connected by stretches of DNA. As chromatin becomes more compact, these units fold further, allowing DNA to be efficiently packaged inside the nucleus.

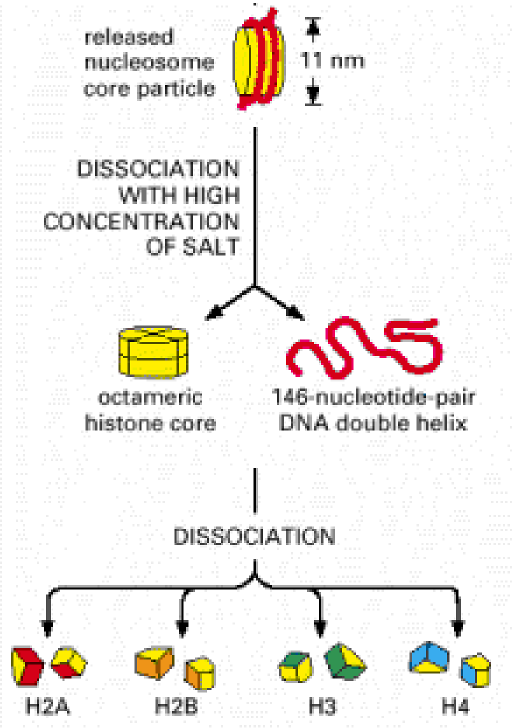
- Histone proteins form a structure called an **octamer.** The prefix **octa- means eight** and **-mer means unit**, so an octamer consists of eight histone proteins. Specifically, it is composed of four different histone types: (H2A, H2B, H3, H4) **=> (are two copies of each histone, giving a total of eight histone molecules).**

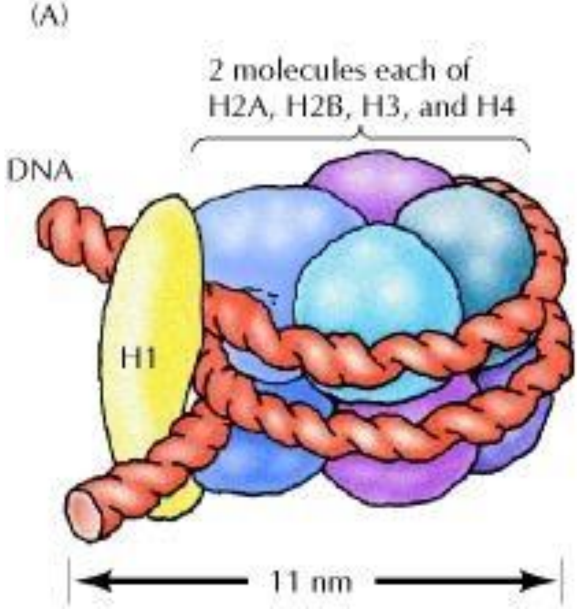
- DNA wraps around this histone octamer **twice**. Between adjacent octamers, there is an extension of DNA that is not associated with histones. This region is called linker DNA because it connects/links one nucleosome to the next.

Nucleosomes

Another histone, histone H1 (locates out the octamer). It acts like a seal , stabilizing the DNA wrapped around the histone core. Although H1 is not required for nucleosome formation, it plays an important role in stabilizing chromatin.

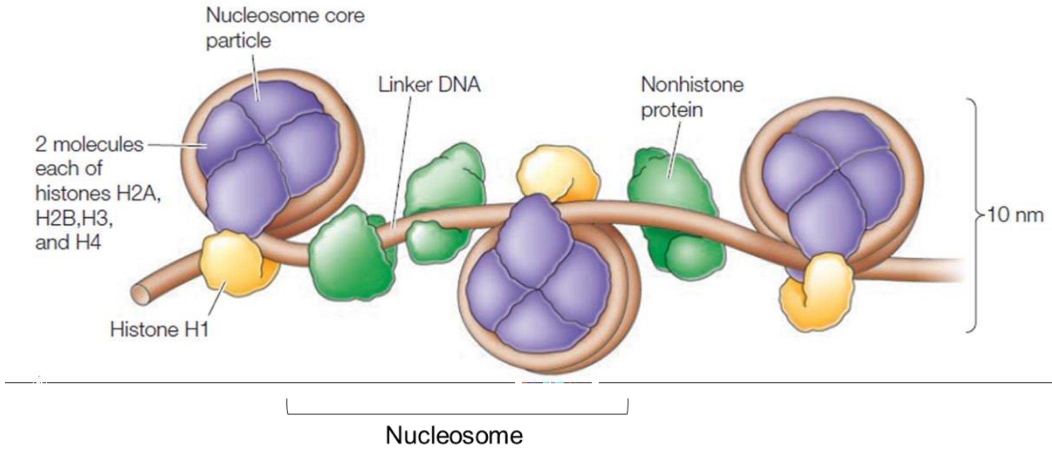
- The histone core particle is an octamer (two molecules of histones H2A, H2B, H3, and H4) and the DNA wrapped around it.
- Addition of histone H1 to the octamer and the wrapped DNA creates a chromatosome).
- Free DNA, called linker DNA, links two nucleosomal core particles to each other, forming a nucleosome.





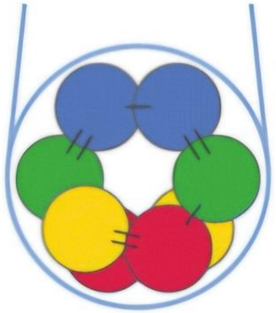
- Histones are positively charged facilitating DNA interaction and charge neutralization.

Therefore, histones bind to DNA through **electrostatic interactions** at any place.

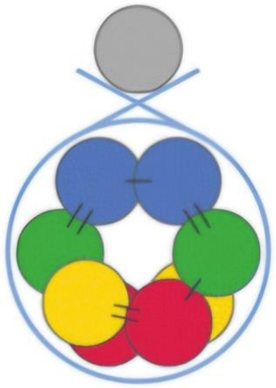


- **There are different structures :**

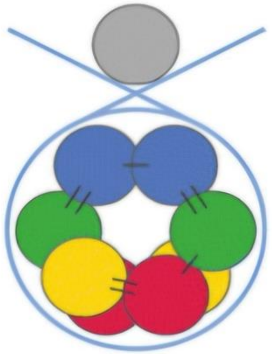
1. **Nucleosome core particle**
   Consists of the **histone octamer** (2 × H2A, 2 × H2B, 2 × H3, and 2 × H4) with **DNA wrapped** around it, does not include histone H1 or linker DNA.

