Chromosome structure and organization

M.Sc. Microbiology, 2nd Semester
MCB 202 : Genetics and Gene regulation
Gr. A: Fundamental Genetics

by
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The total length of DNA in the haploid chromosome in non-dividing cells of mammals corresponds to about 1 meter.

It needs to squeeze into 15µm nucleus reducing its length as much as 10,000 fold

How does it do this?

DNA in prokaryotic and eukaryotic cells are organized into chromosomes.

A chromosome is a deoxyribonucleic acid (DNA) molecule with part or all of the genetic material (genome) of an organism associated with different proteins.

Why is chromosome organization important?

- *Chromosomes are compact forms of DNA—allows DNA to fit inside a cell*
- *Chromosomes stabilize DNA and protect it from damage*
- *Allows for equal partitioning of DNA into daughter cells during cell division*
- *Organizes the accessibility of other proteins to DNA*
- *Critical for the regulation of DNA replication and transcription*

Prokaryotic and Eukaryotic cells have different mechanisms for compacting DNA

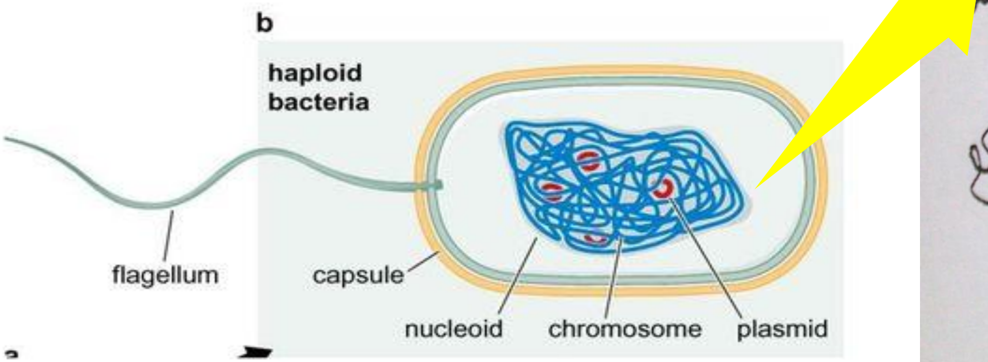
Prokaryotic chromosome

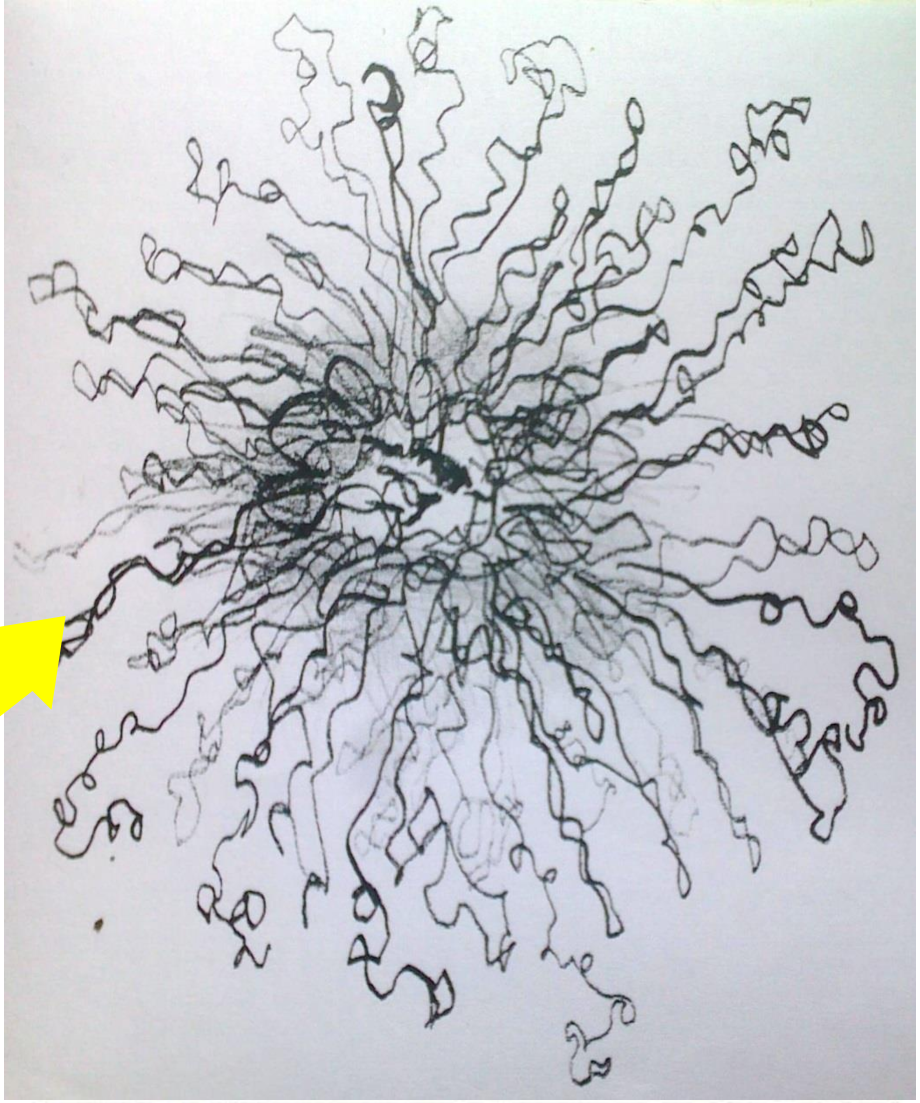
- Most prokaryotic chromosomes contain a circular DNA molecule – there are no free ends to the DNA. Free ends would otherwise create significant challenges to cells with respect to DNA replication and stability.
- The DNA of a bacterial cell is a circular double-stranded molecule often referred to as the **bacterial chromosome**.
- The circular DNA is packaged into a region of the cell called the **nucleoid** where it is organized into 50 or so loops or domains that are bound to a central protein scaffold, attached to the cell membrane.
- The DNA is negatively supercoiled, that is, it is twisted upon itself.
- It is associated with several DNA-binding proteins, the most common of which are proteins HU, HLP-1 and H-NS. These are histone-like proteins.

Prokaryotic Chromosome Organization

Prokaryotic Chromosomes:

- Prokaryotic circular DNA molecules are much larger than the bacteria cell (x1500)
- Bacterial DNA is compacted and organized into a nucleoid. A nucleoid contains DNA, proteins and RNA



