Epigenetics

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Genetics –

"We are what our parents are"

Continuity

Epigenetics –

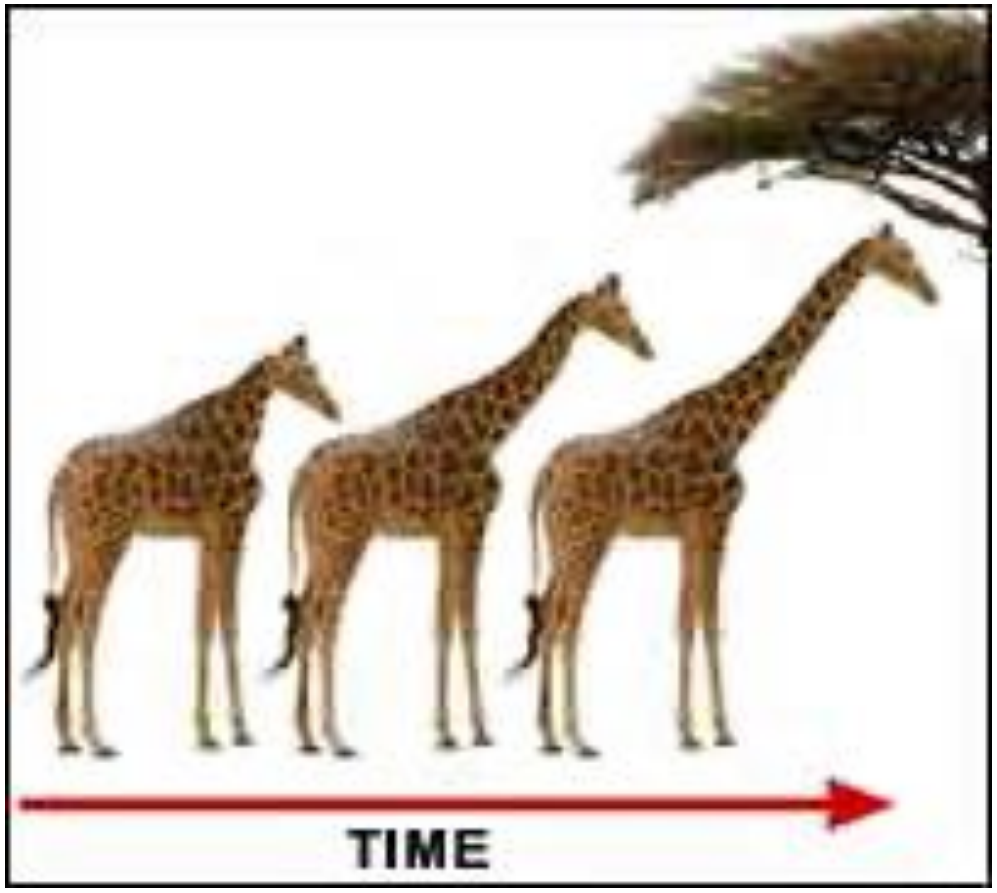
"Changes at the cellular level in response to our environment that we can pass

to our children"

Lamarckian theory (1700's):

Change Through Use and Disuse

"Heritability of acquired characteristics"



Take home message:

Open-mindedness

The “wrong” answers of today could be a Nobel prize of tomorrow”

GENETICS:

The study of heredity (in the past) of mostly DNA coded information from cell to cell, generation to generation.

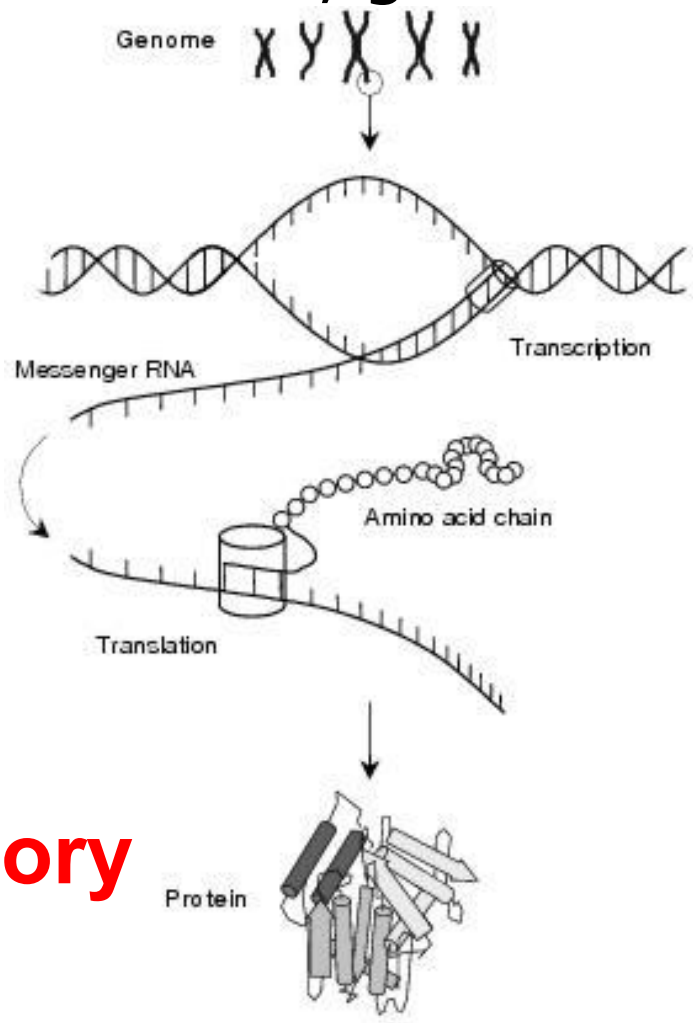
CENTRAL DOGMA:

Genes/DNA

→ RNA (Transcription)

→ Protein (Translation)

→ Functions/Traits



DNA is only part of the story

Chromosome-wide regulation:
X inactivation in mammals

Female: XX Male: XY

Bar body:

- One of the two Xs in the female stays highly condensed.

-Transcription is inactivated on the Bar body.

-The inactivated X contains hypermethylated on DNA.