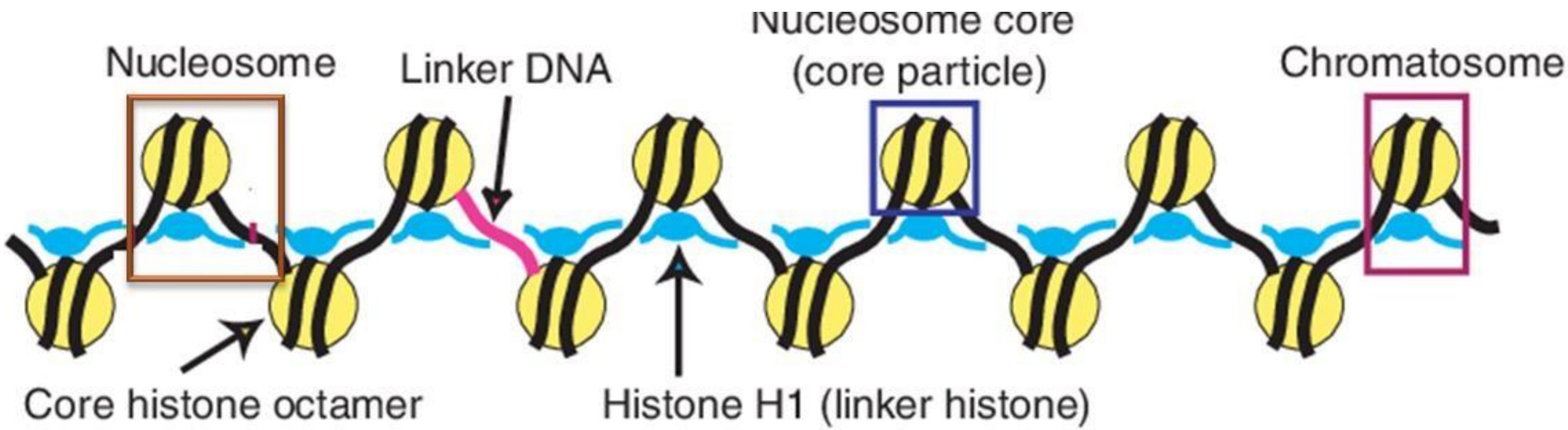


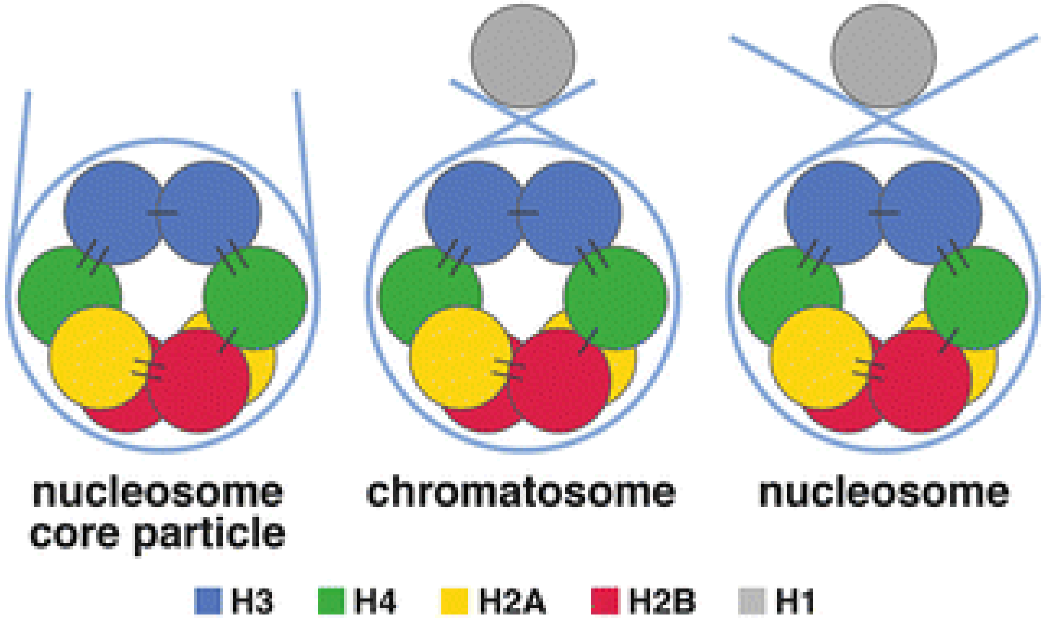
2. **Chromatosome**
   Consists of the **nucleosome core particle** plus **histone H1**,H1 stabilizes the DNA wrapped around the histone core.



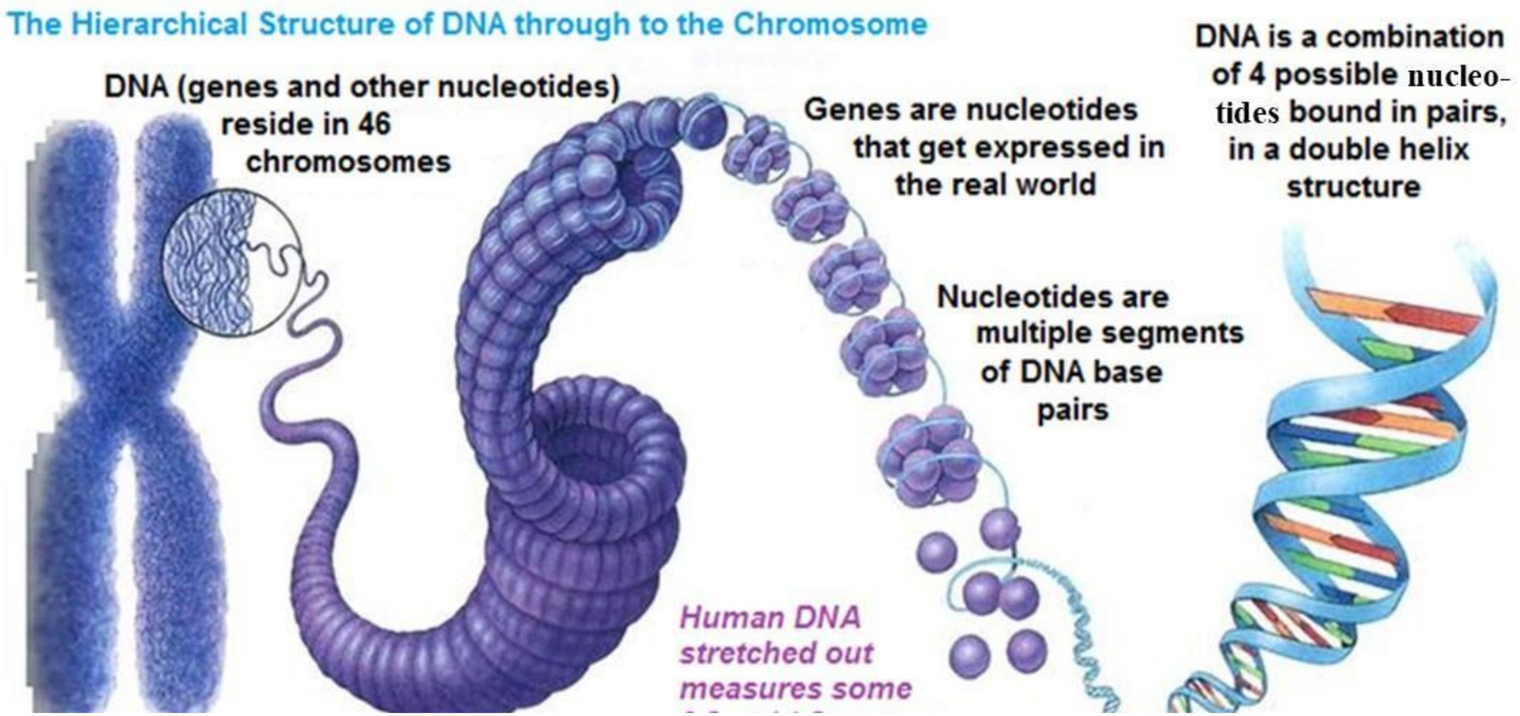
3. **Nucleosome**
   Consists of the **chromatosome** plus **linker DNA**. Linker DNA connects adjacent nucleosomes.