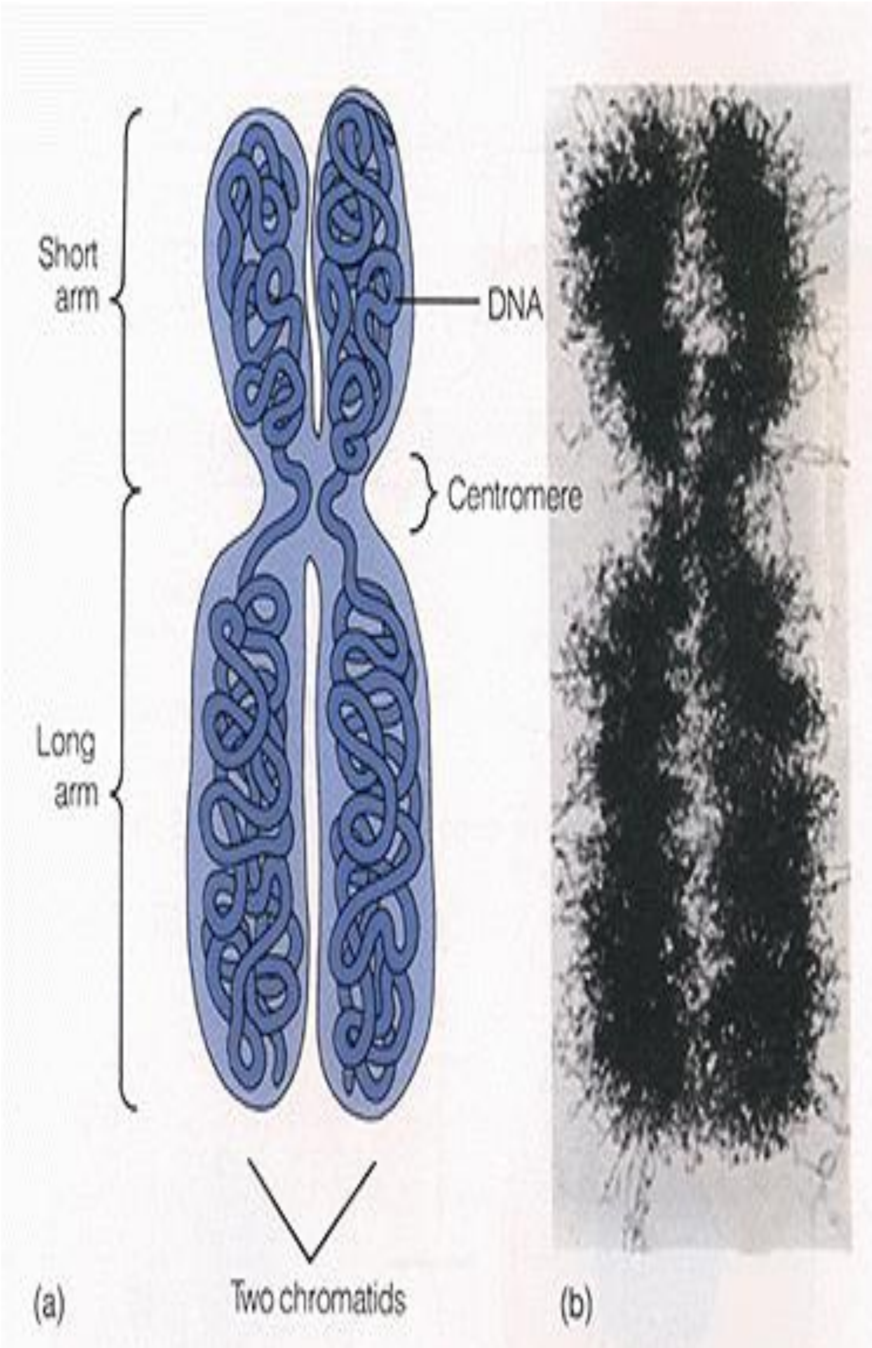


- Prokaryote species generally have one copy of each major chromosome, but many cells can easily survive with multiple copies.

Eukaryotic chromosome

- Each eukaryotic chromosome is made up of DNA tightly coiled many times around proteins called **histones** that support its structure.
- Chromosomes are not visible in the cell's nucleus—not even under a microscope—when the cell is not dividing.
- However, the DNA that makes up chromosomes becomes more tightly packed during cell division and is then visible under a microscope.
- Most of what researchers know about chromosomes was learned by observing chromosomes during cell division.

- In eukaryotes, nuclear chromosomes are packaged by proteins into a condensed structure called chromatin.
- This allows the very long DNA molecules to fit into the cell nucleus.
- The structure of chromosomes and chromatin varies through the cell cycle.
- Chromosomes must be replicated, divided, and passed successfully to their daughter cells so as to ensure the genetic diversity and survival of their progeny.



Estimated number of base pairs on each human chromosome

Chromosome	Total base pairs	% of bases
1	247,199,719	8.0
2	242,751,149	7.9
3	199,446,827	6.5
4	191,263,063	6.2
5	180,837,866	5.9
6	170,896,993	5.5
7	158,821,424	5.2
8	146,274,826	4.7
9	140,442,298	4.6
10	135,374,737	4.4
11	134,452,384	4.4
12	132,289,534	4.3
13	114,127,980	3.7
14	106,360,585	3.5
15	100,338,915	3.3
16	88,822,254	2.9
17	78,654,742	2.6
18	76,117,153	2.5
19	63,806,651	2.1
20	62,435,965	2.0
21	46,944,323	1.5
22	49,528,953	1.6
X	154,913,754	5.0
Y	57,741,652	1.9
Total	3,079,843,747	100.0

Chromosome number of some species

Sr. no	Scientific name	Common name	Chromosome number	
			Somatic	Gametic
1	*Homo sapiens*	Human	46	23
2	*Oryza sativa*	Rice	24	12
3	*Rattus norvegicus*	rat	42	21
4	*Pisum sativum*	Pea	14	7
5	*Daucus carota*	Carrot	20	10
6	*Allium cepa*	Onion	16	8
7	*Zea mays*	Maize	20	10
8	*Apis mellifera*	Honey bee	32	16
9	*Musca domestica*	House fly	12	6
10	*Felis domesticum*	Cat	38	19
11	*Drosophila melanogaster*	Fruit fly	8	4
12	*Neurospora Crassa*	Bread mold	14	7

Euchromatin and Heterochromatin

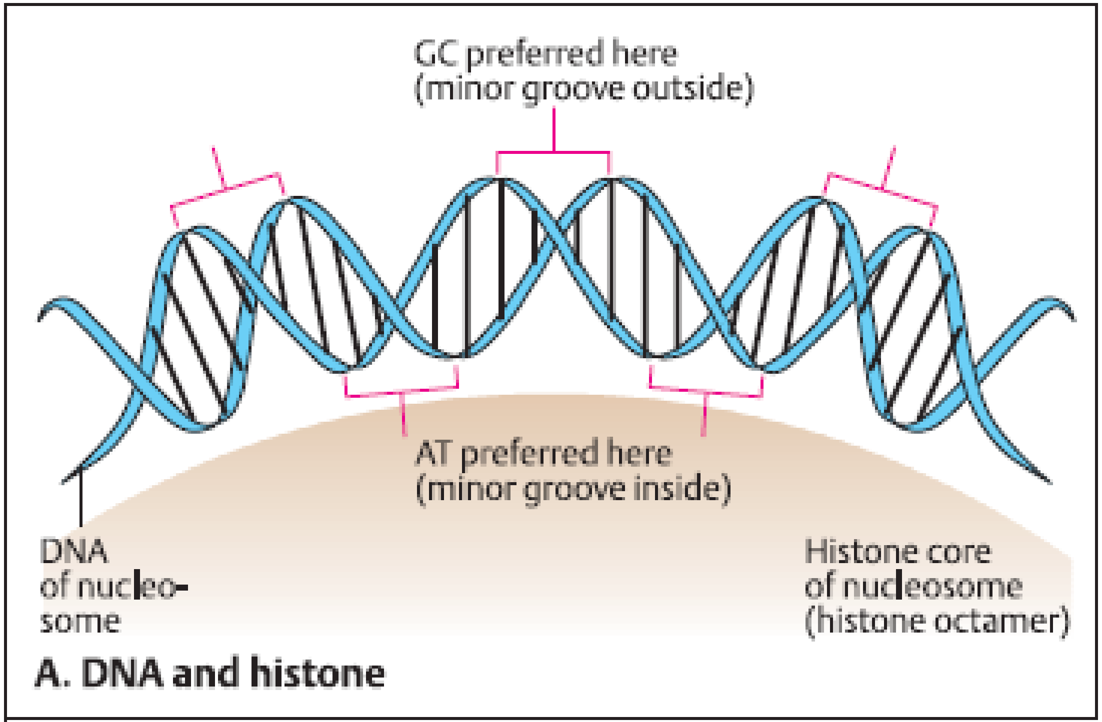
- *During interphase (the period of the cell cycle where the cell is not dividing), two types of chromatin can be distinguished:*
- **Euchromatin,** which consists of DNA that is active, e.g., being expressed as protein.
- **Heterochromatin,** which consists of mostly inactive DNA. It seems to serve structural purposes during the chromosomal stages. Heterochromatin can be further distinguished into two types:
  - Constitutive heterochromatin, which is never expressed. It is located around the centromere and usually contains repetitive sequences.
  - Facultative heterochromatin, which is sometimes expressed.

