Genomics, Bioinformatics & Medicine

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Epigenetics

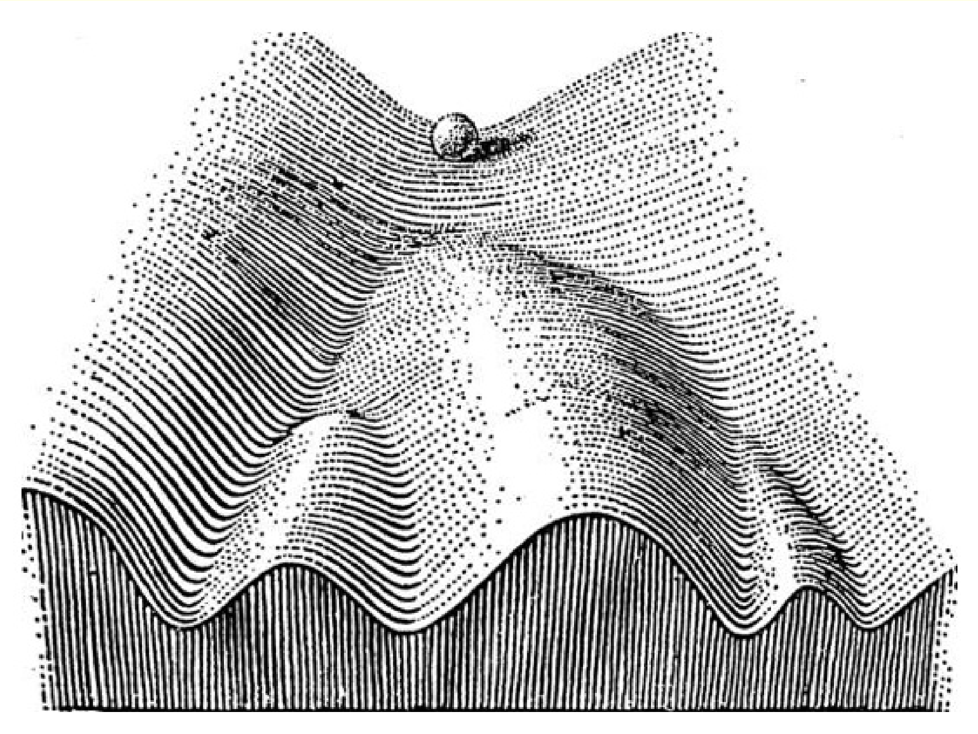
http://biochem158.stanford.edu/Epigenetics.html

Doug Brutlag
Professor Emeritus of Biochemistry & Medicine
Stanford University School of Medicine

What is Epigenetics?

- C.H. Waddington coined the term epigenetics to mean above or in addition to genetics to explain differentiation.
- How do different adult stem cells know their fate?
  - Myoblasts can only form muscle cells
  - Keratinocytes only form skin cells
  - Hematopoietic stem cells only become blood cells
  - But all have identical DNA sequences.

C.H. Waddington



Waddington's Epigenetic Landscape

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- Modern definition is non-sequence dependent inheritance.
- How can identical twins have different natural hair colors?

Identical Twins with Different Hair Color

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- How can a single individual have two different eye colors?

Mosaicism:
An Individual with Two Different Eye Colors

"Diego"

Mosaicism: An Individual with Two Different Eye Colors

“Josie Too”

Mosaicism: An Individual Eye with Two Colors

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Coat Colors of Genetically Identical Agouti Mice Liter Mates

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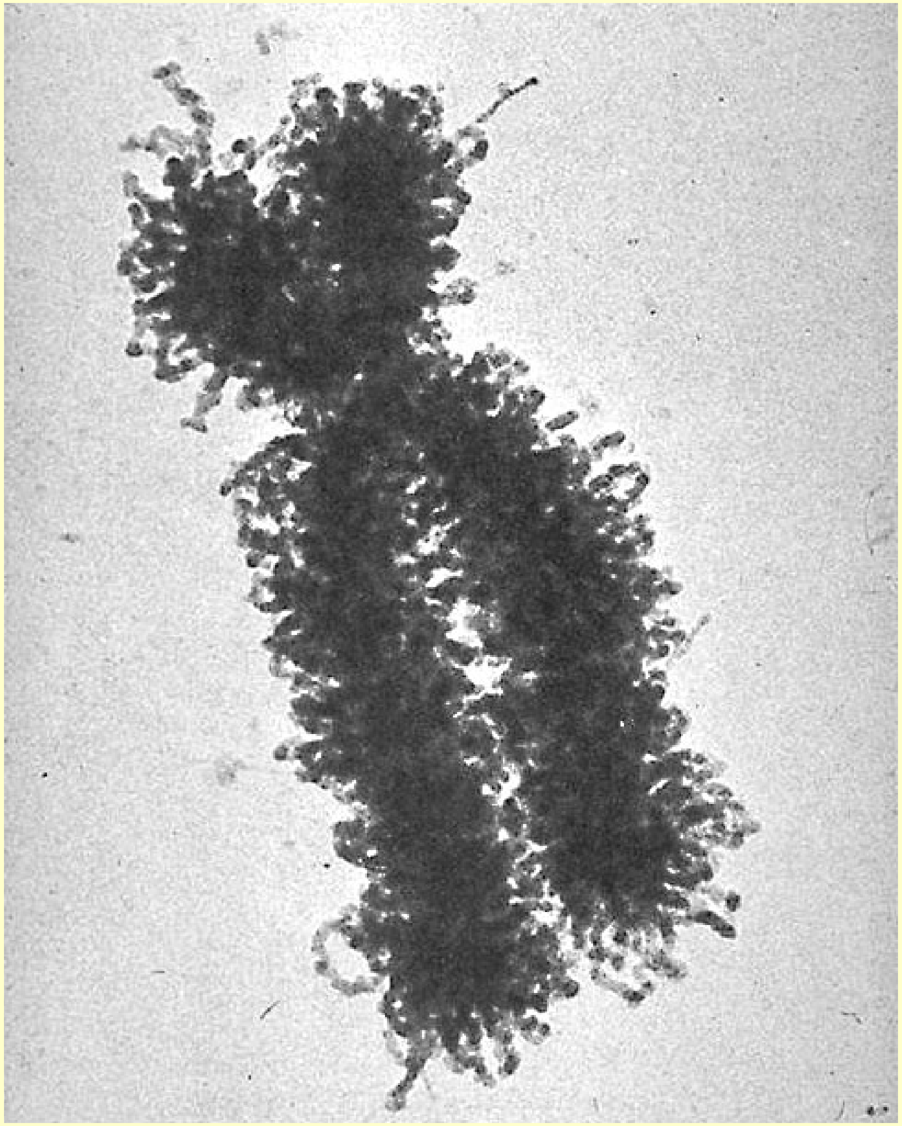
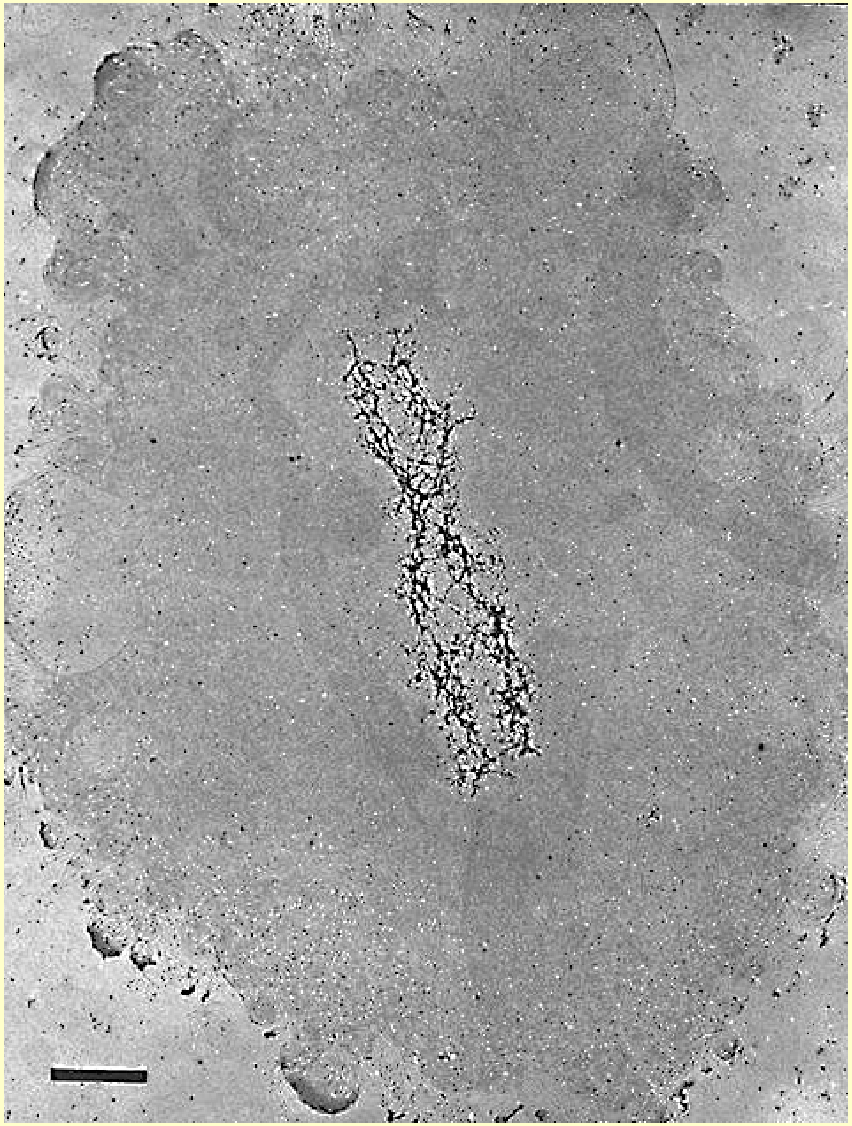
- How can identical twins have different natural hair colors?
- How can a single individual have two different eye colors?
- How can identical twin liter mates show different coat colors?
- How can just paternal or maternal traits be expressed in offspring? This is called genetic imprinting.
- How can females express only one X chromosome per cell?
- How can acquired traits be passed on to offspring?
- Some changes in gene expression that are, in fact, heritable!

Human Mitotic Chromosome

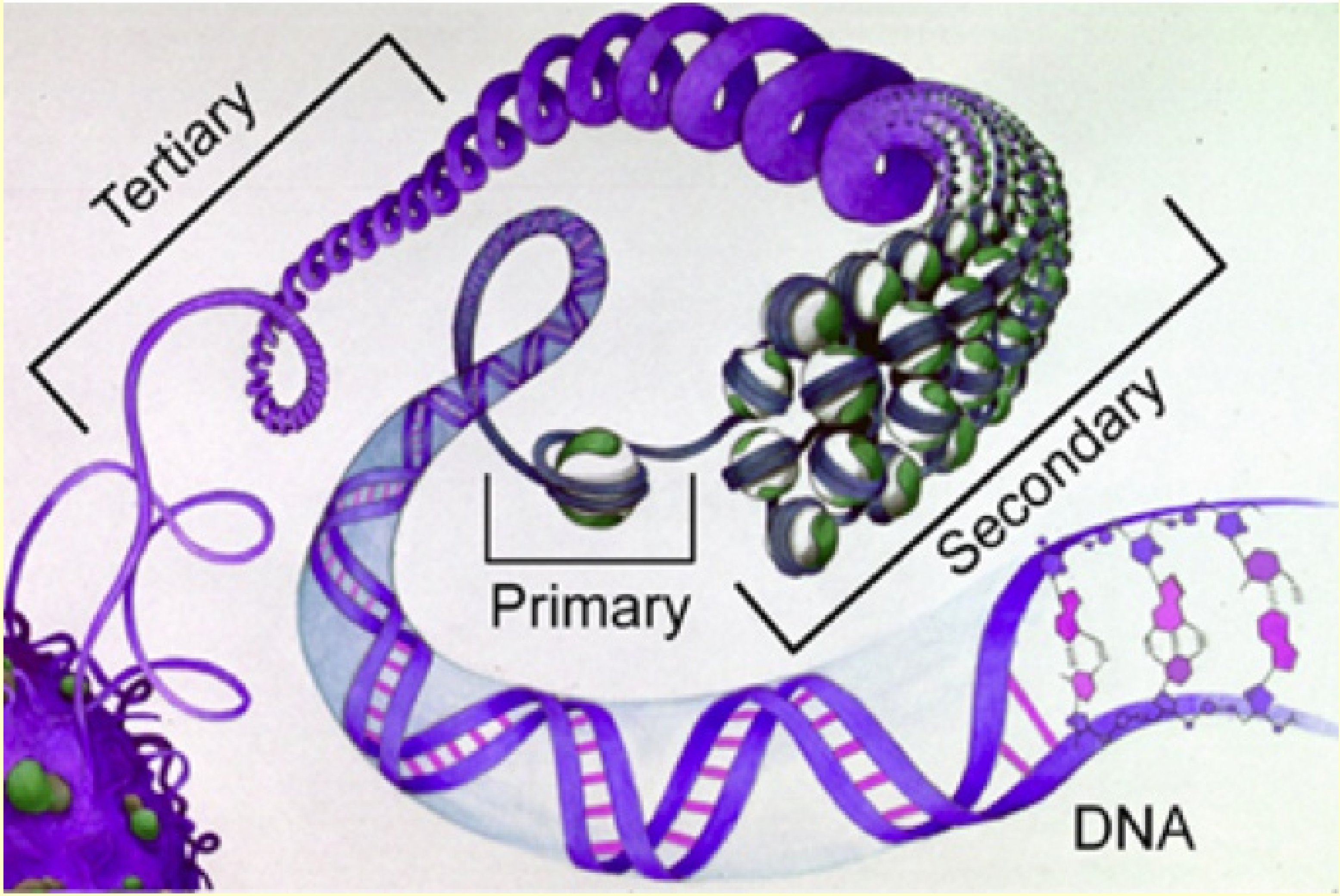


DNA in a Human Chromosome

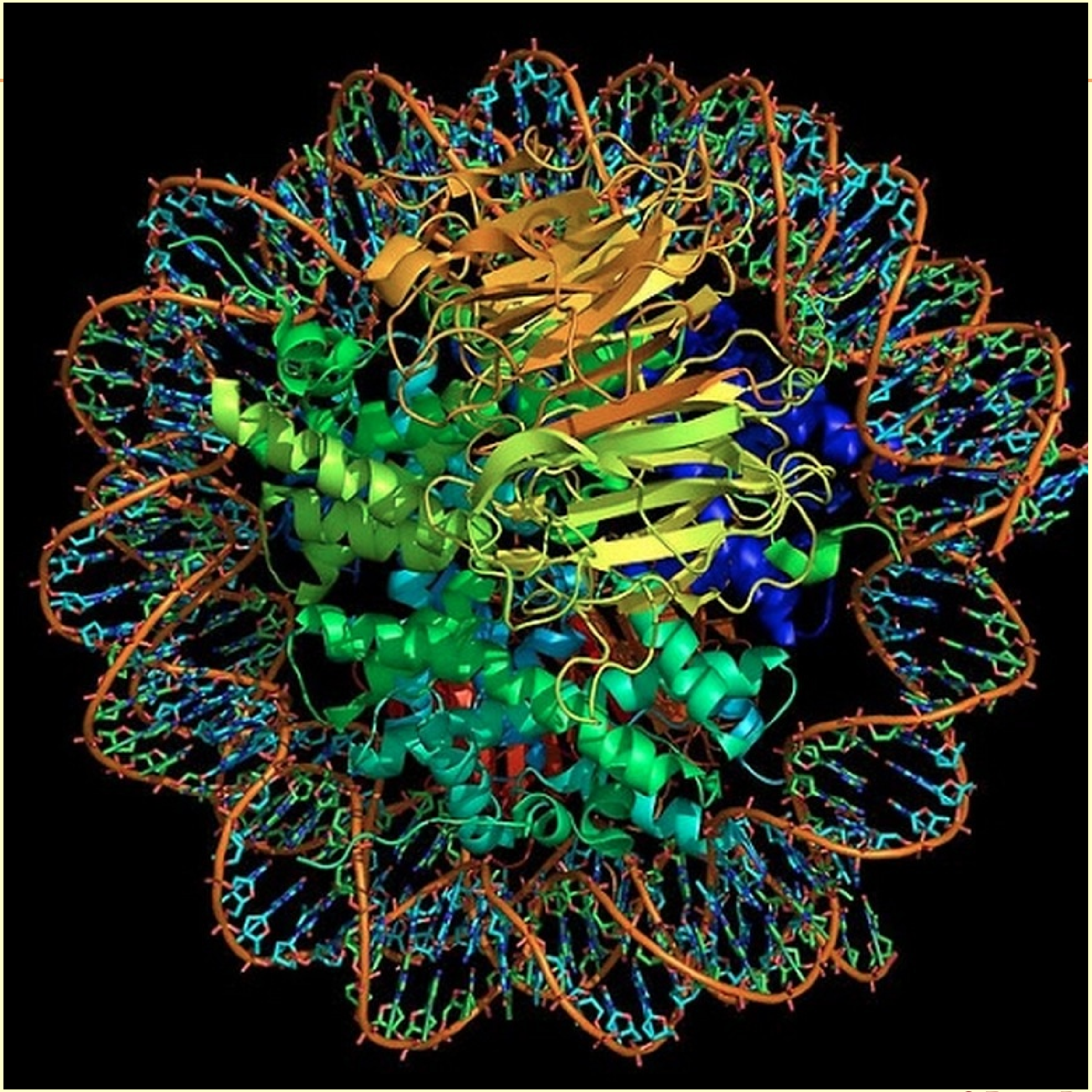


DNA in a Human Chromosome

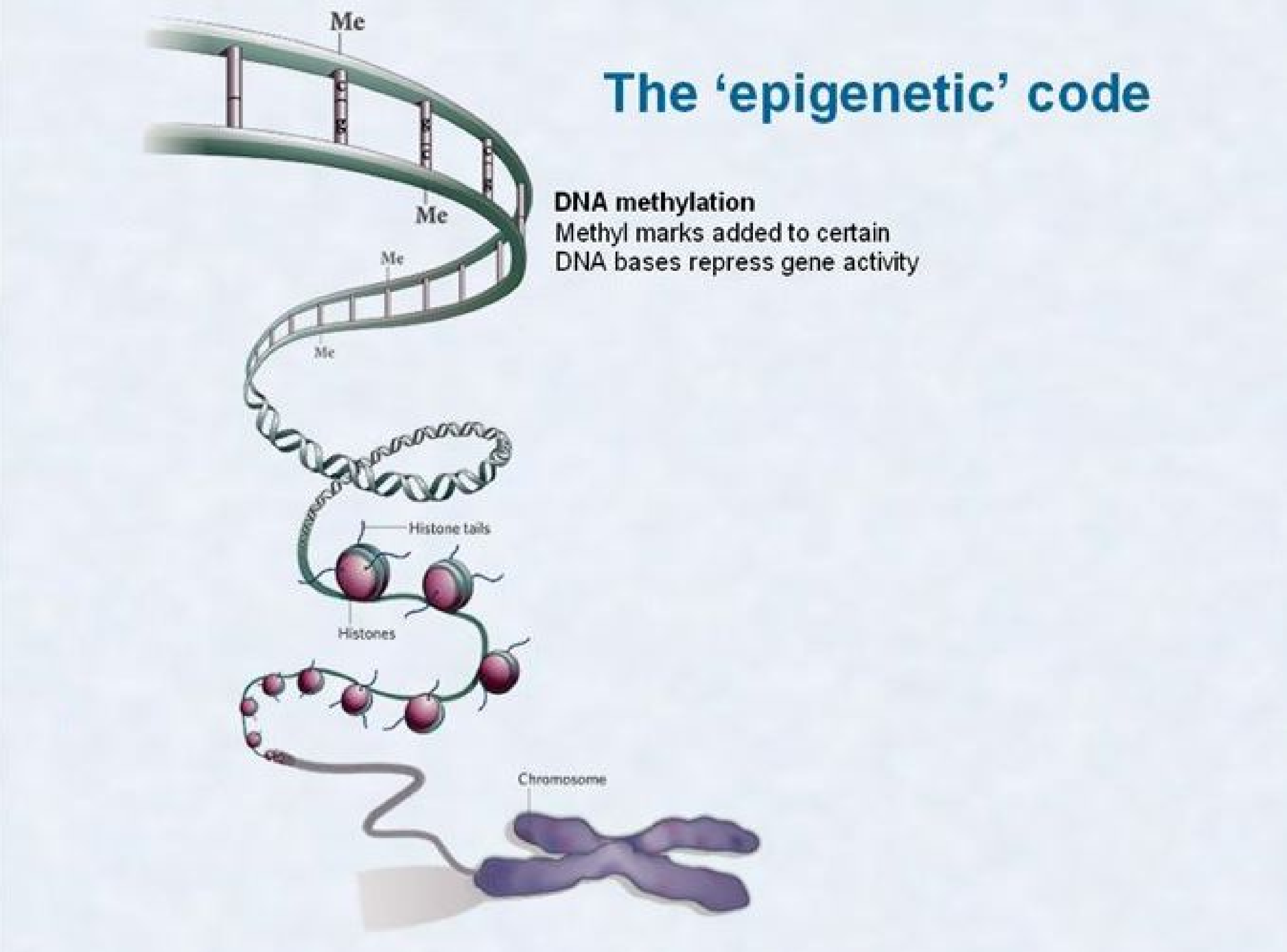
Three Levels of Folding of DNA in Chromatin