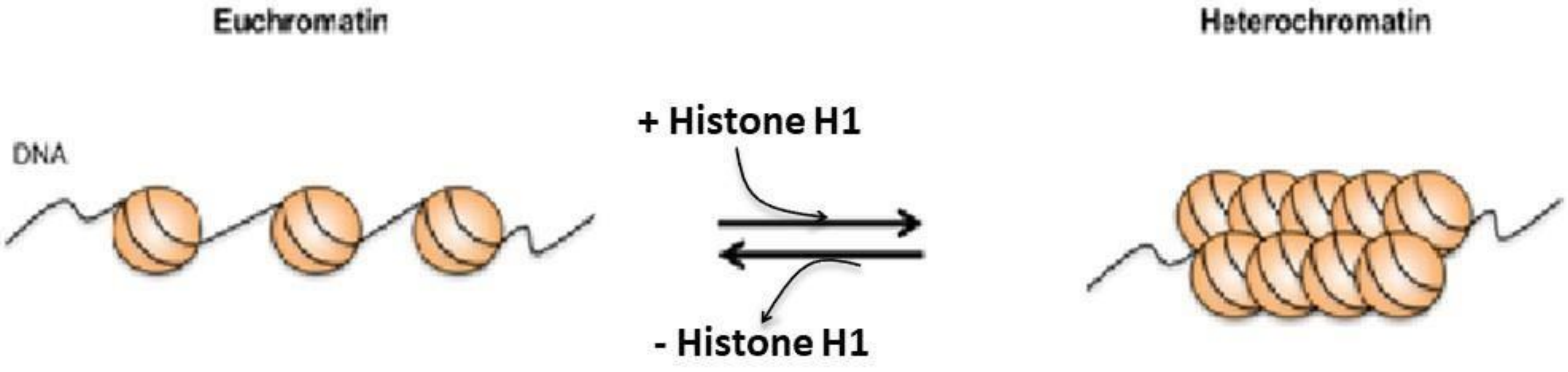



Nucleosome
Linker DNA
Nucleosome core
(core particle)
Chromatosome
Core histone octamer
Histone H1 (linker histone)


nucleosome
core particle
chromatosome
nucleosome
H3
H4
H2A
H2B
H1

Higher organization of DNA and histone H1

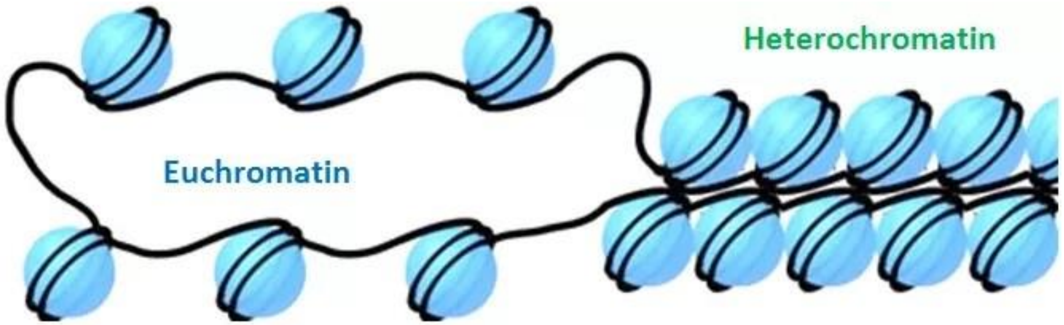




- **H1** plays an important role in determining the degree of DNA **compaction**. When histone H1 is **present**, it promotes tighter **packing** of chromatin, making the DNA highly **compact**. In contrast, when histone H1 is **absent**, chromatin remains more **relaxed** and **flexible**.

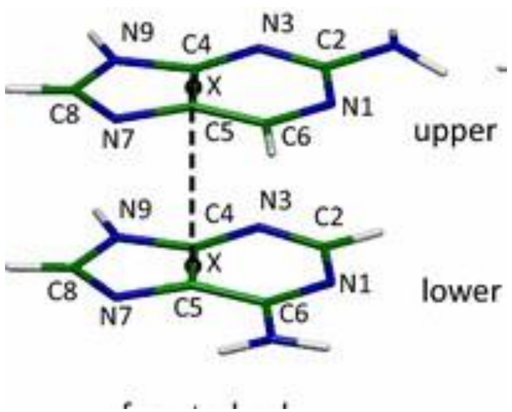
- Therefore, chromatin exists in **two** structural forms:
  Euchromatin: the less condensed **(relaxed)** form of chromatin, which contains little or no histone H1. Euchromatin is transcriptionally **active**, meaning that the genes in these regions are accessible and can be expressed.
  Heterochromatin: the highly condensed **(compact)** form of chromatin, which is associated with the presence of histone H1. Heterochromatin is generally transcriptionally **inactive**, as the tightly packed DNA is inaccessible to the transcription machinery.

- Although all cells in the body contain the same DNA and the same set of genes, not all genes are active in every cell type. Different cells express different subsets of genes according to their specialized functions,so the higher-order organization of chromatin differs among cell types, depending on which genes need to be active. **Histone H1** is one of the major factors .

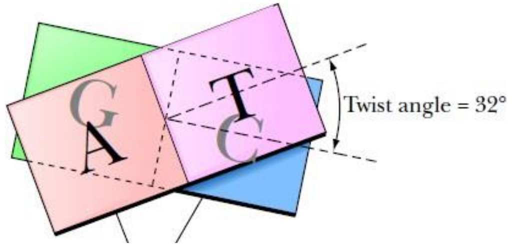


Additional image

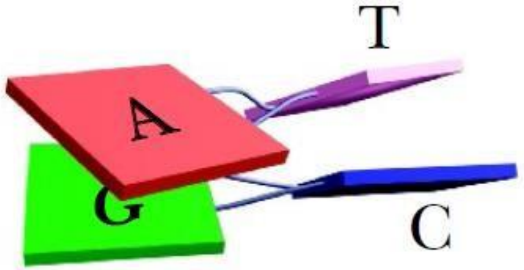
the resons of imperfect helix / DNA-stabilizing forces



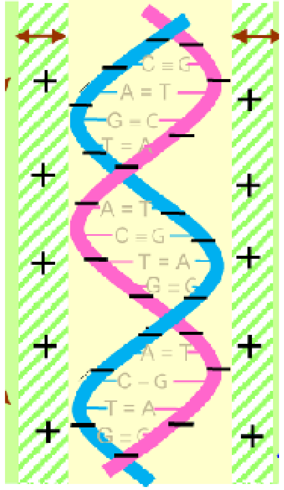
- Hydrogen bonds between complementary bases
- **Hydrophobic stacking:** The hydrophobic rings of the bases that lie on top of each other interact with each other via hydrophobic interactions and van der Waals interactions.
- Helical twists: Each base pair is rotated with respect to the preceding one for maximal base pairing.



- Propeller twists: The bases twist for optimal base stacking.



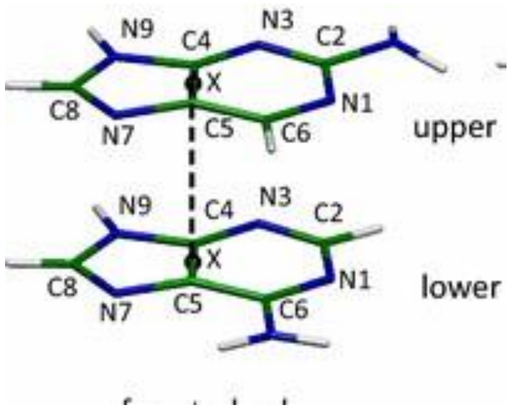
- DNA-binding proteins (e.g., histones)
- Ions such as Na^+ or Mg^{2+} (and histones) reduce the repulsion created by the negatively-charged phosphates of the DNA.