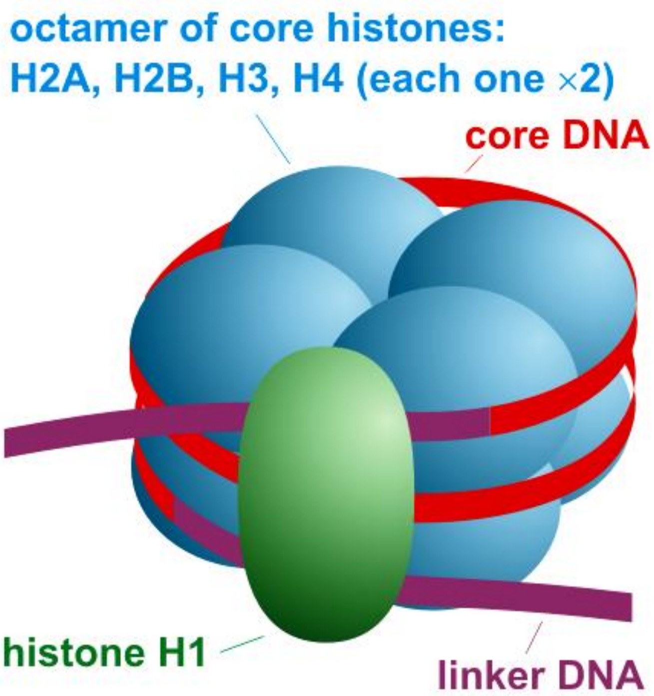
- In 1928 Emil Heitz observed that certain parts of the chromosomes of a moss (*Pellia epiphylla*) remain thickened and deeply stained during interphase, as chromosomes otherwise do only during mitosis.
- He named these structures heterochromatin, as opposed to euchromatin, which becomes invisible during late telophase and subsequent interphase.
- Functionally, heterochromatin is defined as a region in which few or no active genes lie and in which repetitive DNA sequences occur. When active genes become located close to the heterochromatin, they usually become inactivated.

- In eukaryotes the genetic materials are found packaged within a nuclear membrane, unlike the case in prokaryotes.
- This membrane consists of a DNA double helix bound to an octamer of core histones (2 dimers of H2A, H2B, H3 and H4).
- Together, the DNA bound around this histone core forms what is known as the nucleosome.
- About 147 base pairs of DNA coil around 1 octamer, and ~20 base pairs are sequestered by the addition of the linker histone (H1), and various length of "linker" DNA (~0-100 bp) separate the nucleosomes.

- Packaging of DNA is facilitated by the electrostatic charge distribution: phosphate groups cause DNA to have a negative charge, while the histones are positively charged.
- Most eukaryotic cells contain histones. Histones are positively charged molecules as they contain lysine and arginine in larger quantities and DNA is negatively charged. So they make a strong ionic bond in between them to form nucleosome.

Nucleosome





Histone Type	Molecular Weight	Number of Amino Acids	Approx. Content of Basic Amino Acids
H1	17,000–28,000	200–265	27% lysine, 2% arginine
H2A	13,900	129–155	11% lysine, 9% arginine
H2B	13,800	121–148	16% lysine, 6% arginine
H3	15,300	135	10% lysine, 15% arginine
H4	11,300	102	11% lysine, 4% arginine

Types of Histones

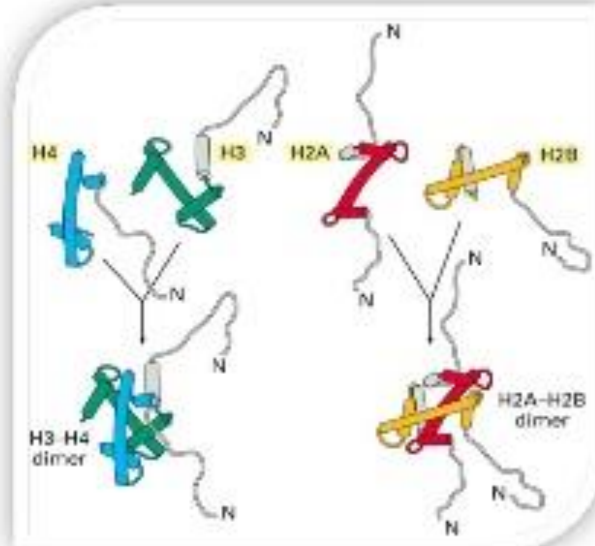
❑ Histone proteins are of two types:

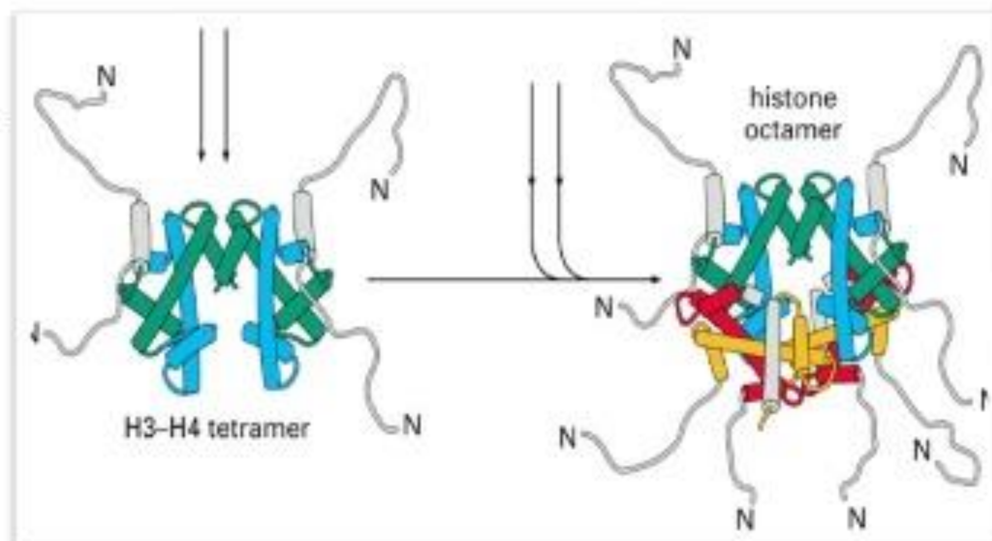
- **Core Histones -** H2A, H2B, H3, and H4
- **Linker Histones -** H1

➢ The eight histones in the core are arranged into a **(H3)2(H4)2 tetramer** and a pair of **H2A–H2B dimers.**

➢ The tetramer and dimers come together to form a left-handed superhelical ramp around which the DNA wraps.

➢ Hydrogen bonds between the DNA backbone and the amide group on the main chain of histone proteins





Histone Modification

- **N-terminal tails** of histones are the most accessible regions of these peptide as they protrude from the nucleosome and possess no specific structure.

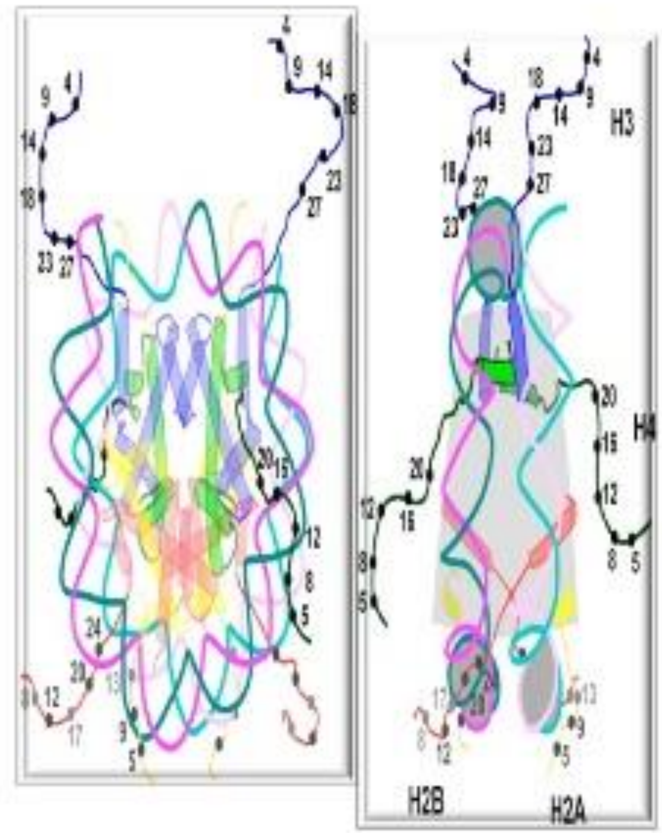
- The major function of PTMs is to either **create sites for the recruitment of specific factors or modify existing sites so as to abolish previous interactions.**

- Chromatin must be first made relaxed to allow access of cellular machineries to chromatin DNA.