- 

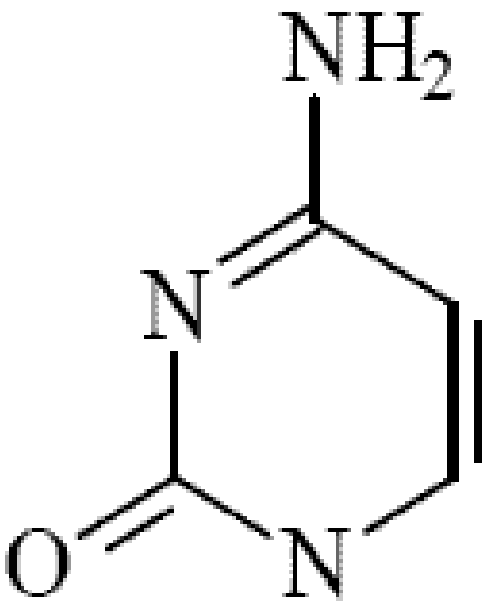
random or skewed
X inactivation

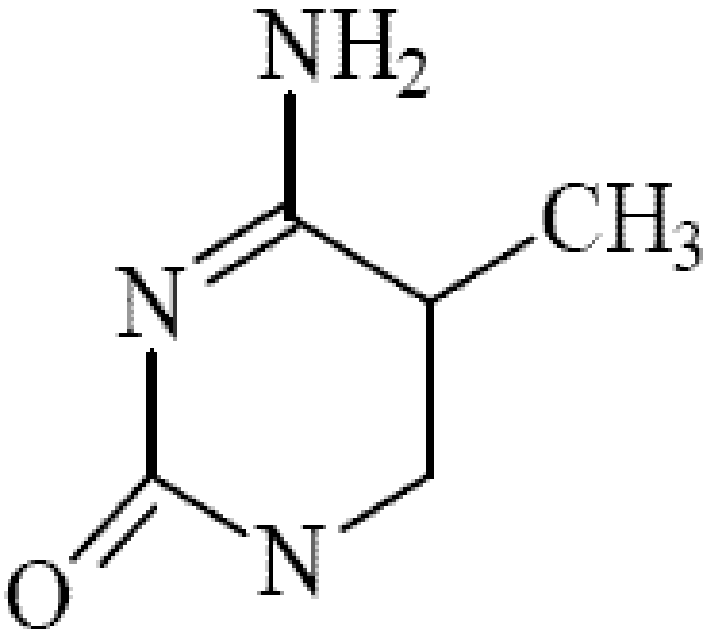
-Recent concept: a large number of genes can variably escape silencing on one or both chromosomes (aging).

-X-chromosome vulnerability

-X has enriched immune-related genes → Age-dependent autoimmune diseases

DNA Methylation



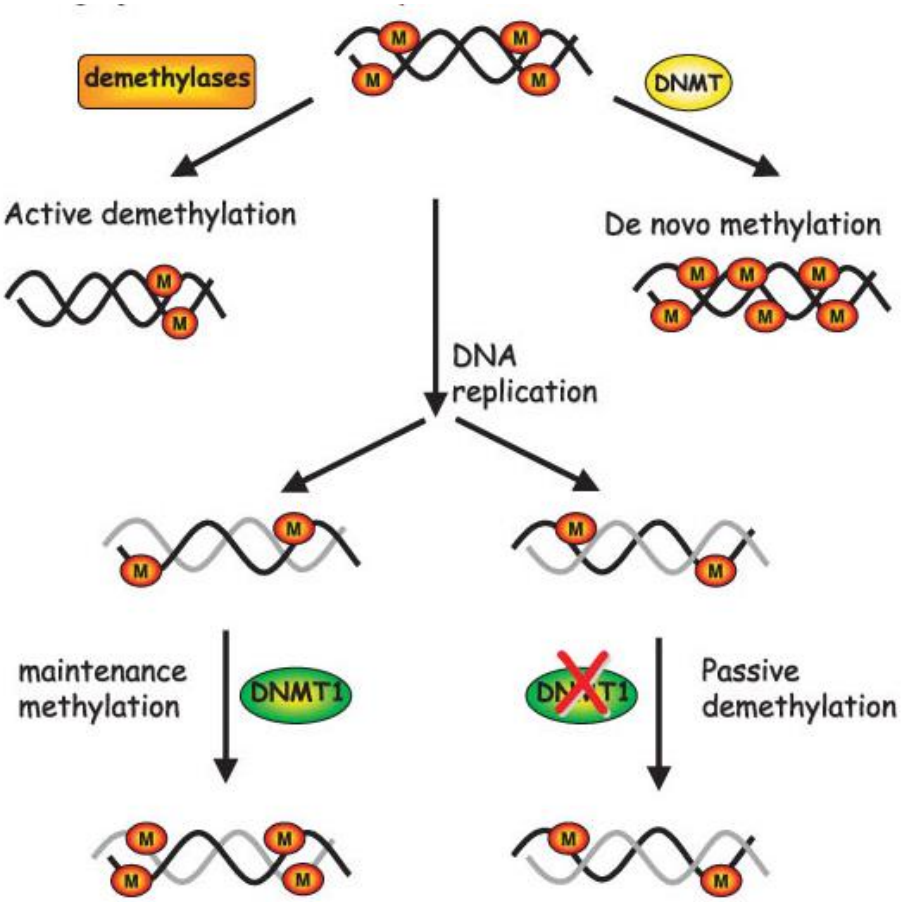


Cytosine —DNMT→ 5’-methylated cytosine

DNA methyl transferase (DNMT)

De novo vs. maintenance methylation of DNA

Massive demethylation occurs in early embryos.



This is followed by de novo Methylation.

Then, maintenance methylation.

Maternal nutritional influences on the fetal epigenome

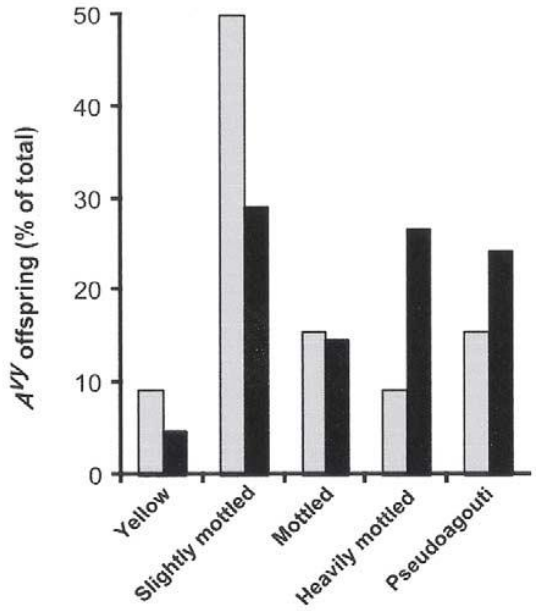
A

Agouti^{vy} or A^{vy}
a metastable epiallele

Coat colors
Yellow: Hypo-methylation of *A^{vy}*
increased expression of *A^{vy}*