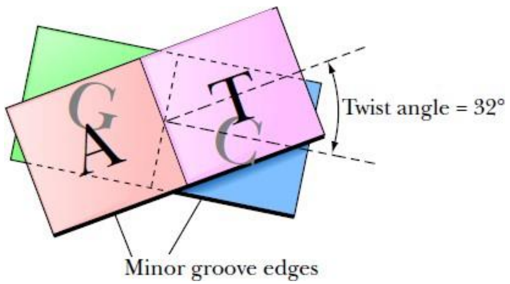
The non-covalent interactions within the DNA molecule and between its components contribute to its three-dimensional conformation, resulting in the formation of the characteristic major and minor grooves rather than a perfectly uniform helix.

- The double-helical structure of DNA is stabilized by multiple non-covalent interactions that collectively produce its characteristic three-dimensional structure. The first and most familiar interaction is hydrogen bonding between complementary nitrogenous bases. Adenine (A) forms two hydrogen bonds with thymine (T), whereas guanine (G) forms three hydrogen bonds with cytosine (C).

- In addition to hydrogen bonding, bases which lie on top of each other interact through hydrophobic stacking (stacking interactions). Since the nitrogenous bases are hydrophobic, they tend to stack on top of one another. These hydrophobic stacking interactions are one of the major forces that stabilize the DNA double helix.

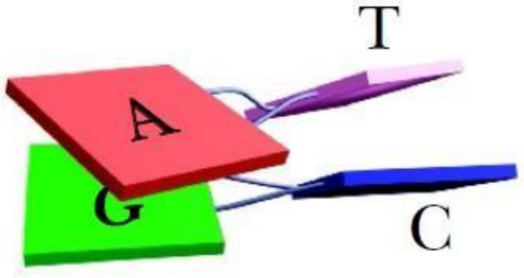


- However, the bases are not perfectly aligned directly above one another. Instead, each base pair is slightly rotated relative to the previous one, producing the characteristic helical twists of DNA. This rotation is responsible for the shape of the double helix , so the bases aren't stacked on top of each other perfectly.

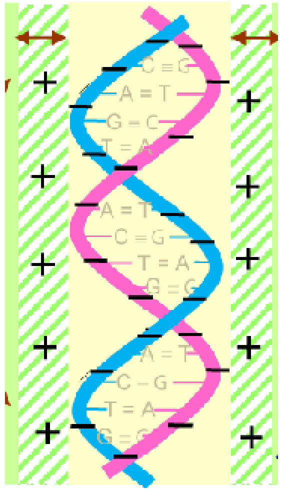


- Furthermore, the base pairs are not perfectly perpendicular to the sugar-phosphate backbone. Instead, they are slightly bent, a feature known as the propeller twist. This improves base stacking and optimizes the non-covalent interactions that stabilize the DNA molecule.

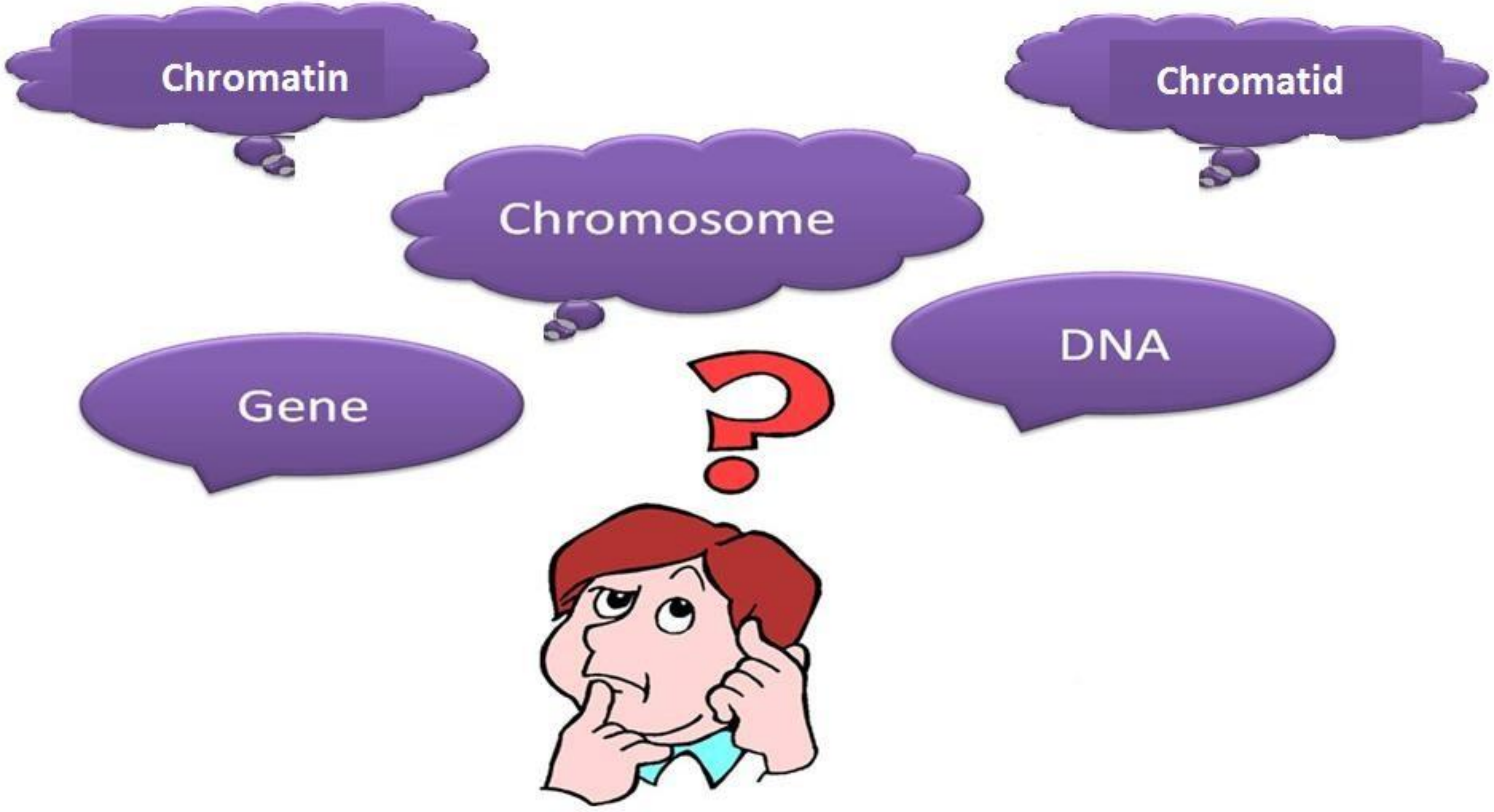
- In addition to these interactions, the structure of DNA is influenced by DNA-binding proteins, which help organize and stabilize DNA within the cell.



- Finally, positively charged ions, particularly sodium (Na^+) and magnesium (Mg^{2+}) ions, interact with the negatively charged phosphate groups of the DNA backbone. These ions neutralize the negative charges, reducing electrostatic repulsion and contributing to the stability of the DNA structure.