- The amino-terminal portion of the core histone proteins contains a flexible and highly basic tail region, which is conserved across various species and is subject to various **PTM.**

- Chromatin can be highly packed or loosely packed, and correlated to the gene expression levels.

- Post-translational modification (PTM) of histones is a **crucial step in epigenetic regulation of a gene.**

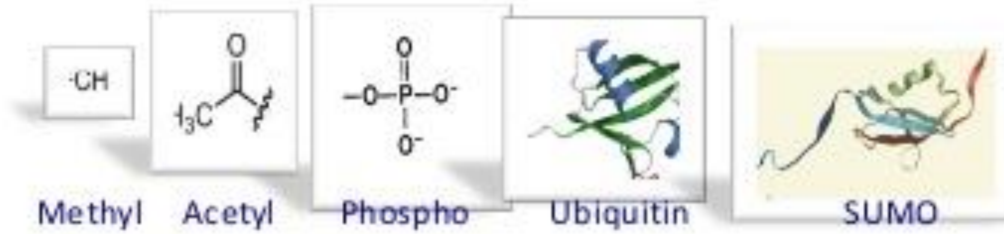


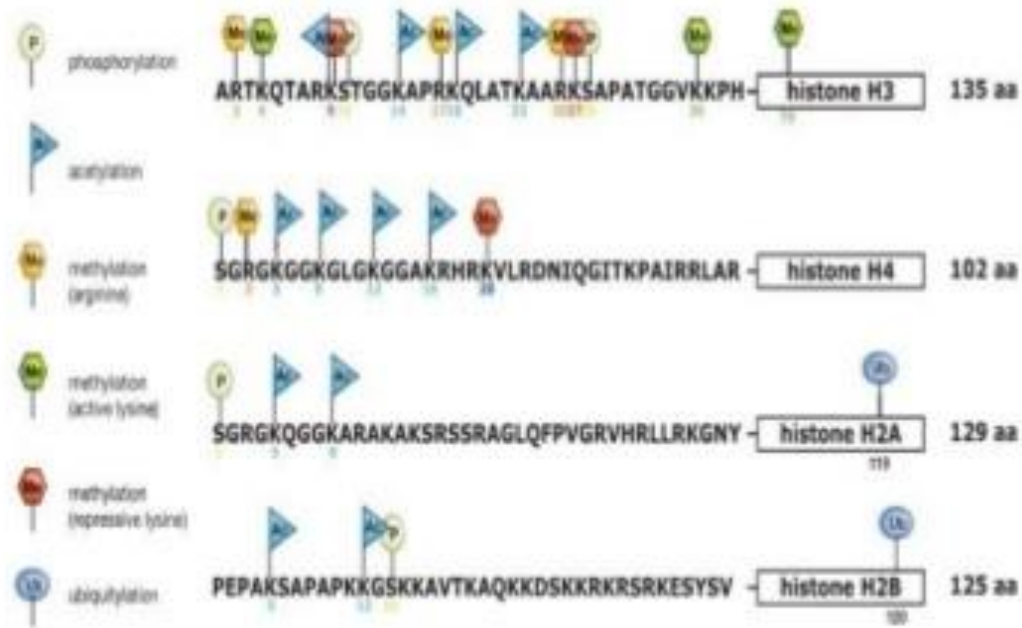
N-termini of the core histones

Types of Histone Modification

❑ N-terminal tails of all histones are particularly of interest since they protrude out of the compact structure. These N-terminal tails are often subjected to a variety of post-translational modifications such as,

1. Acetylation
2. Methylation
3. Phosphorylation
4. Ubiquitination
5. Sumoylation
6. ADP ribosylation

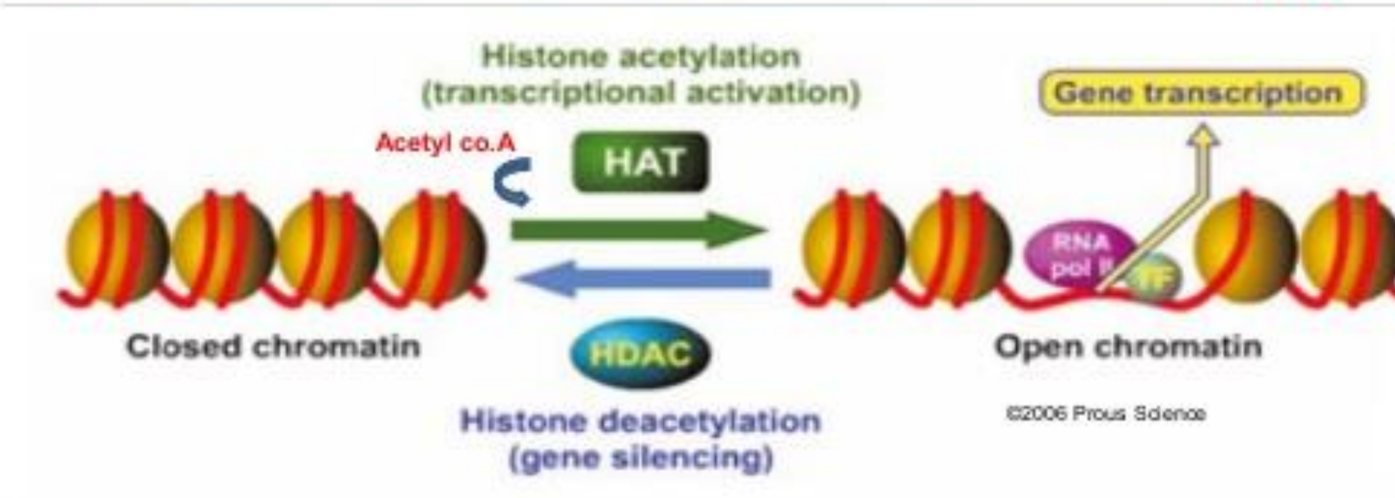




➢ It has been proposed that these modifications result in a **'code'** which can be read by proteins involved in gene expression and other DNA translations

Role in Gene regulation

	Acetylation	**Deacetylation**
	Histone acetylation	**Histone deacetylation**
Enzyme	Histone acetyl transferases **(HATs)**	Histone deacetylases **(HDACs)**
Group	**Adds acetyl groups** to histone tails	**Removes acetyl groups** from histone tails
Interacion with DNA	Reduces positive charge and **weakens** interaction of histones with DNA	**Increases** interaction of DNA and histones
	Allows transcription	**Repress transcription**



Covalent Modification of core histone tails
Acetylation of lysines
Mythylation of lysines
Phosphorylation of serines

Histone acetyl transferase (HAT)
Histone deacetylase (HDAC)

