

Heterochromatin: Types, organization, formation and significance

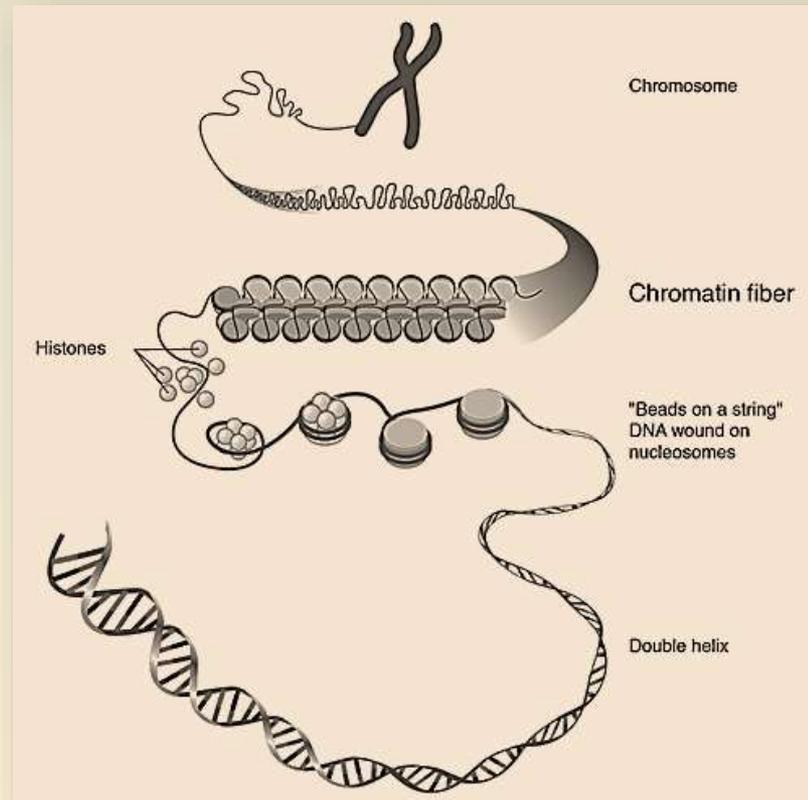
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Introduction

- ❑ It is the structural form of DNA which is found in the periphery of the nucleus as opposed to euchromatin which is found in the inner body of the nucleus..
- ❑ It is a part of chromatin which is densely packed – as opposed to euchromatin, which is lightly packed.
- ❑ The term heterochromatin and euchromatin was coined by Emil Heitz in 1928 who found heterochromatin as densely stained part of the chromosomes.
- ❑ The heterochromatin has variable forms, such as constitutive heterochromatin and facultative heterochromatin.
- ❑ Only 10% of the genome though to be present as heterochromatin; rest is euchromatin.
- ❑ It is epigenetically marked by specific histone modifications.
- ❑ Compact nature of heterochromatin makes it inaccessible to the proteins which are involved in the gene expression.
- ❑ It is transcriptionally silent part of the chromosomes mostly located at the centromeric and telomeric regions.
- ❑ Compact nature of heterochromatin makes it protected from crossing over during cell division.

What is chromatin?

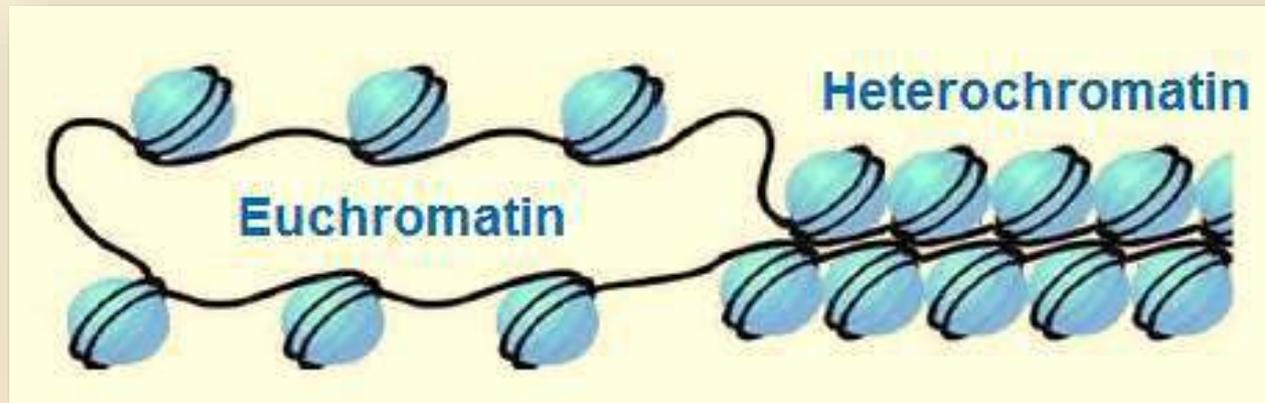
- ❑ As the term suggests, it is complex of DNA and protein (nucleoprotein) within the nucleus of eukaryotic cells (Greek – Chromos meaning 'coloured', tene meaning 'ribbon').
- ❑ It looks like threaded structure or beads on a string (string of nucleosome and linker DNA fragments).
- ❑ It makes the entire chromosome.
- ❑ It is categorized into base on the compactness in the chromosome, i.e., euchromatin and heterochromatin.