Nucleosome Core Structure



DNA Methylation & the Epigenetic Code



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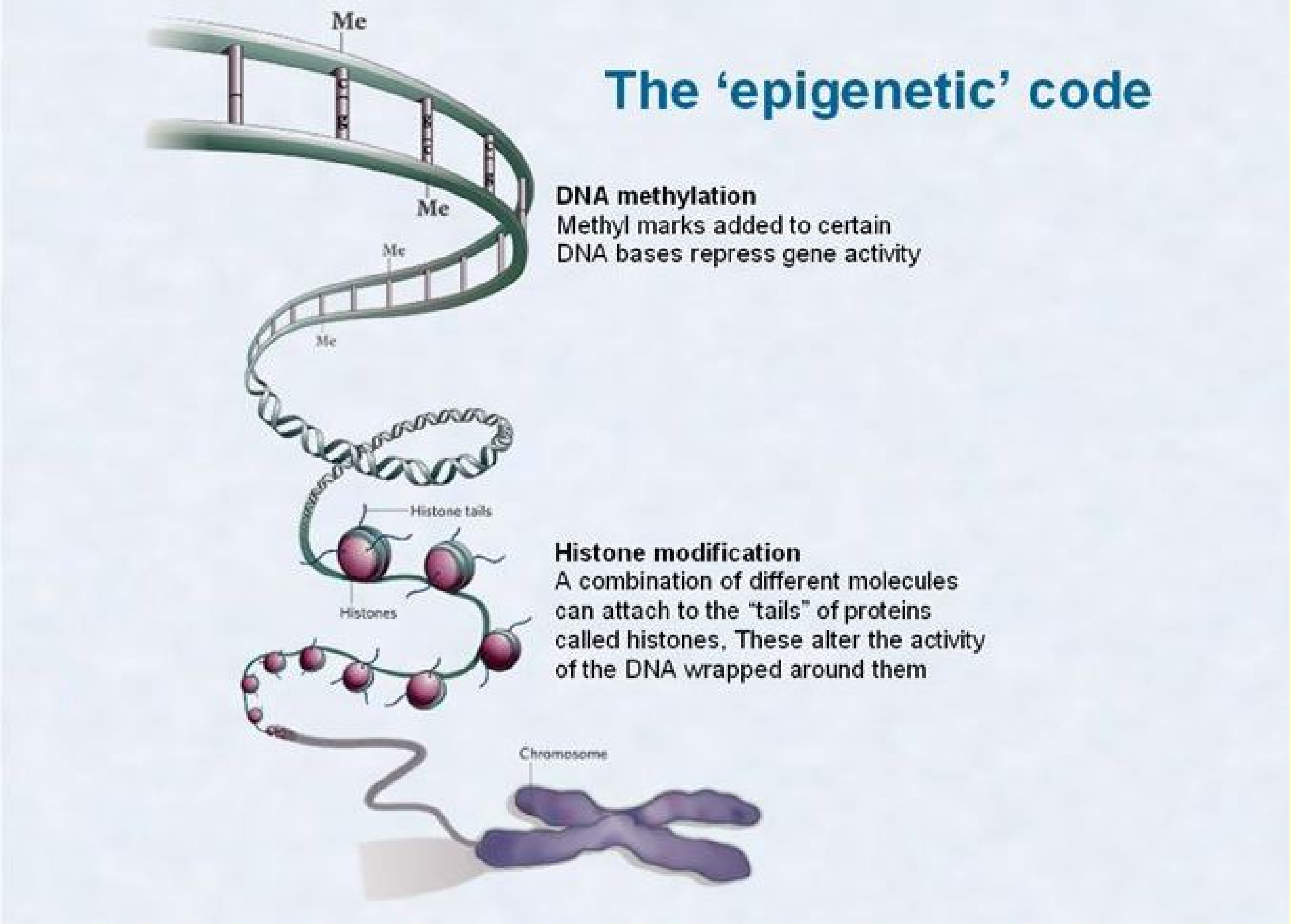
DNA Methylation & Histone Modifications Form the Epigenetic Code



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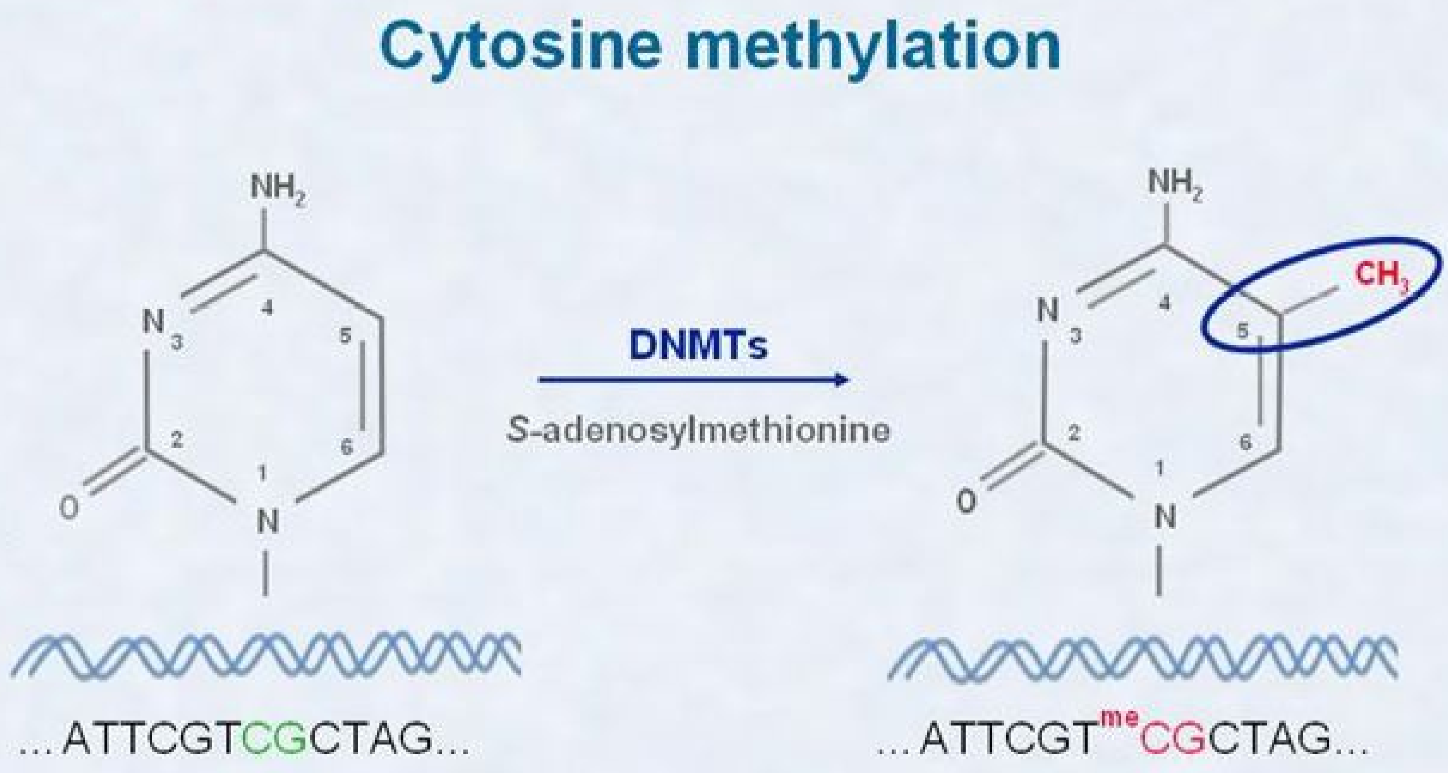
Methylation of Cytosine in DNA



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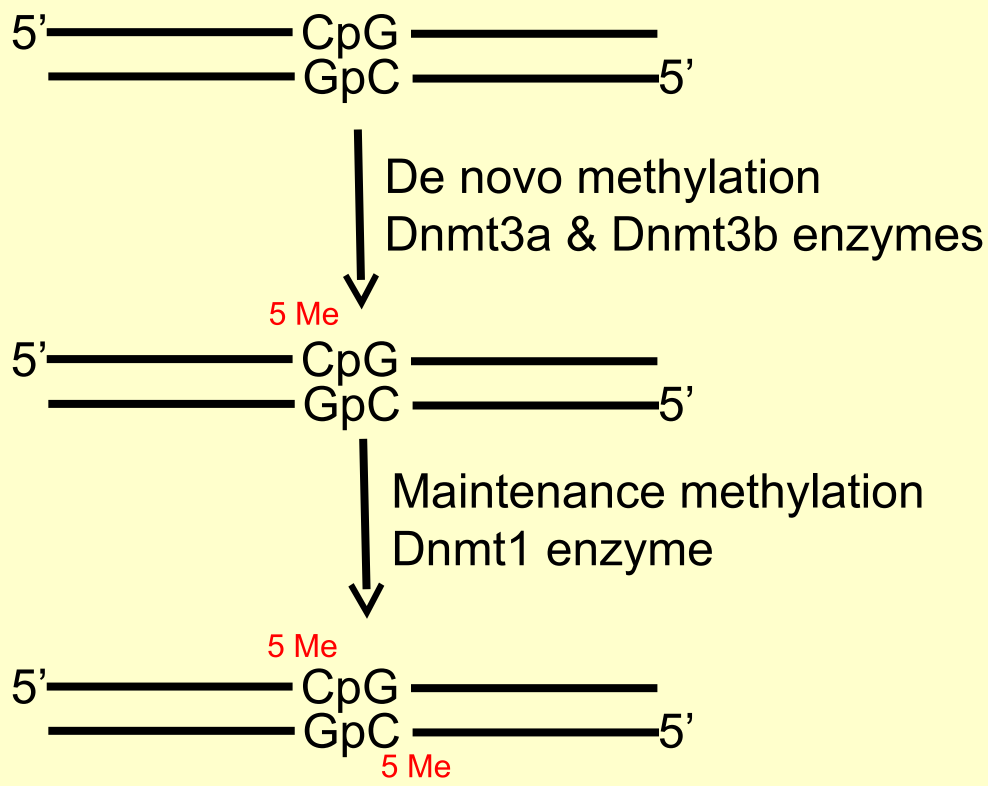
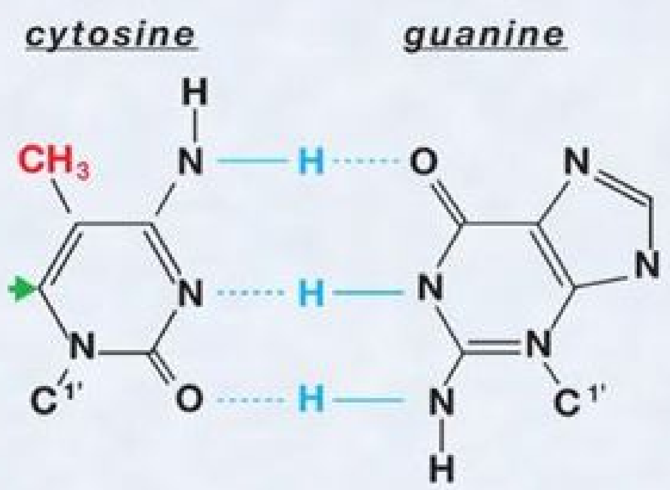
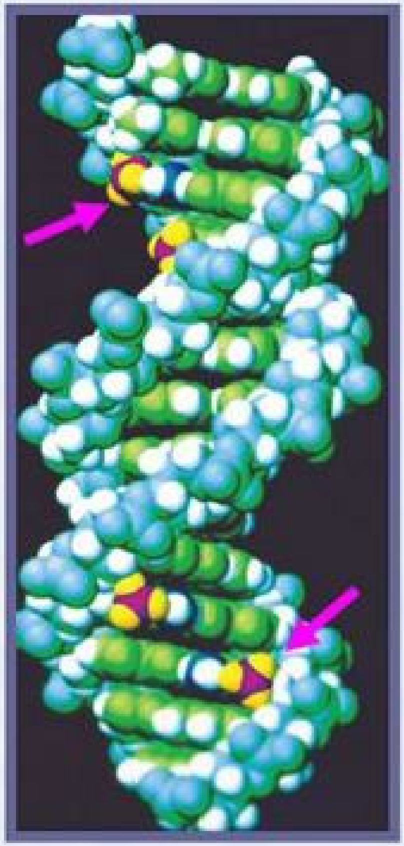
Only Cs in CG sequences are Methylated



5-Methyl Cytosine in DNA

Cytosine methylation





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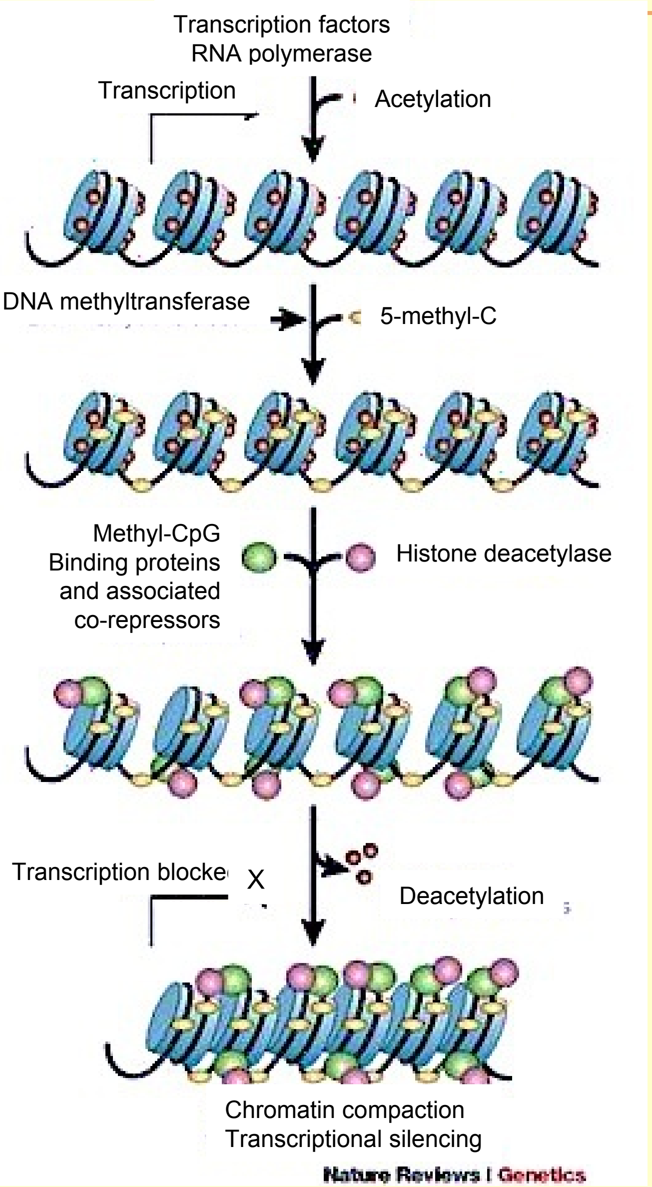
Cytosine Methylation Maintains Inactive-Condensed Chromatin State



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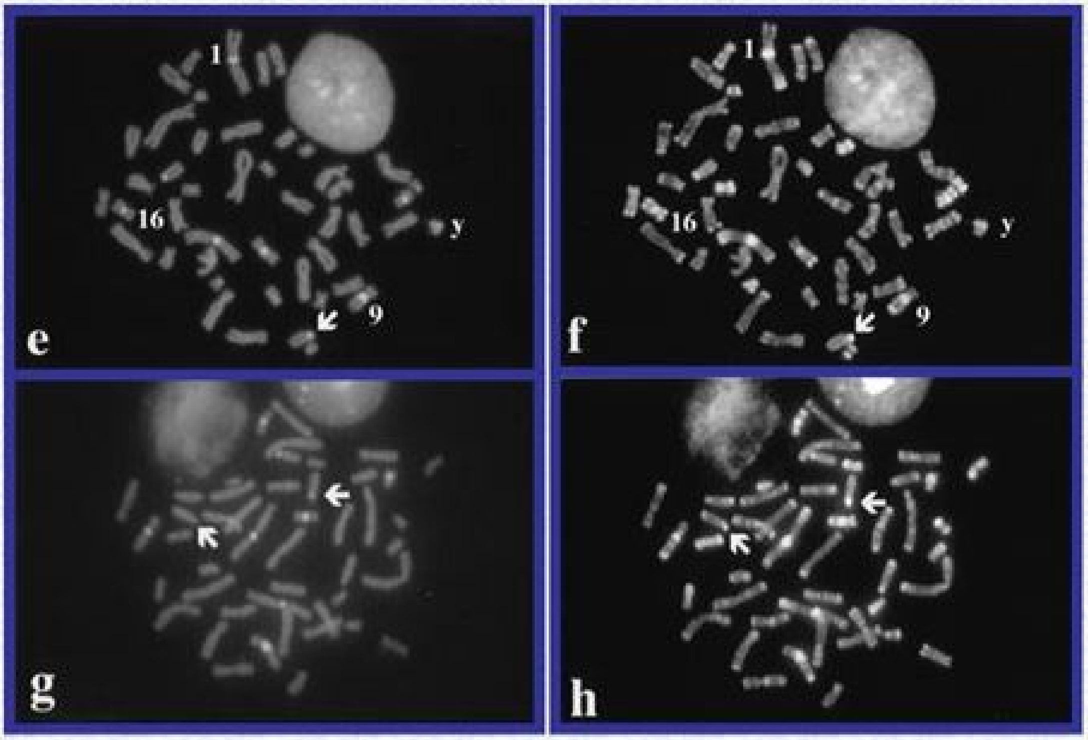
Henry Stewart Talks

5-Methyl Cytosine is Found in Heterochromatic Regions

The distribution of cytosine methylation in mammals

- Heterogeneity visible at cytogenetic scale
- Associated with heterochromatic regions

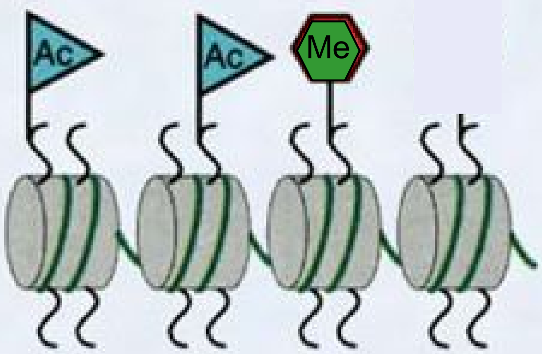


PMID: 9609658

Structure & Epigenetics of Euchromatin versus Heterochromatin

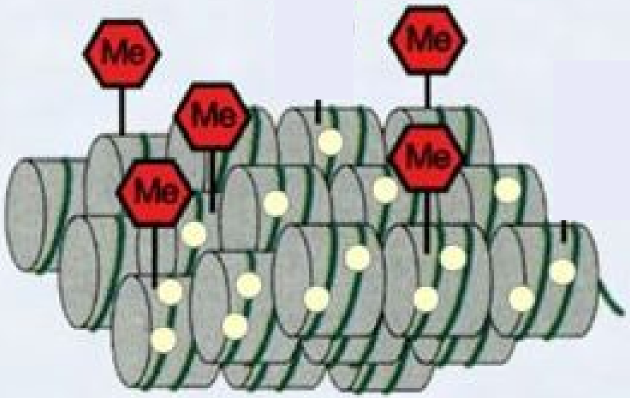
DNA methylation and histone modifications help to compartmentalize the genome into domains of different transcriptional potentials

Euchromatin



- High histone acetylation
- Low DNA methylation
- H3-K4 methylation

Heterochromatin



- Low histone acetylation
- Dense DNA methylation
- H3-K9 methylation

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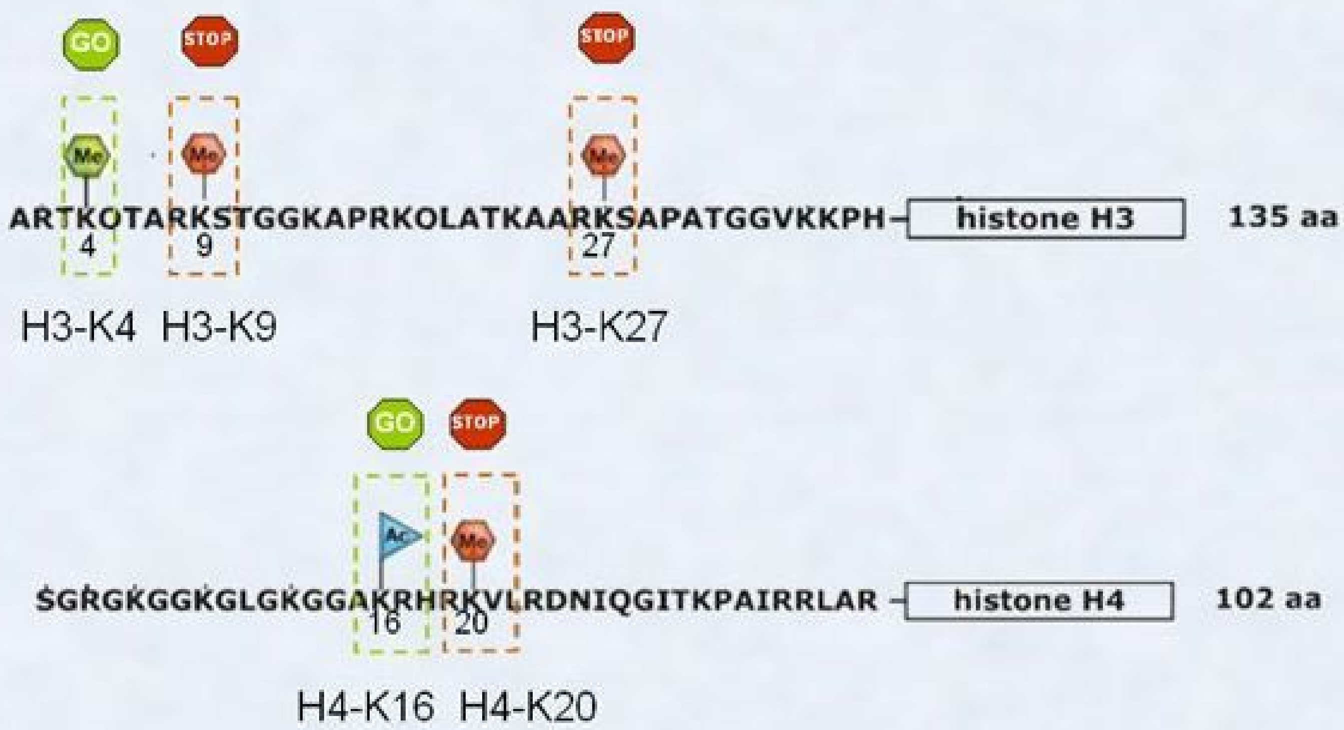
Histone Code