Black: hyper-methylation of *A^{vy}*
decreased expression of *A^{vy}*

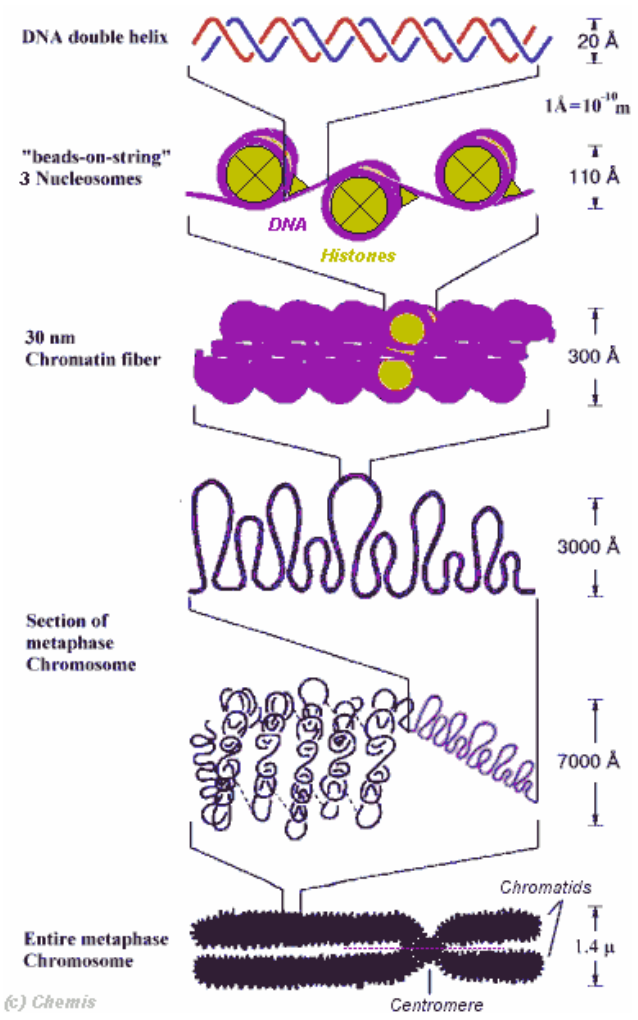
B



1. Maternal diet supplements affect pups' coat colors

Grey bar: NIH31 diet
Black bar: NIH31 supplemented with methyl donors and cofactors

Epigenetic information is also embedded in Chromatin (DNA + histones)