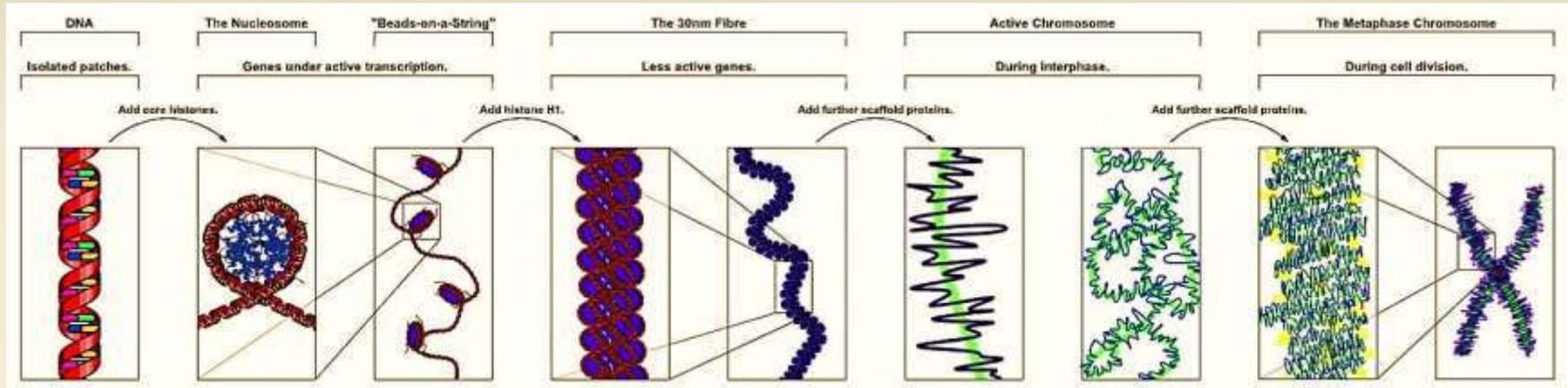
Greek, '*eu-*' means good, well or true; '*hetero-*' (English) means different.

What is euchromatin?

- ❑ Euchromatin is the tightly (lighter than heterochromatin) packed chromatin fiber that is rich in gene concentration.
- ❑ Euchromatin represents transcriptionally active part of the chromosomes.
- ❑ Being transcriptionally active is due to the loose wrapping or light condensation of nucleoprotein so that the DNA is easily accessed by the proteins involved in the transcription.
- ❑ It is simple chromatin fiber of nucleoprotein complex which appears as an elongated open 10nm microfibril as noted from electron micrograph.



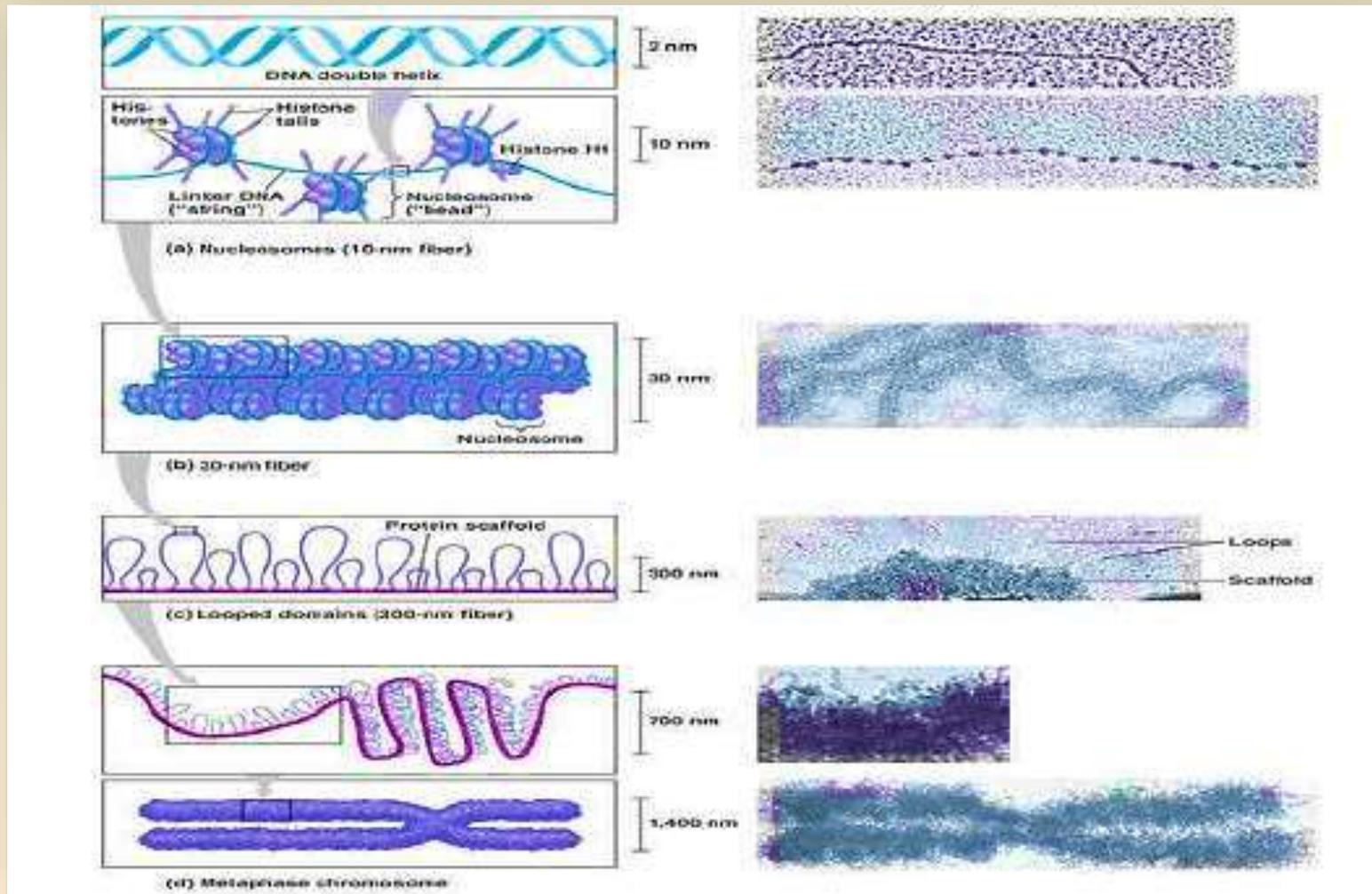
Packaging of DNA molecules into chromatin