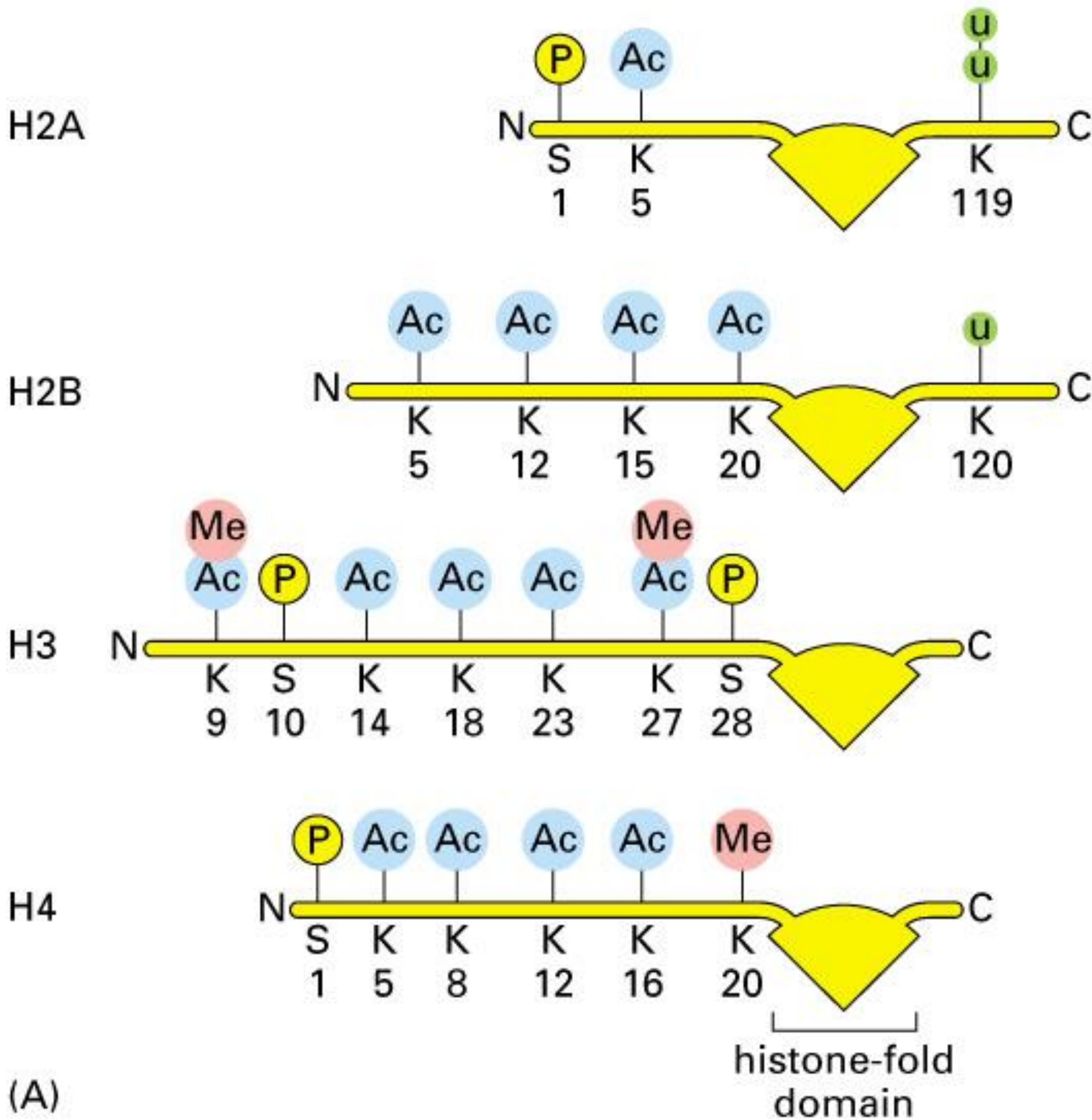
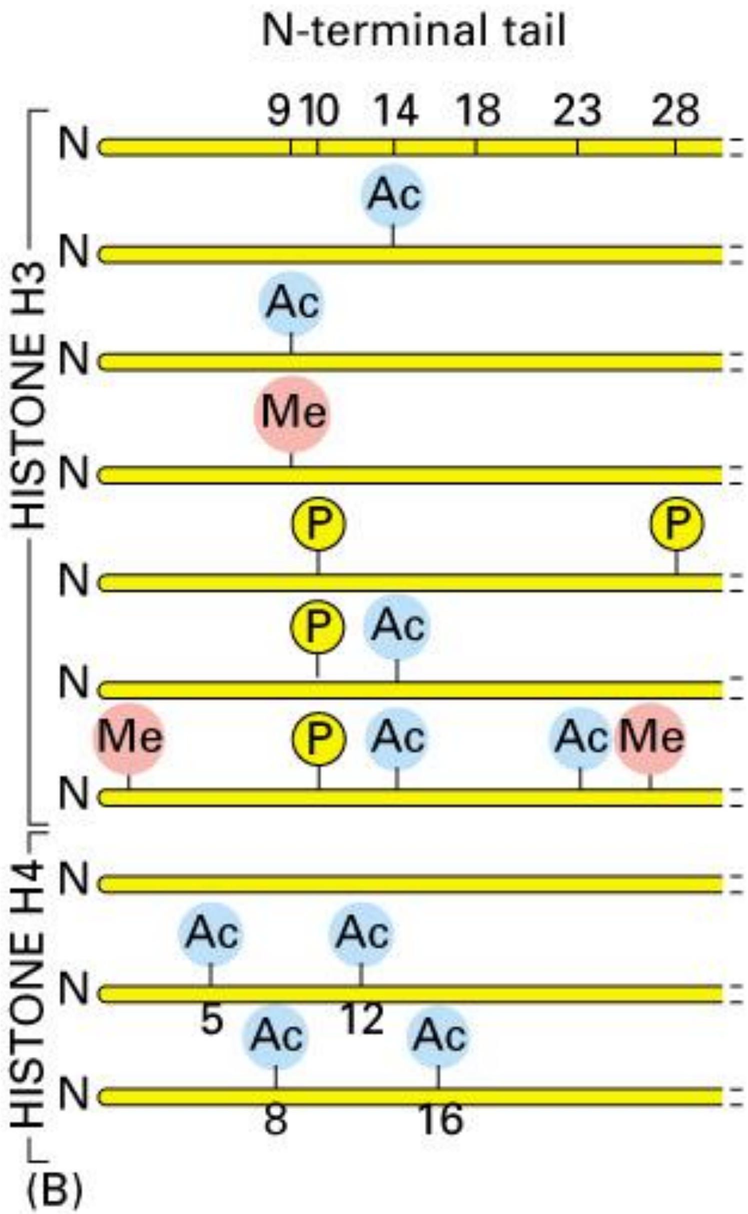


Figure 4–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.



modification state	"meaning"
unmodified	gene silencing?
acetylated	gene expression
acetylated	histone deposition
methylated	gene silencing/ heterochromatin
phosphorylated	mitosis/meiosis
phosphorylated/ acetylated	gene expression
higher-order combinations	?
unmodified	gene silencing?
acetylated	histone deposition
acetylated	gene expression

