

Epigenetics: concepts and mechanisms

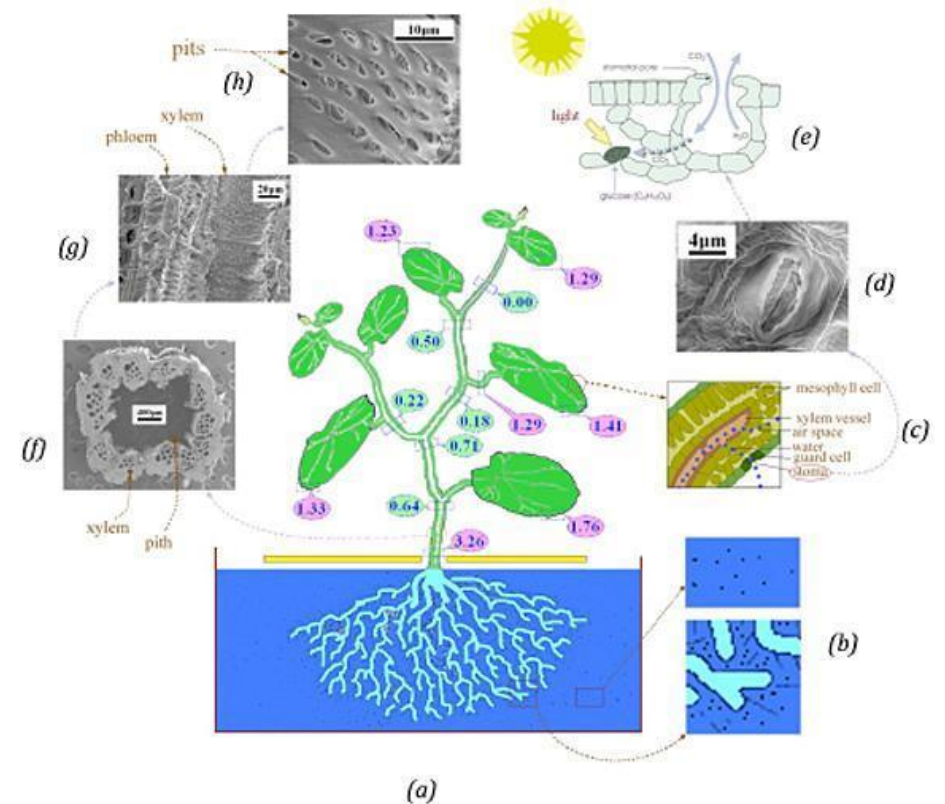
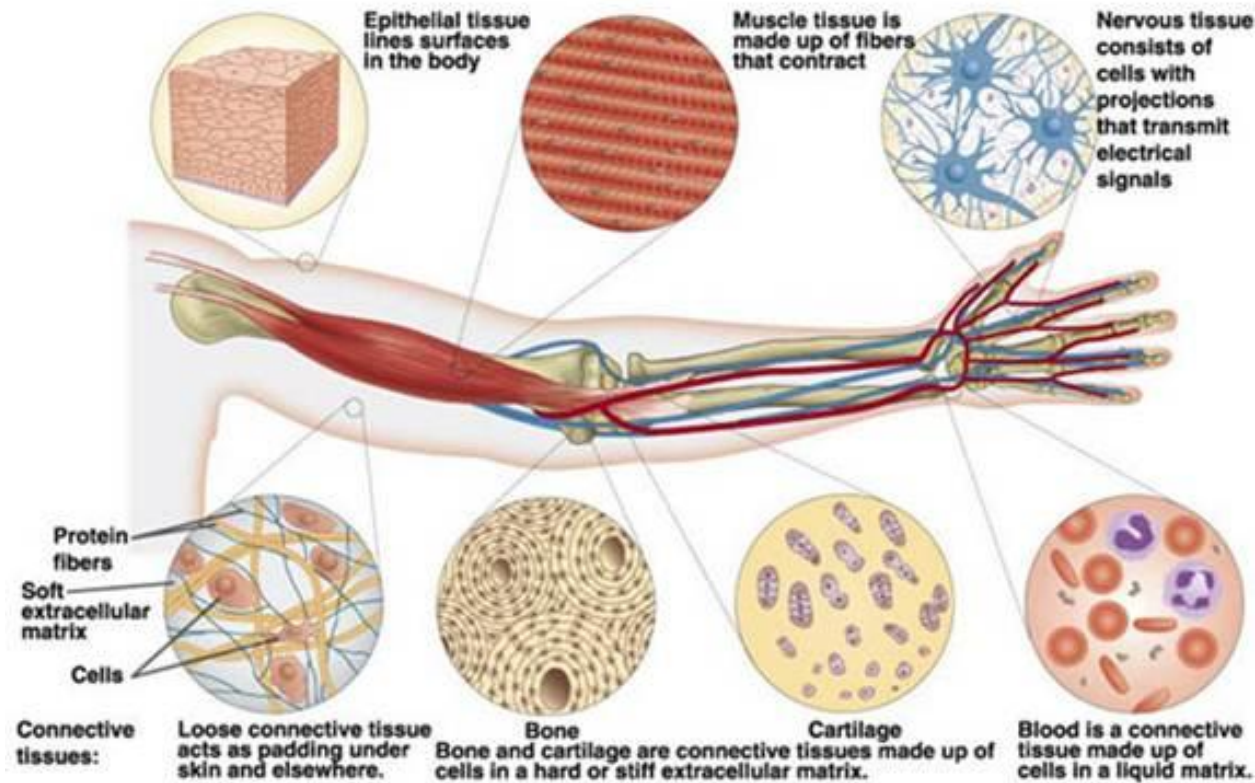
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Begining of modern EPI-genetics

- Conrad Weddington - "cells can start so simply, and then develop specialised functions, yet they have the same genetic material"
- diversity of phenotypes of differentiated cells
- how can specific cell programming be achieved and maintained during adult life?

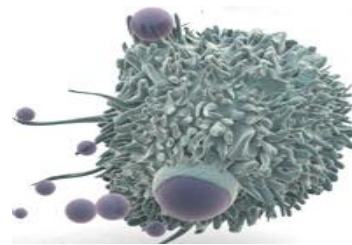
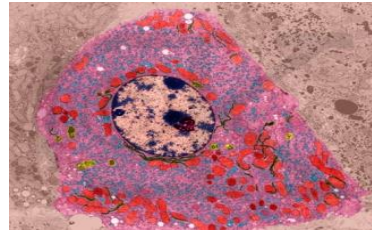
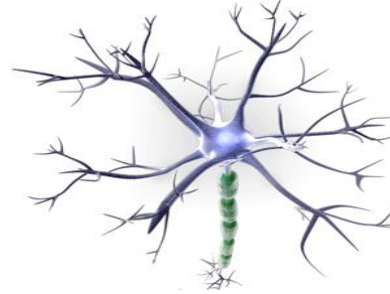
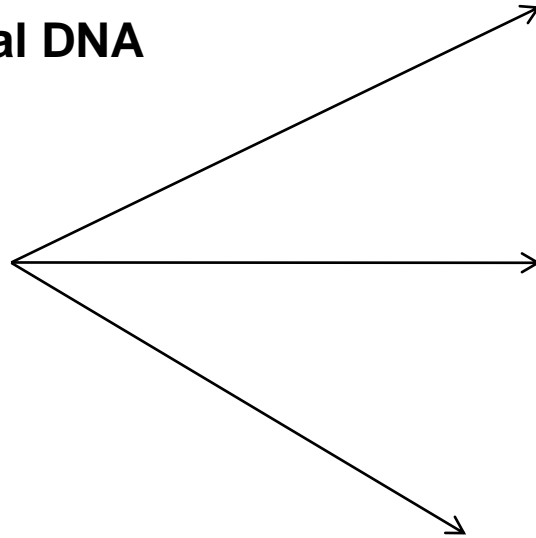
- **1949 EPIGENETIC CONCEPT "SWITCH ON-SWITCH OFF"**