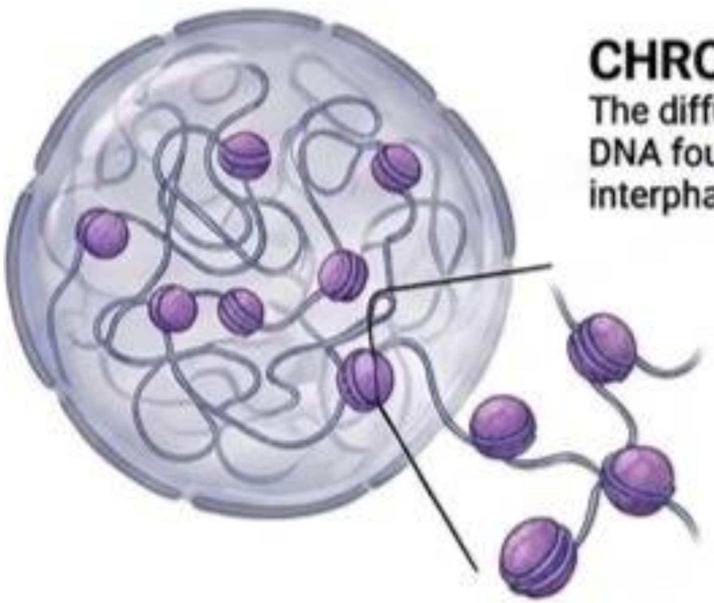


Terms to know



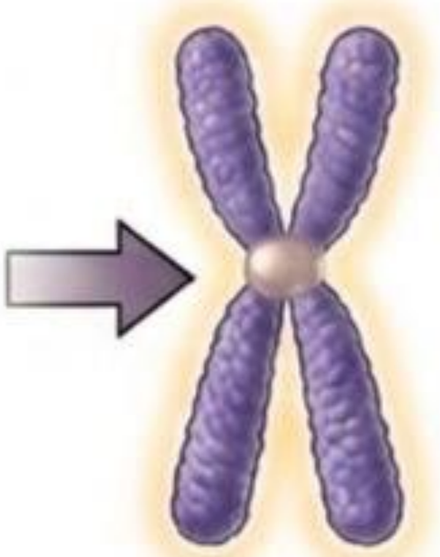
Terms to know

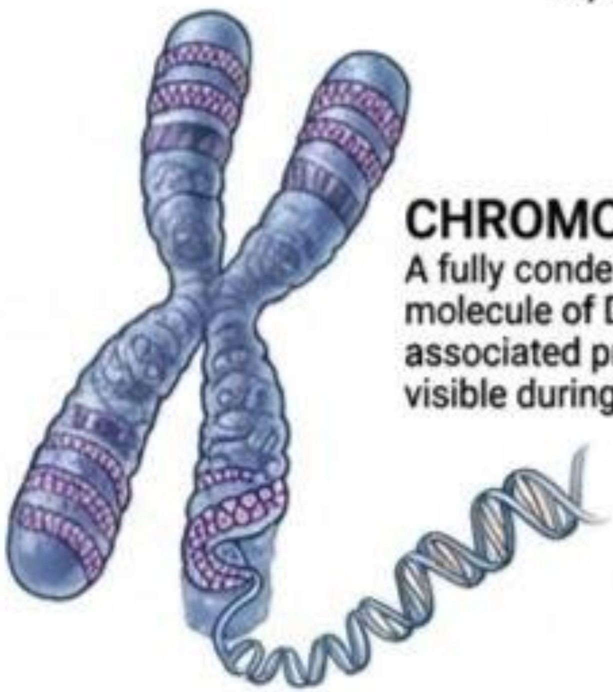
Additional image



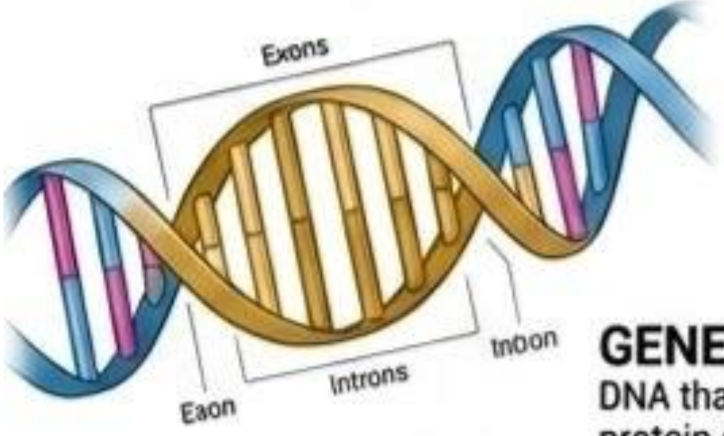
CHROMATIN:
The diffused, uncoiled form of DNA found in the nucleus during interphase.

CHROMATID:
One of the two identical copies of a chromosome formed during DNA replication.

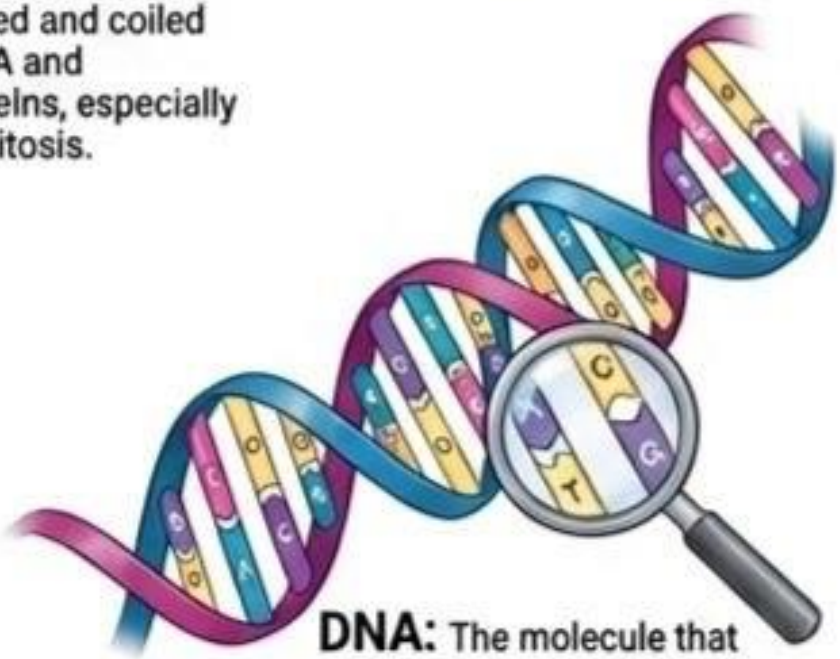




CHROMOSOME:
A fully condensed and coiled molecule of DNA and associated proteins, especially visible during mitosis.



GENE: A specific segment of DNA that codes for a specific protein or characteristic.