<u>Chromatin of varying compaction</u>

Bead-on-strings

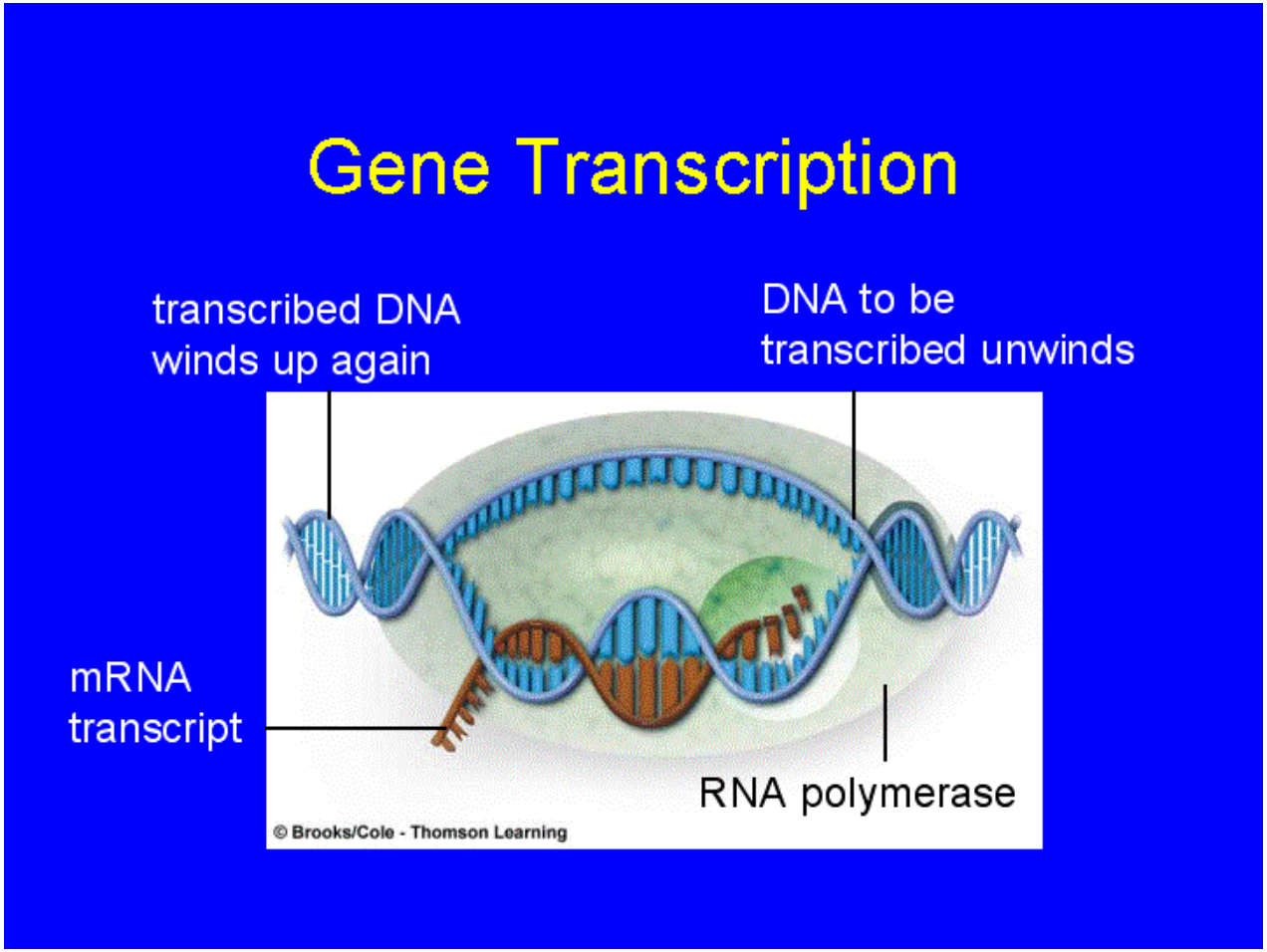
30 nm fibers

Chromatin loops

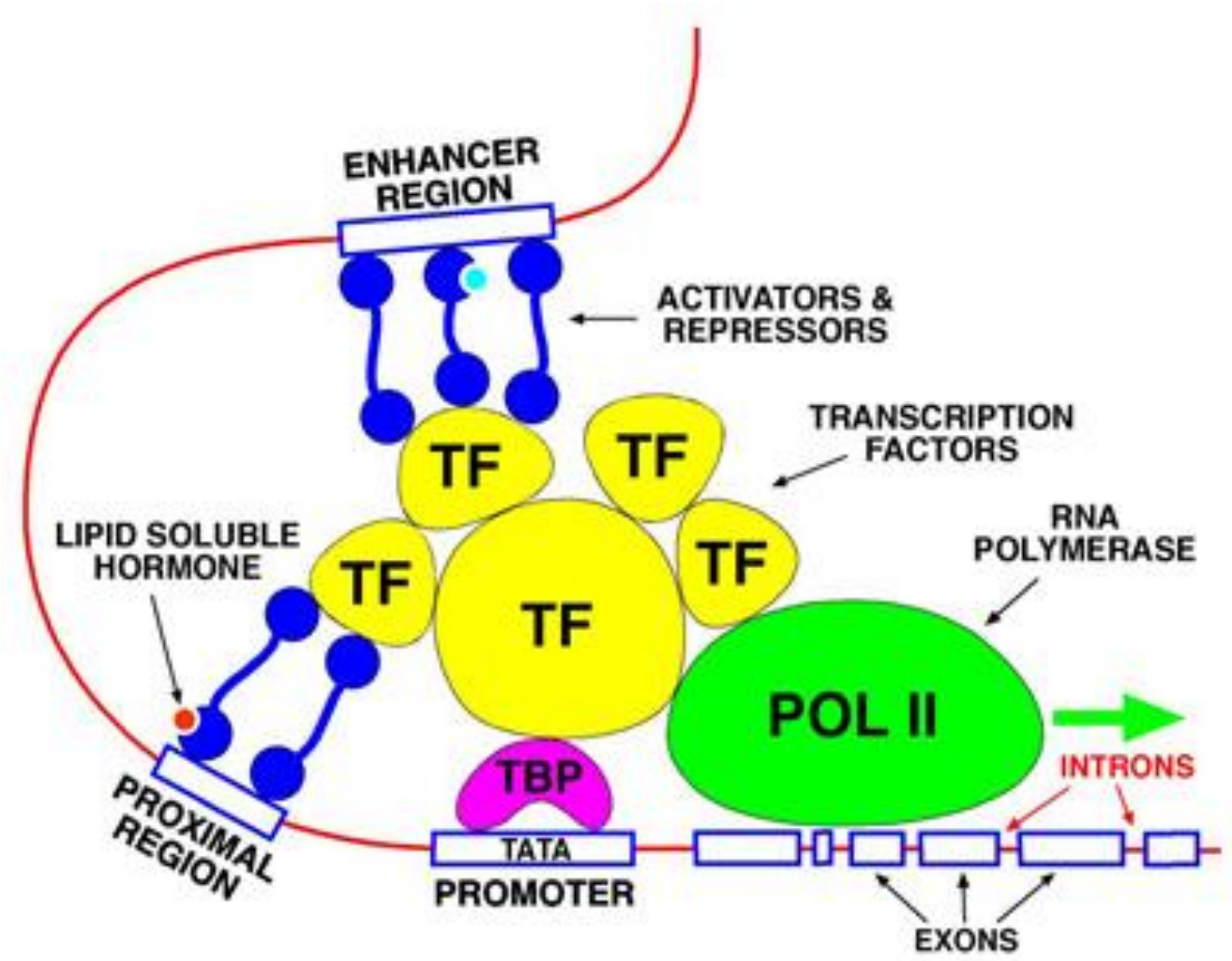
Partially condensed chromatin

Mitotic chromosome (fully condensed)

Chromatin affects promoter access to proteins involved in transcription



Chromatin affects enhancer-promoter interaction



Epigenetic information –

Chemical modifications on DNA & histones

-- Direct the formation of chromatin structure

-- Influence the transcription of genes

Txn = Transcription
Tln = Translation

EPIGENETICS:

A new branch of genetics. Heredity of non-DNA sequence coded information from cell to cell, generation to generation.

Modified Central Dogma

GENOME = The whole collection of DNA sequence info

+

EPIGENOME = The whole collection of epigenetic information on chromatin or elsewhere, including:

- Modifications on DNA
- Modifications on Histones
- Histone variants
- Chromatin associated proteins
- Non-coding or micro RNAs (carried in sperm)

CHROMATIN STRUCTURE → Txn → RNA → Protein → Cell → Function/Trait

EPIGENETICS:

"The study of heritable alternations that result in gene expression changes without changes in DNA sequences"

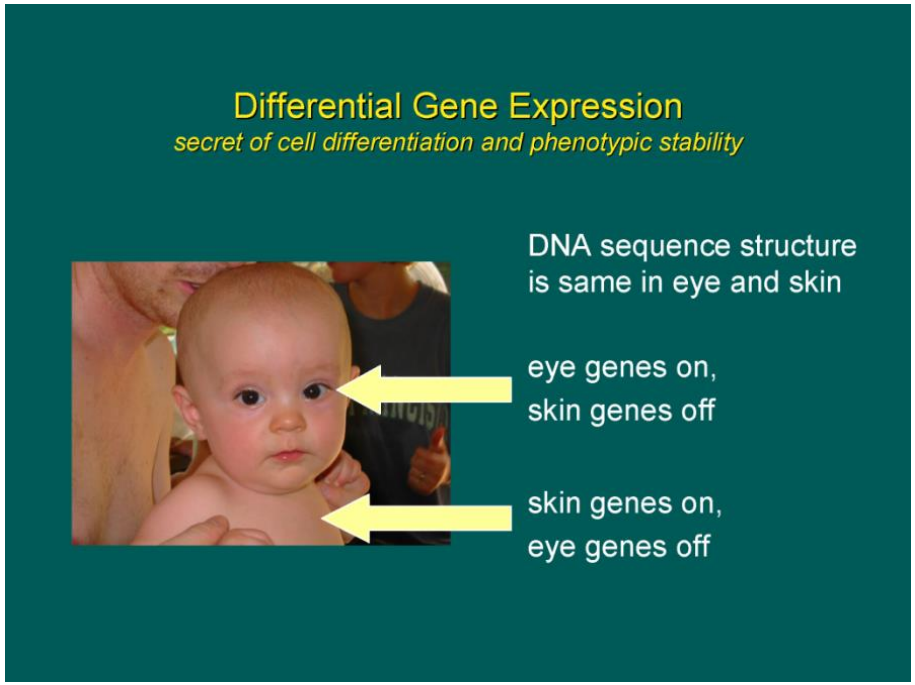
"The study of heritable changes in gene function that cannot be explained by changes in DNA sequence"

Heredity of non-DNA coded information.