Epigenetics is associated with developmental biology

but it's own specific pattern of gene expression

Each cell has identical DNA

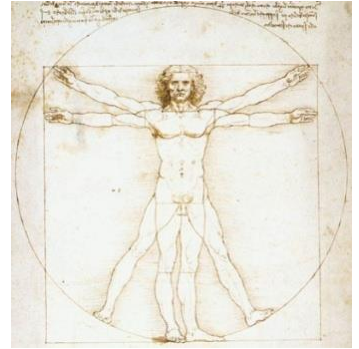


Transcription factors
EPIGENETIC INFORMATION

ZYGOTE

DIFFERENTIATION

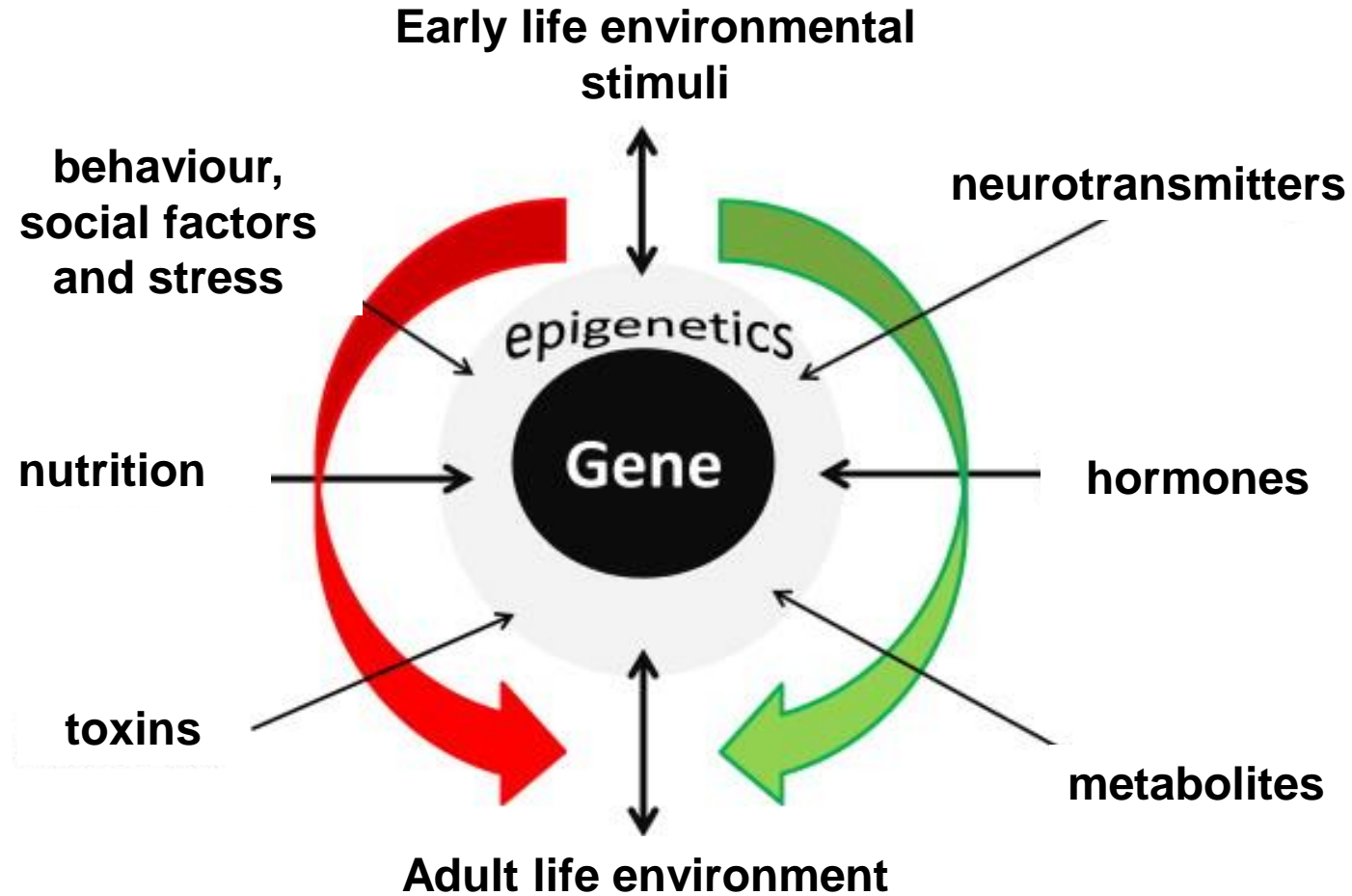
DEVELOPMENT



Homo sapiens

ADULT ORGANISM

EPIGENETICS: a link between environment and genes

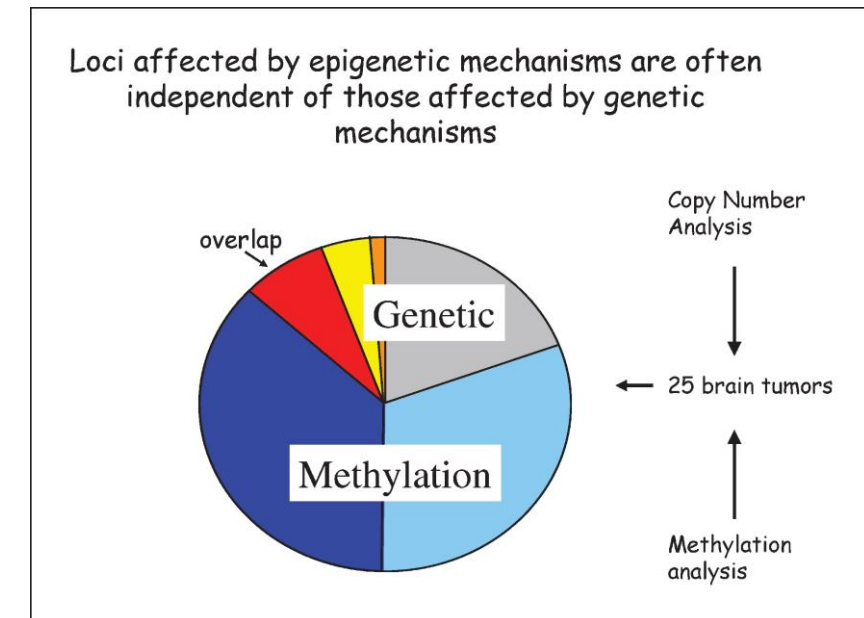


Gene-environment interactions through epigenetic mechanisms constitute a dynamic and reversible process during adult life