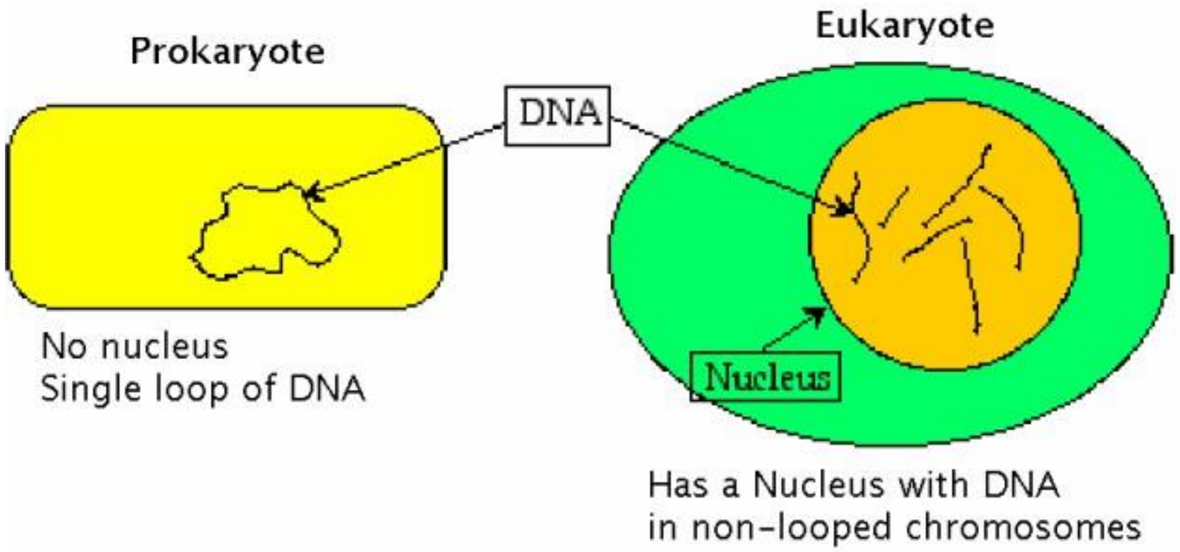


DNA: The molecule that stores genetic information in all living organisms.

The genome of prokaryotes versus eukaryotes

- Genome: the total genetic material of a living being (bacteria vs. human), a species (monkey vs. human) , an individual (me vs. you), or a cell (brain vs. liver), etc.
- Prokaryote: an organism that lacks a nucleus or other organelles.
- Eukaryote: an organism that has a true (clearly defined) nucleus.

Genome is the total collection of DNA in an organism or in a cell.



Bacterial chromosome and plasmids / Bacterial Genome

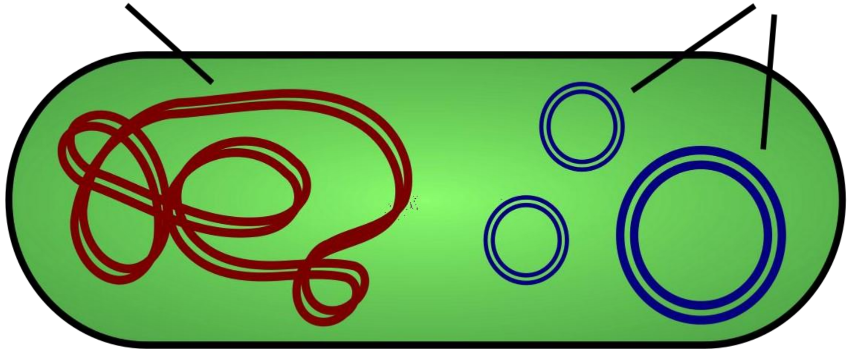
A Chromosome is a full DNA unit

But in humans, it is divided into 46 chromosomes (23 pairs). Each pair contains one chromosome inherited from the mother and one from the father. When all 46 chromosomes are considered together, they constitute the human genome.

The **genetic materials** of **bacteria** are of 2 types:

1. The chromosome: **One circular** chromosome of double-stranded DNA.

- The entire chromosome of the bacterium Escherichia coli is composed of a single circular double-stranded DNA molecule, contains >4 × 10^6 bp (length of 2 mm) carrying 4200 genes.



2. Plasmids: 1) Small, circular DNA molecules, 2) can replicate autonomously independent of the genomic chromosomes, 3) not infectious like viruses, 4) can carry genes, some of which confer resistance to antibiotics, and 5) exist as different types but one plasmid type per cell, 6) can exist as multiple copies, and 7) can transfer among bacterial cells.

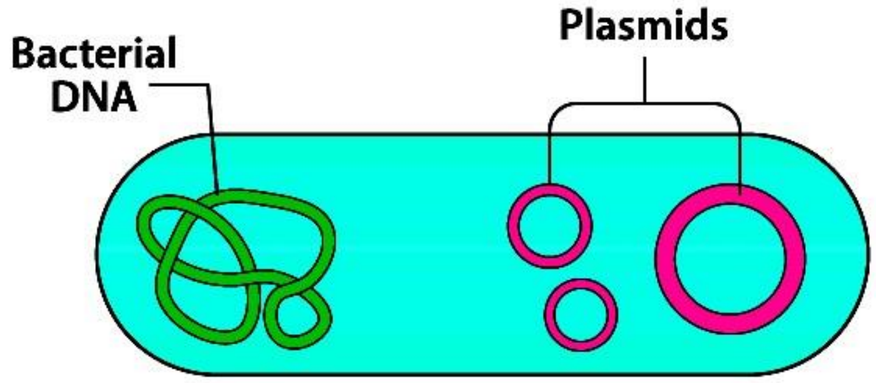
These are the different characteristics of plasmids.

- In addition to the chromosome, bacteria also have extra-chromosomal DNA, which is small, circular DNA called a plasmid. A bacterium may contain multiple copies of a plasmid.

- Plasmids are small, circular DNA molecules that carry genes encoding proteins that provide an **advantage** to the bacteria. For example, they may contain genes that confer **resistance** to certain antibiotics, or genes that allow bacteria to **communicate** with one another and establish connections. These plasmids are present in bacteria in addition to their main chromosome.