<https://biologydictionary.net/heterochromatin/>

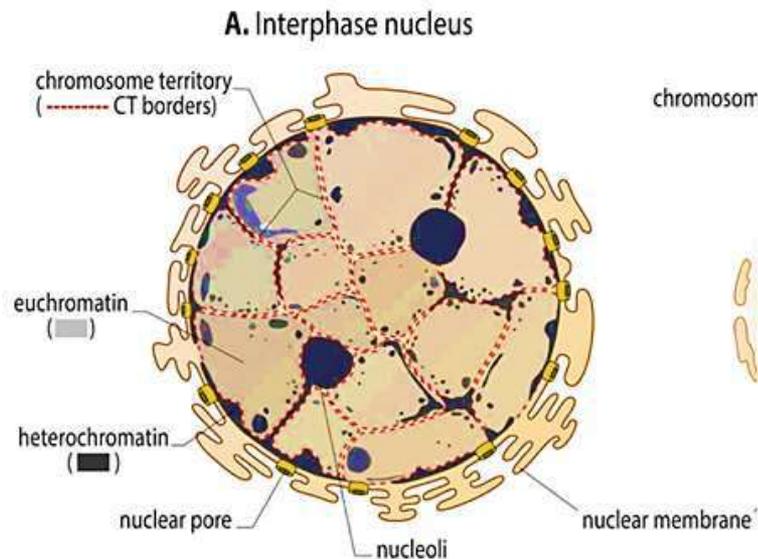
- ❑ Double-stranded helical DNA (first illustration) is coiled around histones, forming nucleosomes (second illustration)
- ❑ Nucleosome constitute the euchromatin or beads-on-a-string structure (third illustration).
- ❑ Euchromatin is further condensed into heterochromatin or 30-nm fibers (fourth and fifth illustrations).
- ❑ The last four illustrations depict more tightly condensed DNA in the form of active and metaphase chromosomes.

Chromatin structure



Structure of heterochromatin

Lighter stained euchromatin (transcriptionally active) and the patches of darker heterochromatin (transcriptionally silent) are easy to visualize.



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- Heterochromatin mainly consists of genetically inactive satellite sequence where many genes are repressed, while many can't be expressed.
- Both centromere and telomere are heterochromatic, as is the Barr body of the second, inactivated X-chromosome in a female.

Types of heterochromatin

Heterochromatins are mainly of two types; constitutive heterochromatin and facultative heterochromatin.