Histone Code

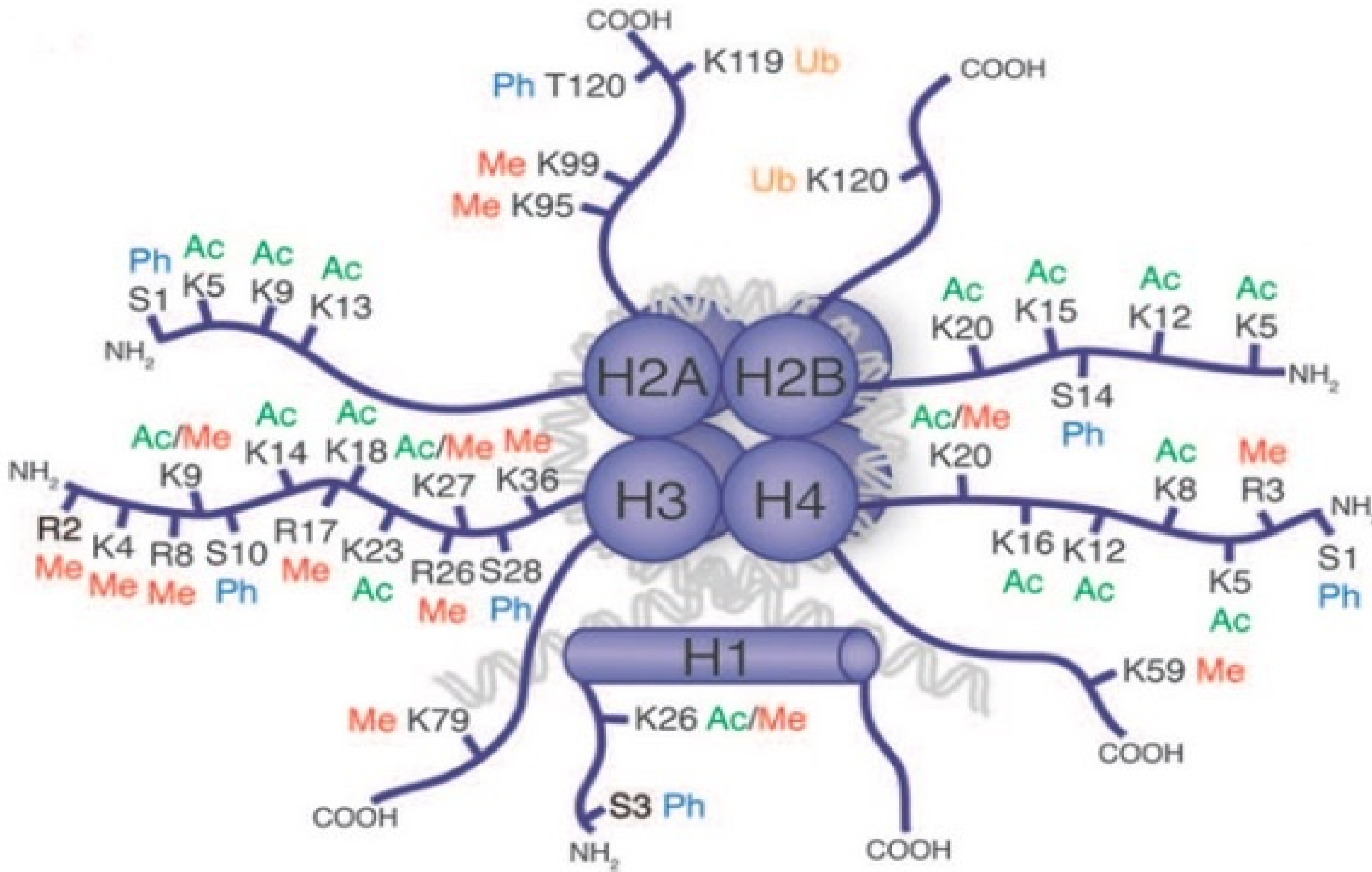


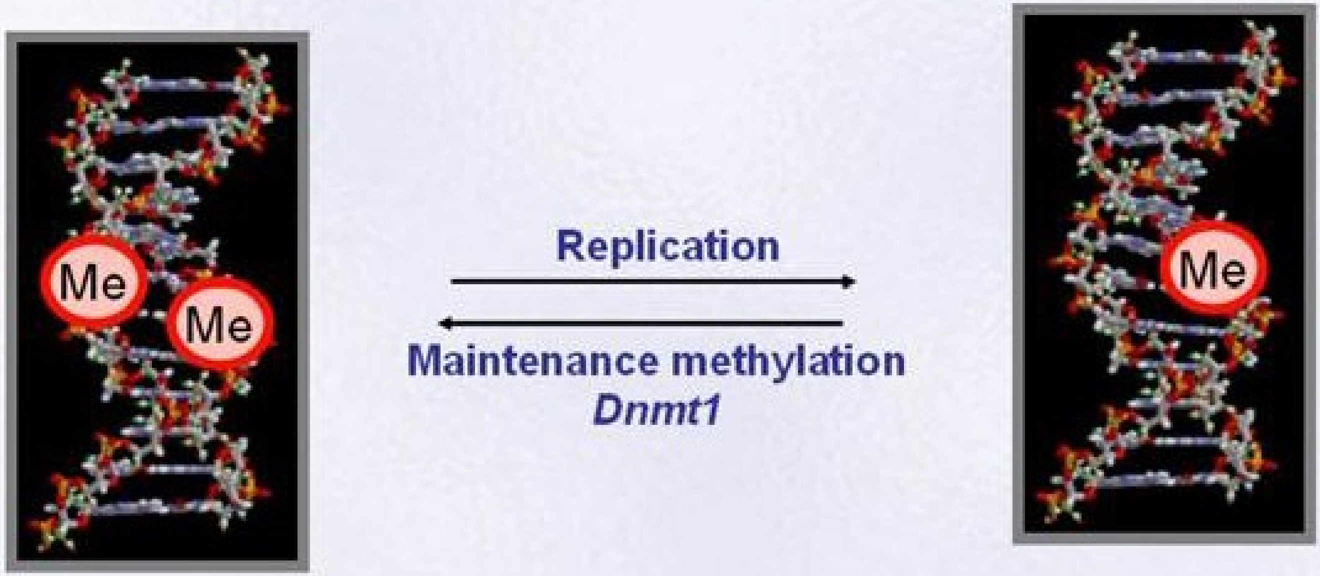
FIGURE 4.

Nucleosome with histone posttranslational modifications (Adapted from 1)

"Pluripotent Stem Cells", book edited by Deepa Bhartiya and Nibedita Lenka

Maintenance of Cytosine Methylation

Establishment and maintenance



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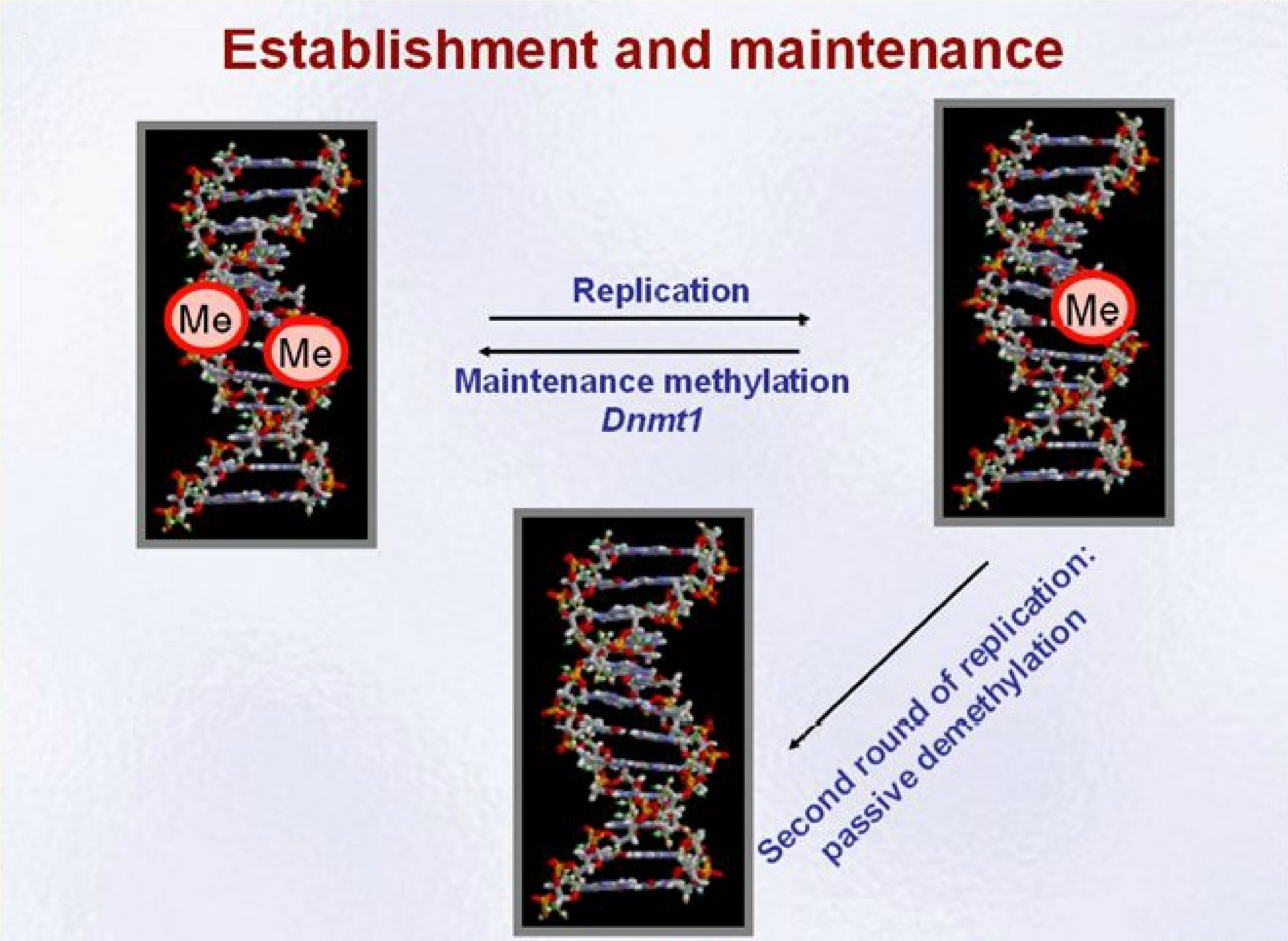
Passive Demethylation of 5-Methyl-Cytosine



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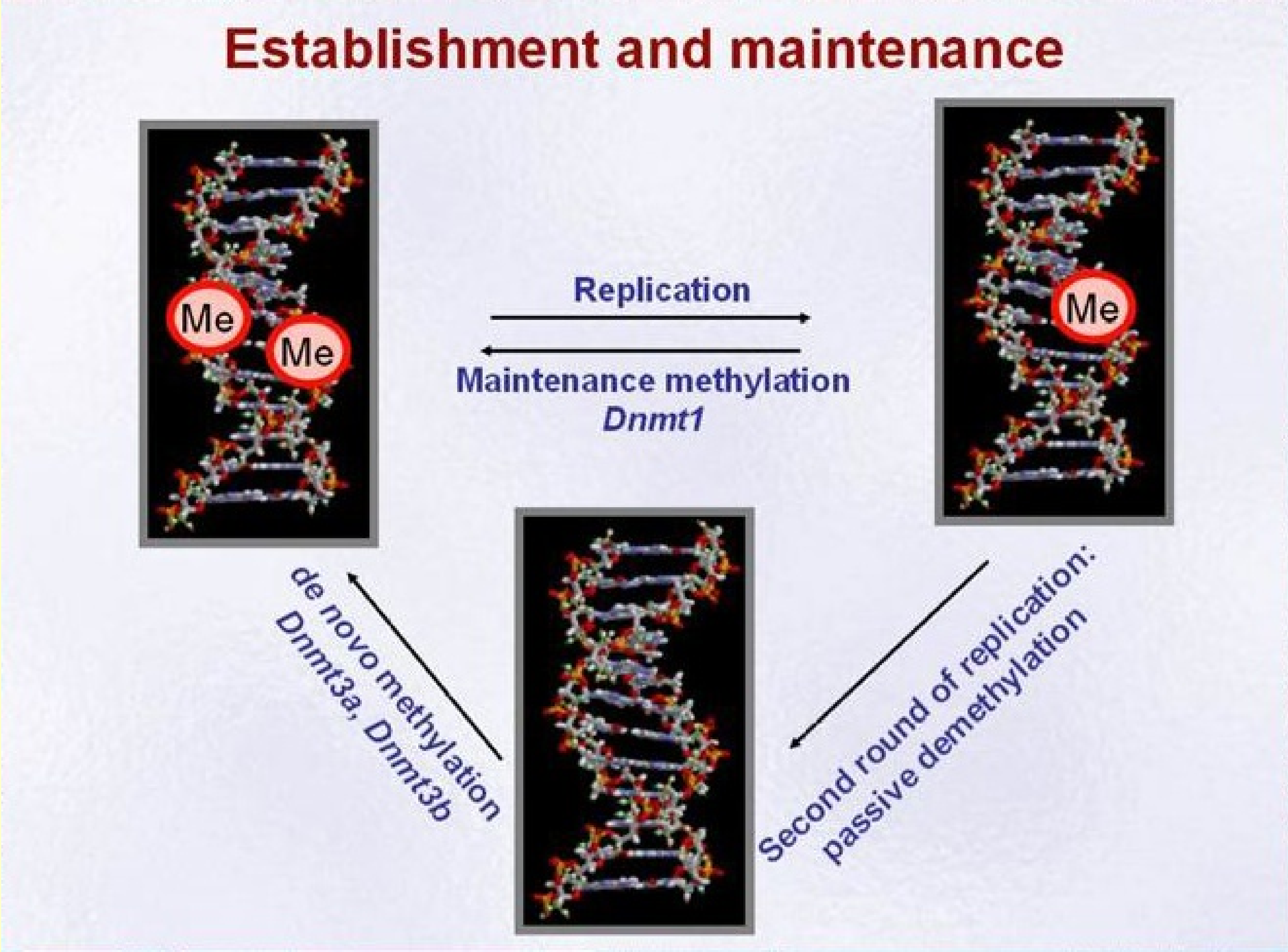
Establishment and Maintenance of Cytosine Methylation



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Some DNA Methyl Transferases are Essential

Mammalian Dnmts are essential

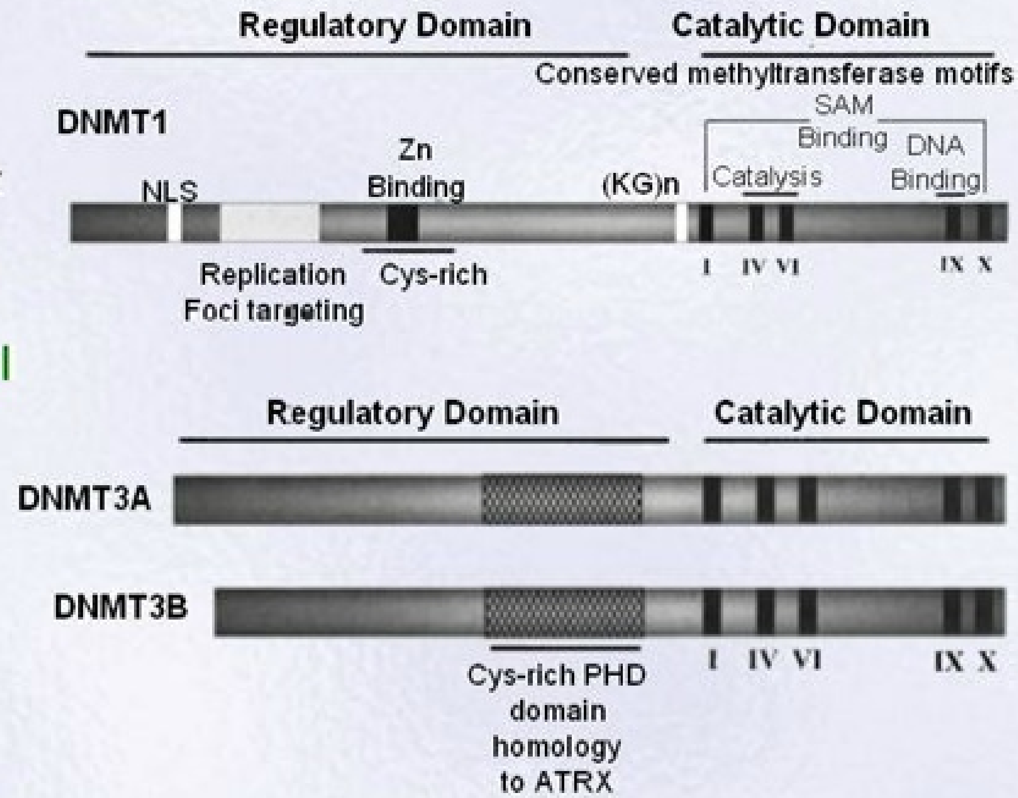
Dnmt1: embryonic lethal

Dnmt2: no obvious effect

Dnmt3a: perinatal death

Dnmt3b: embryonic lethal

Dnmt3l: no imprints

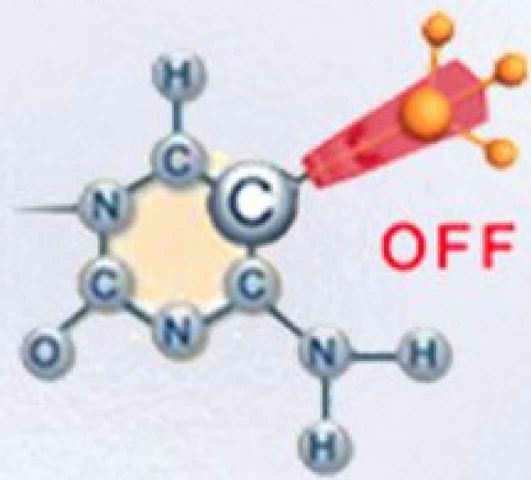


Robertson, KD, *Oncogene* 2002

Some DNA Methyl Transferases are Essential

Cytosine methylation in mammals

- Gene expression
- Chromosomal stability
- Cell differentiation
- Imprinting
- X-Inactivation
- Carcinogenesis
- Aging



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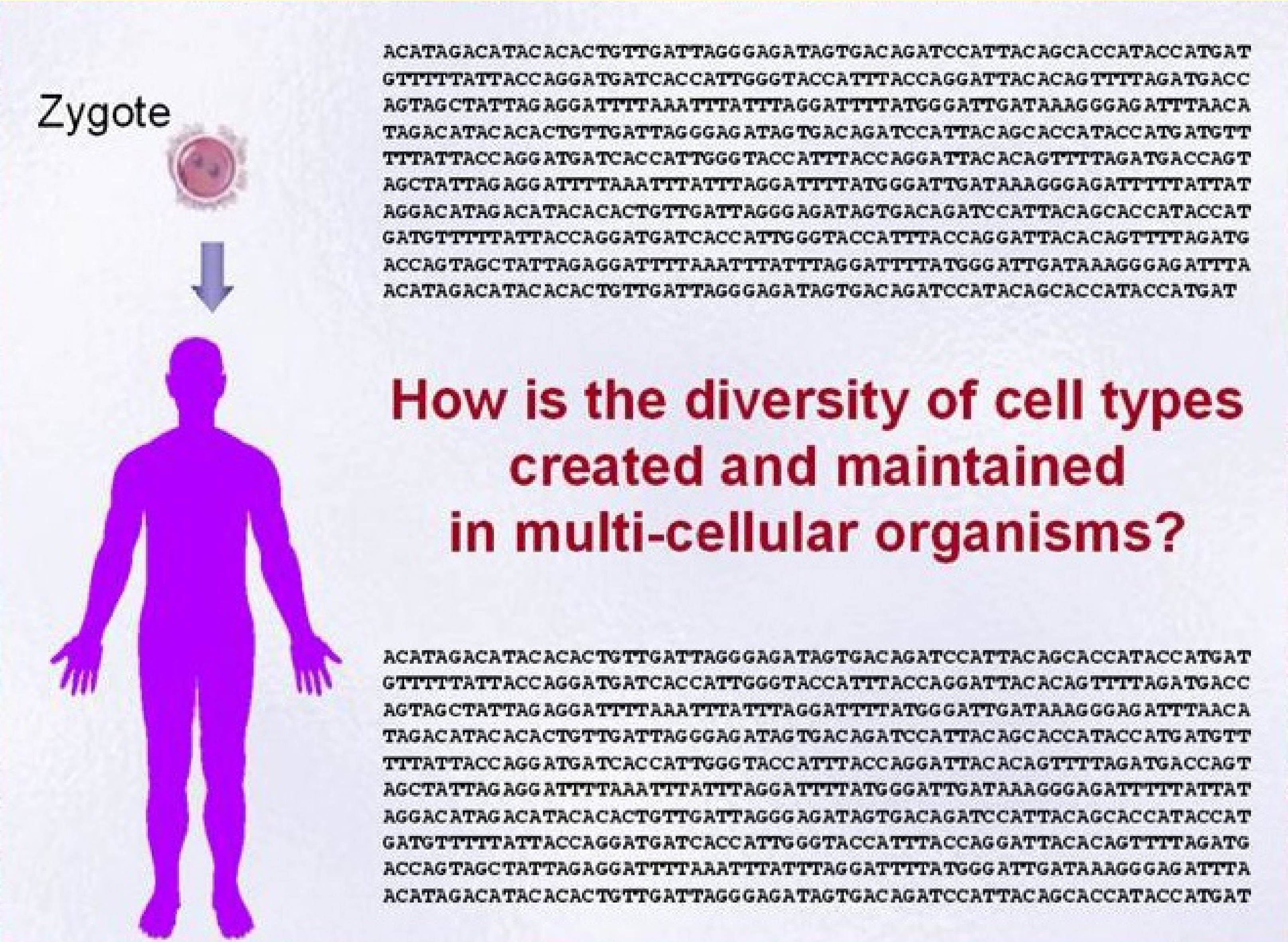
Methylated DNA from Zygote to Adult