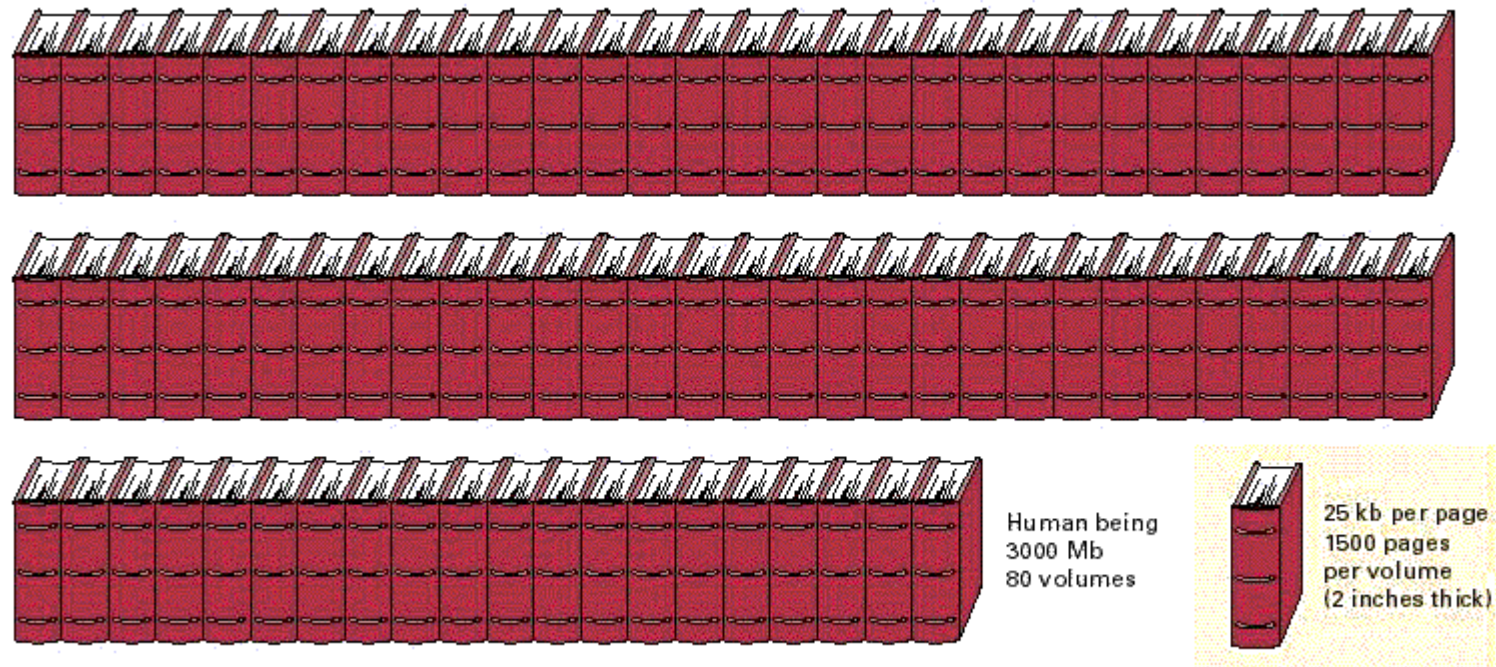
EPIGENETICS ON THE SCENE

- Sequencing of the human genome and genomes of model organisms - genes will tell us everything!
- Only 5% of the human diseases are due to genetic mutations
- Majority of human population has genetic setup to live long healthy lives
- Much more than 5% of the human population die prematurely which can not be explained with "bad genes"



- Man - 19,000 genes (> 2% of the genome) distributed on 23 chromosome pairs: biblioteca of different set of books which gives different recipes
- 3×10^9 base pairs (A,T,C,G) organised in words, phrases, chapters and books

- What determines which of the different books or which page in the particular book will be red?