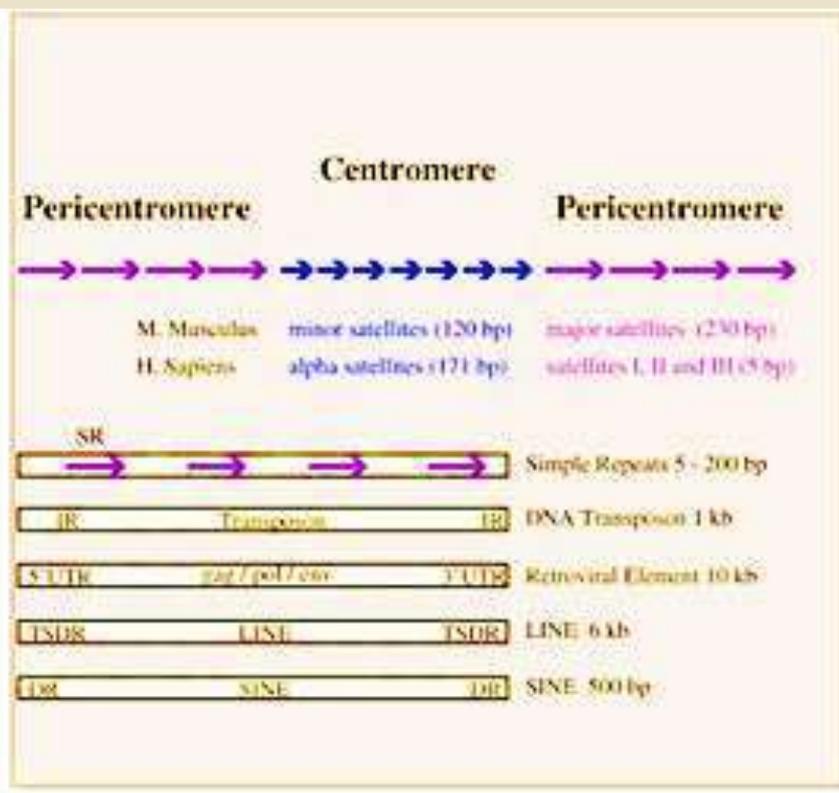
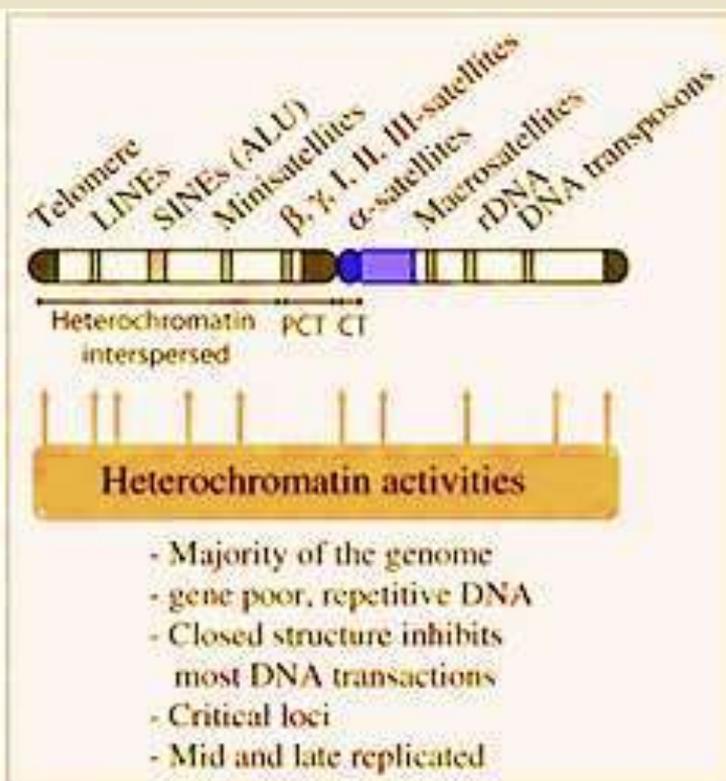
Constitutive heterochromatin

- Constitutive heterochromatin is the stable form of heterochromatin, i.e. it does not loosen up to form euchromatin
- It contains repeated sequences of DNA called satellite DNA.
- It can be found in centromeres and telomeres and throughout the chromosomes in meager amount as well.
- It is made of satellite DNA and is usually involved in structural functions.