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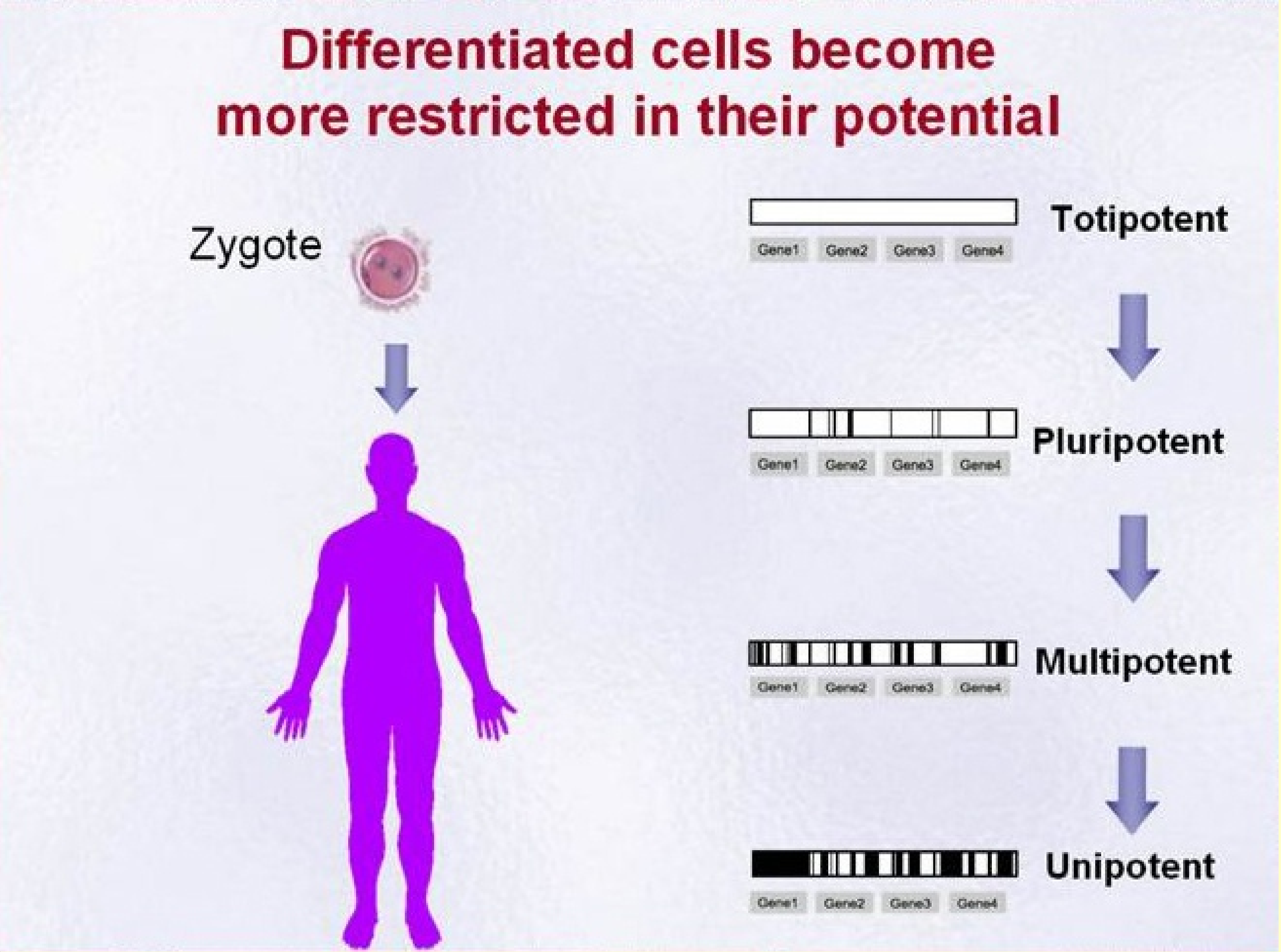

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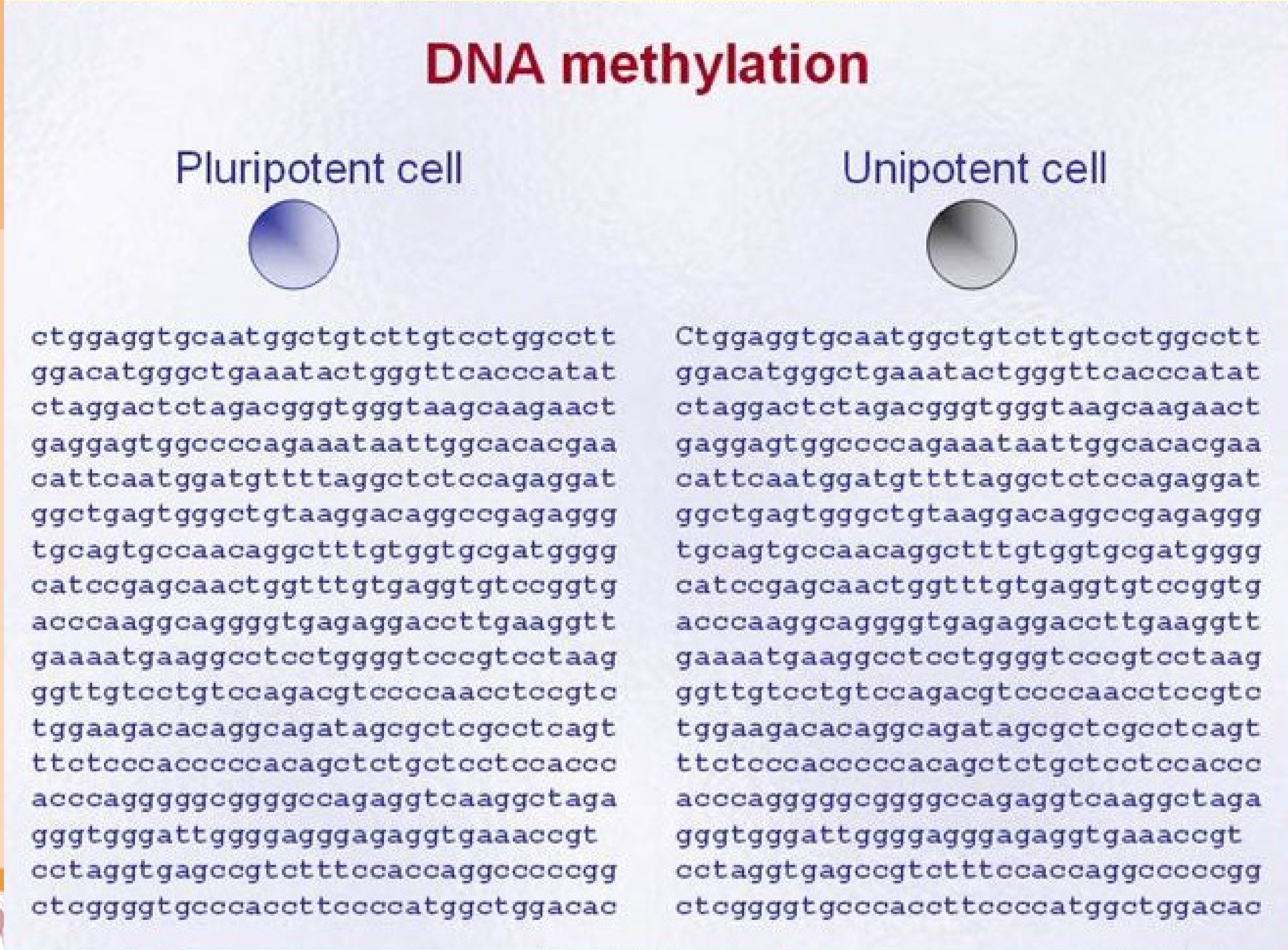
DNA Methylation Differentiates Totipotent Embryonic Stem Cells from Unipotent Adult Stem Cells



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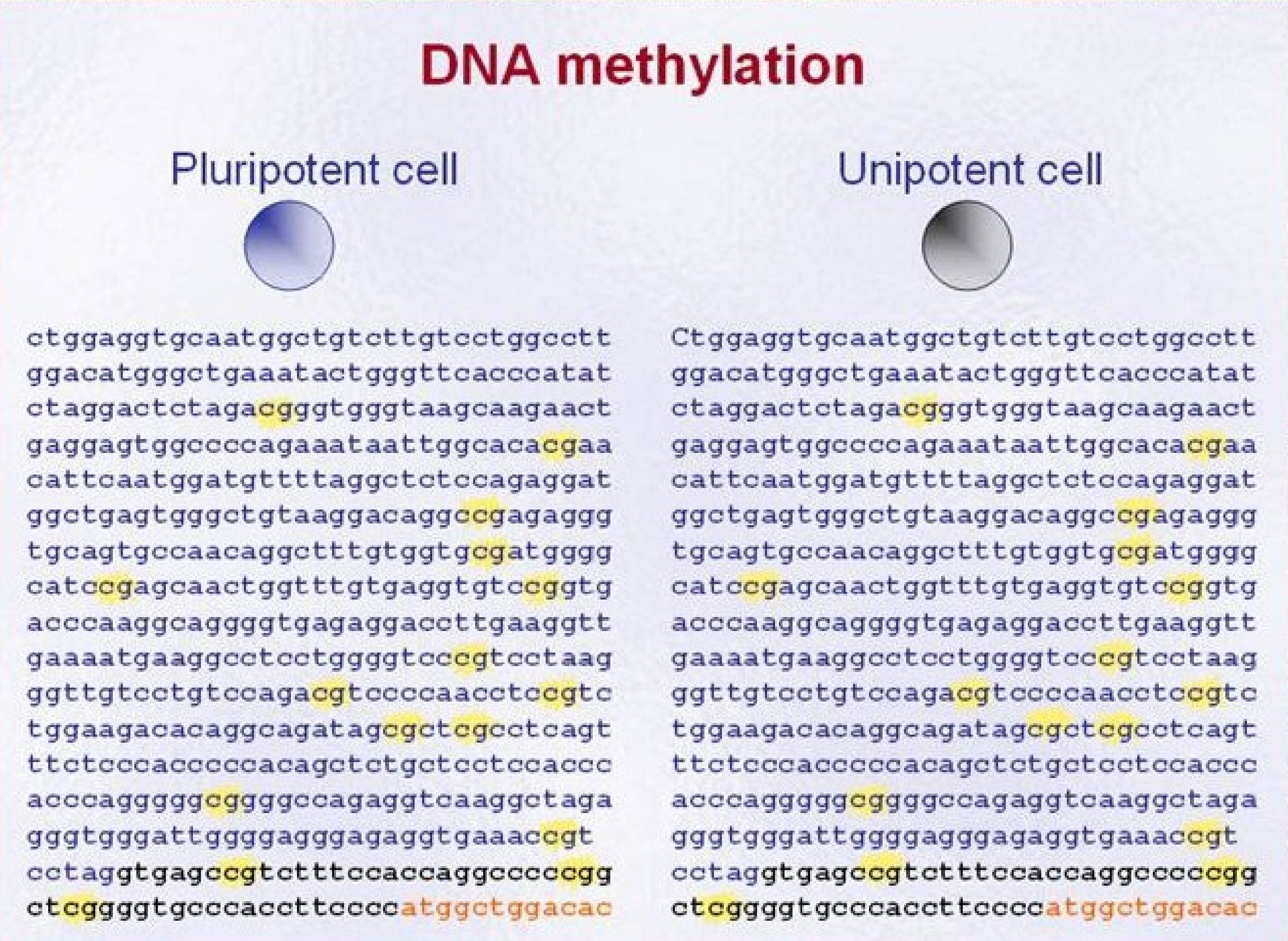

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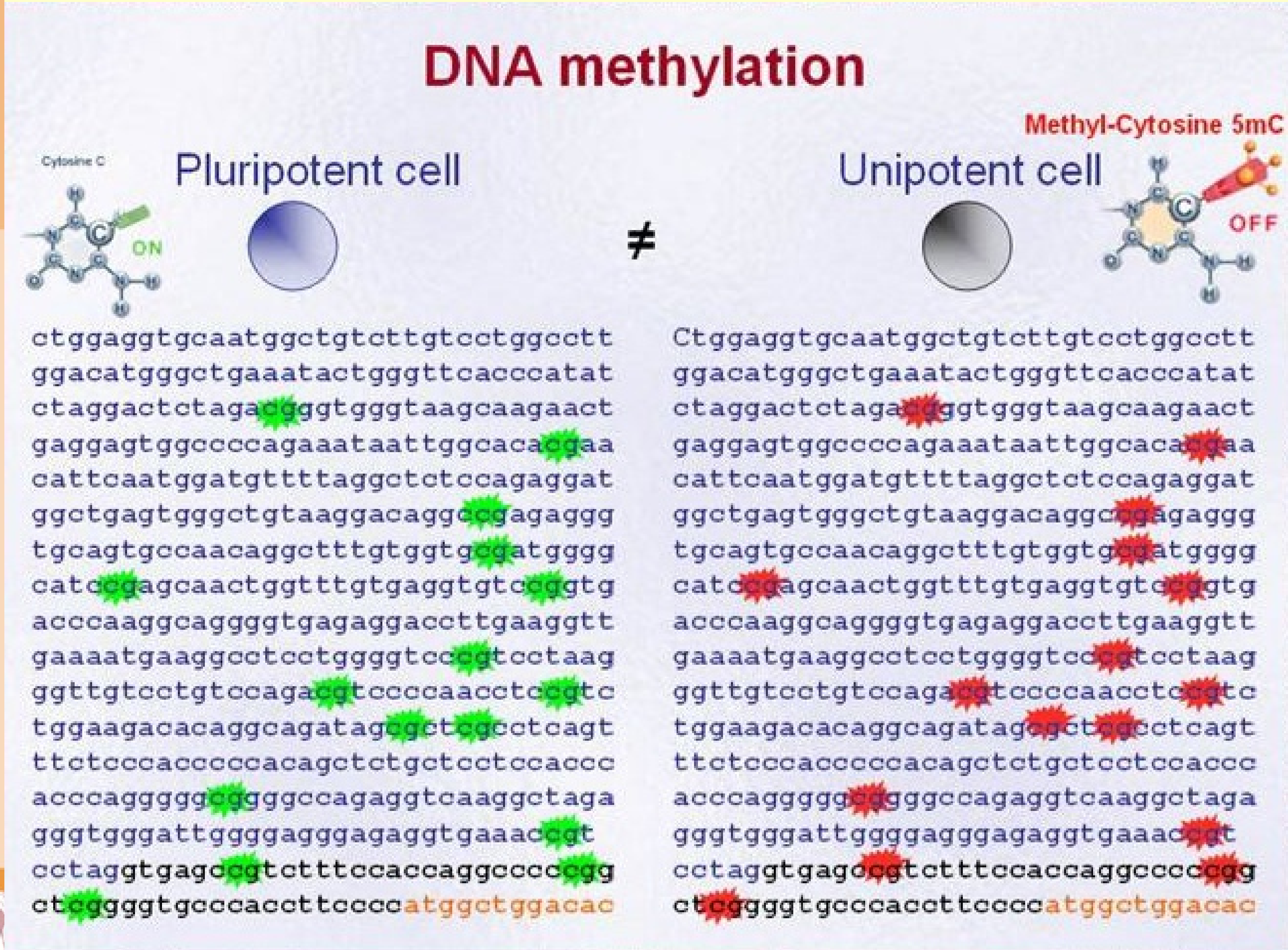

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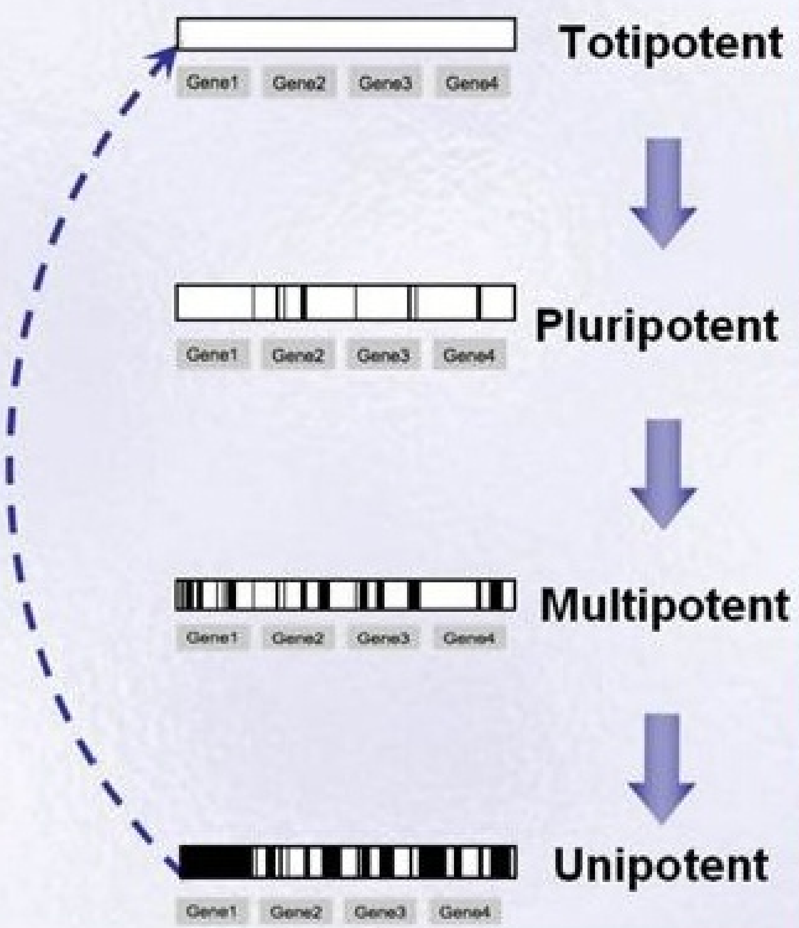
Differentiated Cells can Become Totipotent

Nuclear transplantation demonstrates nuclear equivalence

Briggs and King, 1952
Gurdon, 1960s

"Dolly"

Differentiated cells maintain the potential to generate an entire organism



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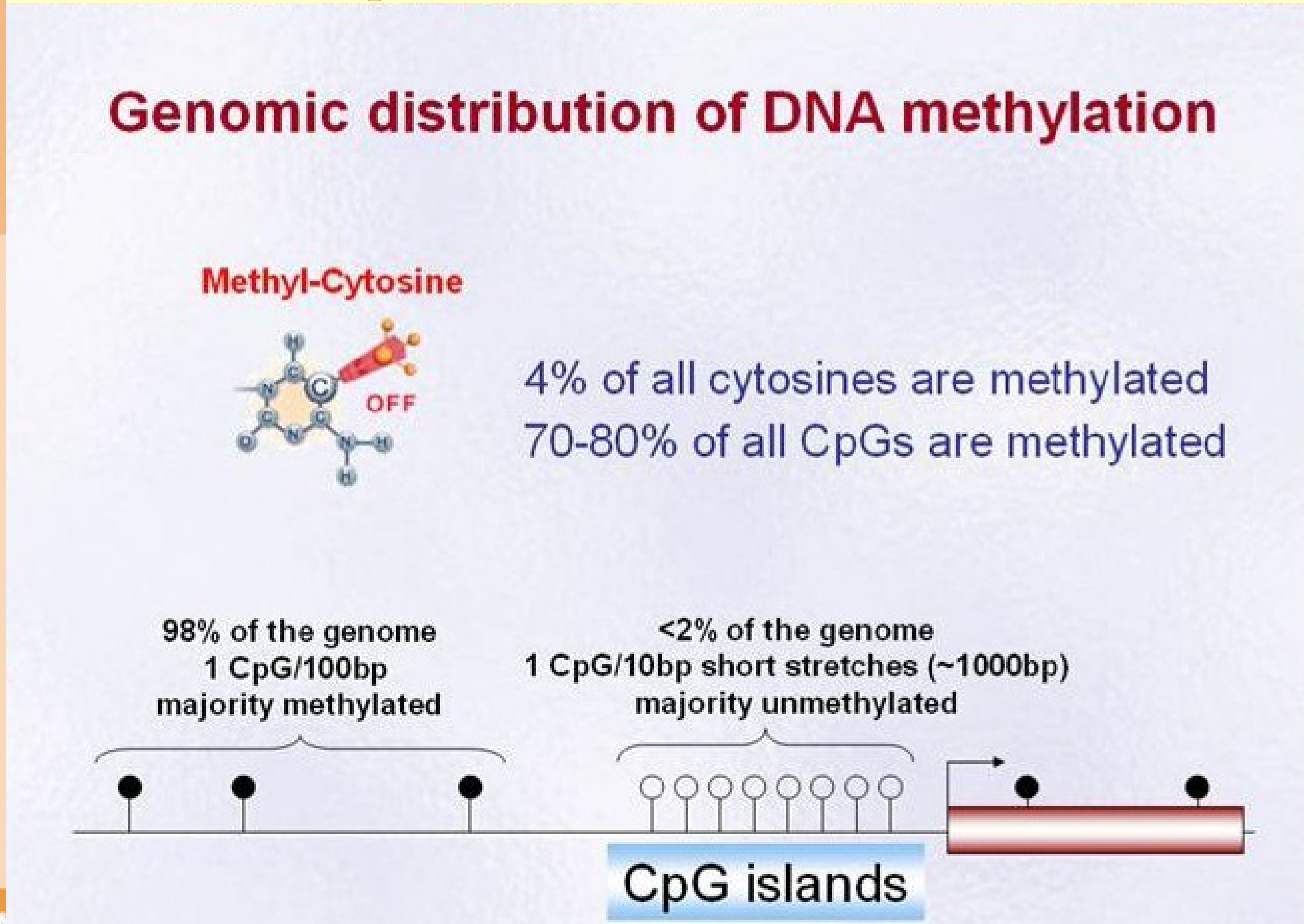
Critical CpG Sequences in CpG Islands Near Promoters