It is time to move beyond genetics

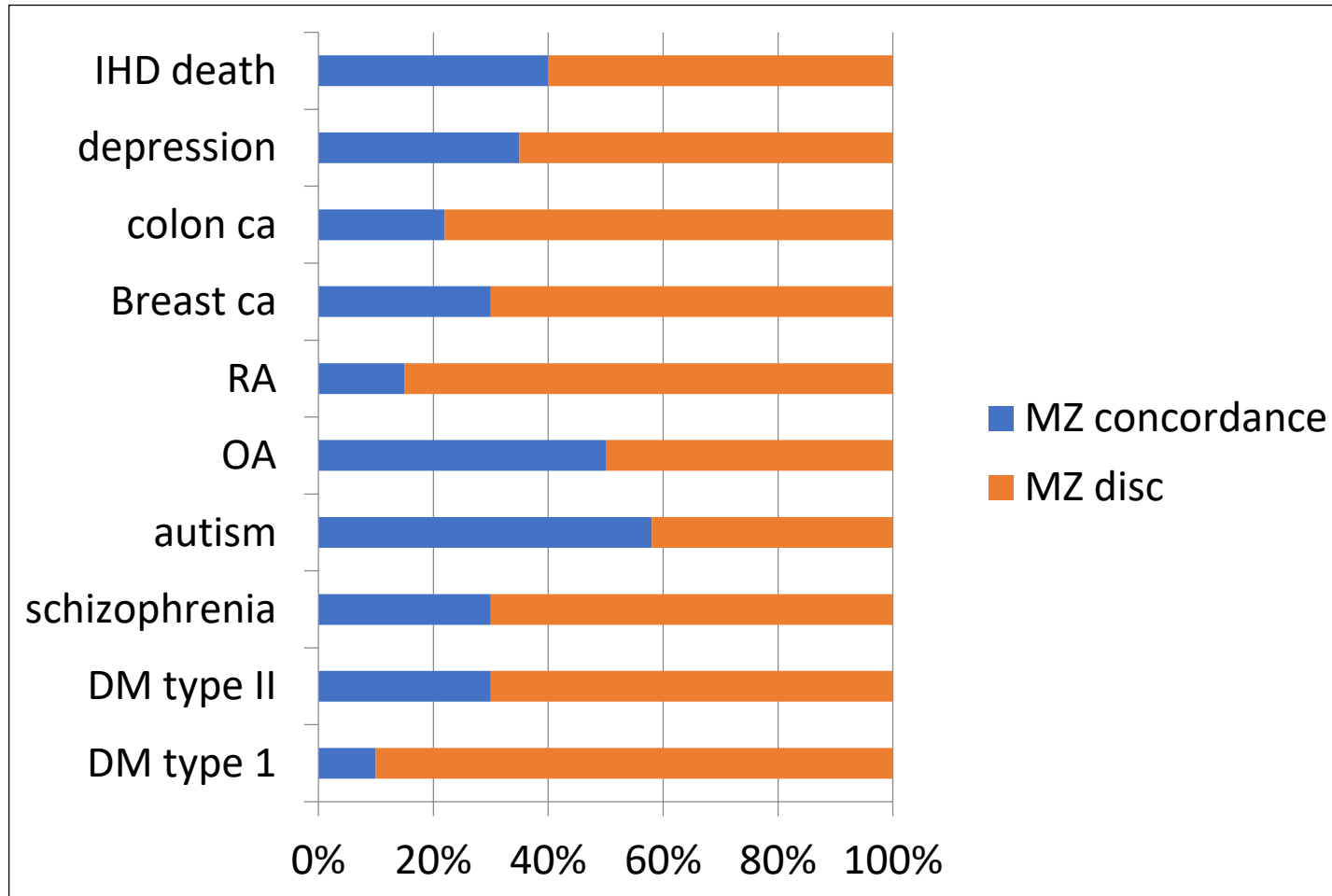
TWINS: in perspective

MZ twins – not exactly the same

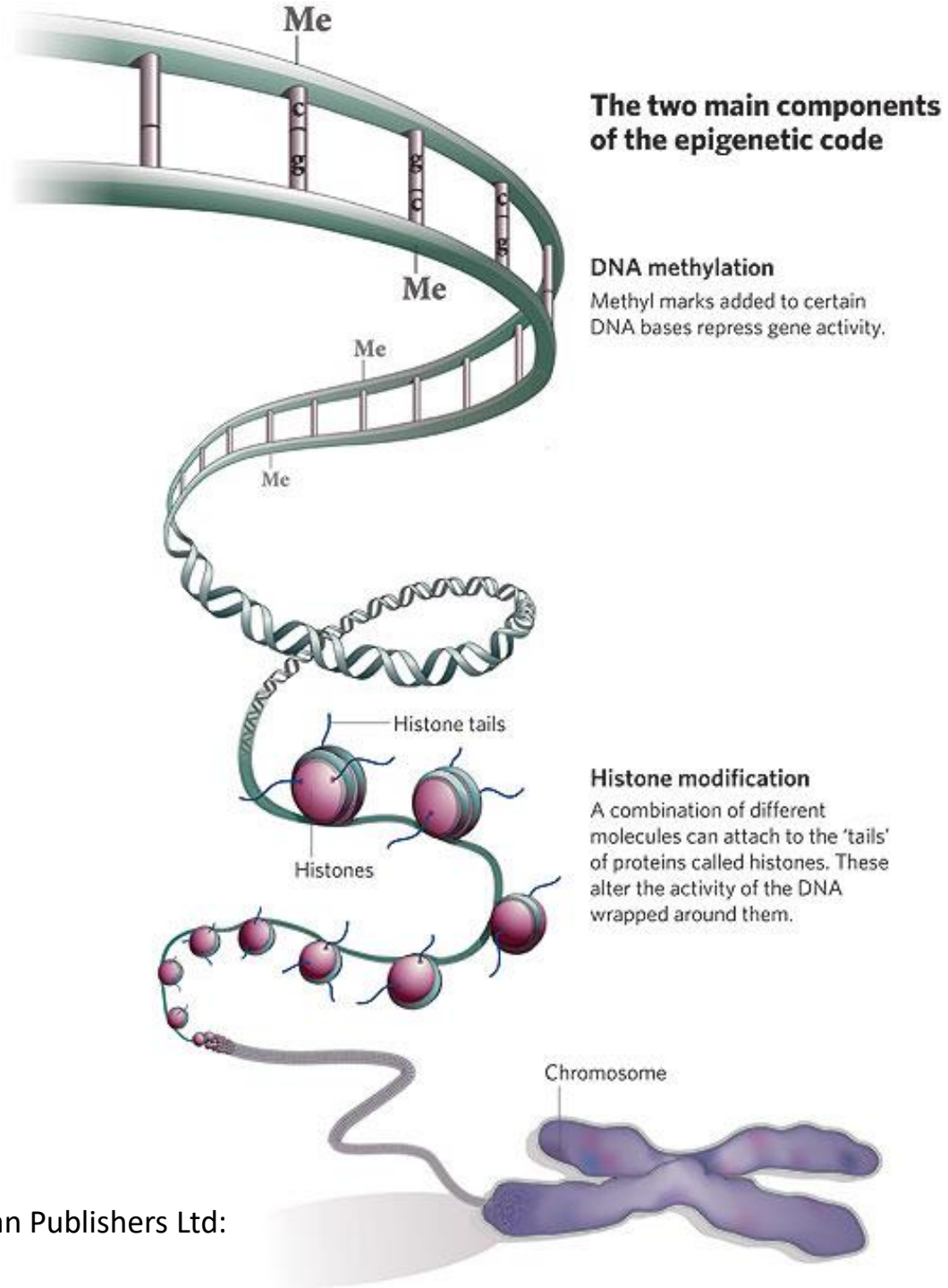


Identical but different-

low concordance rates for common disease in MZ twins



Epigenetics



Animal work - epigenetics

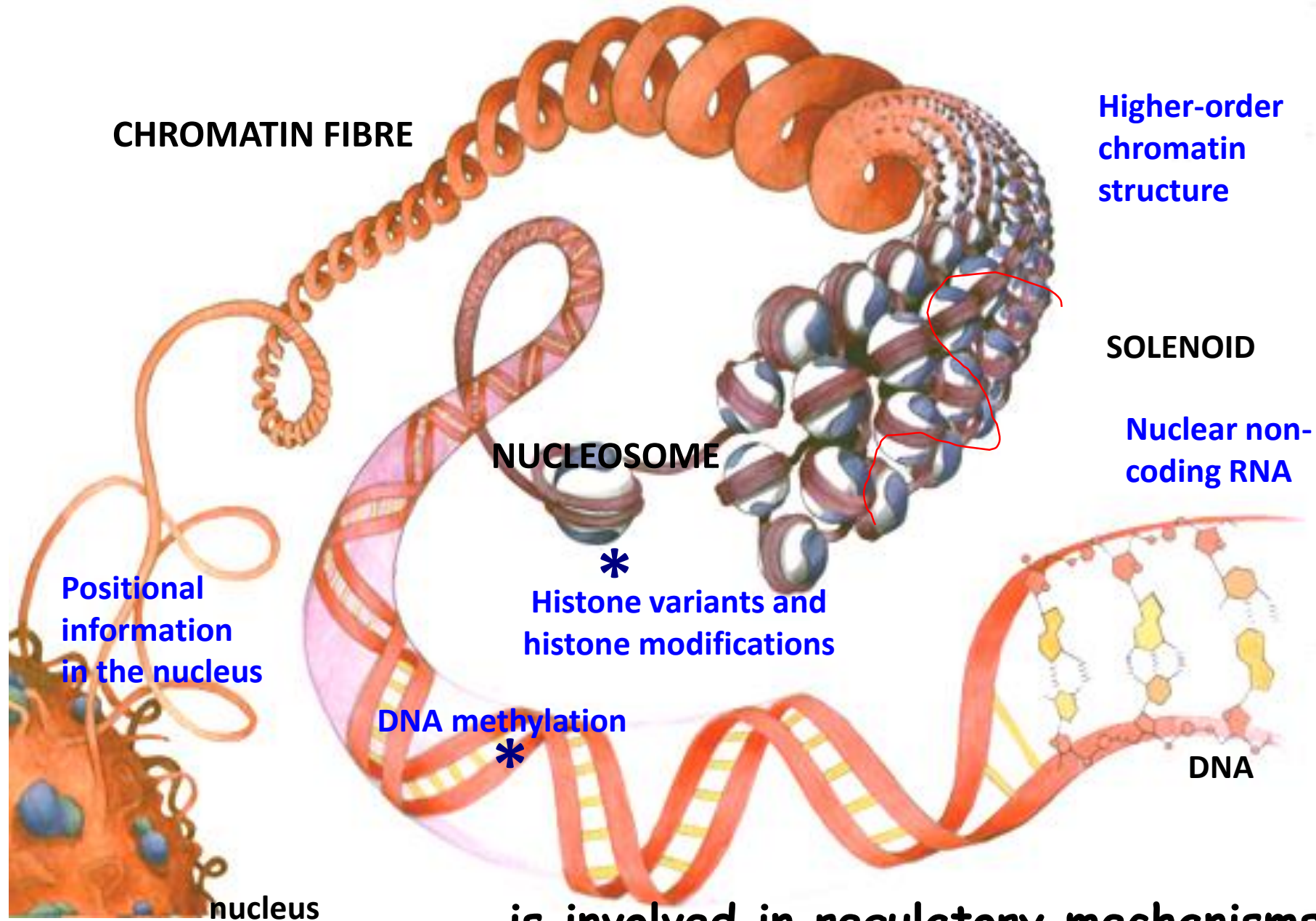


Agouti mouse

-diet influencing coat colour (methyl donor diet)

Twins – MZ allow examination of DNA-matched humans

Epigenetic information at the chromatin level....