Distinction between

Genetic (DNA-coded) versus Epigenetic (non-DNA coded).

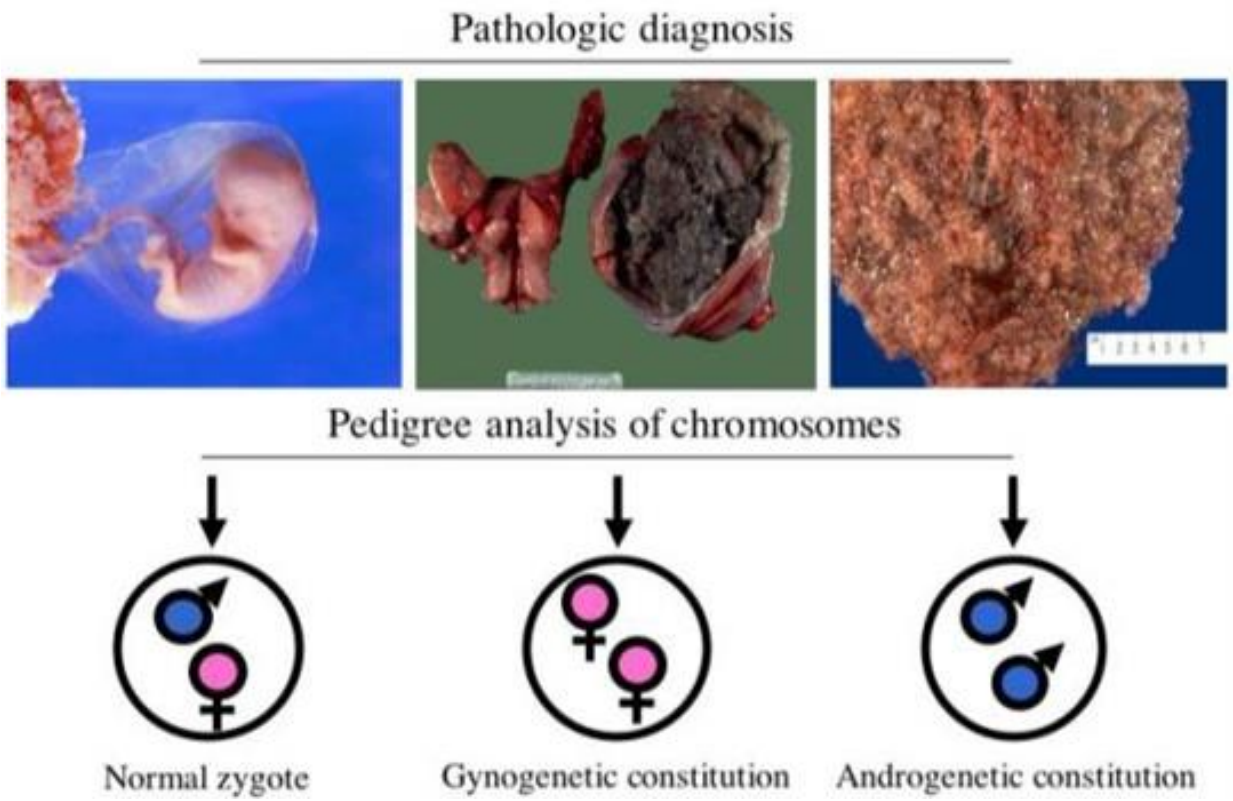
Epigenetic phenomena:
Differential gene expression



Most somatic cells have the same genome, but different epigenomes.

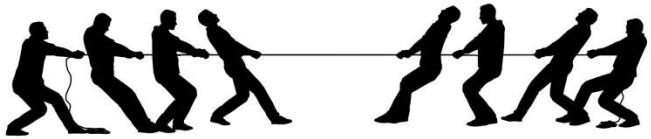
Each cell type has its unique epigenome.

Epigenetic phenomena: Maternal and paternal genomes carry different epigenomes that are TOGETHER required for normal development



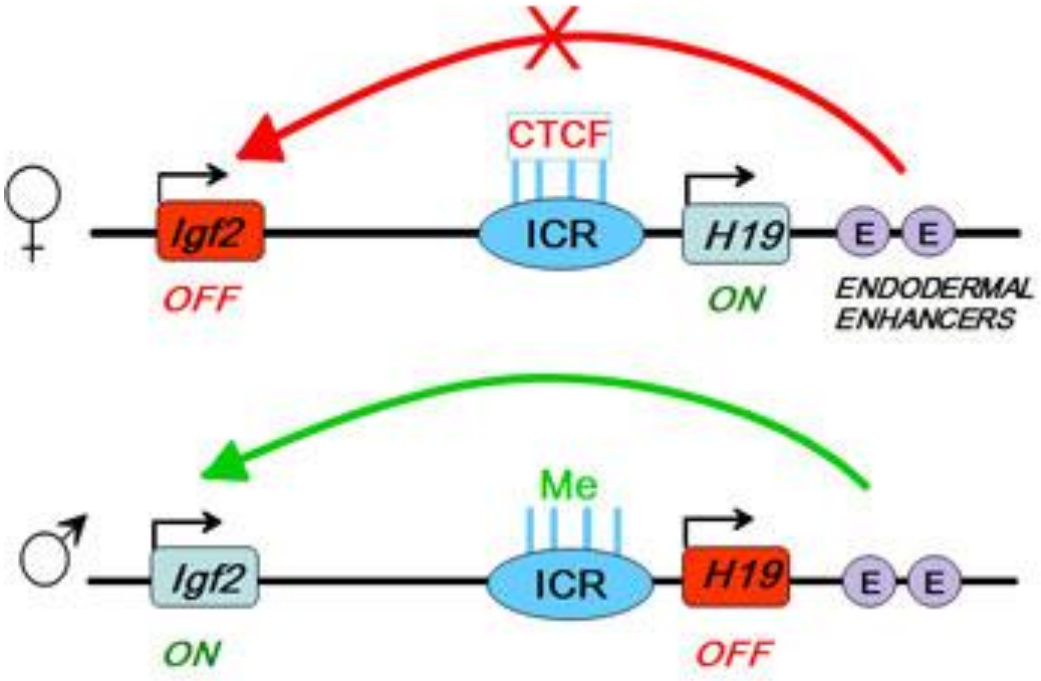
Nm + Np = 2N normal embryo
Nm + Nm = 2N abnormal cell mass
Np+ Np = 2N abnormal cell mass

1.2. Reason for Imprinting – Haig's Tug-of-War hypothesis



- It is better for the father to have large offspring. These will outcompete the offspring from other fathers.
- It is better for the mother to have many small offspring so that they all survive.