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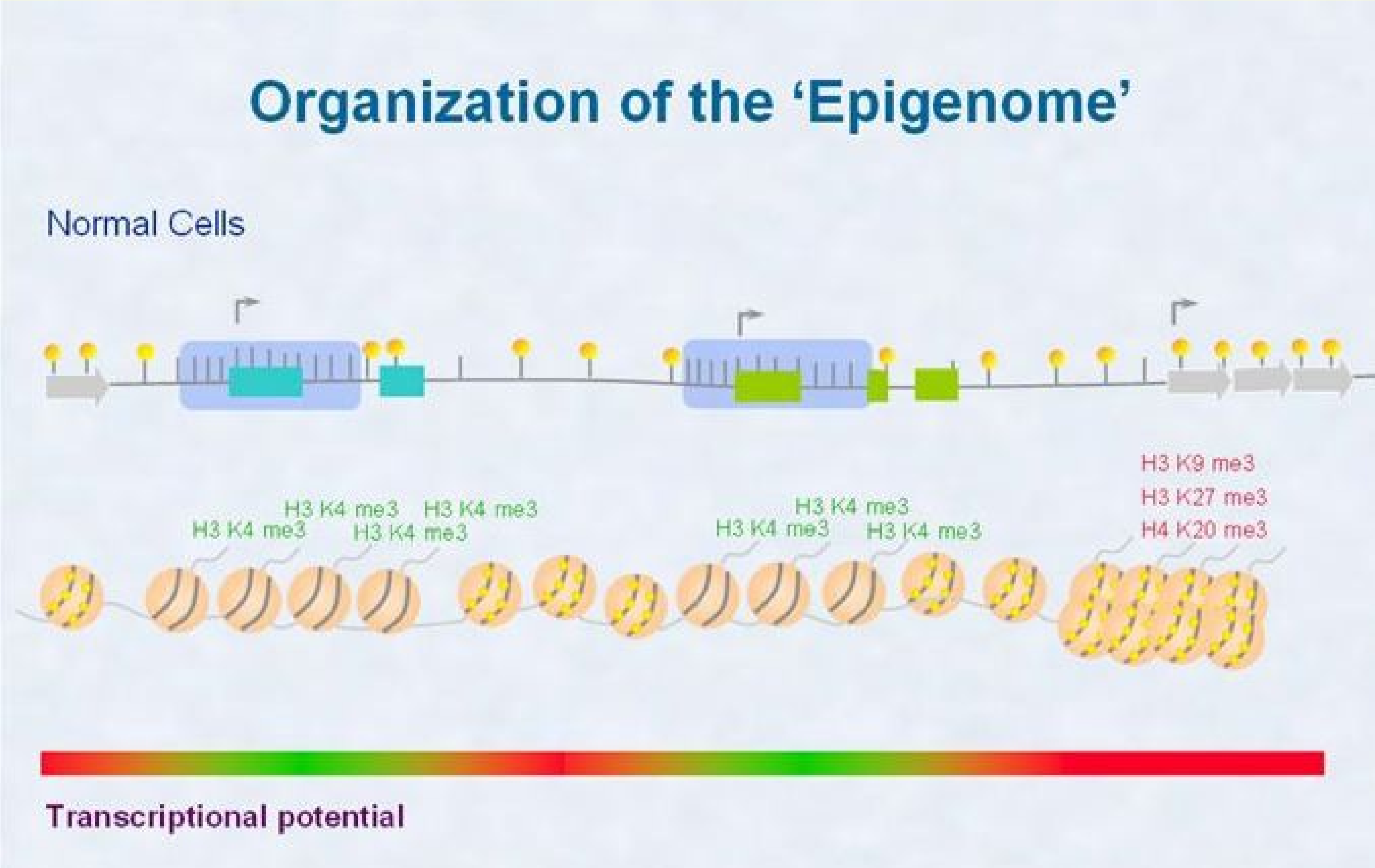
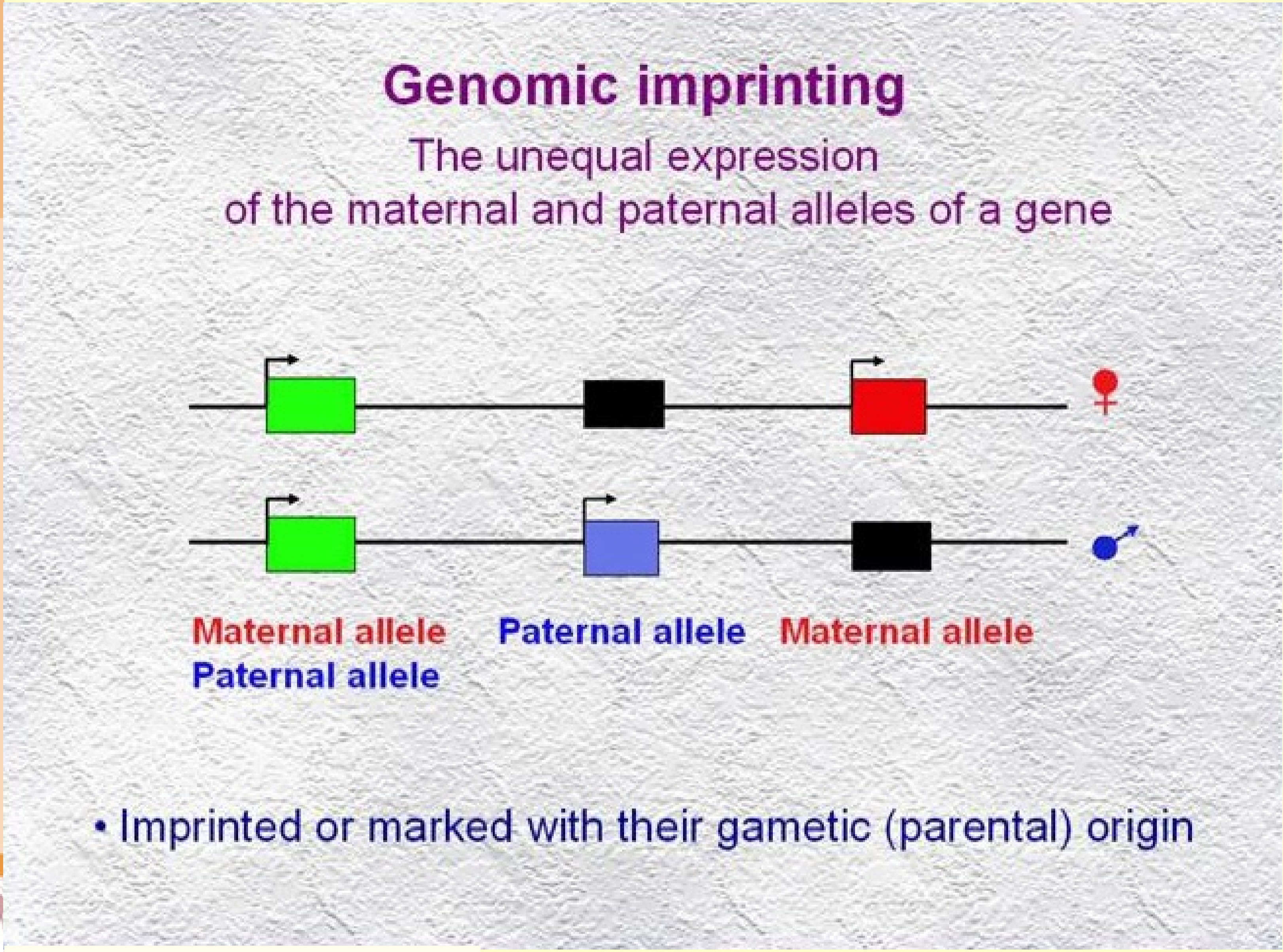
Organization of the Epigenome



Epigenetic Imprinting



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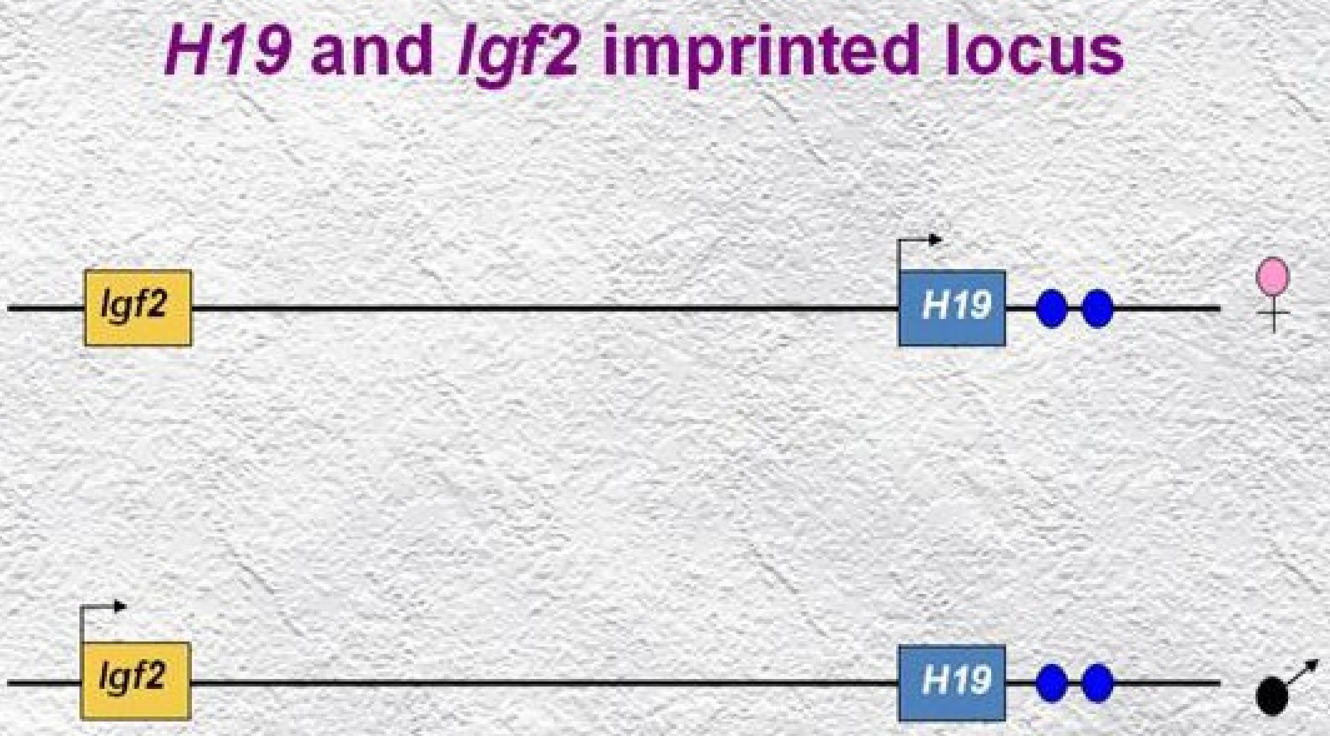
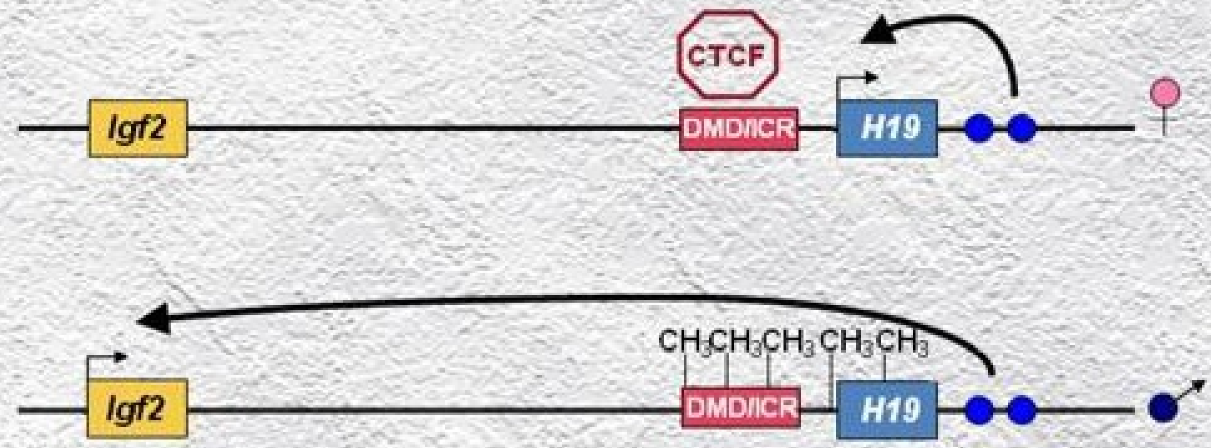
Epigenetic Imprinting of H19 & Igf2 Loci

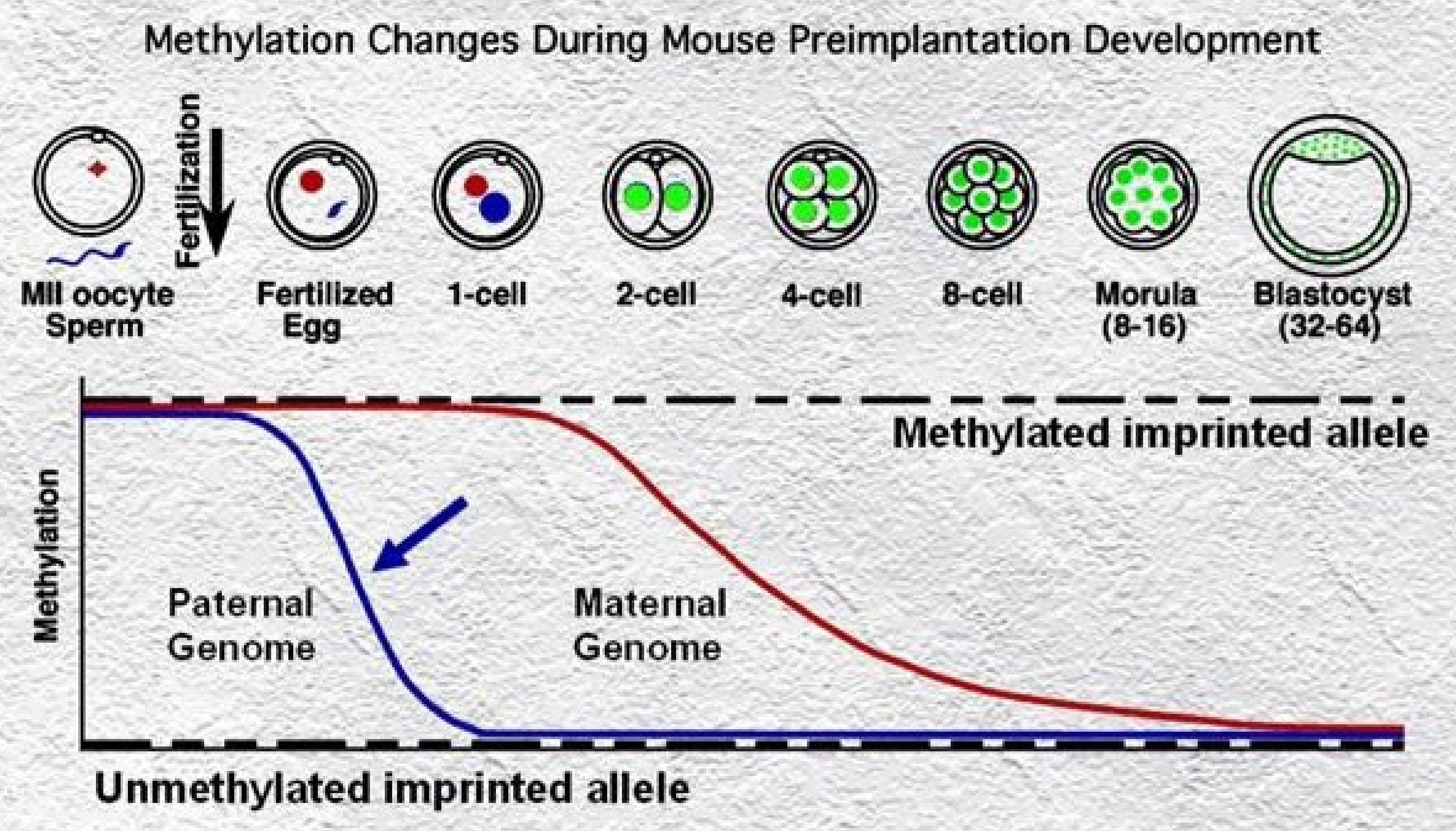


Insulator Model for the Imprinting of H19 & Igf2 Loci

Insulator model for the control of imprinted gene expression at the *H19/Igf2* locus