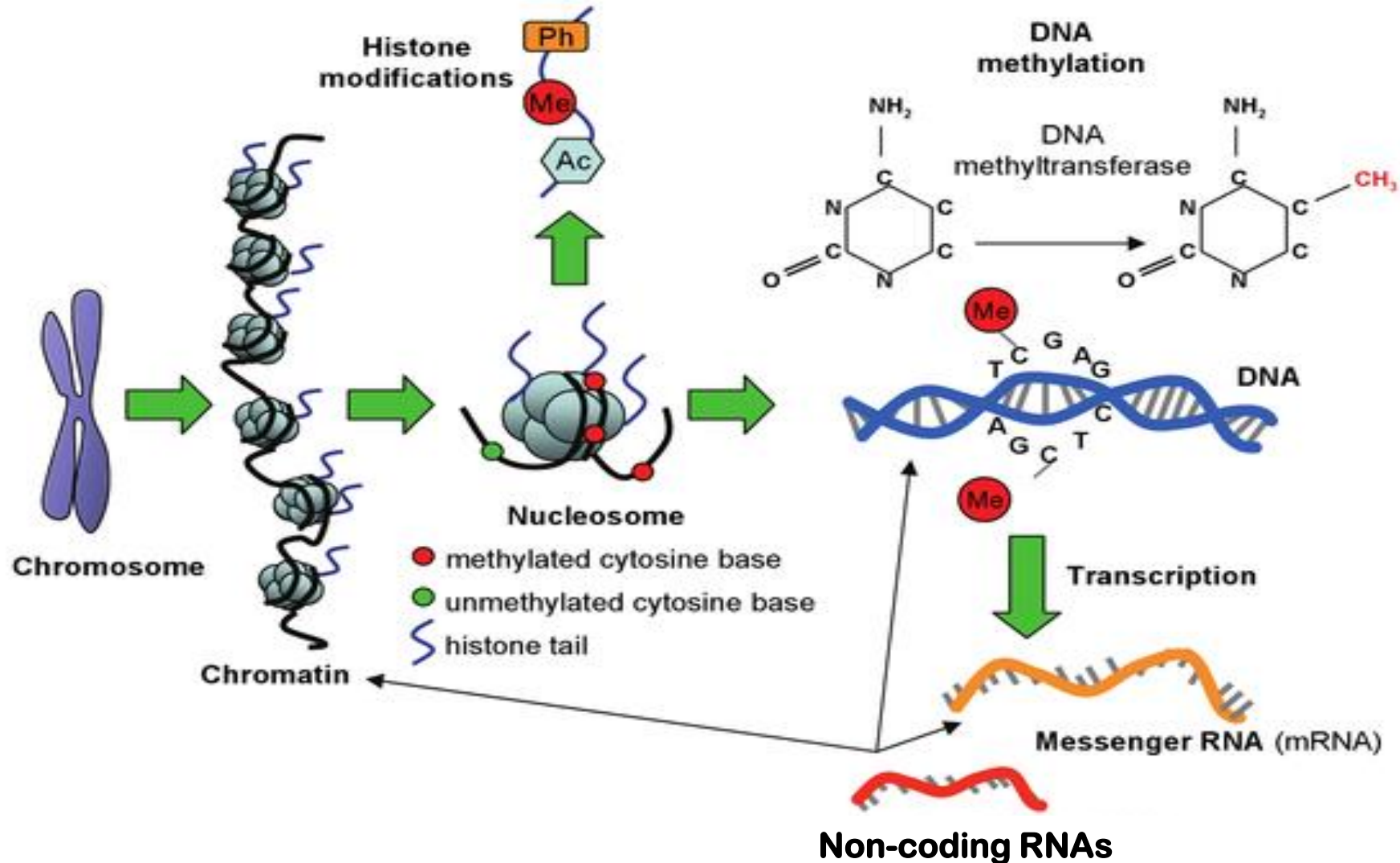


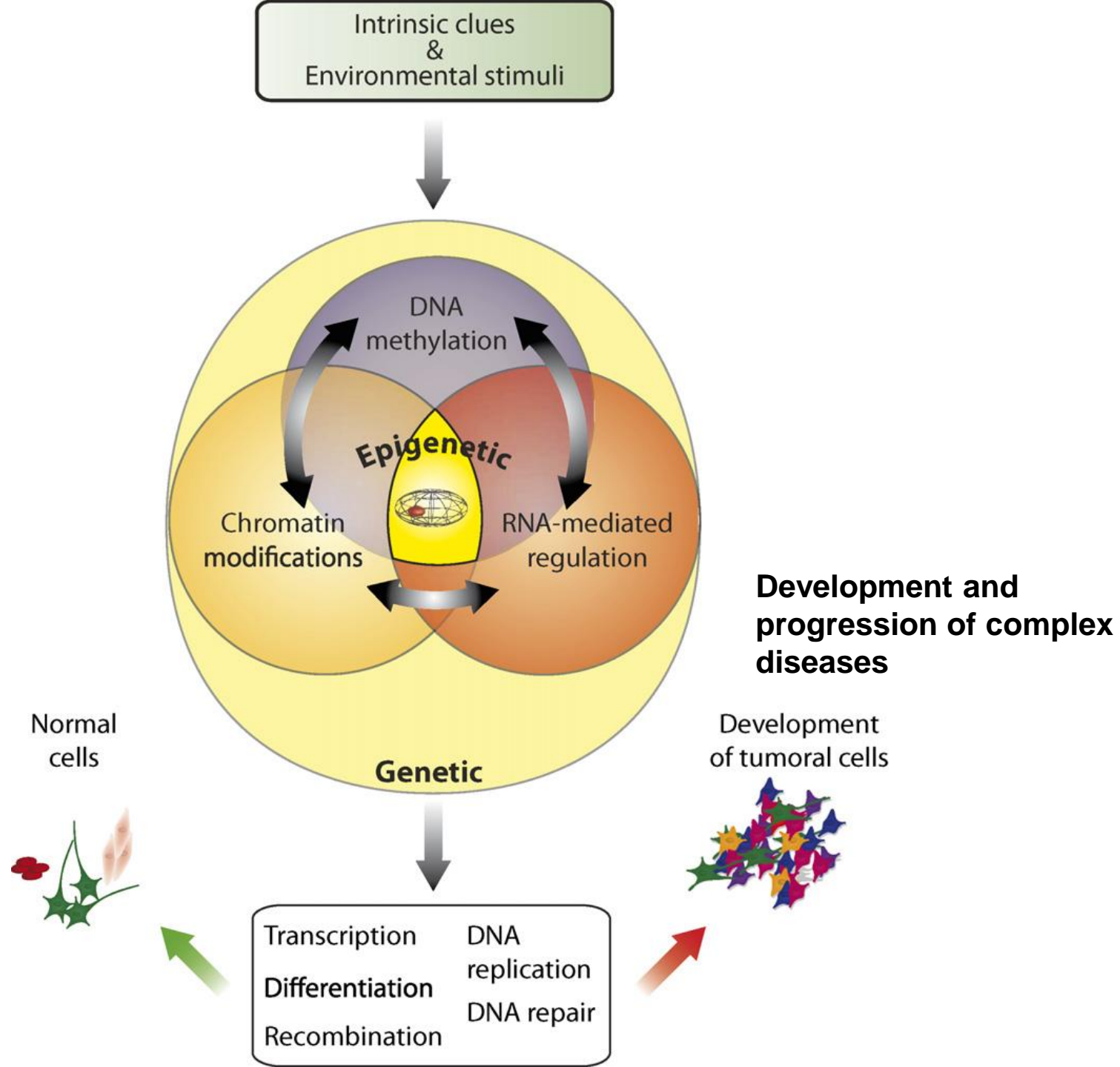
is involved in regulatory mechanisms of the nucleus