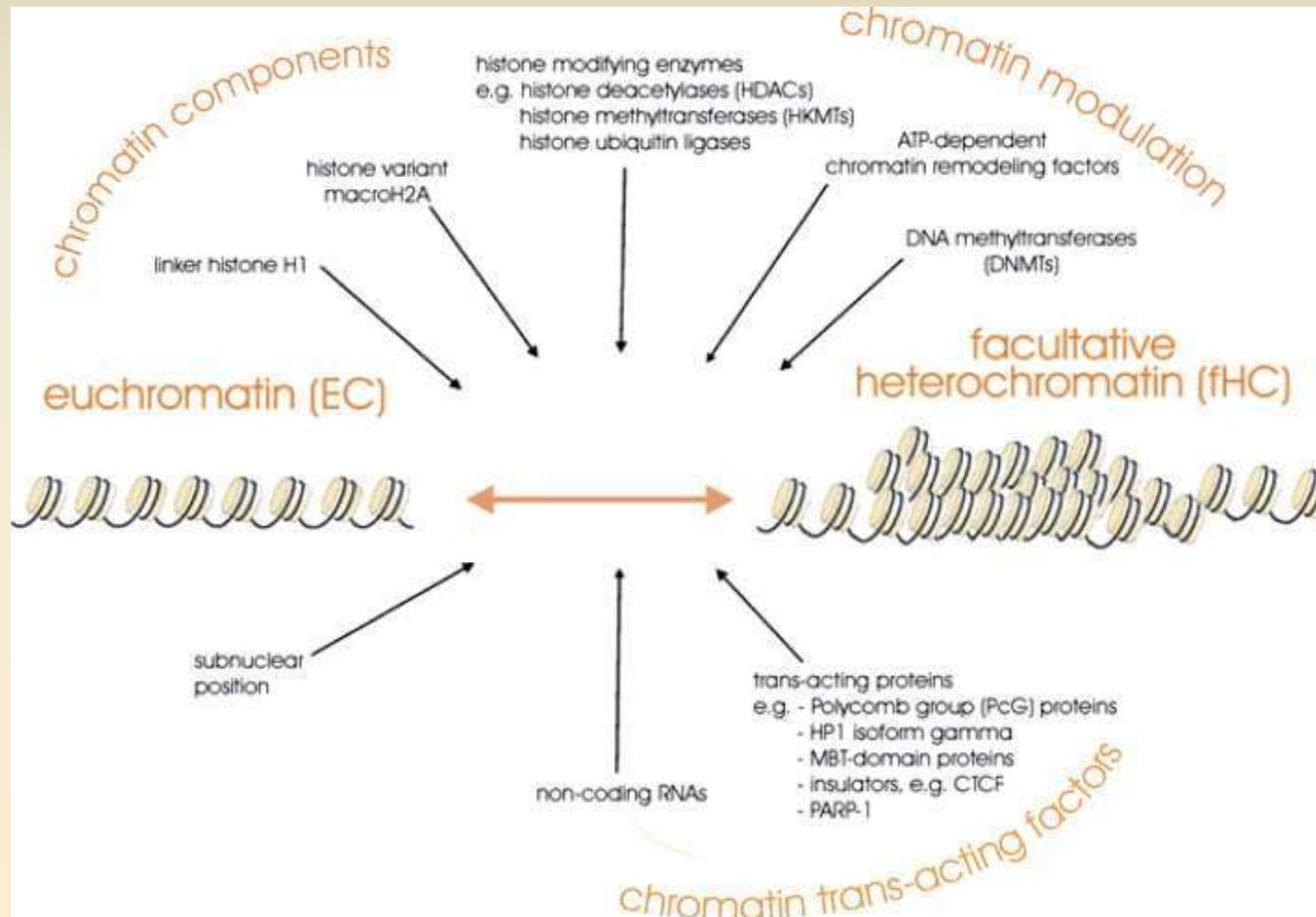
Facultative heterochromatin

- Facultative heterochromatin is reversible, i.e. its structure can change depending on the cell cycle. It may convert to euchromatin..
- It is characterized by the presence of another kind of repeated DNA sequences known as LINE sequences.
- Example is the inactivated X-chromosome (Barr body) of females.

Organization of constitutive heterochromatin



Facultative heterochromatin is flexible

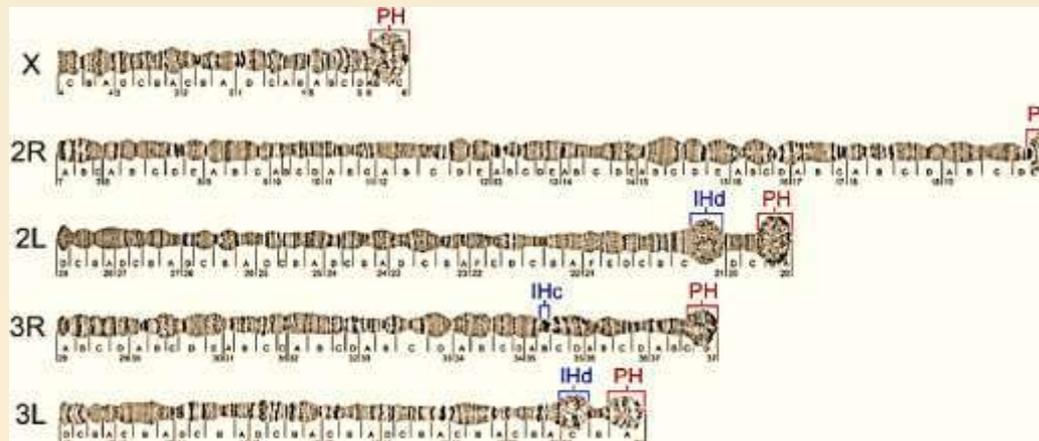


Facultative Heterochromatin Retains the Potential to Convert to Euchromatin

<https://doi.org/10.1016/j.molcel.2007.09.011>

Intercalary heterochromatin

- ❑ Intercalary heterochromatin consists of extended chromosomal domains which are interspersed throughout the euchromatin.
- ❑ It is basically a constitutive heterochromatin that contain silent and or permanently repressed genetic material.
- ❑ It is comparable to that of classic pericentric heterochromatin which are represented by high compaction, late replication and underreplication of genomic material.
- ❑ It also comprises either clusters of functionally unrelated genes or tandem gene duplications.
- ❑ It can be easily visualized in the polytene chromosome.



The pericentric and intercalary heterochromatin of polytene chromosomes . PH – pericentric heterochromatin, IHc – compact intercalary heterochromatin, IHd – diffuse intercalary heterochromatin.

Sharakhova et al. 2010, 11:459

Difference between euchromatin and heterochromatin

	EUCHROMATIN	CONSTITUTIVE HETEROCHROMATIN	INTERCALARY HETEROCHROMATIN
RELATION TO BANDS	IN R-BANDS	IN C-BANDS	IN G-BANDS
LOCATION	CHROMOSOME ARMS	USUALLY CENTROMERIC	CHROMOSOME ARMS
CONDITION DURING INTERPHASE	USUALLY DISPERSED	CONDENSED	CONDENSED
GENETIC ACTIVITY	USUALLY ACTIVE	INACTIVE	PROBABLY INACTIVE
RELATION TO CHROMOSOMES	INTERCHROMOMERIC	CENTROMERIC CHROMOSOMES	IINTERCALARY CHROMOSOMES