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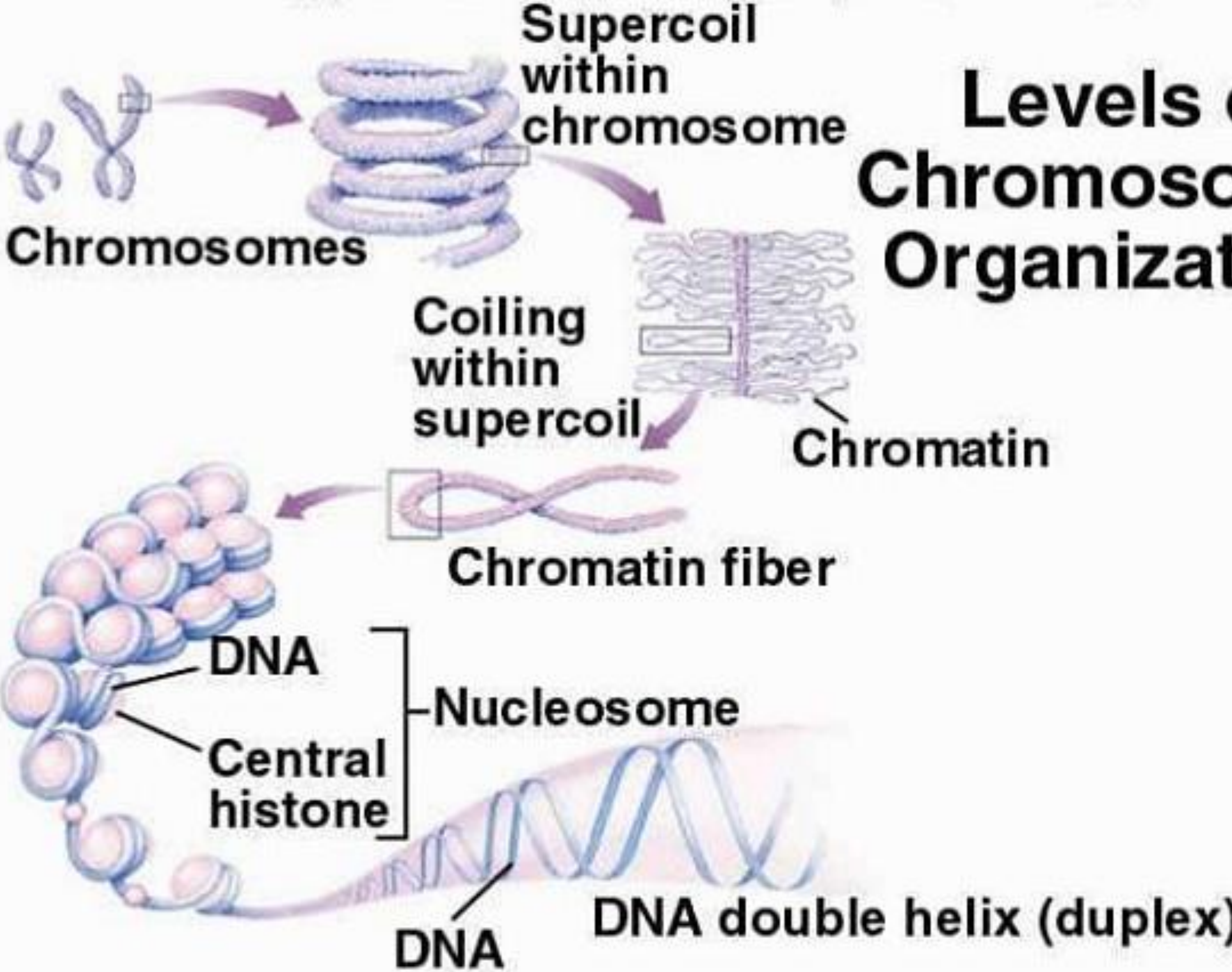
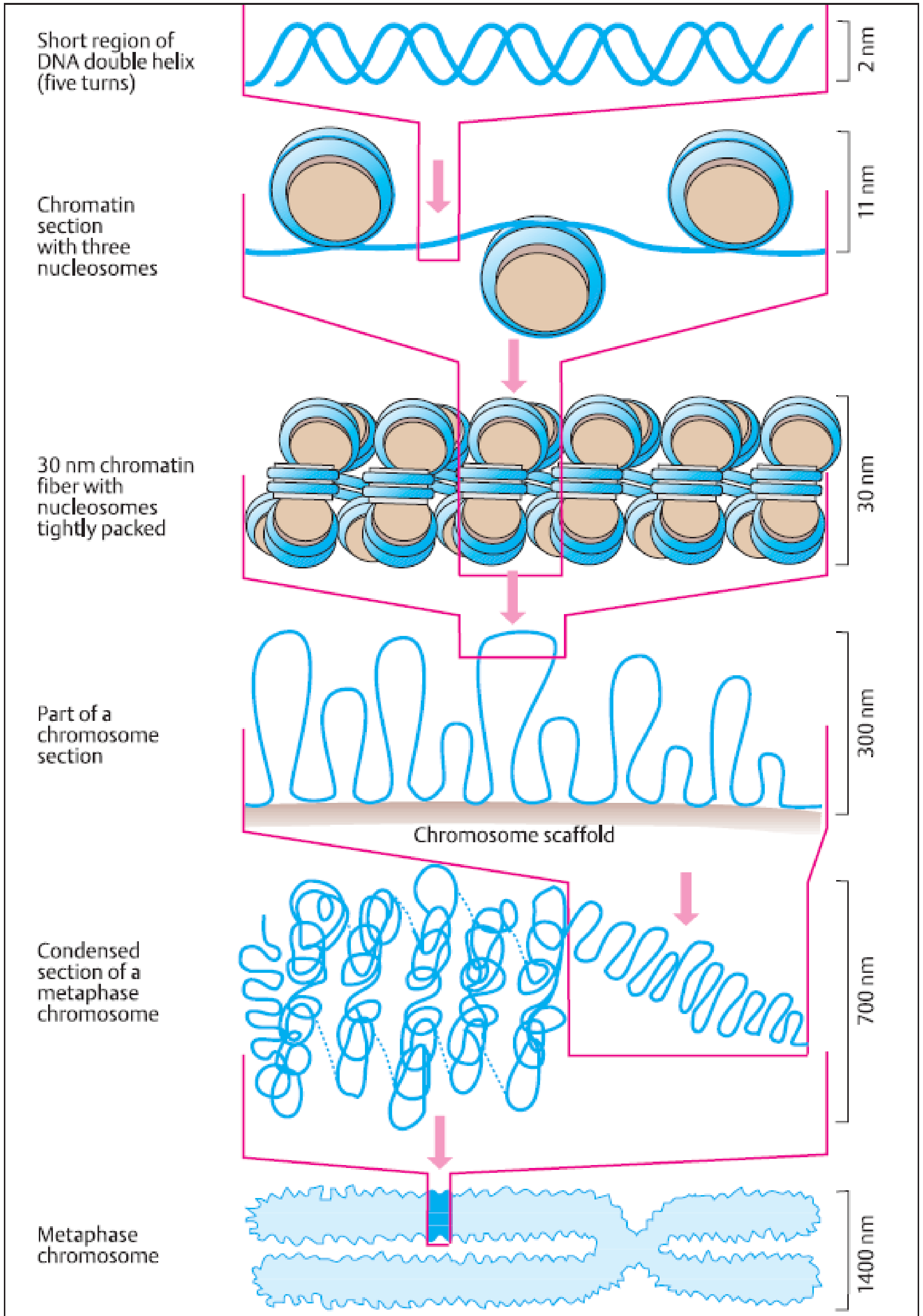
Levels of Chromosomal Organization





A. DNA in a metaphase chromosome

- Chromosomal DNA is folded and packed in an efficient manner. Schematically, several levels of packing of DNA in a metaphase chromosome can be differentiated.
- The figure shows (at the top) a segment of DNA double helix from part of a chromatin segment.
- The chromatin segment consists of several nucleosomes connected by so-called linker stretches of DNA.
- The folding of a chromatin segment produces a chromatin fiber of 30 nm diameter.
- It consists of a series of tightly packed nucleosomes. These in turn form a part of a chromosome segment of about 300 nm diameter in the extended stage.
- A further packing level is represented by a thickened segment of a metaphase chromosome. This is called a condensed chromosomal segment.
- This segment corresponds to only a small part of one chromatid of a metaphase chromosome.

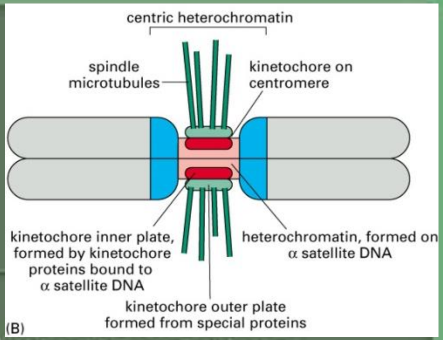
Chromosome structure

- **Structurally chromosomes consists of seven parts**

1. Centromere
2. Chromatid
3. Secondary constriction and satellite
4. Telomere
5. Chromomere
6. Chromonema
7. Matrix

Chromatid

- Each metaphase chromosome appears to be longitudinally divided into two identical parts each of which is called **chromatid**.
- Both the chromatids of a chromosome appear to be joined together at a point known as **centromere**.
- The two chromatids of chromosome separate from each other during mitotic anaphase (and during anaphase II of meiosis) and move towards opposite poles.
- Since the two chromatids making up a chromosome are produced through replication of a single chromatid during synthesis (S) phase of interphase, they are referred to as **sister chromatids**.
- In contrast, the chromatids of homologous chromosomes are known as **non-sister chromatids**.