PLASMIDS

Additional image

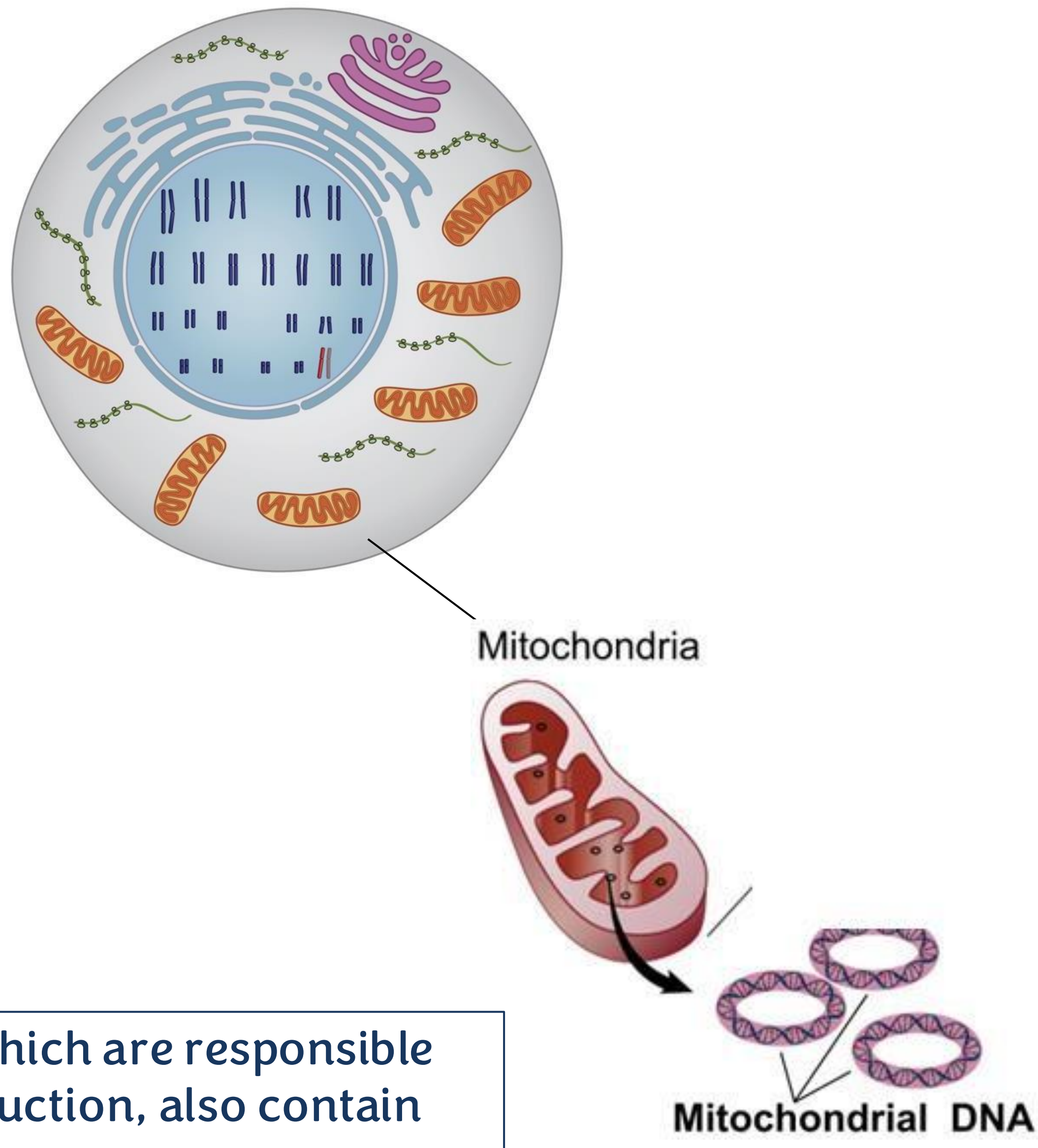


The human genome

- The genetic material of humans is of 2 types:
  - The nuclear genome: organized as linear chromosomes that consist of ~3 x 10^9 nucleotides in germline cells (sperm and egg), with a length of 1 meter per germline cell and that carry ~20000 genes.
  - The mitochondrial genome, which constitutes less than 0.1% of the total DNA in a cell (~16500 bp) and encodes 37 genes for proteins involved in the respiratory chain reaction.

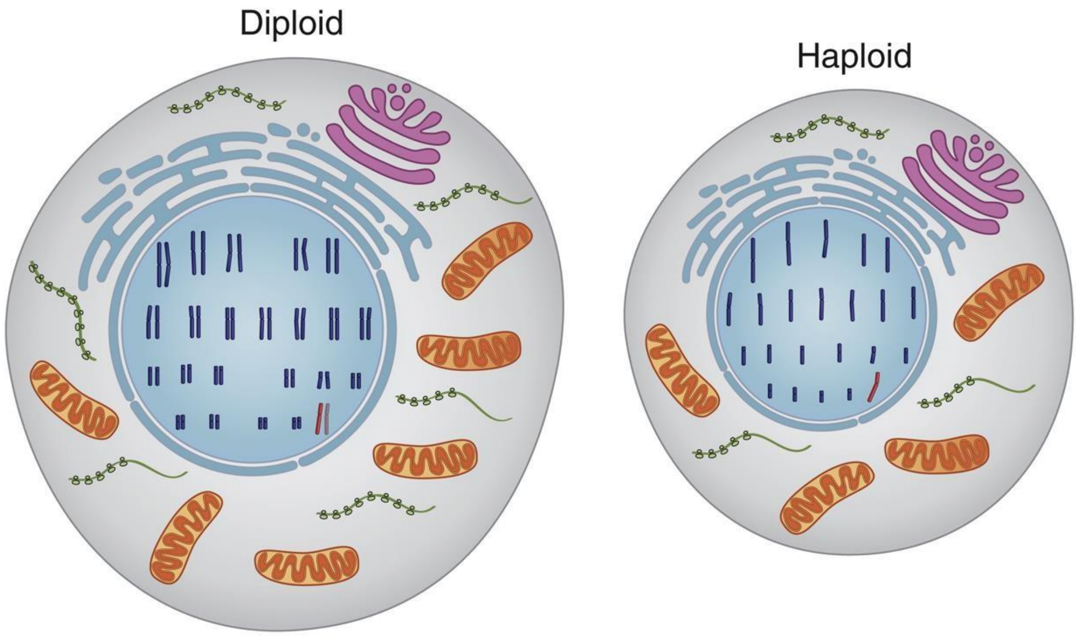
which is located in the nucleus

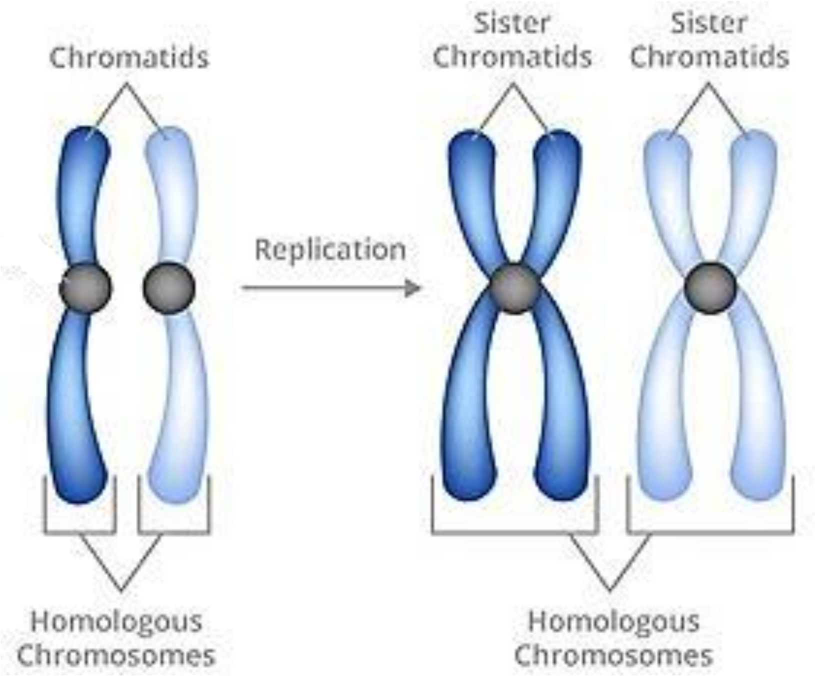
Mitochondria which are responsible for energy production, also contain their own DNA.