Chromatin - an indexing platform

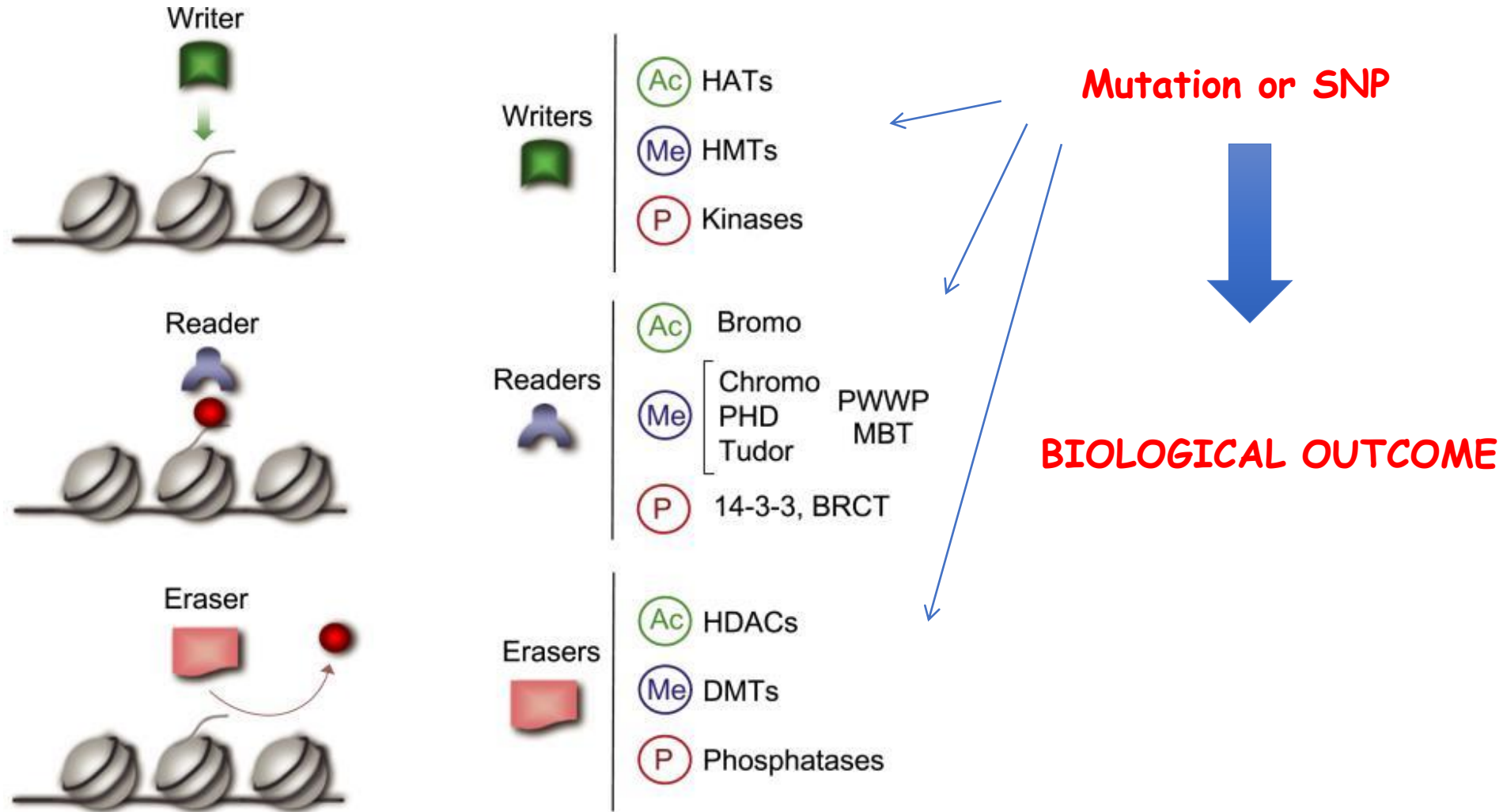


Genome "behaviour": epigenetic mechanisms

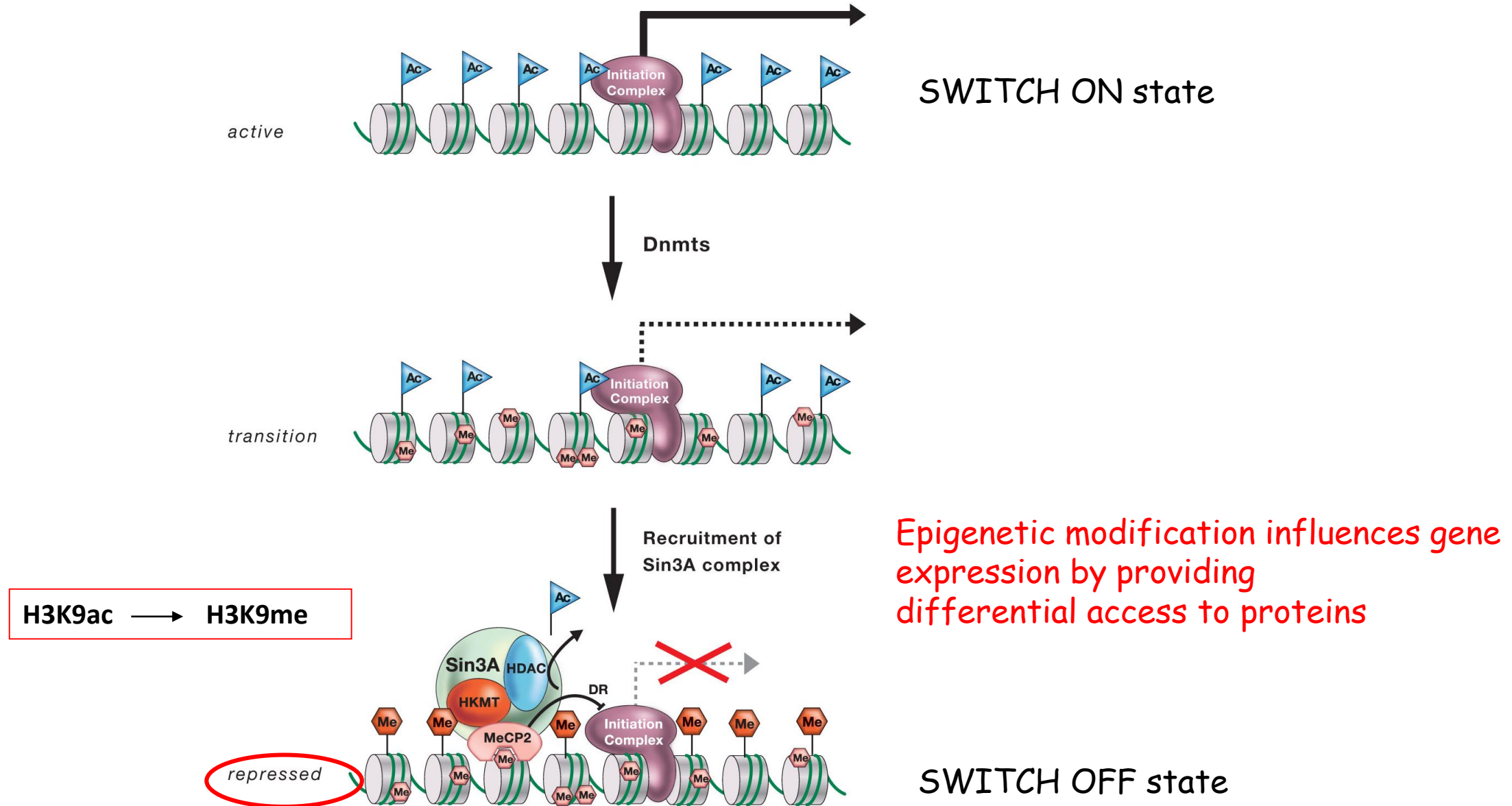




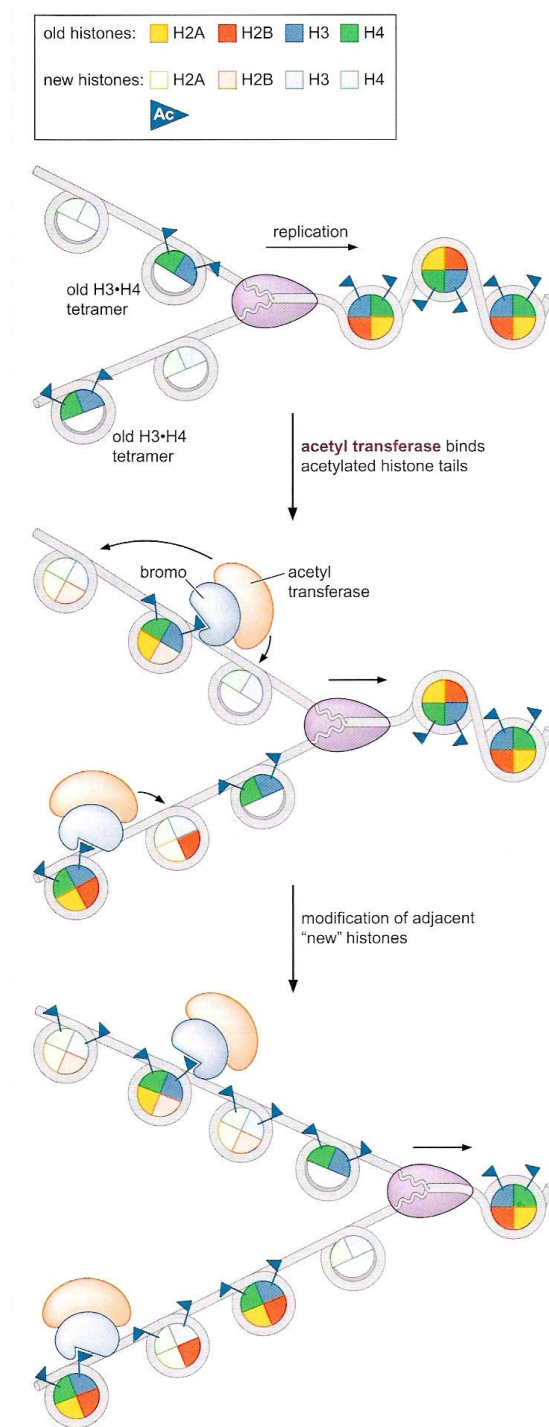
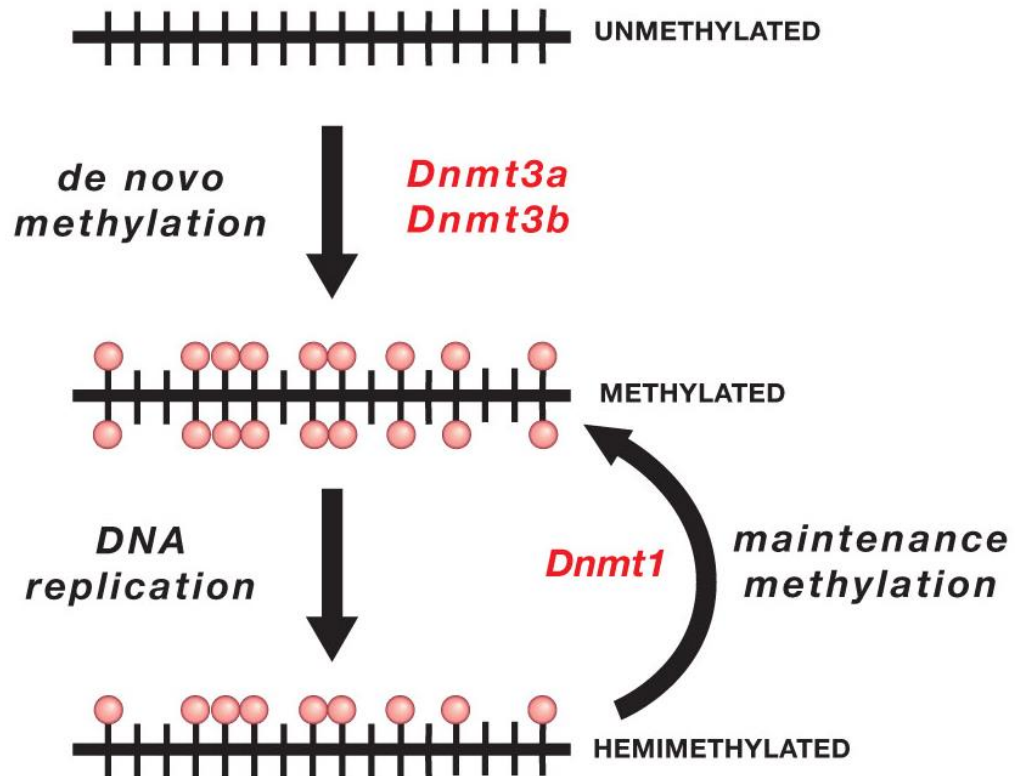