Centromere (Primary constriction)

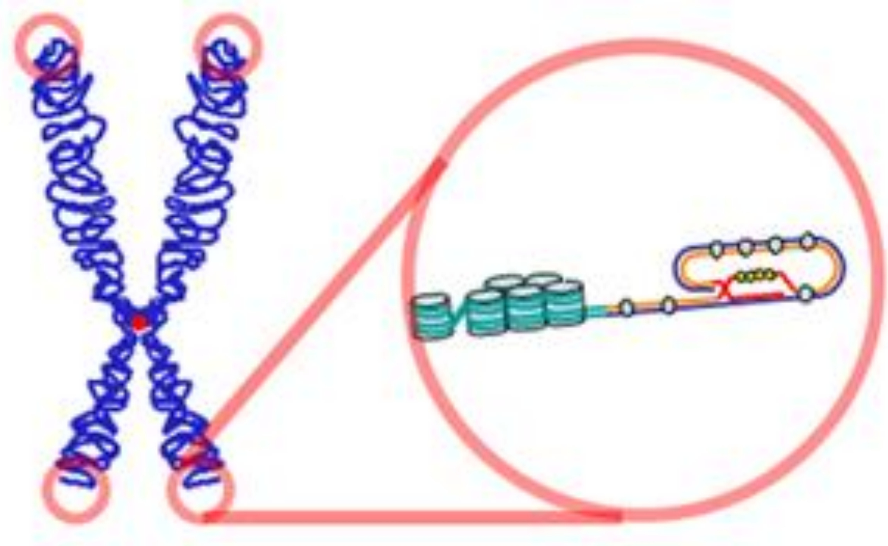
- Centromere is the landmark for identification of chromosome.
- Each chromosome has a constriction point called the **centromere** (Synonym: **Kinetochore**), which divides the chromosome into two sections or arms.
- The **short arm** of the chromosome is labeled the **"p"** arm. The **long arm** of the chromosome is labeled the **"q"** arm.

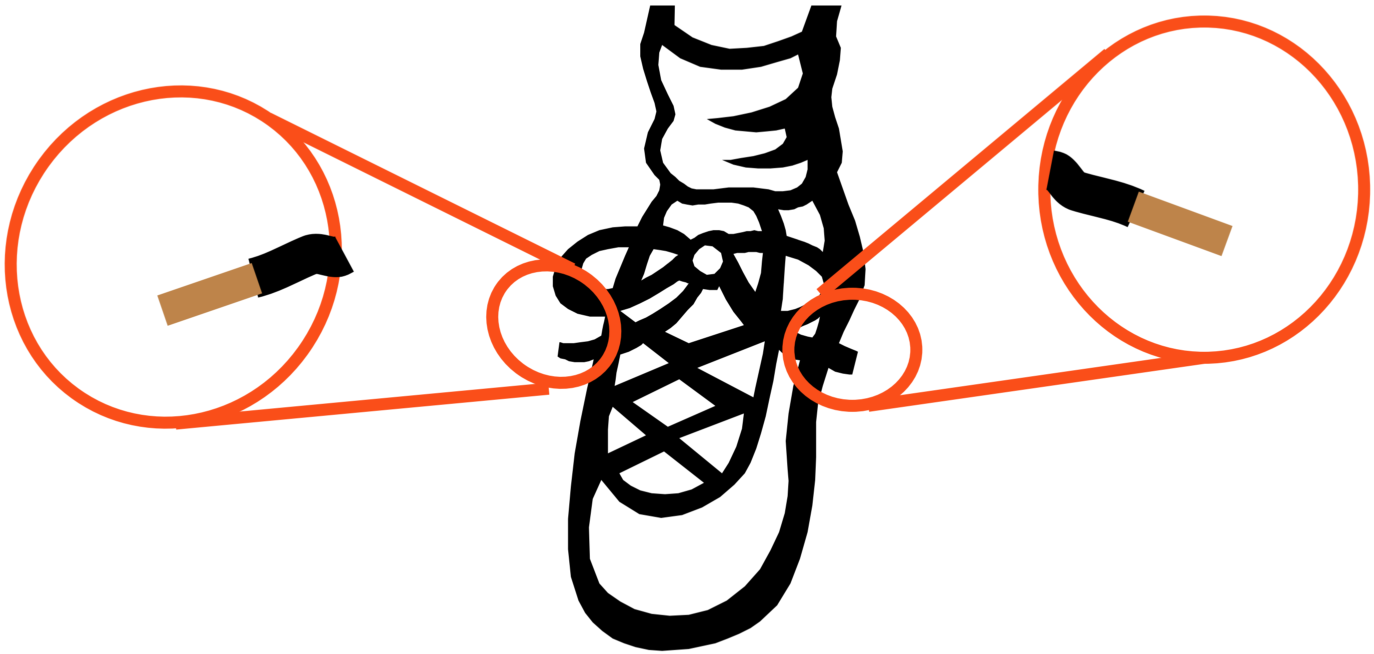
Telomere

- The two ends of a chromosome are known as telomeres, they play critical roles in chromosome replication and maintenance of chromosomal length.
- The telomeres are highly stable and telomeres of different chromosomes do not fuse.
- The telomeric region of chromosome is made up of repeatative sequence of **T** and **G** bases

Special Structure at the Ends of a Chromosome: the Telomere

- Unlike the circular chromosomes of bacteria, bacteriophages, plasmids, and mitochondrial DNA, the chromosomes of eukaryotes are linear. Each end is ”sealed” by a specialized region, the telomere. Telomeres stabilize chromosomes at both ends.
- DNA at the telomeres consists of G-rich tandem sequences (5'-TTAGGG-3' in vertebrates, 5'-TGTGGG-3' in yeast, 5'-TTGGGG-3' in protozoa). The G-strand overhangs are important for telomeric protection by formation of a duplex loop
- Two features characterize the telomere: telomerase activity to compensate for replication-related loss of nucleotides at the chromosome ends and telomeric DNA loop formation to stabilize the chromosome ends. Telomerase is a modified reverse transcriptase consisting of protein and about 450 nucleotides of RNA. Near the RNA 5' end are sequences complementary to telomeric DNA repeat sequences.