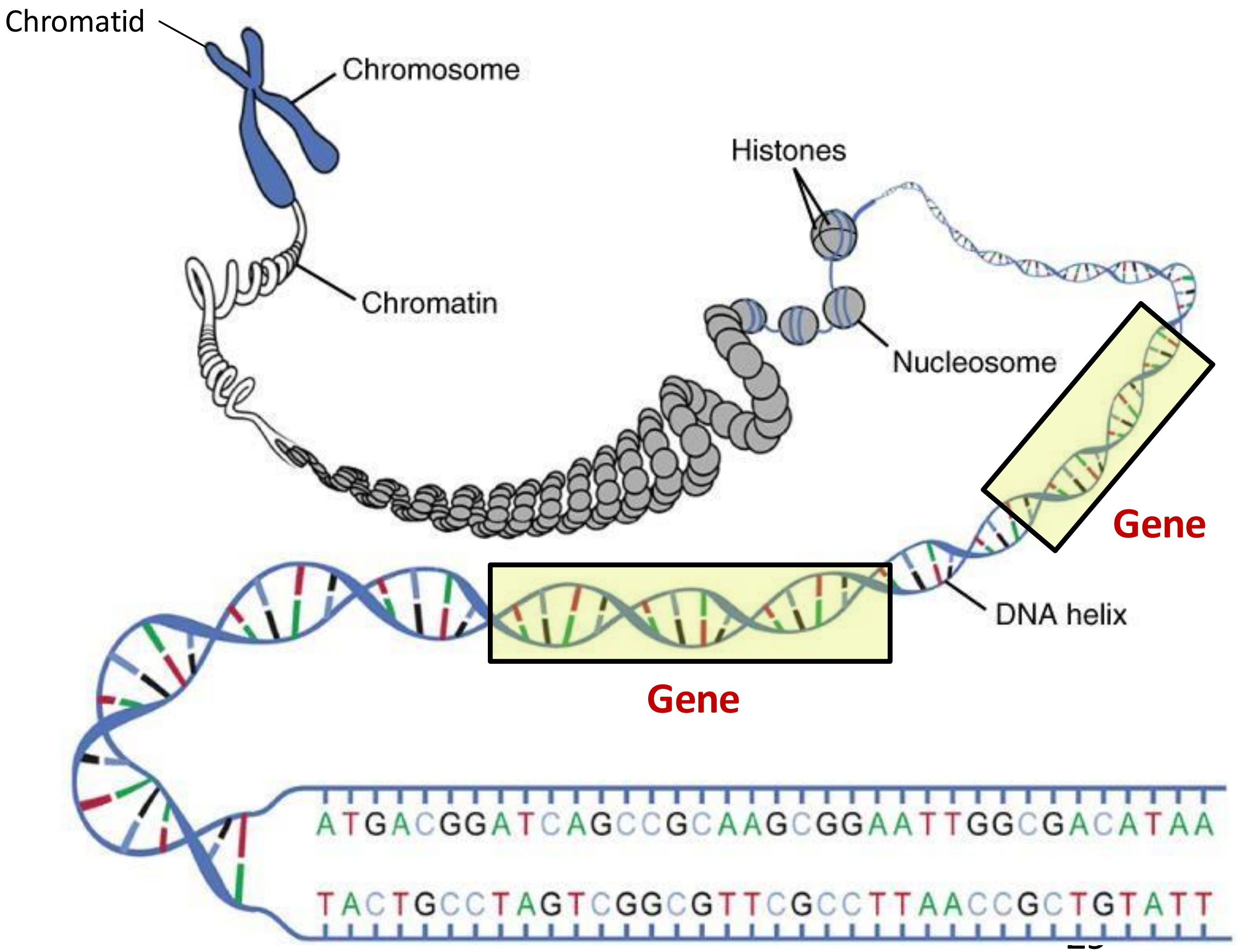
More eukaryotic terms

- Germline cells are **haploid** (1n) cells having **one copy** of every chromosome (either maternal or paternal).
- Somatic cells are **diploid** (2n) having **two copies** of every chromosome (maternal AND paternal) called homologous chromosomes.





- Each chromosome can be made of one chromatid or sister chromatids.

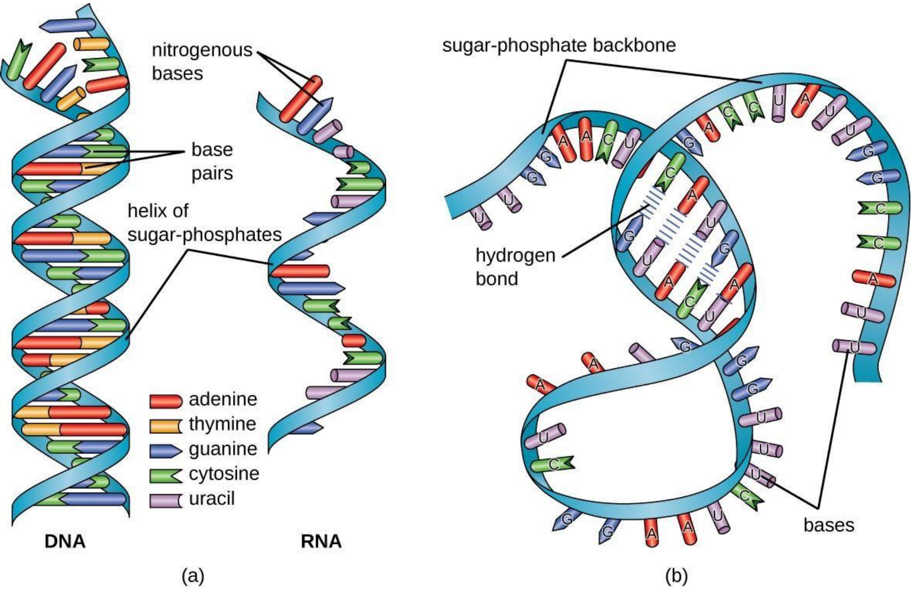


A gene is a specific region of DNA that undergoes transcription, or RNA synthesis.

RNA

These are the characteristics of RNA, as well as the differences between RNA and DNA

- It consists of long, unbranched chains of nucleotides joined by phosphodiester bonds between the 3'-OH of one pentose and the 5'-PO_4^- of the next.
- The pentose unit is a ribose (it is 2-deoxyribose in DNA).
- The pyrimidine bases include uracil and cytosine (thymine and cytosine in DNA).
- In general, RNA is single-stranded (DNA is double-stranded), but can form double-stranded regions. If complementary.



RNA does not have a precise structure, but it can fold on itself forming hydrogen bonds within the same molecule, if complementary.

Some RNAs can act as enzymes, known as ribozymes.

Types of RNA

For this table, you do not need to memorize all of it. All you need to know is that there are different types of RNA molecules in our cells, and they have different functions.

Symbol	Non-Coding RNAs	Functions
* tRNA	Transfer RNA	mRNA translation (structural)
* rRNA	Ribosomal RNA	mRNA translation (structural)
* miRNA	micro RNAs	Post-transcriptional transposon repression
piRNA	Piwi-interacting RNA	DNA methylation, transposon repression
* siRNA	Short interfering RNA	RNA interference
snoRNA	Small nucleolar RNAs	RNA modification, rRNA processing
PROMPT's	Promoter upstream transcripts	Associated with chromatin changes
tiRNAs	Transcripton initation RNAs	Epigenetic regulation
lincRNAs	Long intergenic ncRNA	Epigenetic regulators of transcription
rasiRNA	Repeat associated small interfering RNA	Involved in the RNA interference (RNAi) pathway
eRNA	Enhancer-like ncRNA	Transcriptional gene activation
T-UCRs	Transcribed ultraconserved regions	Regulation of miRNA and mRNA levels
NATs	Natural antisense transcripts	mRNA stability
PALRs	Promoter-associated long RNAs	Chromatin changes
tasiRNA	Trans-acting siRNA	Represses gene expression
* lncRNA	Long noncoding RNA	Regulation of gene transcription

Test yourself:)

<u>Quiz</u>

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

Prof . Mamoun Ahram live lecture (nucleic acids)

Extra References for the Reader to Use:

Marks' Basic Medical Biochemistry

كان النَّبيُّ ﷺ وقت الشِّدة يقول

إني عبد الله ولن يُضيعني .