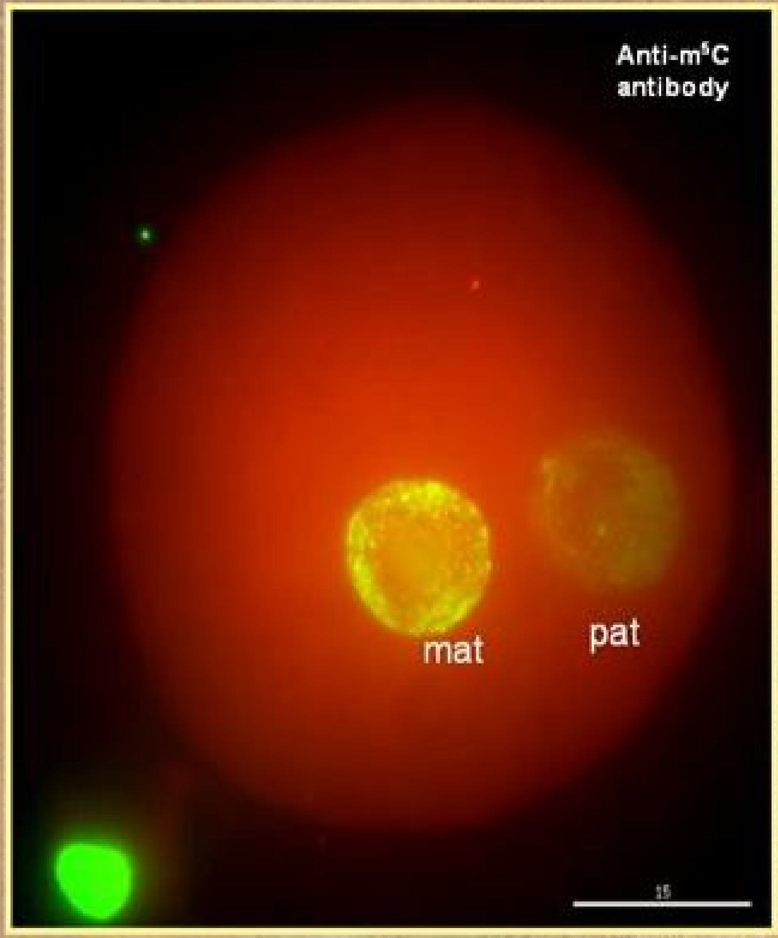


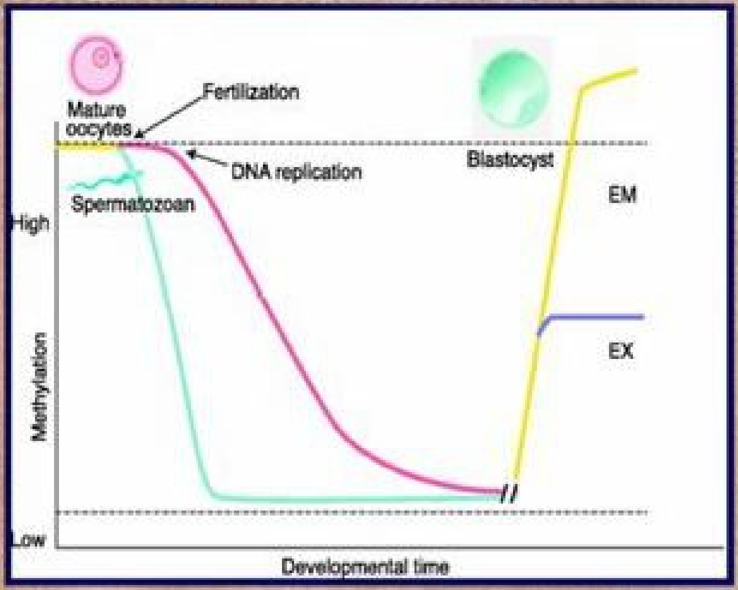
Methylation Changes During Development



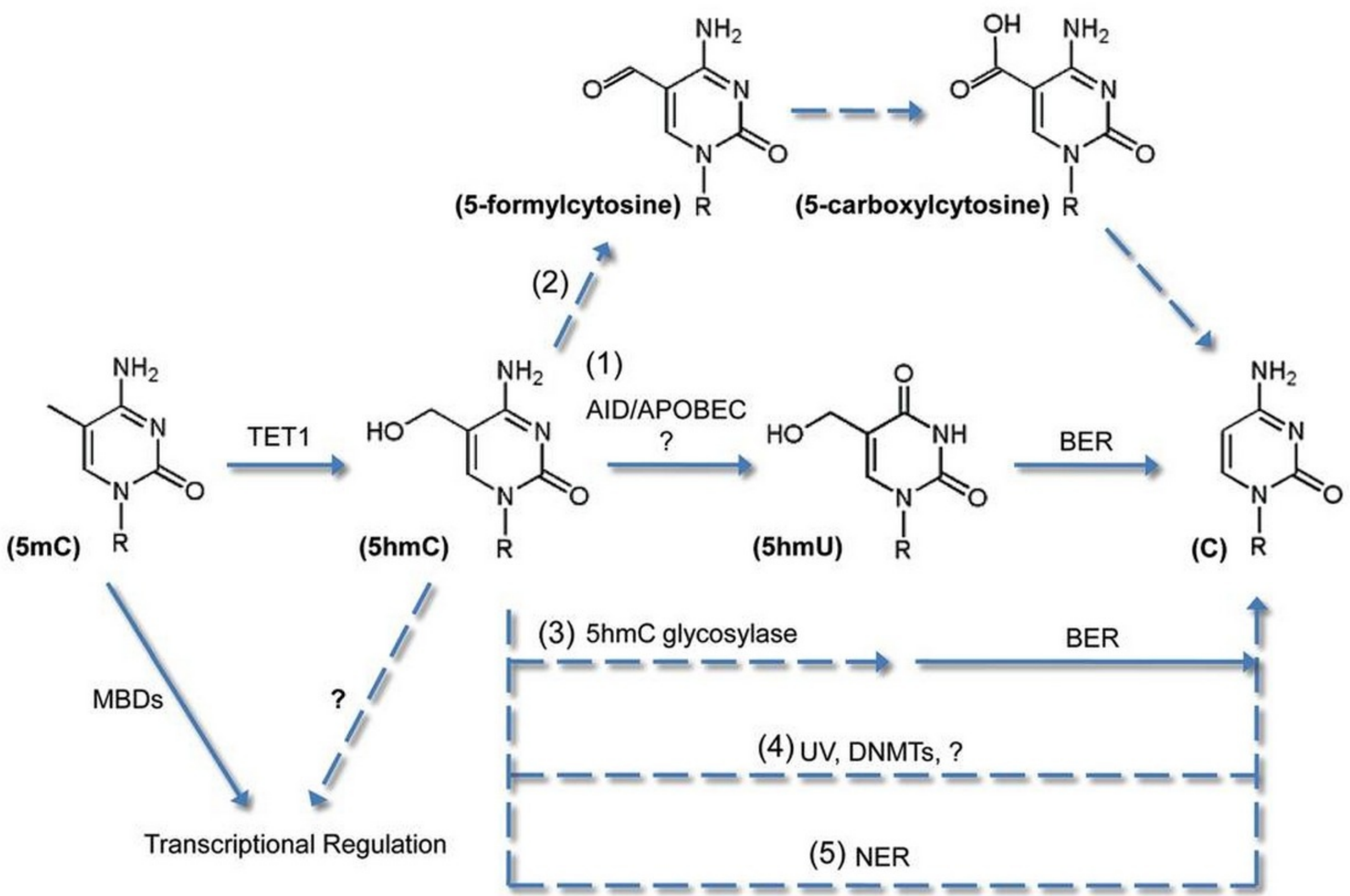
Demethylation of the Paternal Genome

De-methylation of the paternal pronucleus in the one-cell embryo of mouse



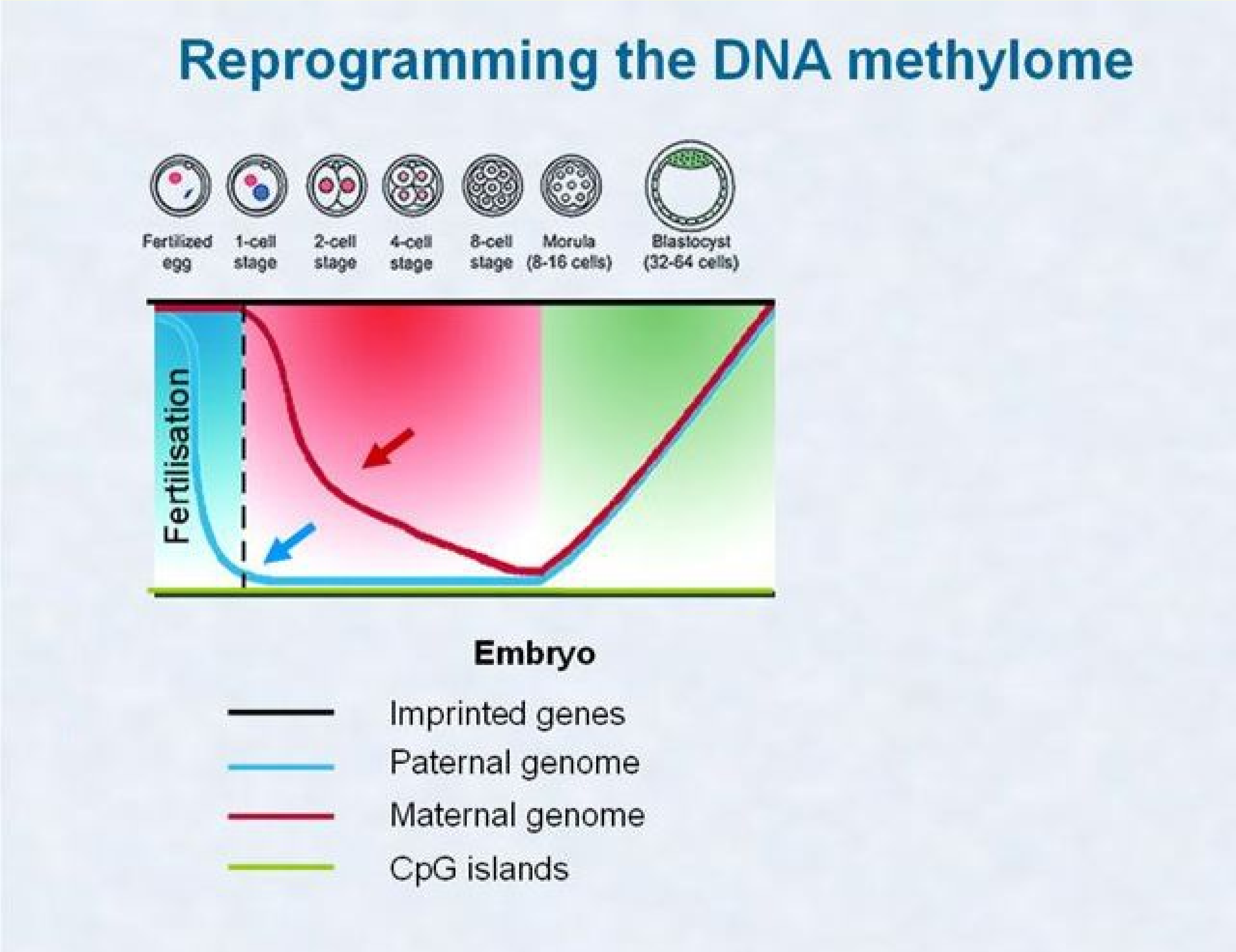


Tet Proteins Modify 5-Methyl-Cytosine Leading to Removal by DNA Repair

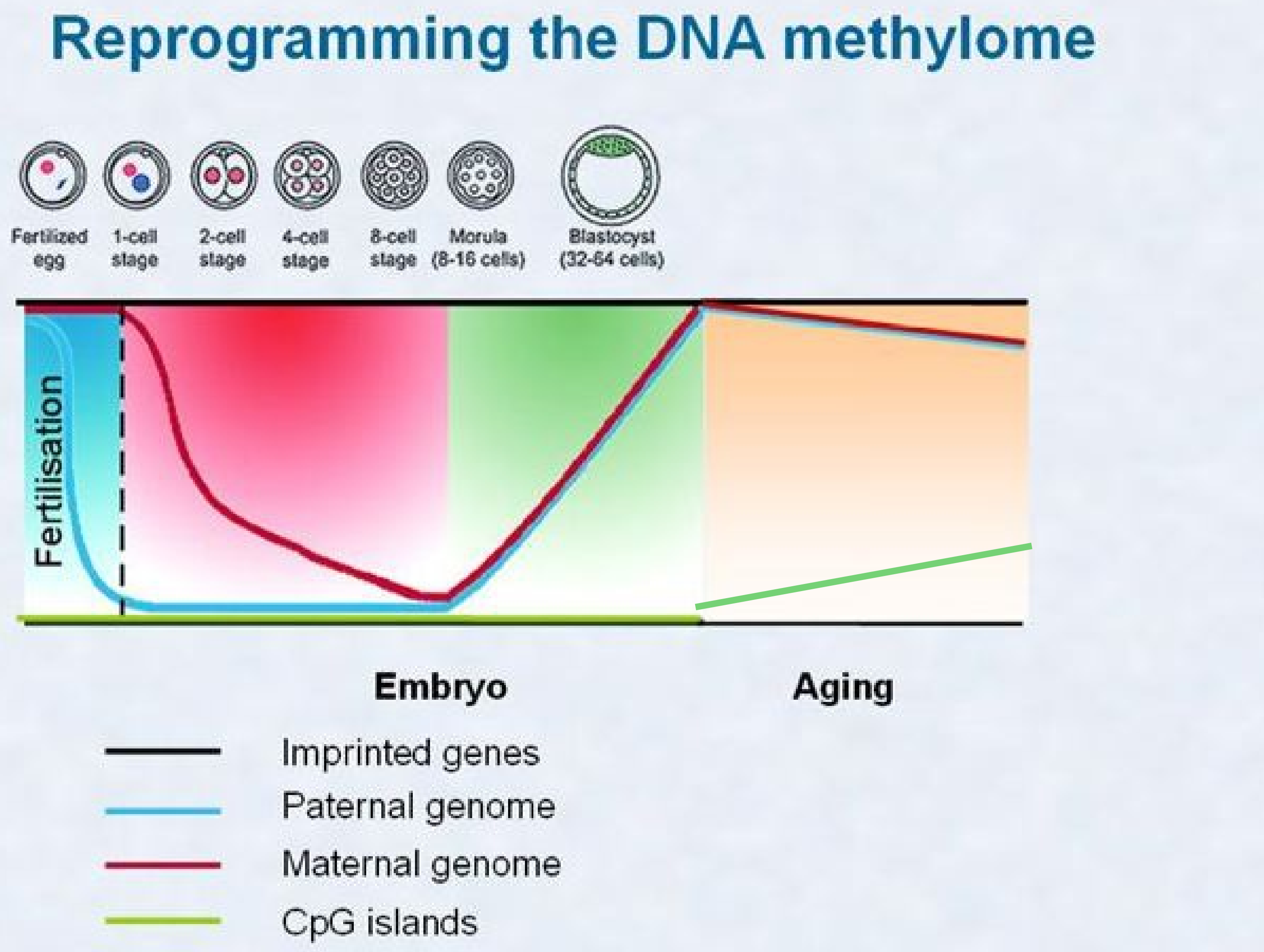


Guo et al, Cell Cycle. 2011 August 15; 10(16): 2662–2668.

Methylation Changes During Development



Methylation Changes During Development



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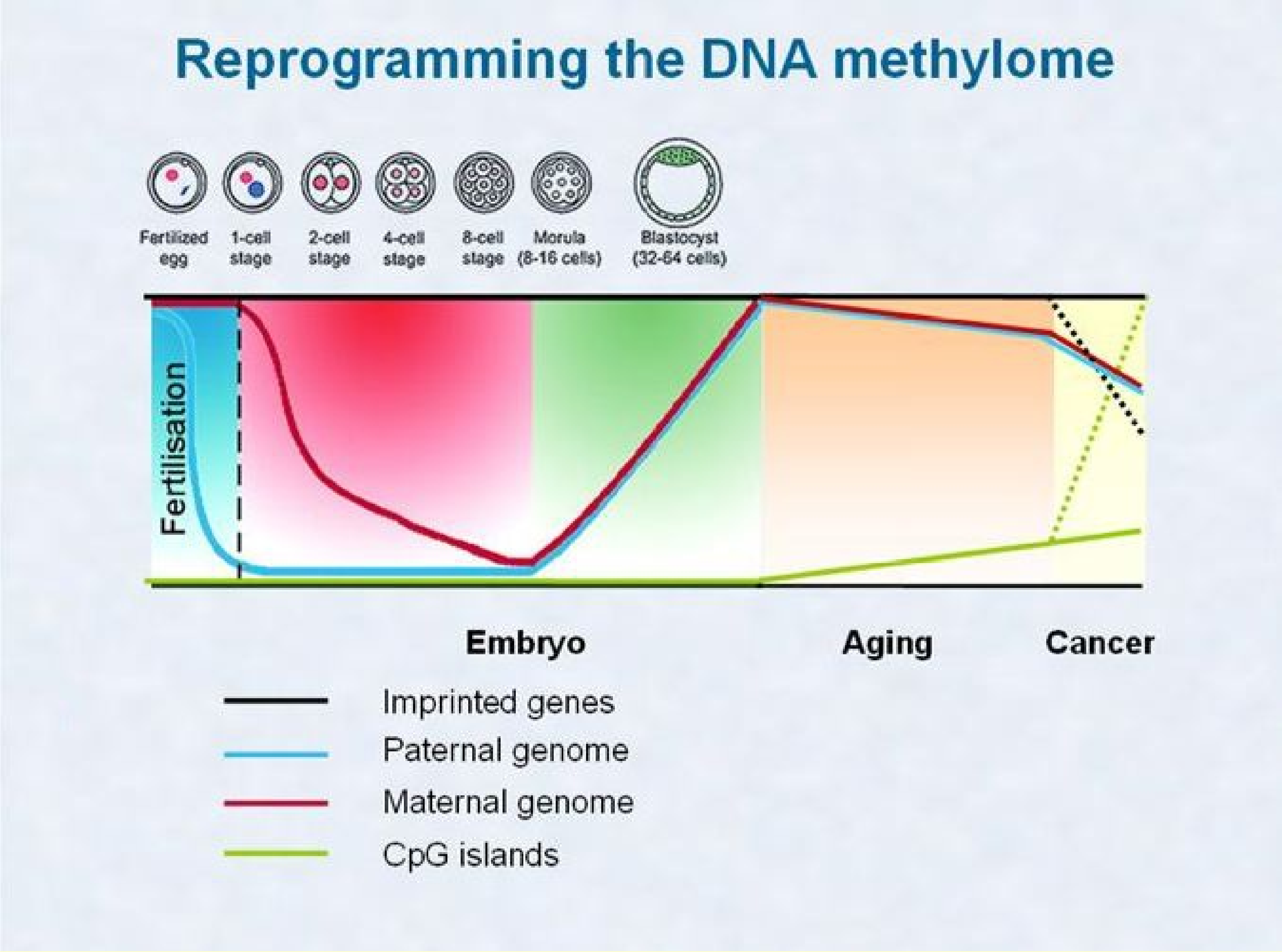
Methylation Changes During Development



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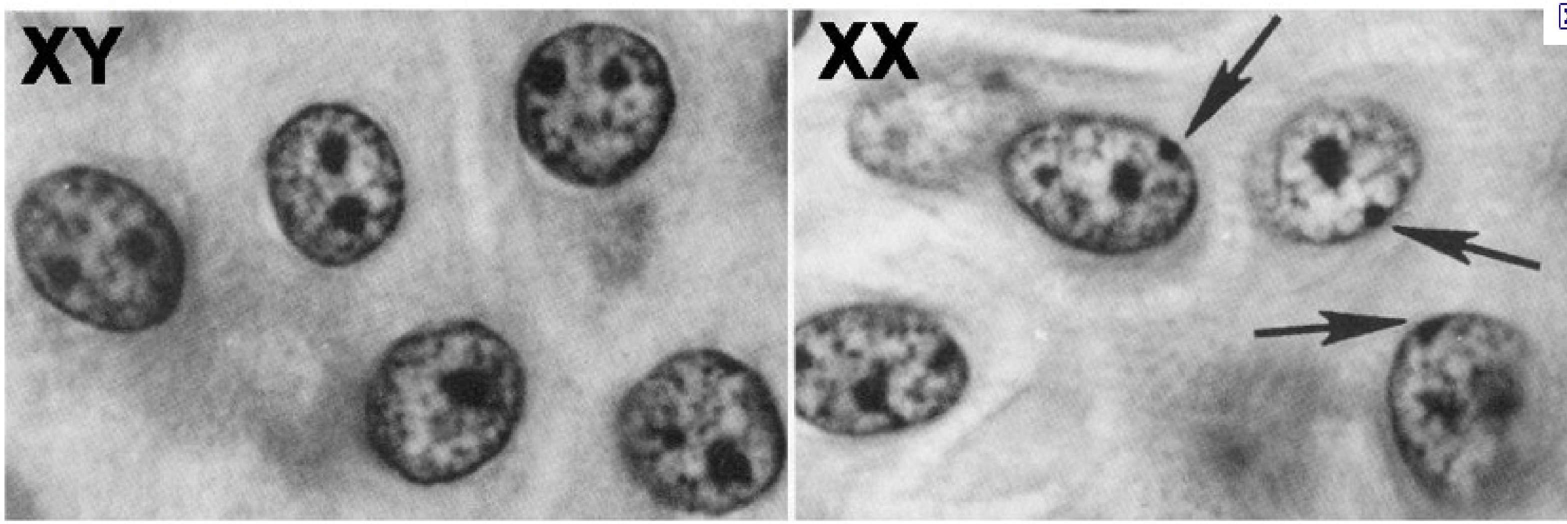
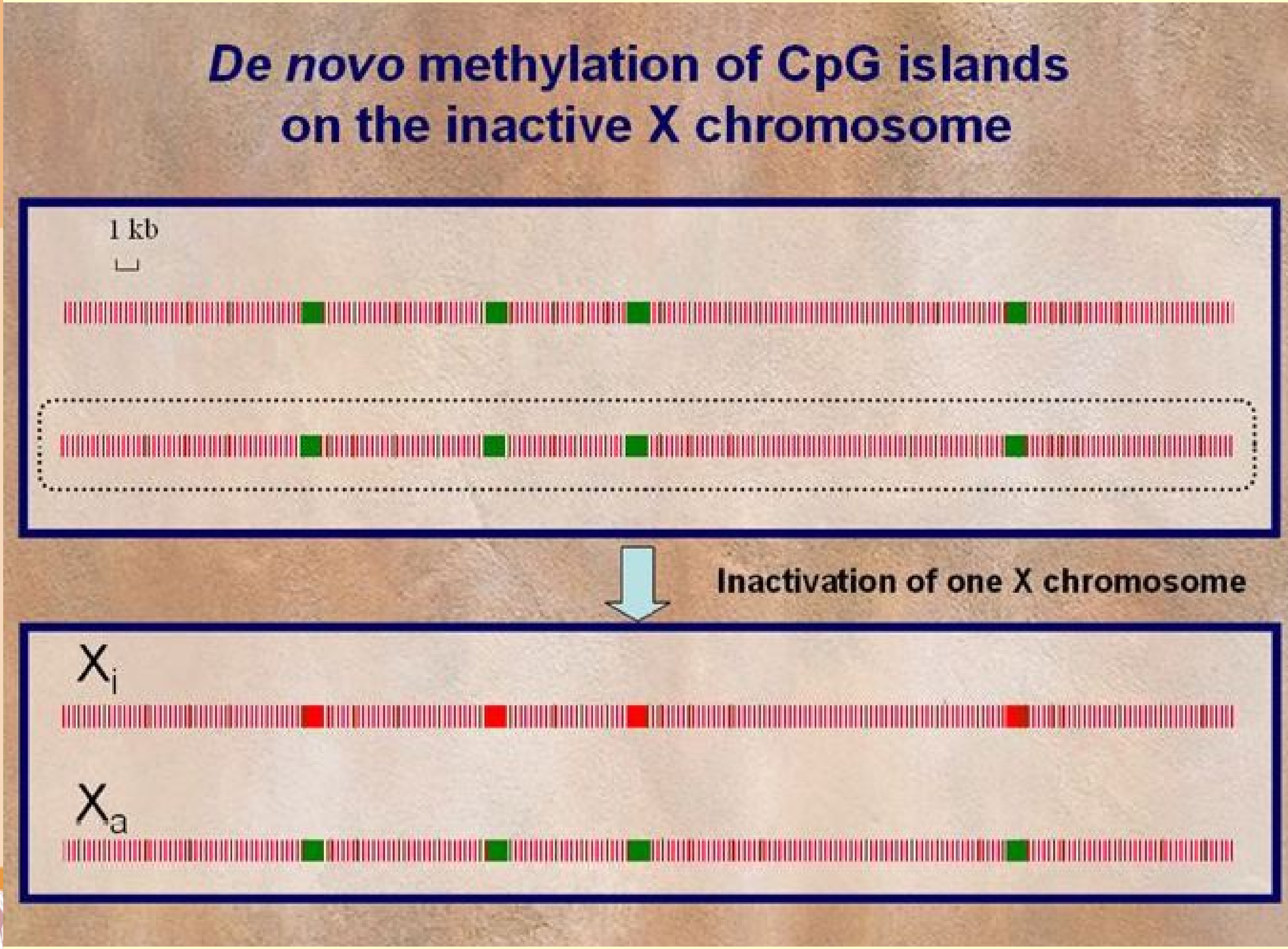
X Chromosome Inactivation: Barr Bodies



Barr, M. L., Bertram, E. G., (1949), A Morphological Distinction between Neurons of the Male and Female, and the Behavior of the Nucleolar Satellite. *Nature.* ***163*** *(4148): 676-7.*

Lyon, M. F., (2003), The Lyon and the LINE hypothesis. j.semcdb 14, 313-318. (Abstract)