"Epigenetic indexing code": writers, readers and erasers



Orchestra of different epigenetic mechanisms



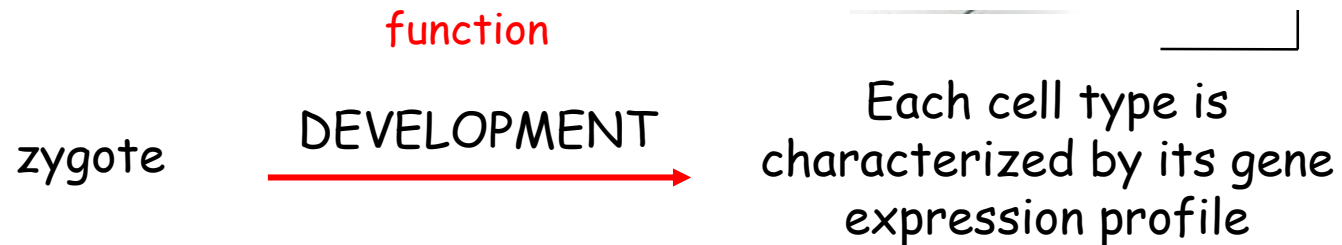
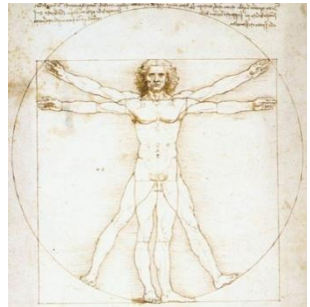
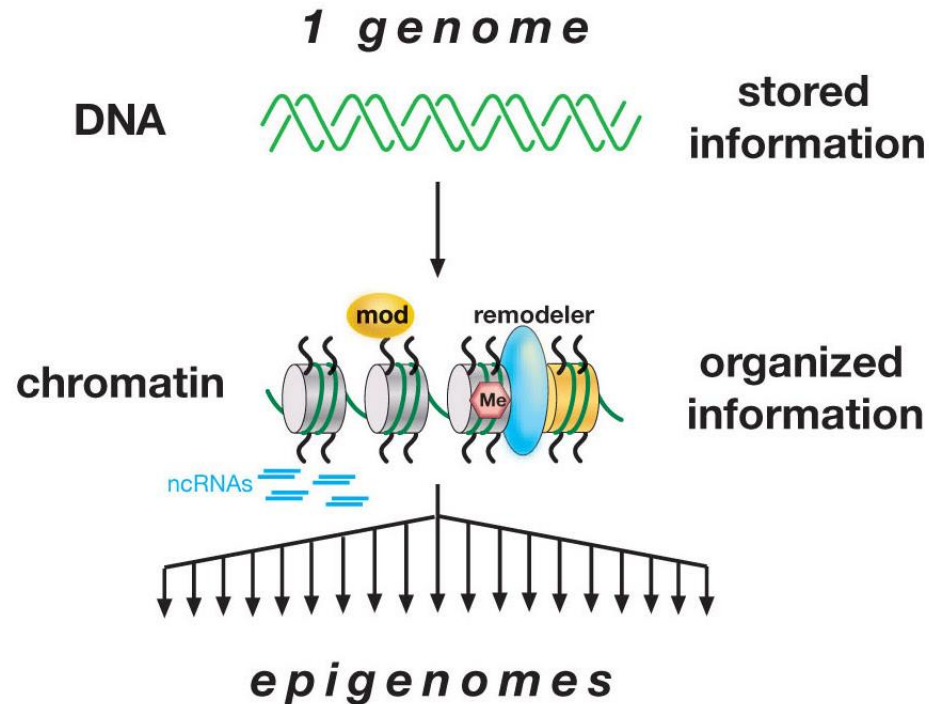
Heritability of epigenetic information - CELL MEMORY