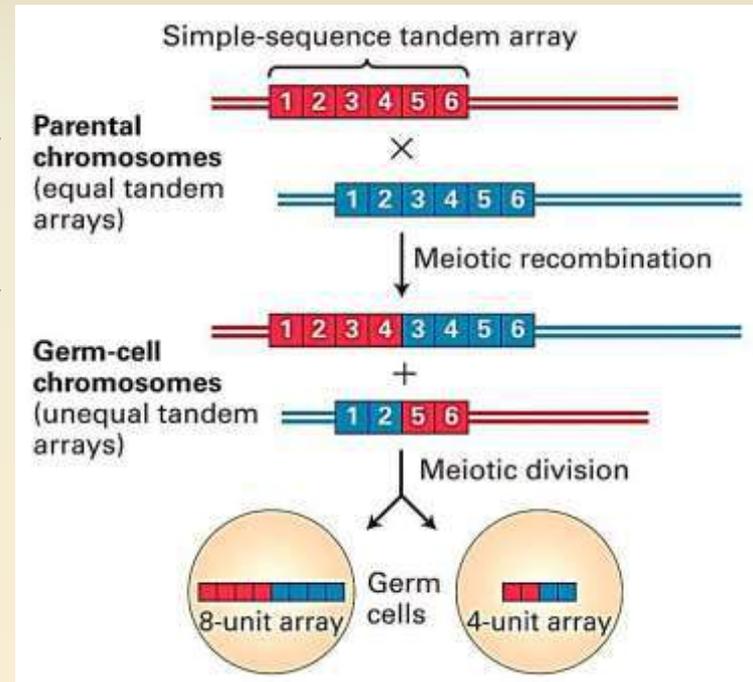
Source: Mir Harris

Satellite DNA or repetitious DNA

Satellite DNA is classified into 3 categories based on length.

- Satellite DNA consists of 14-500 bp sequence units that tandemly repeat over 20-100 kb lengths of genomic DNA.
- Minisatellite DNA consists of 15-100 bp sequence units that tandemly repeat over 1-5 kb stretches of DNA.
- Microsatellite DNA consists of 1-13 bp units that can repeat up to 150 times.

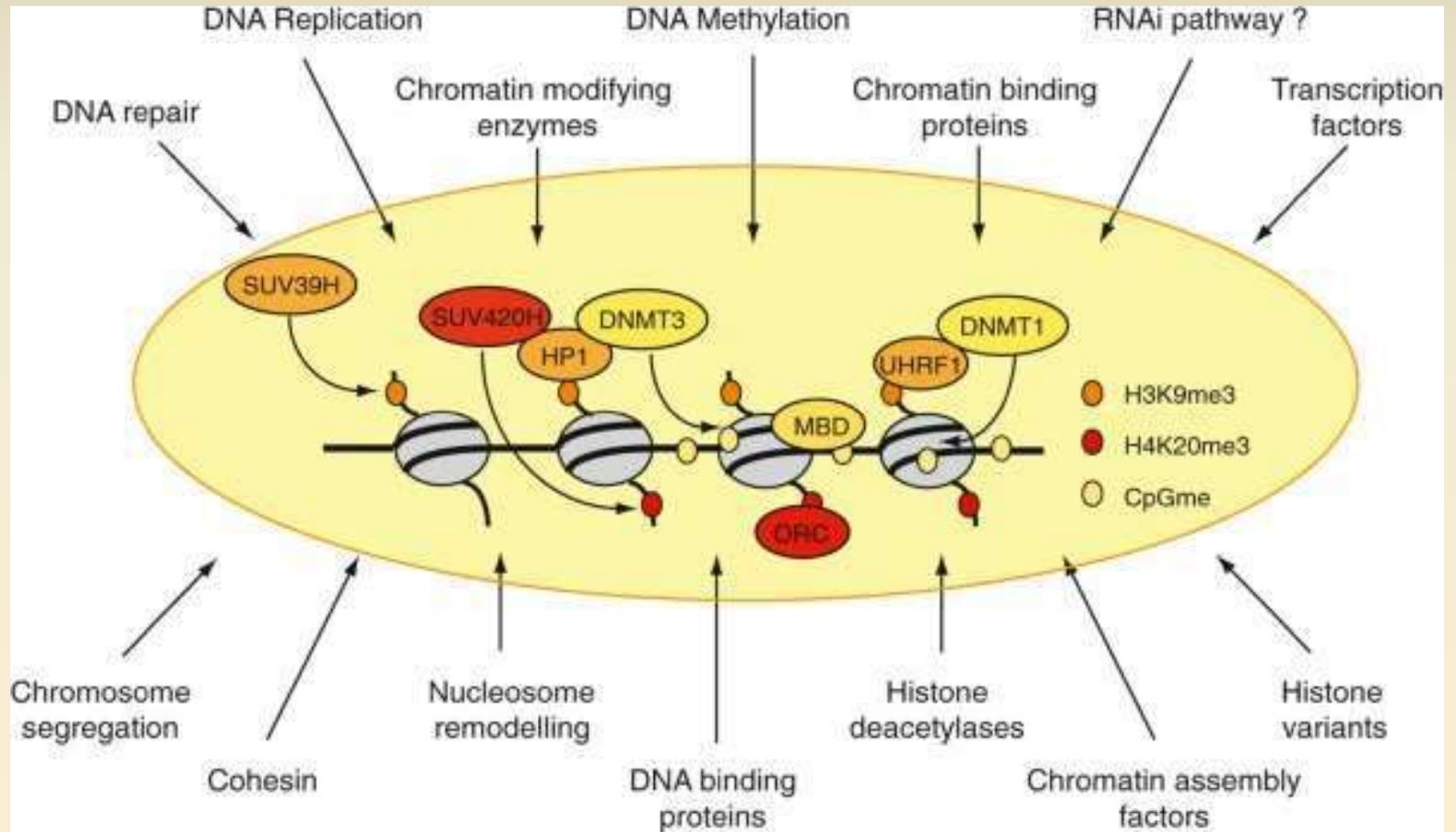
Although the sequences of satellite DNA are highly conserved, the number of tandem copies at each locus is highly variable between individuals.