X Chromosome Inactivation: CG Island Methylation



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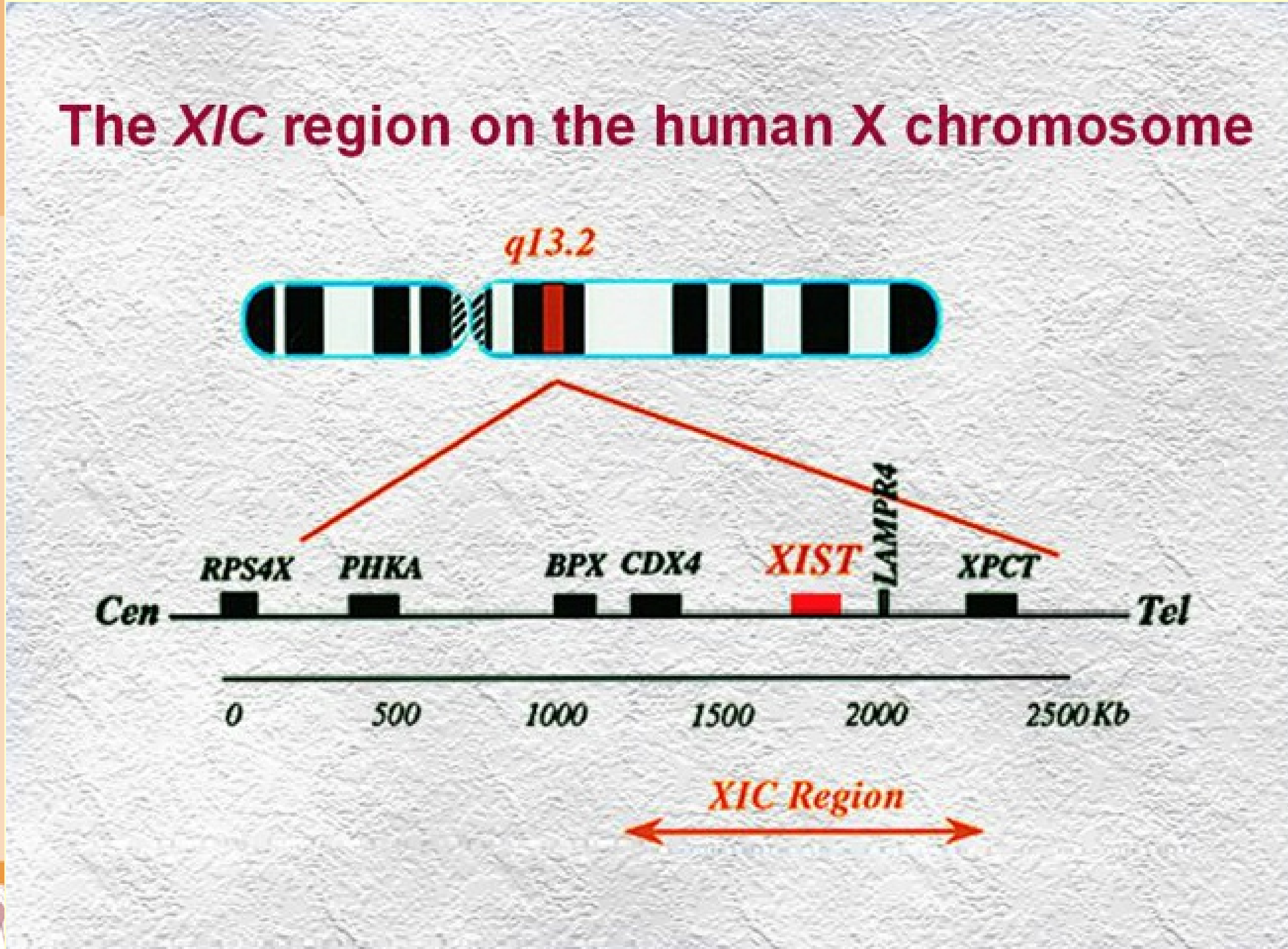
XIC Region



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Characteristics XIST Gene

Characteristics of *XIST*

- Located in the XIC
- Transcribed *only* from the *inactive* X
- 20kb cDNA with no ORF, remains intranuclear, surrounding the *Barr body*
- *The* XIC gene responsible for Cis inactivation

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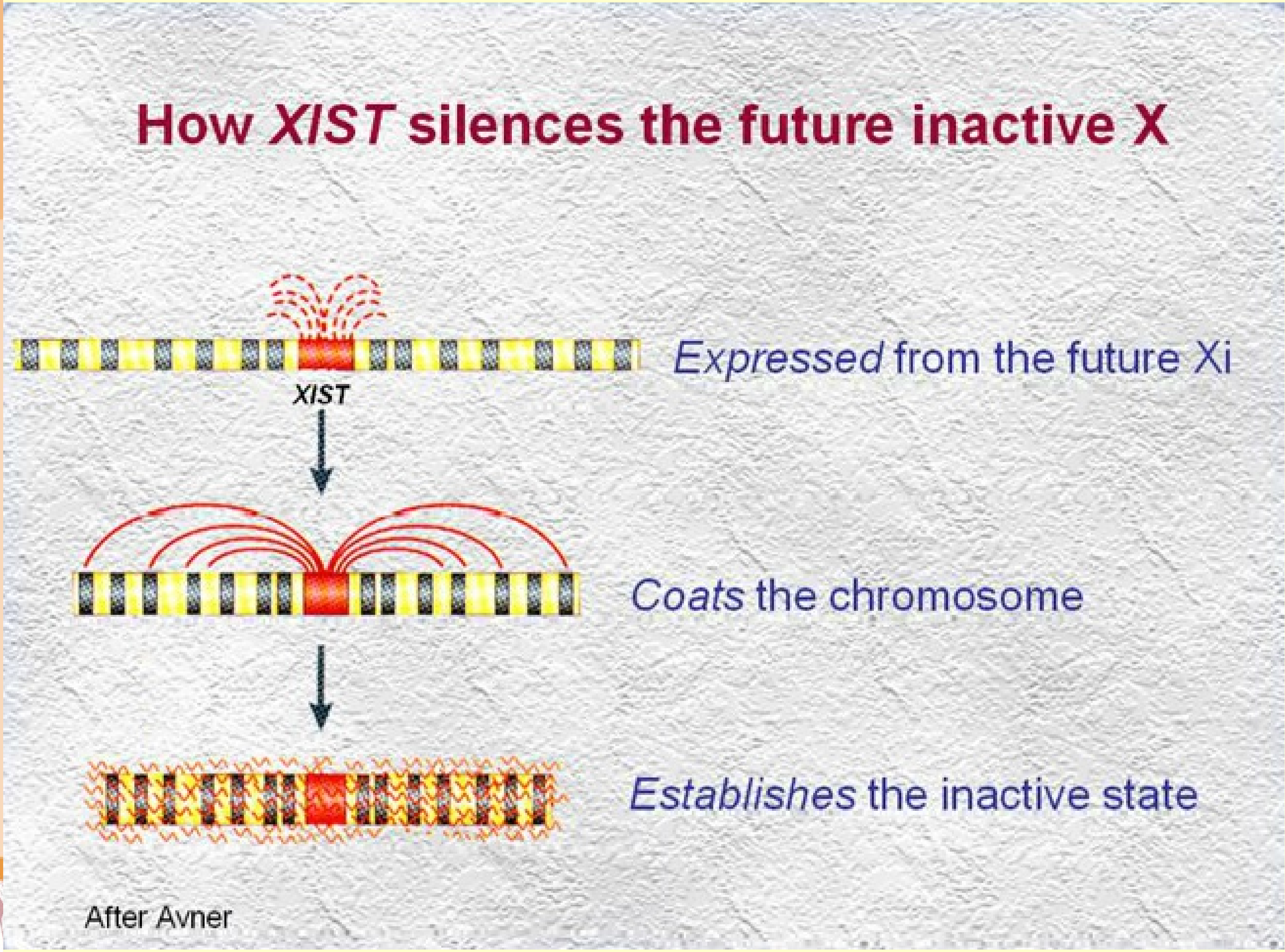
Xist Works in Cis



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Only one X is active

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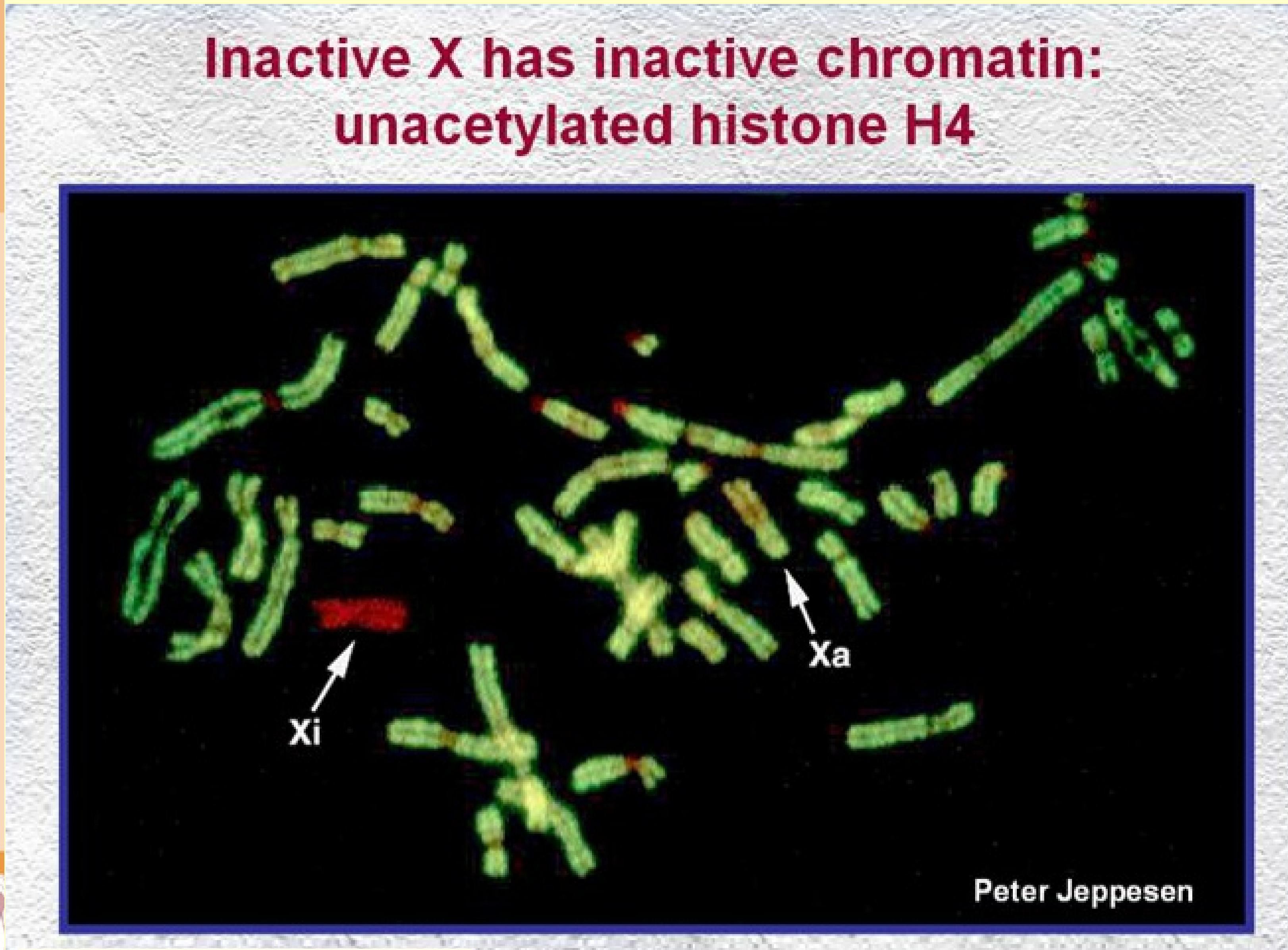
Inactive X has unacetylated histone H4



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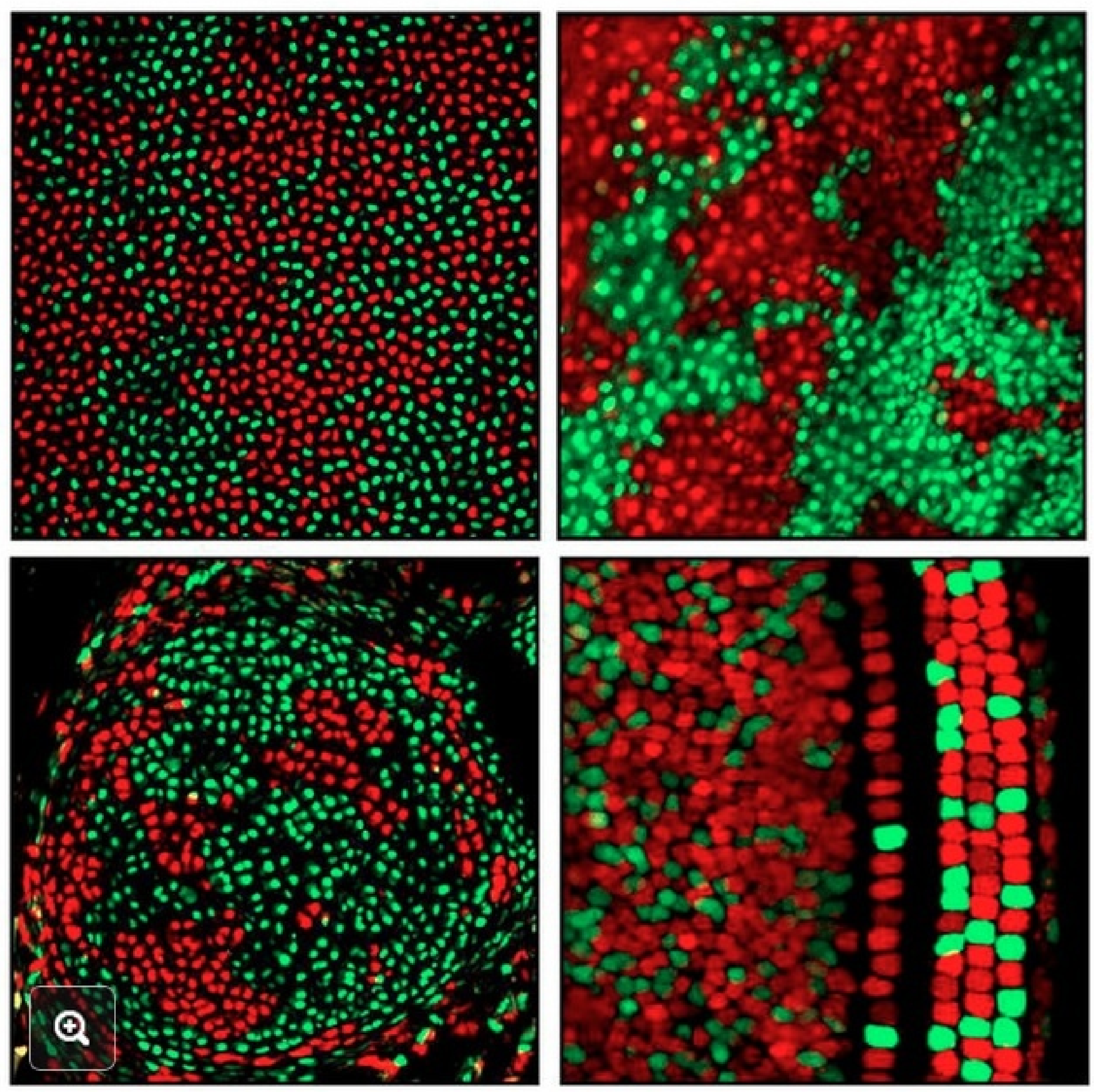
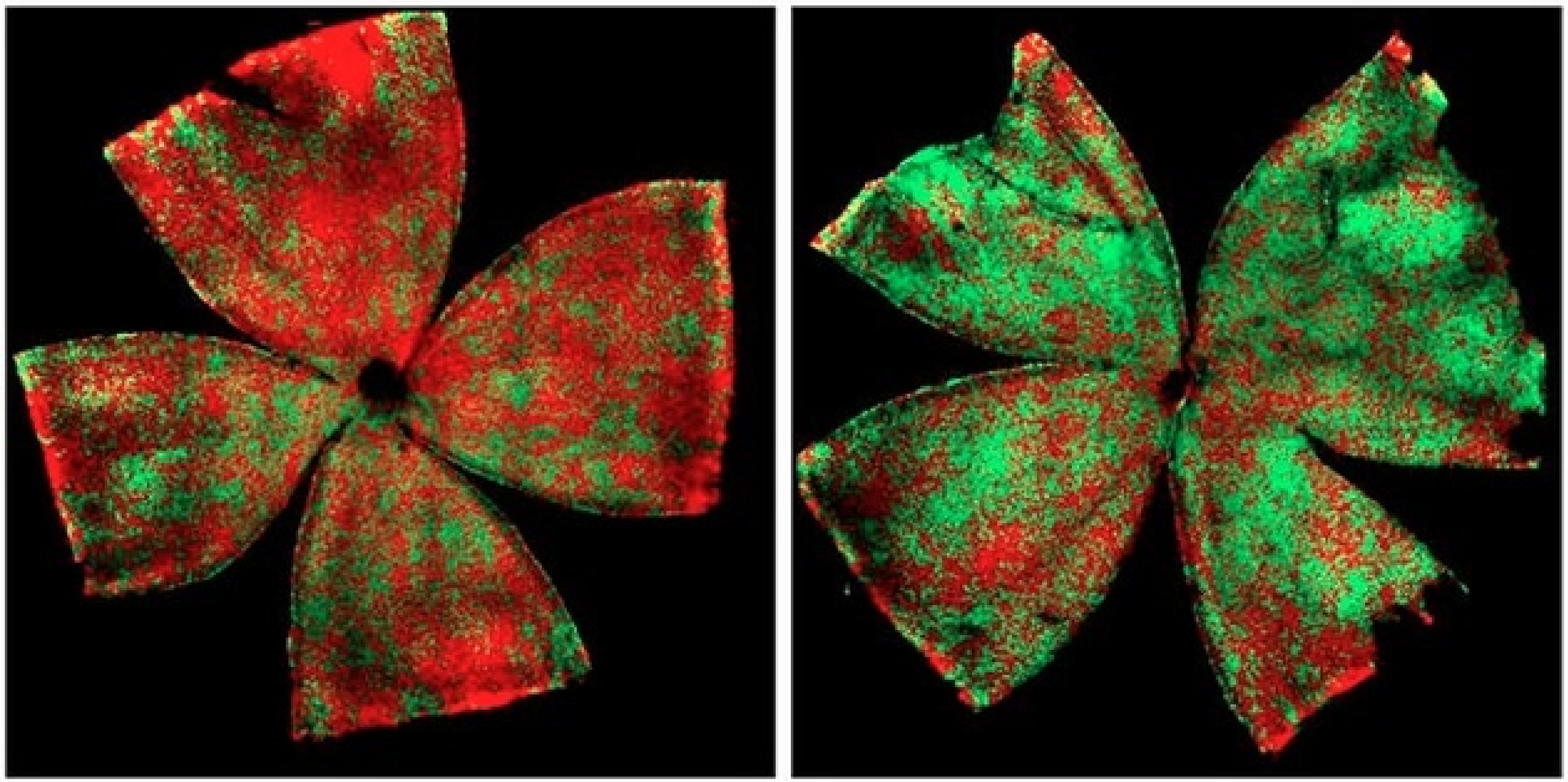
Female X chromosome Mosaicism (cornea, skin, cartilage & inner ear)



Female X chromosome Mosaicism Left and Right Retina



Distinguishing features of Xi and Xa

Table 1. Distinguishing features of chromatin on inactive and active X chromosomes

Feature	Xi	Xa	References
Barr body formation	+	−	[30]
XIST expression/association	+	−	[3–6]
CpG islands methylation	+	−	[43,44]
Methylated H3 K-9/27	+	−	[59,61,62,65]
Methylated H3 K-4	−	+	[59,60]
Histone tail acetylation	−	+	[55–58]
Elevated levels mH2A1/2	+	−	[69,71,72]
Elevated levels histone H1	+	−	[49]
Elevated levels HMG-I/Y	+	−	[49]
Elevated levels of HP1	+	−	[49]
H2A-Bbd presence	−	+	[68]
Replication timing	Late	Early	[94,95]

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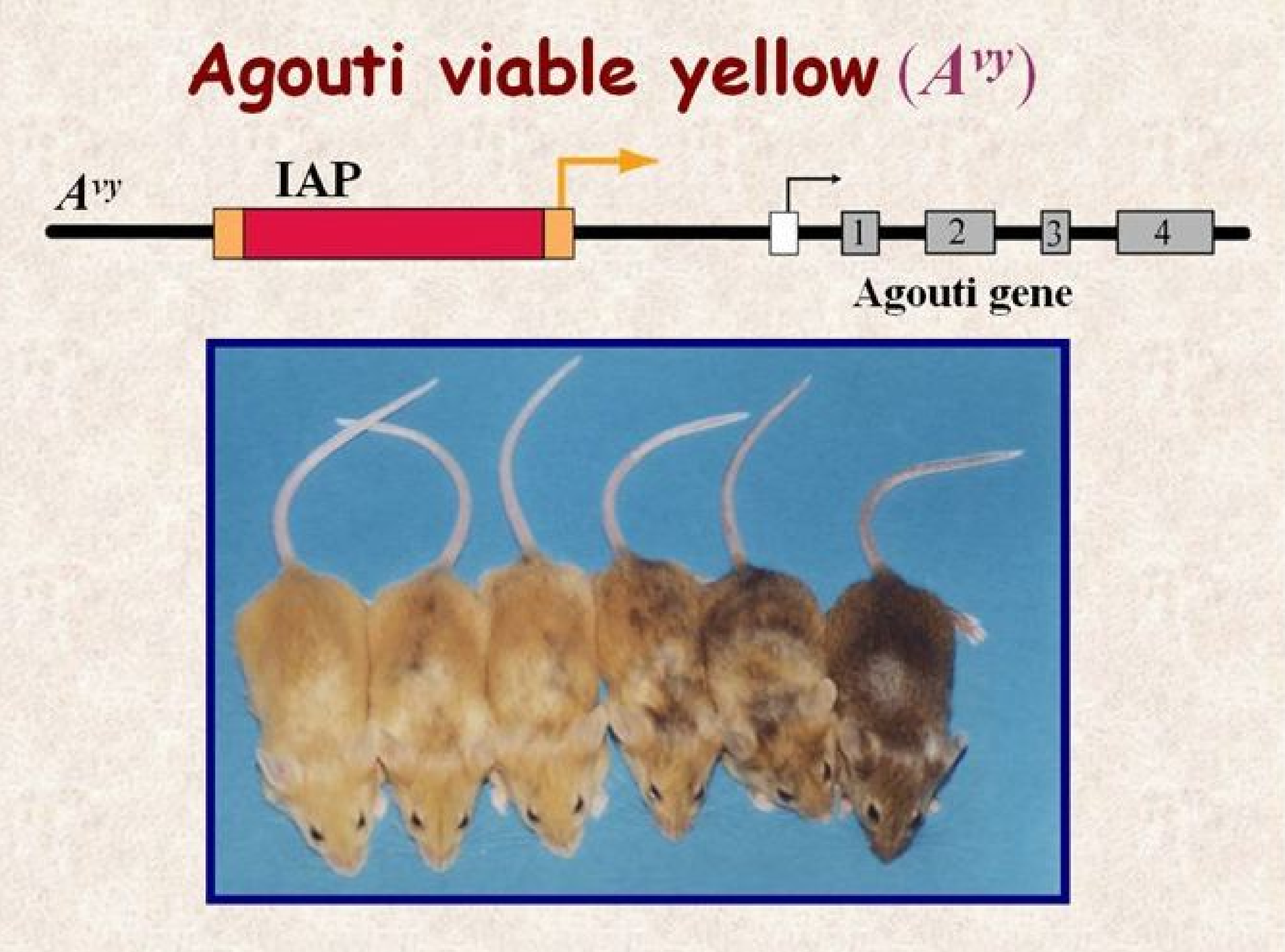
Agouti Genes in Mice