Imprinting Growth Factor Genes



Germlines have their unique epigenetic markers

Eggs and sperm carry different epigenetic markers that are complementary in function in supporting the development of full term babies.

Human imprinting diseases

Prader-Willi Syndrome

- Hypotonia
(low muscle tone,
lack of sucking at birth)
- Small stature
- Small hands & feet
- Chronic hunger
- Late sexual maturity

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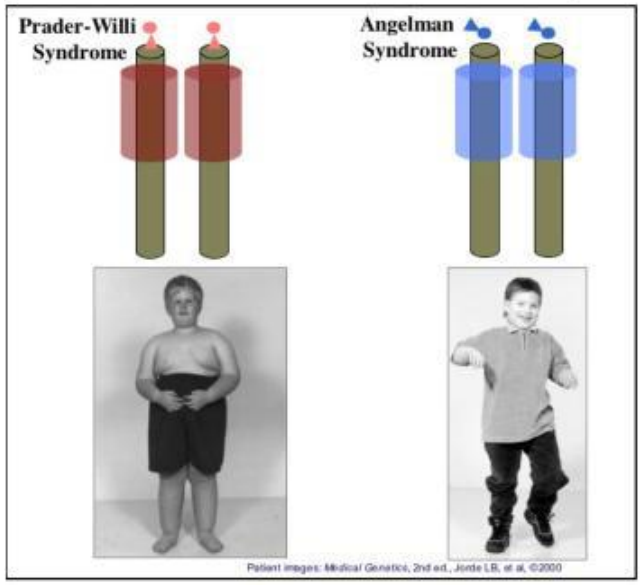
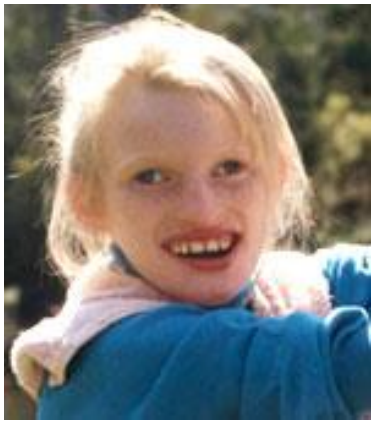
Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome

Robert D. Nicholls*†‡, Joan H. M. Knoll†, Merlin G. Butler§, Susan Karam‖ & Marc Lalande*†¶



Angelman Syndrome



- Neurological disorder
- Mental retardation
- Facial anomaly
- Muscular anomaly

Imprinting gene(s) in 15q11-13

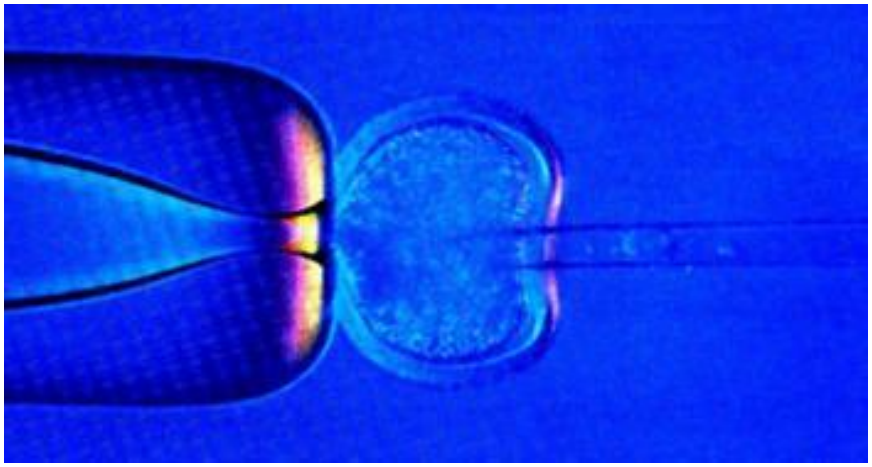
Parent-of-origin effects/traits

Liger – offspring of
female tiger and male lion

Swimming – a tiger characteristics

Tigon – offspring of
male tiger and female lion

Epigenetic phenomena: Animal cloning errors



Cloned animals are unhealthy. Some are obese, and some have lung defects, neurological problems and premature aging, etc.

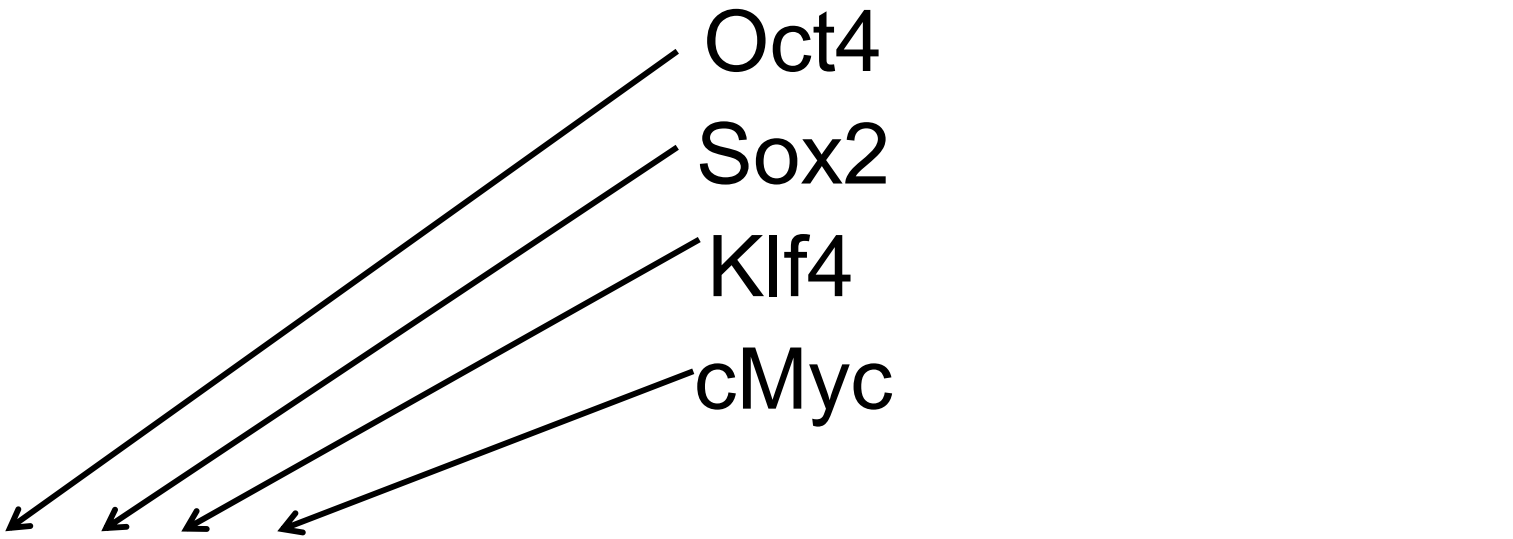
EPIGENETIC REPROGRAMMING:

Epigenetic information of a somatic nucleus/DNA has to be erased and replenished with those characteristic of the germ cells to ensure normal development. Otherwise, normal genes could be mis-regulated, thereby disrupting development or health.

iPS cells: induced pluripotent stem cells

EPIGENETIC REPROGRAMMING

by four transcription factors:



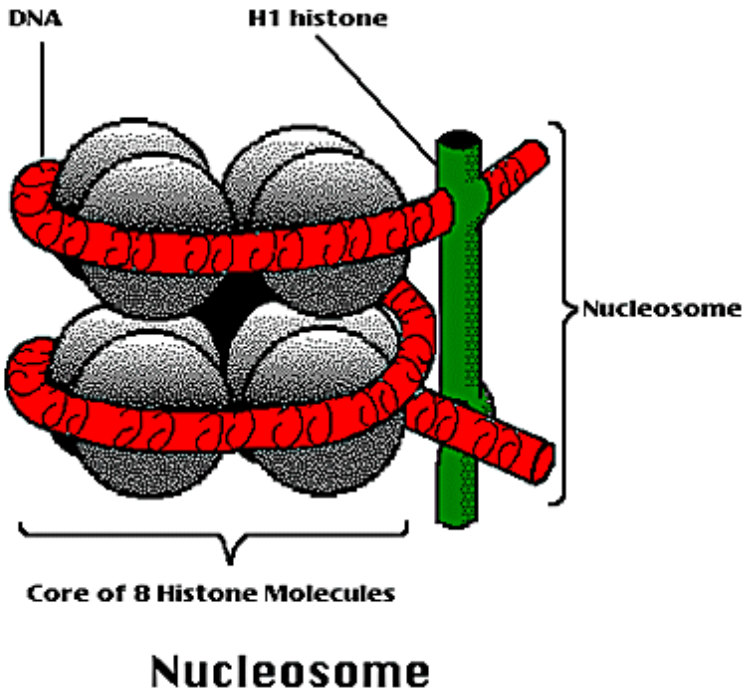
Fibroblasts → Changing the epigenetic states

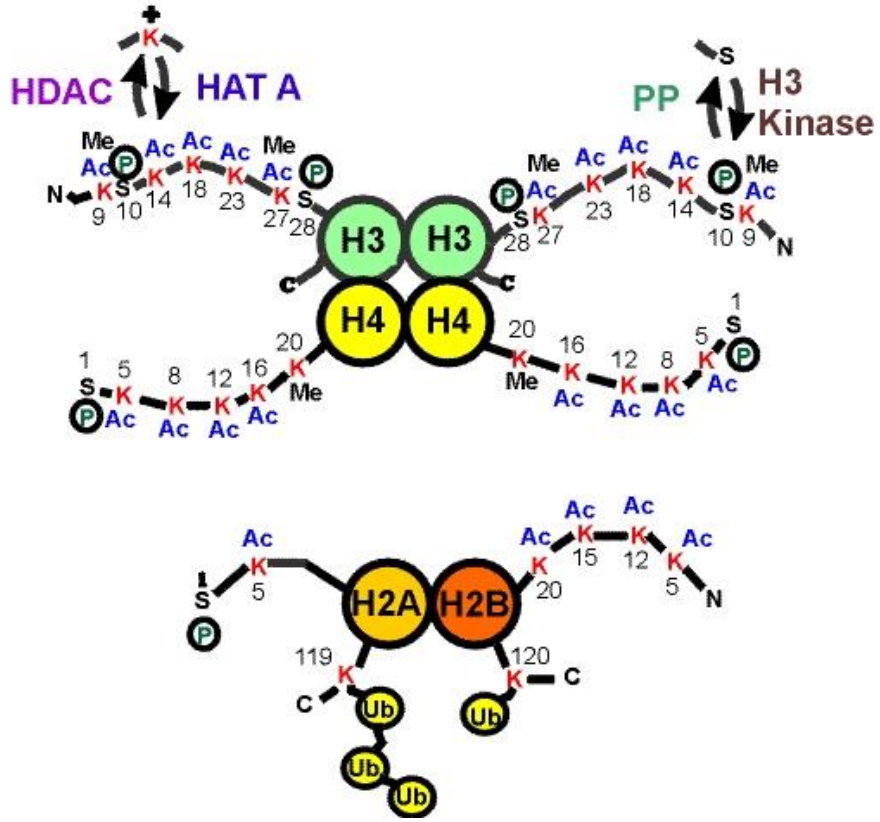
→ embryonic stem cells

What happened to Dolly

- Cloned from a nucleus of a 6-yr old sheep
- Had 20% shorter telomere length
- Gave birth to Bonnie and triplets in the old fashioned way (with normal telomere length)
- Died 14 Feb 2003 at 6 yr of age (~ ½ of normal life span)
- Suffering from arthritis, lung disease, etc
- Preserved and on display at the National Museum of Scotland.