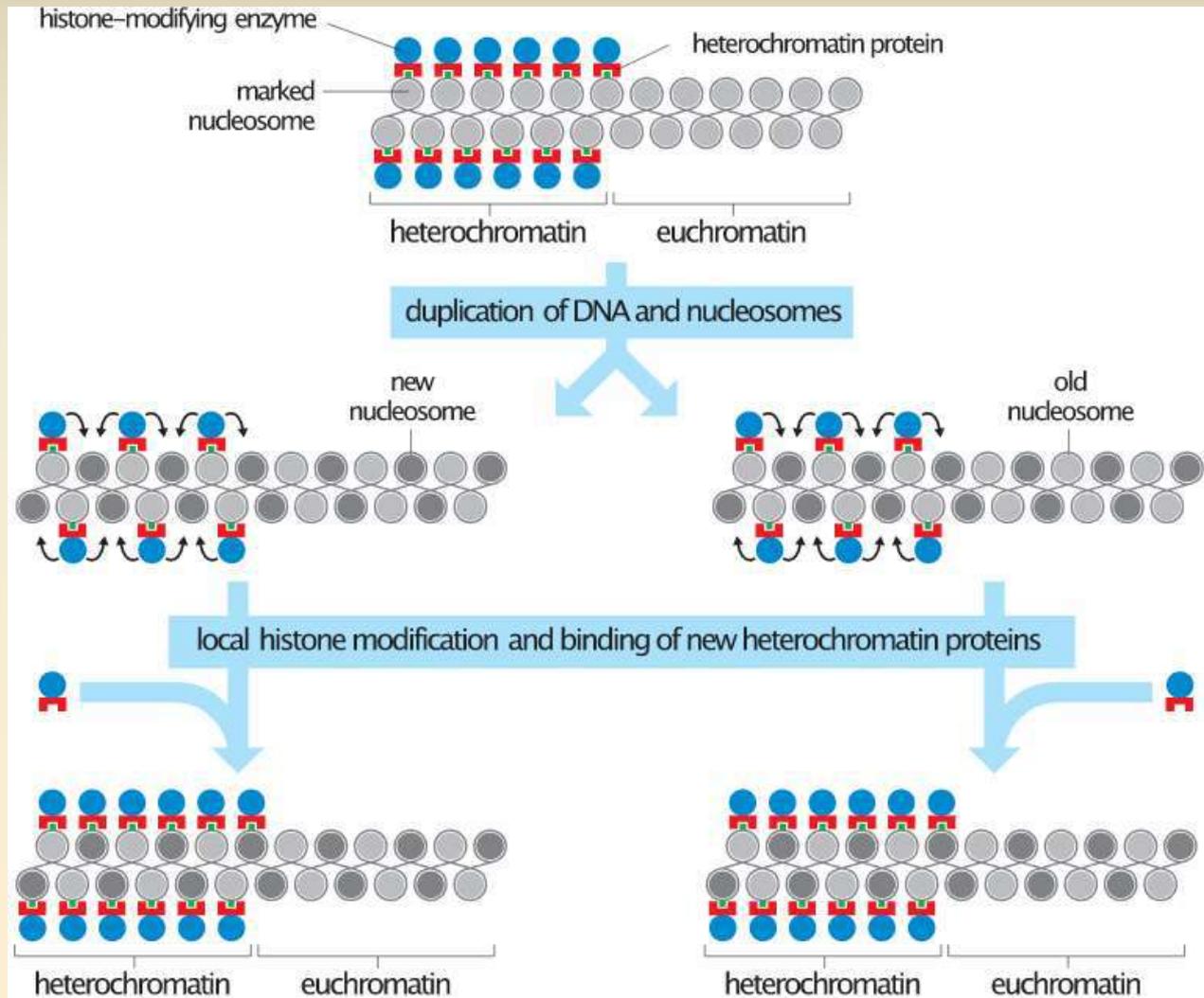
*It carries a variable **AT-rich** repeat unit that often forms arrays up to 100 Mb.*

Every repetitive DNA is not a satellite DNA.

Formation of heterochromatin



Replication of heterochromatin



Properties of heterochromatin

- Heterochromatin is condensed.
- Heterochromatin DNA is late replicating.
- Heterochromatin DNA is methylated.
- Histones are hypo-acetylated in heterochromatin.
- Histone H3 in heterochromatins is methylated on lysine 9.
- Heterochromatin is transcriptionally inactive.
- Heterochromatin does not participate in genetic recombination.
- Heterochromatin has a gregarious instinct.