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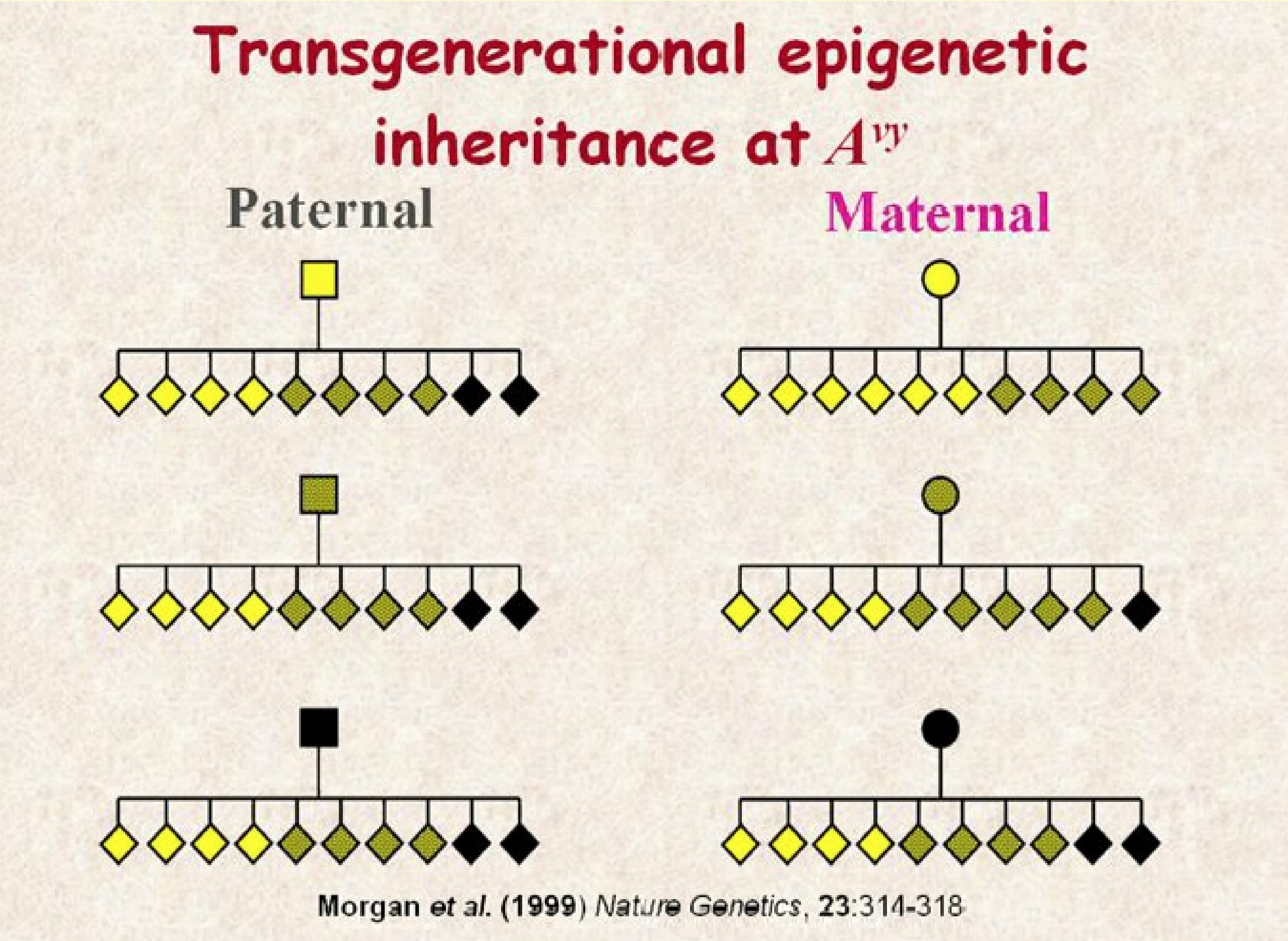
Epigenetic Inheritance



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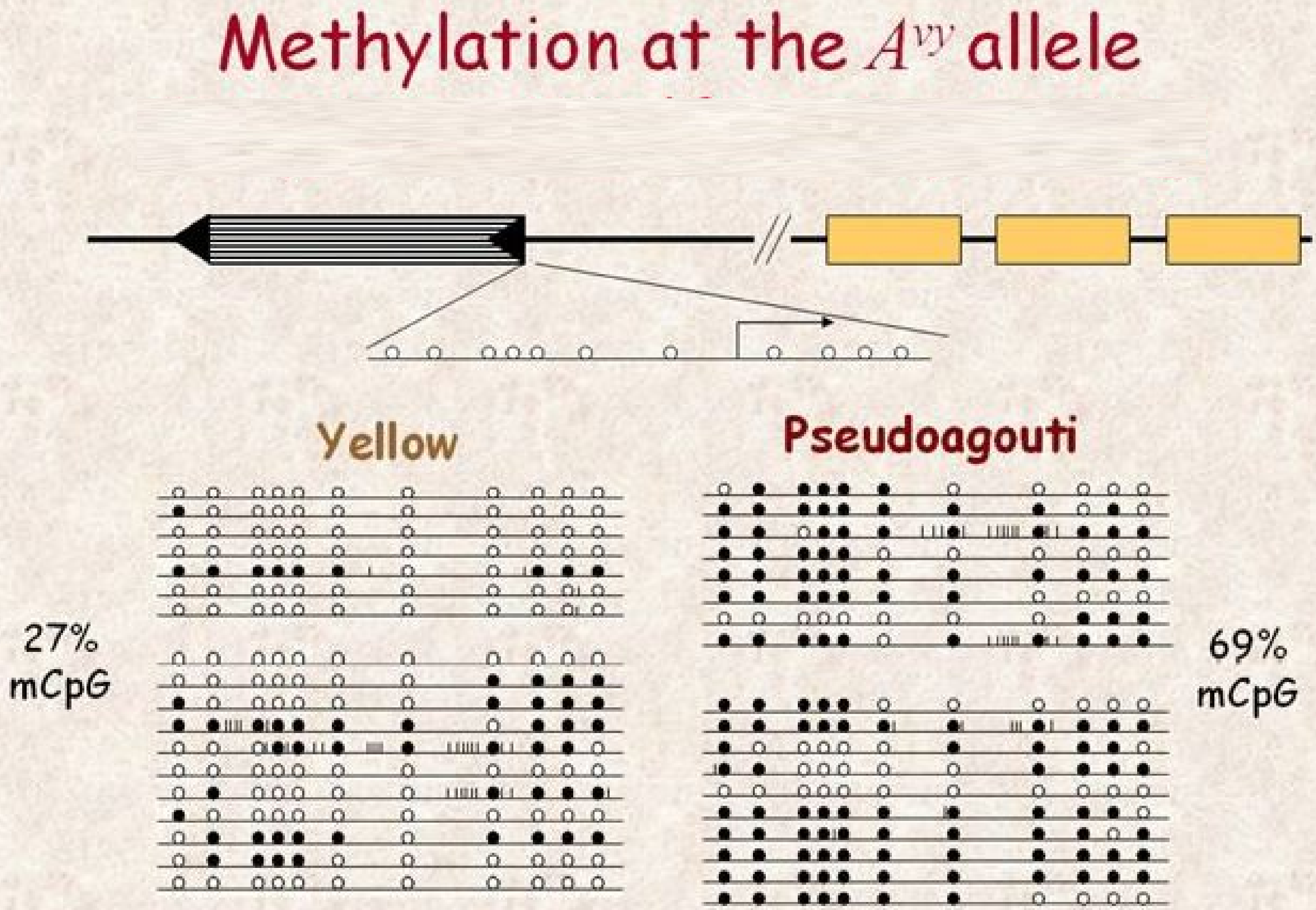
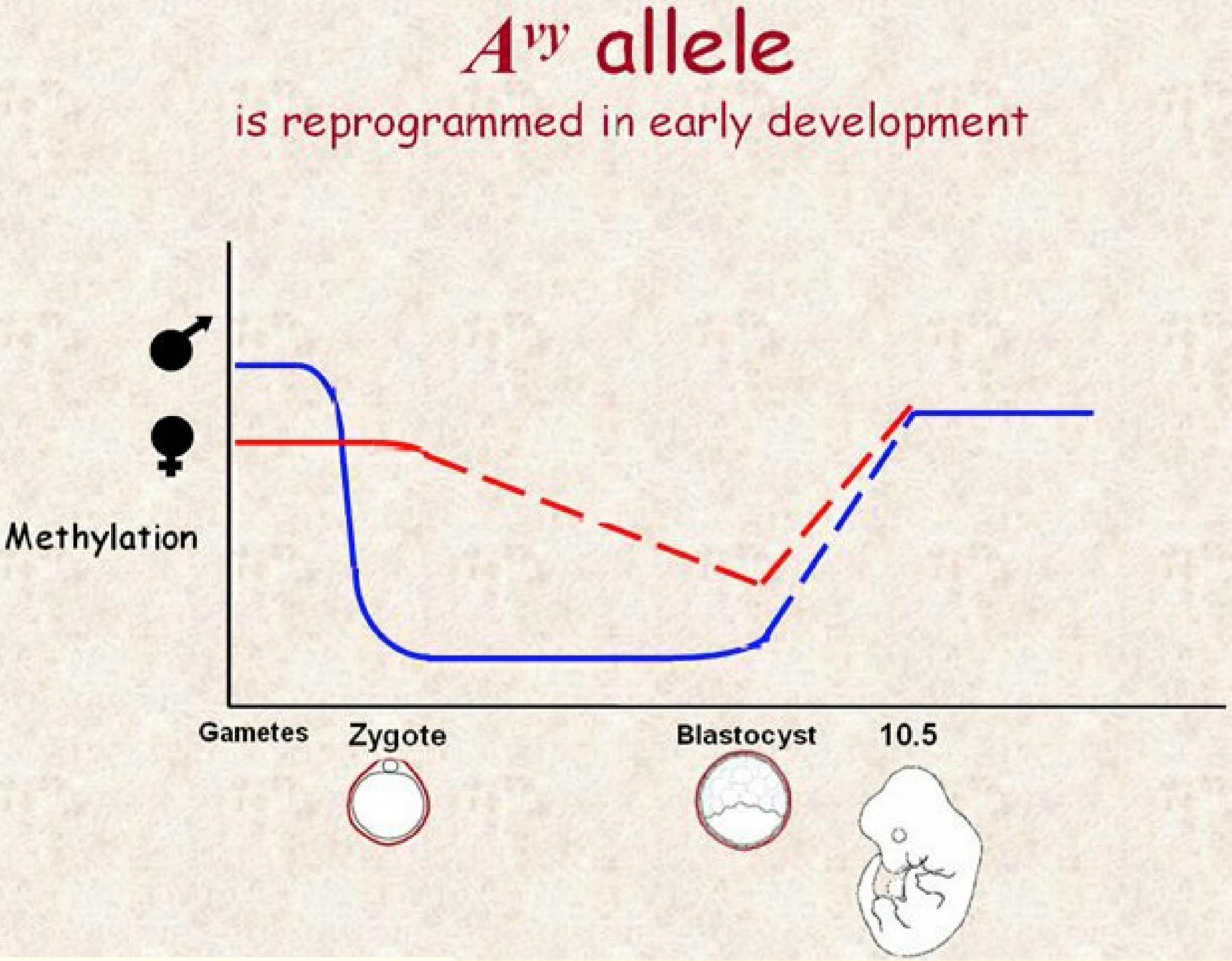
Methylation of Agouti Genes in Mice



Reprogramming of A^{vy} Allele in Development



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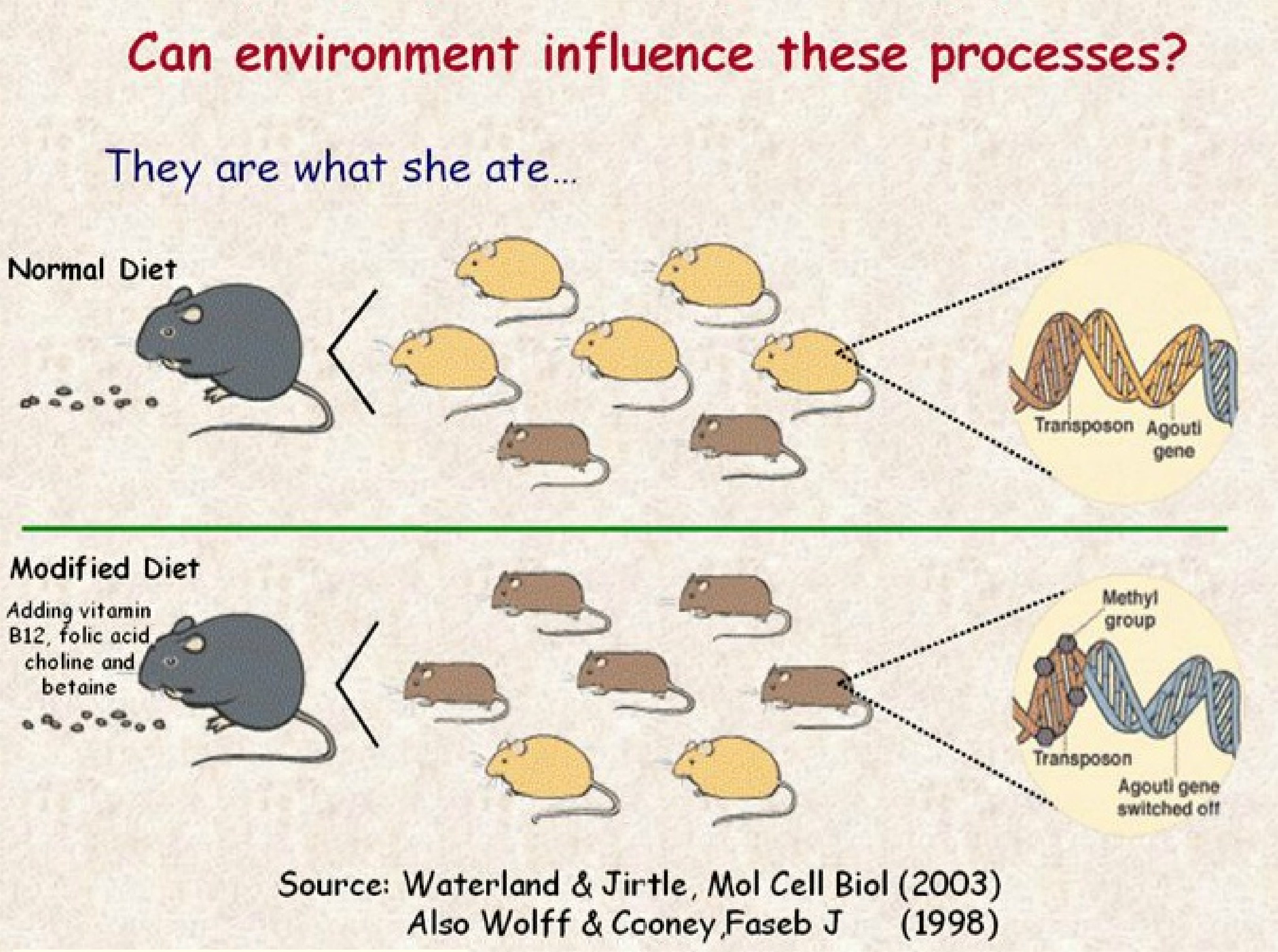
Environment can Influence Epigenetic Changes



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Hongerwinter 1944

- German's blocked food to the Dutch in the winter of 1944.
- Calorie consumption dropped from 2,000 to 500 per day for 4.5 million.
- Children born or raised in this time were small, short in stature and had many diseases including, edema, anemia, diabetes and depression.
- The Dutch Famine Birth Cohort study showed that women living during this time had children 20-30 years later with the same problems despite being conceived and born during a normal dietary state.

Epigenome Roadmap

http://www.nature.com/collections/vbqgtr

Epigenome Roadmap

Search Go

Advanced search

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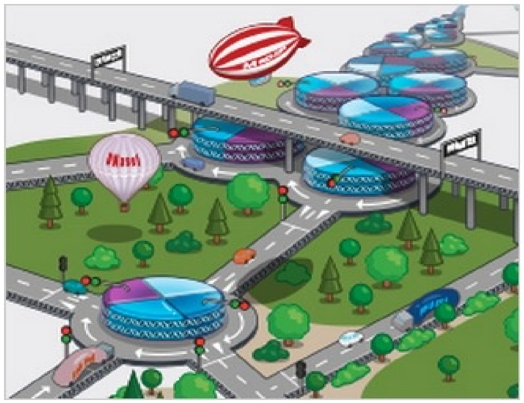


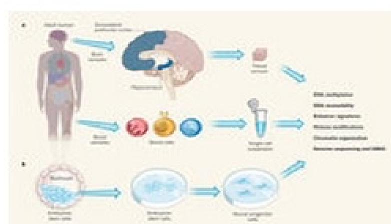
Welcome to the Epigenome Roadmap! Here, we have collected research papers describing the main findings of the NIH Roadmap Epigenomics Program, the aim of which was to systematically characterize epigenomic landscapes in primary human tissues and cells. The papers are complemented by eight threads each of which highlights a topic that runs through more than one paper. Threads are designed to help you explore the wealth of information collectively published across several Nature Publishing Group journals. Each thread consists of relevant paragraphs, figures and tables from across the papers, united around a specific theme.

We invite you to explore the research content, the News & Views, the video and other associated material.

News and Multimedia

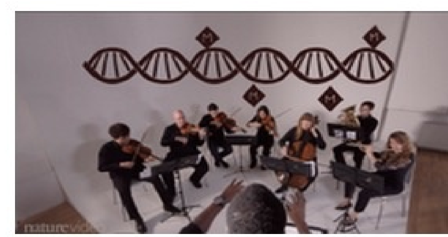
Nature News | Editorial

Beyond the genome



Nature | News and Views

Epigenomics: Roadmap for regulation



Nature News | News

Epigenome: The symphony in your cells

Epigenome Roadmap

http://www.nature.com/collections/vbqgtr

Thread articles | **Research papers**

THREAD 1

1. Annotation of the non-coding genome

Highlight referenced papers ▶

THREAD 2

2. Relationship between different epigenomic marks: DNA accessibility and methylation, histone marks, and RNA

Highlight referenced papers ▶

THREAD 3

3. Epigenomic changes during differentiation and development

Highlight referenced papers ▶

THREAD 4

4. Regulatory models: networks, motifs, modules, sequence drivers and predictive models

Highlight referenced papers ▶

THREAD 5

5. Interpreting variation: GWAS, cancer, genotype, evolution and allelic

Highlight referenced papers ▶

Nature

Conserved epigenomic signals in mice and humans reveal immune basis of Alzheimer's disease

Elizabeta Gjoneska, Andreas R. Pfenning, Hansruedi Mathys, Gerald Quon, Anshul Kundaje *et al.*

◀ Highlight associated threads

Nature Communications

The meta-epigenomic structure of purified human stem cell populations is defined at cis-regulatory sequences

N. Ari Wijetunga, Fabien Delahaye, Yong M. Zhao, Aaron Golden, Jessica C. Mar *et al.*

◀ Highlight associated threads

Nature

Genetic and epigenetic fine mapping of causal autoimmune disease variants

Kyle Kai-How Farh, Alexander Marson, Jiang Zhu, Markus Kleinewietfeld, William J. Housley *et al.*

◀ Highlight associated threads

Nature Communications

Epigenomic footprints across 111 reference epigenomes reveal tissue-specific epigenetic regulation of lincRNAs

Viren Amin, R. Alan Harris, Vitor Onuchic, Andrew R. Jackson, Tim Charnecki *et al.*

◀ Highlight associated threads

Nature Communications

Intermediate DNA methylation is a conserved signature of genome regulation

GiNell Elliott, Chibo Hong, Xiaoyun Xing, Xin Zhou, Daofeng Li *et al.*

Nature Biotechnology

Large-scale imputation of epigenomic datasets for systematic annotation of diverse human tissues

Jason Ernst, Manolis Kellis

Summary of Epigenetic Gene Regulation

- Patterns of DNA methylation in adult cells parallels cell fate, chromatin structure and gene activation.
- Most DNA methylation is removed at fertilization and re-established during embryogenesis.
- Imprinted genes keep their parental pattern of methylation giving rise to parental patterns of expression.
- Patterns of histone modifications parallel DNA methylation.
- Methylated gene regions are genetically inactive, highly condensed and special histone modifications.
- Active gene regions have little DNA methylation and distinctive histone modifications (acetyl groups and H3K4methyl).
- X chromosome inactivation in females is correlated with extensive CG island methylation on one chromosome, condensation, inactivation and Barr body formation.
- Alterations in gene and CG island methylation patterns are seen in aging and in cancer.
- Most CG islands are not methylated except for X chromosome inactivation and tumor suppressors in cancer.