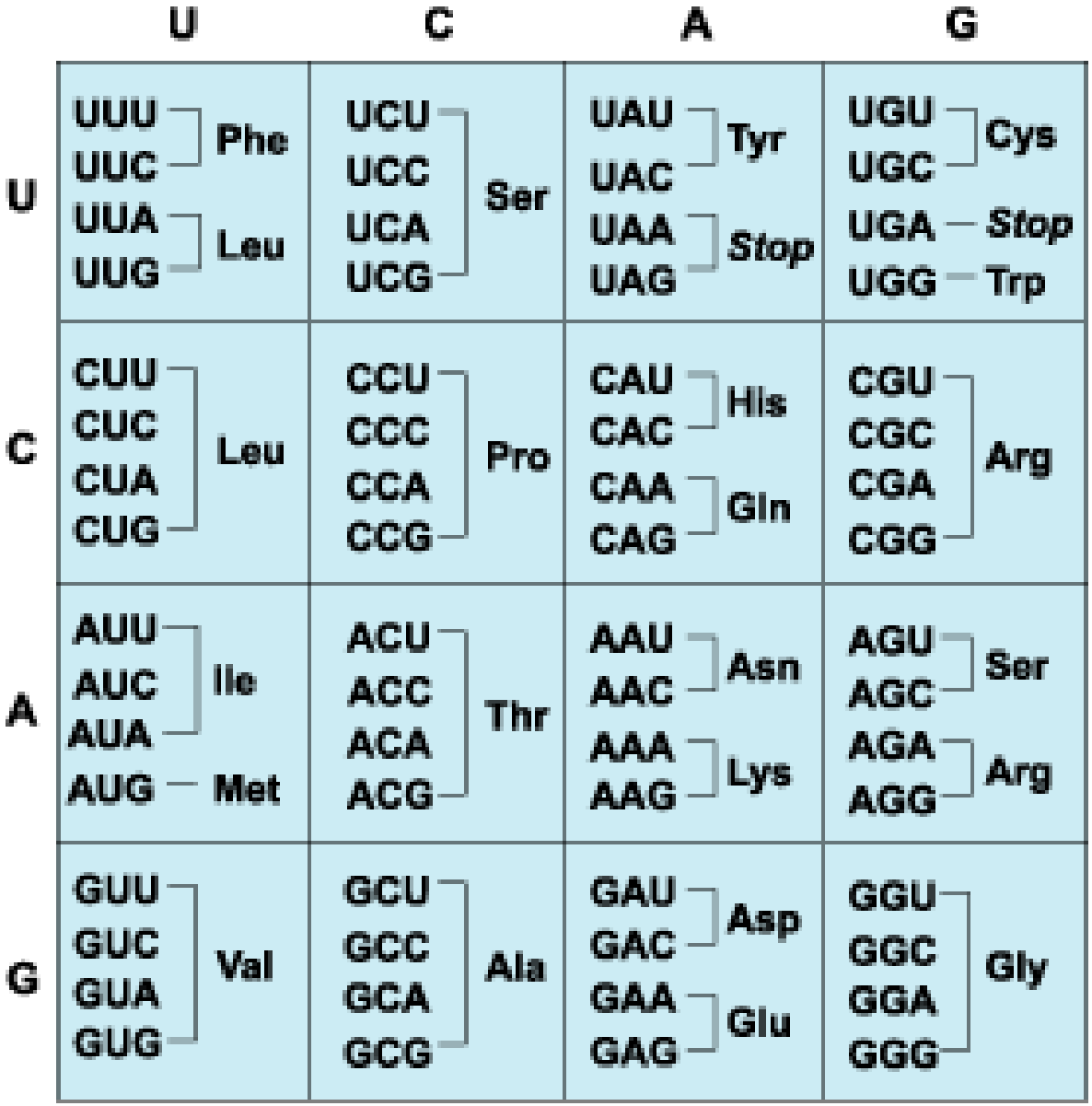
Histone tails:
Major sites of histone modifications





Histone tails: 16 – 25 aa
30% of histone mass
Invisible in crystal structures

Genetic code



Histone code or epigenetic info

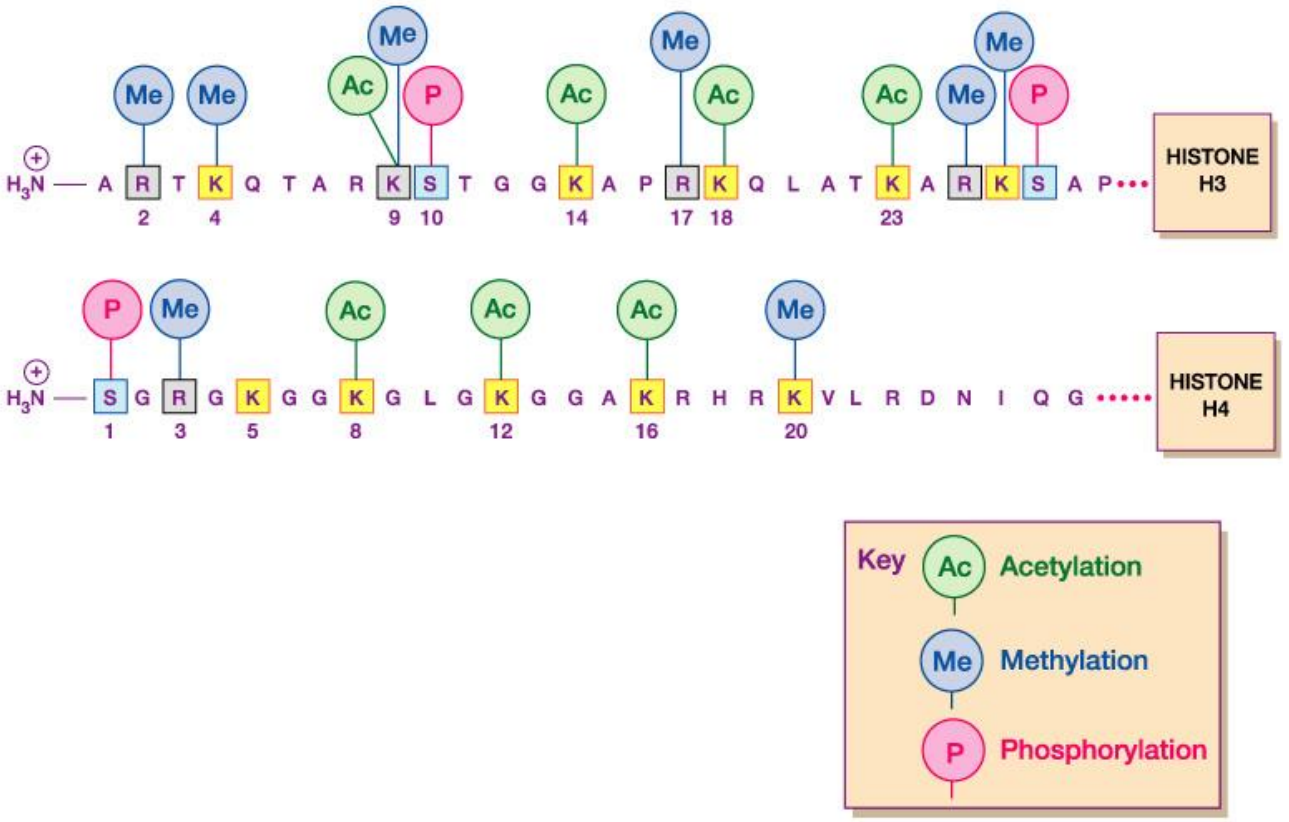


Figure 10-1 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Context dependent meanings

Two key points to remember

- Understand what **hetrochromatin** is and how DNA methylation Histone modification affects the heterochromatin
- Understand how imprinting involves parent of origin specific modifications in the DNA in such a manner that males want big offspring and females want little offspring – **tug of war.**