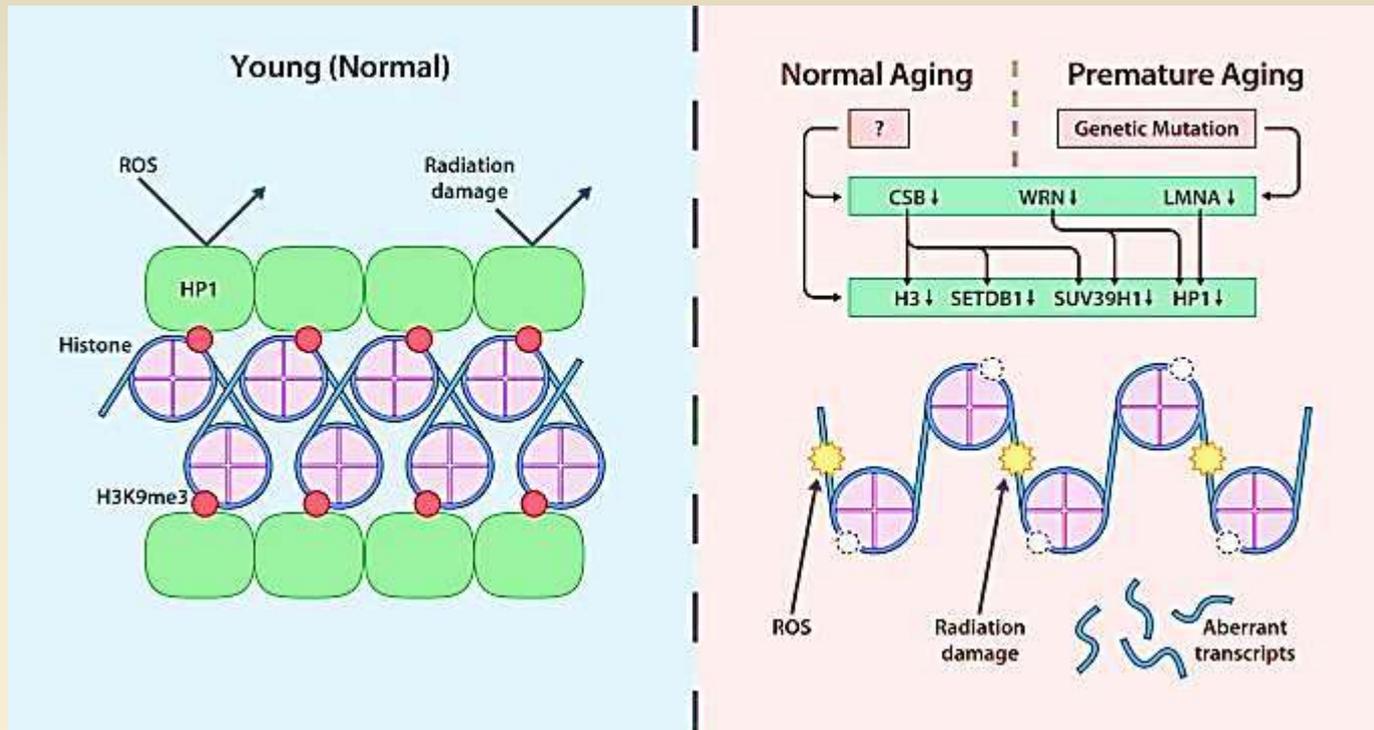
Factors affecting heterochromatization

- ❑ Large arrays of tandemly repeated sequences: Tandem repetition of DNA sequences in a large number itself drives the formation of heterochromatin.
- ❑ Methylation of DNA: Methylation leads to the silencing of DNA and its stabilization.
- ❑ Hypo-acetylation of histones: Hypo-acetylation increases methylation and therefore silencing of DNA.
- ❑ Methylation of H3-K9: Methylation of H3-K9 creates high-affinity binding site for the heterochromatin protein HP1 which enhances methylation of DNA and heterochromatization.
- ❑ Nuclear RNAs: RNAs of those genes which have been repressed or shut down induces the methylation of DNA that may lead to heterochromatization.

Functions of heterochromatin

- ❑ It plays an indispensable role in organization of nuclear domains.
HC is usually localized in the periphery of the nucleus and is attached to the nuclear membrane. In contrast, the active chromatin occupies a more central position.
- ❑ It plays an important role in centromere.
HC is necessary for the cohesion of sister chromatids and that it allows the normal disjunction of mitotic chromosomes.
- ❑ It has profound role in gene repression or epigenetic regulation.
Heterochromatin appears to be involved in controlling the *transcriptability* of the genome. Genes that are usually located in the euchromatin can, therefore, be silenced when they are placed close to a heterochromatic domain.

Heterochromatin and ageing



- Young & healthy individuals exhibit intact heterochromatin, a high level of H3K9me3, and a high level of HP1 bound to H3K9me3, which are factors that stabilize the heterochromatin complex.
- Chronologically, these are reduced resulting in heterochromatin loss, DNA damage accumulation, and expression of aberrant transcripts.

Lee J.-H. et. al. *Exp. Mol. Med.* 2020; 52: 1466-1474.

Heterochromatin diseases

☉ Disease of the constitutive heterochromatin

☐ ICF syndrome or the Roberts syndromes – Constitutional

The ICF syndrome associates **I**mmunodeficiency, **C**entromeric instability and **F**acial anomalies. It is a rare recessive disease that is linked to mutations of the gene DNMT3B, a DNA methyl transferase. The G-C rich satellite DNAs II and III are particularly demethylated, which can cause abnormal segregation of the sister chromatids, formation of multiradial figures, deletions, micronuclei, etc.

☐ Anomalies of the constitutive heterochromatin – Acquired

- Non-Hodgkin's lymphoma and multiple myeloma is associated with anomalies of the secondary constriction of chromosome 1 (similar to those observed in the ICF syndrome). There is a global hypomethylation of the genome (in particular, hypomethylation of DNA satellite II).
- In metastatic breast cancer, there is a decrease in the HP1 alpha protein, which is a protein that is usually localised in the heterochromatic regions of the chromosomes.

☉ Disease of the facultative heterochromatin

- ☐ They can result from a defect in the inactivation of an X chromosome in female somatic cells (mutation in the XIST gene) and may lead to the expression of an X-linked recessive disease in females.
- ☐ They can result from a defect in the condensation of the sex vesicle in male germ cells, leading to a sterility due to pachytene arrest of the meiosis.

Further reading

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