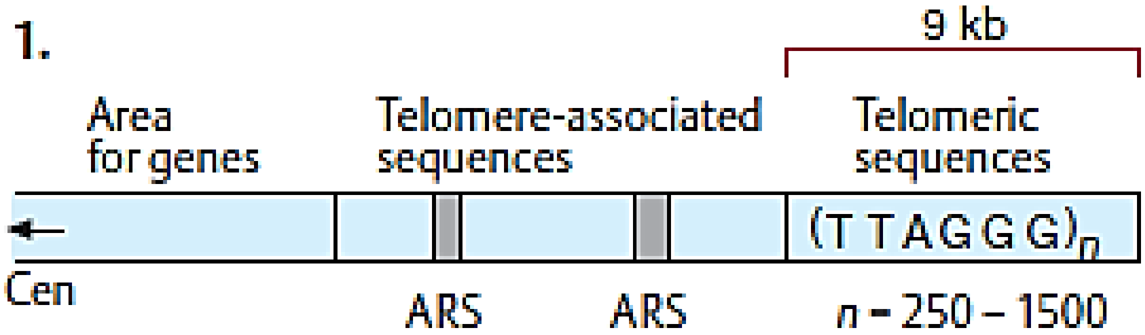




General structure of a telomere

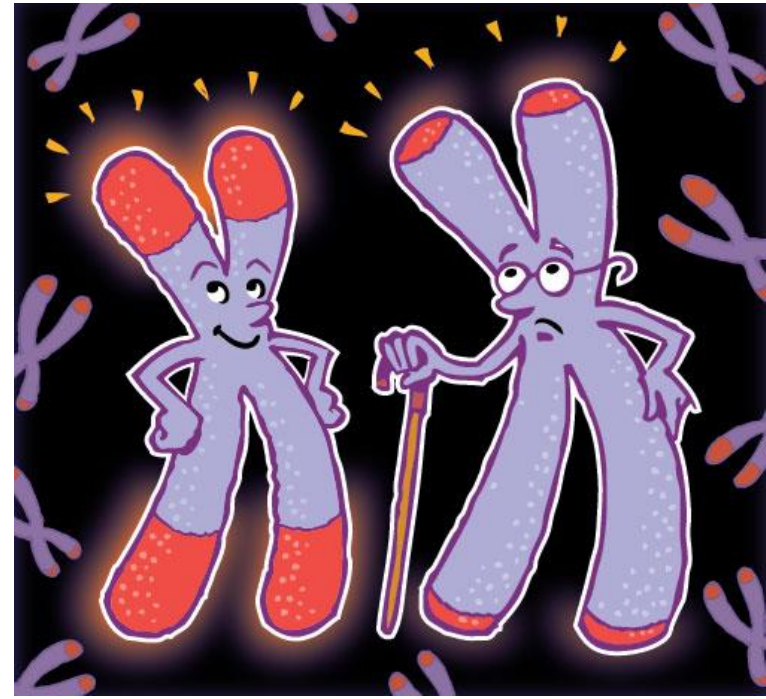
- In the terminal 6–10 kb of a chromosome, telomeric sequences and telomere-associated sequences can be differentiated. The telomere-associated sequences contain autonomously replicating sequences (ARS).
- The telomere sequences consist of about 250 to 1500 G-rich repeats (9 kb). They are highly conserved among different species.
- In vertebrates it occurs mainly in germ cells, and no telomerase activity is found in somatic tissues. The cell division-dependent decrease of telomere length is viewed as being related to aging and death of cells because, ultimately, functional DNA will be lost. Unlike normal cells, many tumors have telomerase activity.

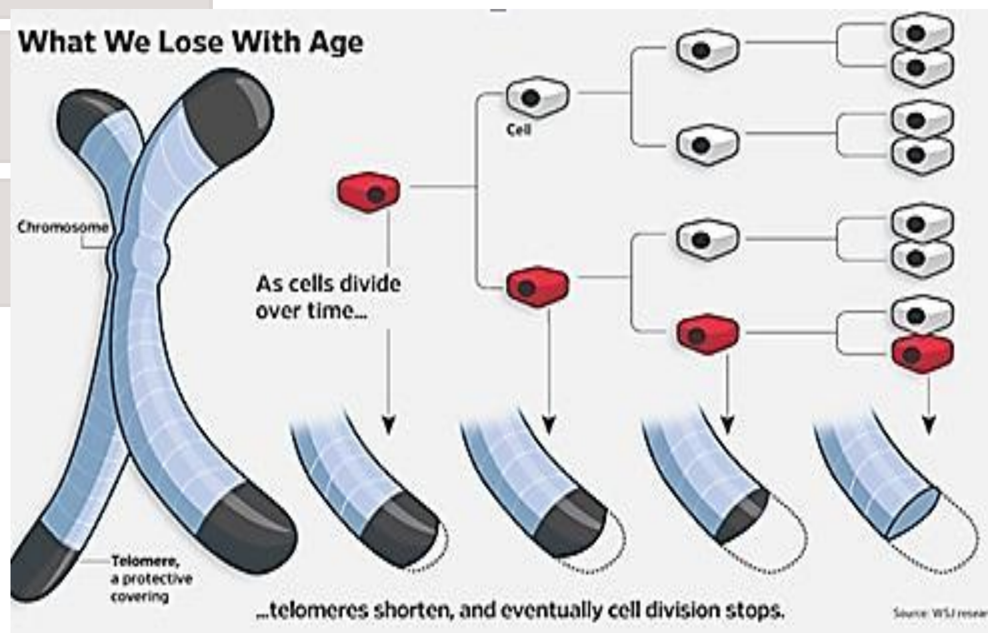
1.



2. Examples of telomeric repeats

Protozoa	e.g., *Tetrahymena* microchromosomes 5' – TTGGGG – 3'	
Yeast	e.g., *Saccharomyces* 5' – TGTGGGG – 3'	
Vertebrates	5' – TTAGGG – 3'	
General	5' – $(T/A)_{1\text{-}4}(G)_{1\text{-}8}$ – 3' (telomere to the right)	





Secondary constriction

- In some chromosome addition to centromere / primary constriction, one or more constrictions in the chromosome are present termed secondary constrictions.

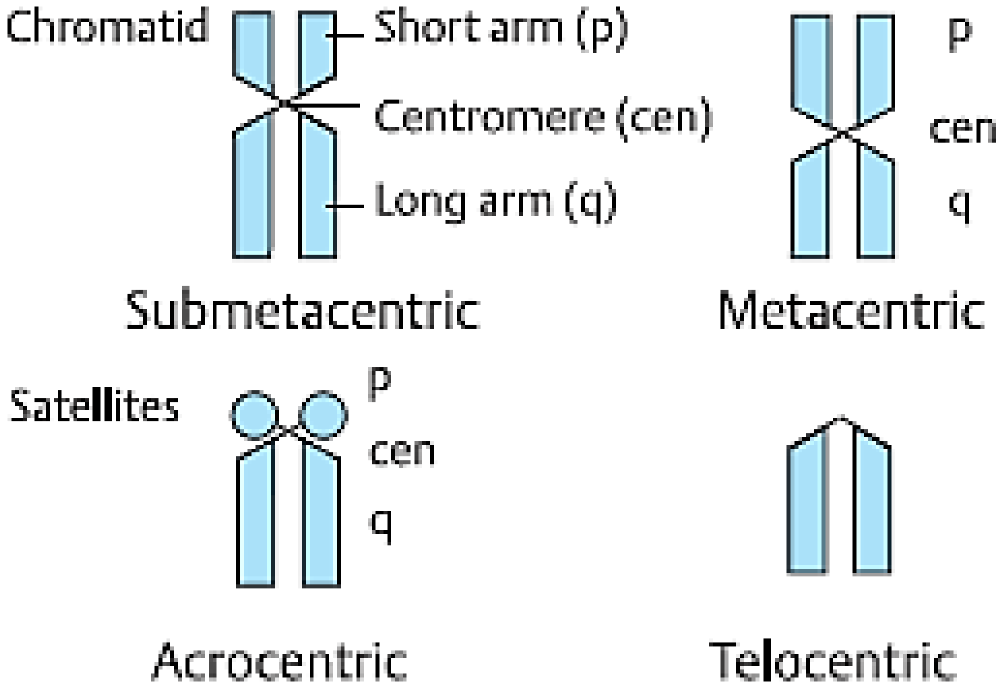
Satellite

- The chromosomal region between the secondary constriction and nearest telomere is called as satellite and chromosomes that possess this region called as **satellite chromosome** or **sat chromosome**.

- A small chromosomal segment separated from the main body of the chromosome by a secondary constriction is called **Satellite**.

Types of chromosome

- According to the relative position of centromere chromosomes are divided into four types



Karyotype

- Karyotype refers to the arrangement of chromosomes in homologous pairs. They are arranged and numbered according to a convention.
- The basis for the arrangement is size of a chromosome, position of the centromere, and the chromosome-specific banding pattern. The karyotype is characteristic for each species.
- Man *(Homo sapiens)* has 22 pairs of chromosomes (autosomes) and in addition either two X chromosomes, in females, or an X and a Y chromosome, in males (karyotype resp. 46,XX or 46,XY).

Idiogram

- A diagrammatic representation of chromosome morphology characteristic of a species or a population is known as Idiogram