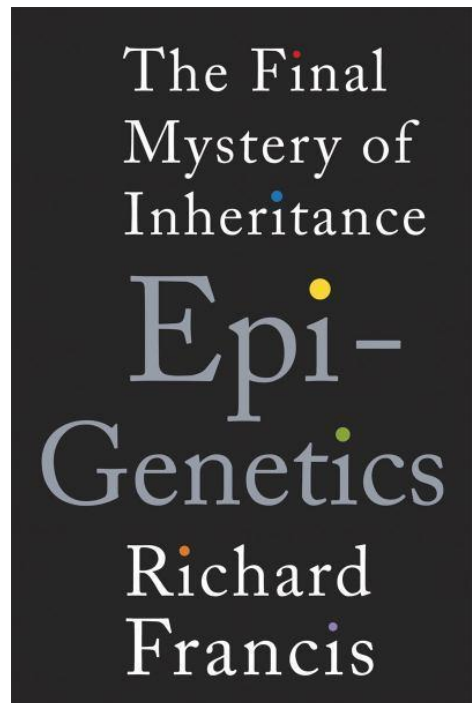
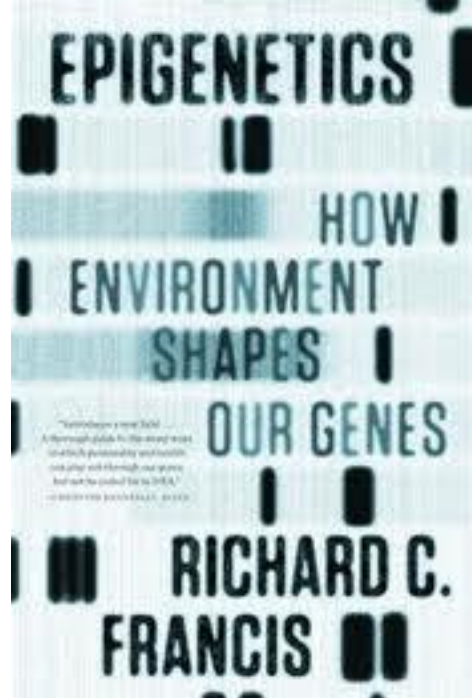


Predetermined epigenetics

Epigenetics defines cellular identity

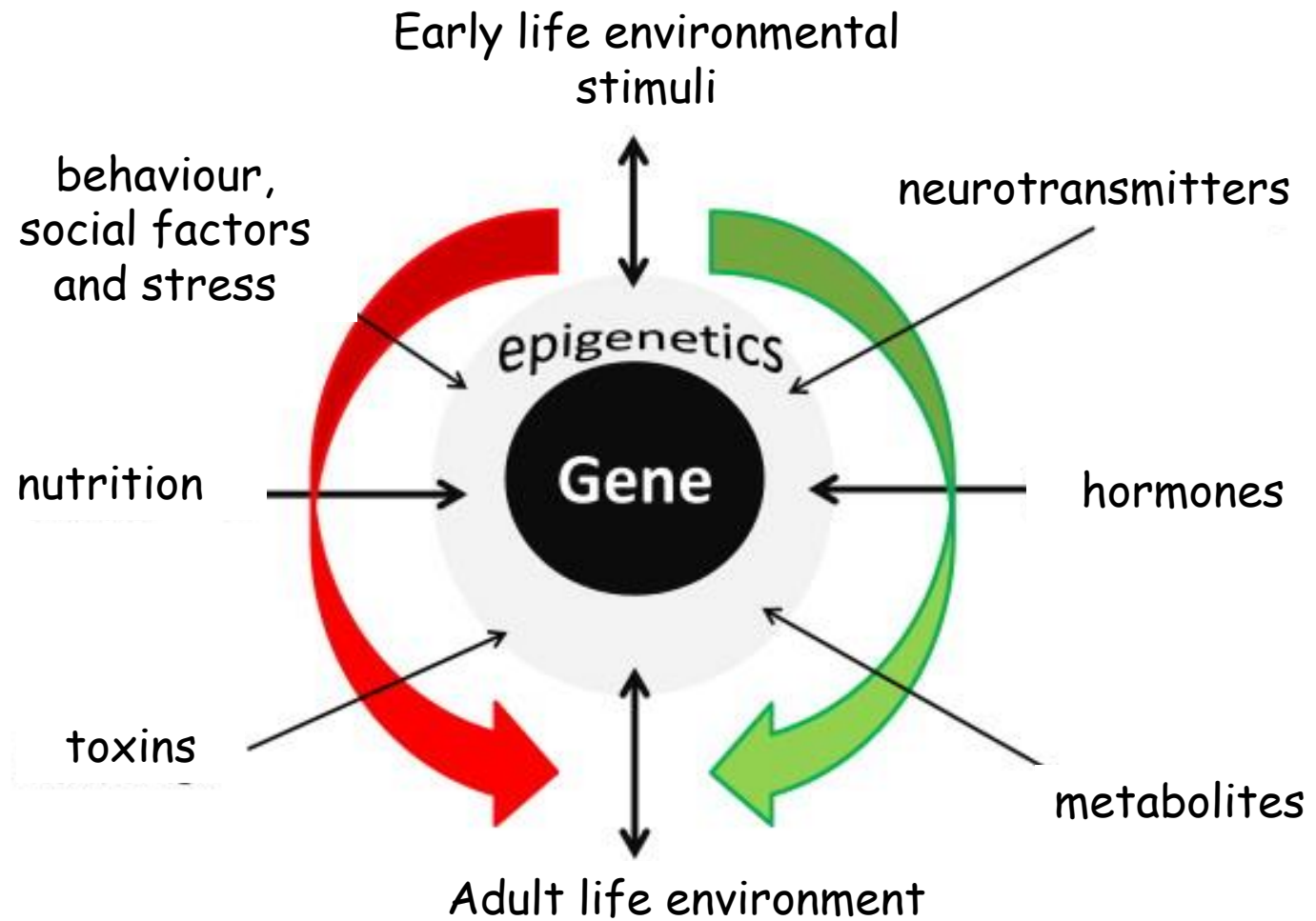
Each cell contains the same DNA





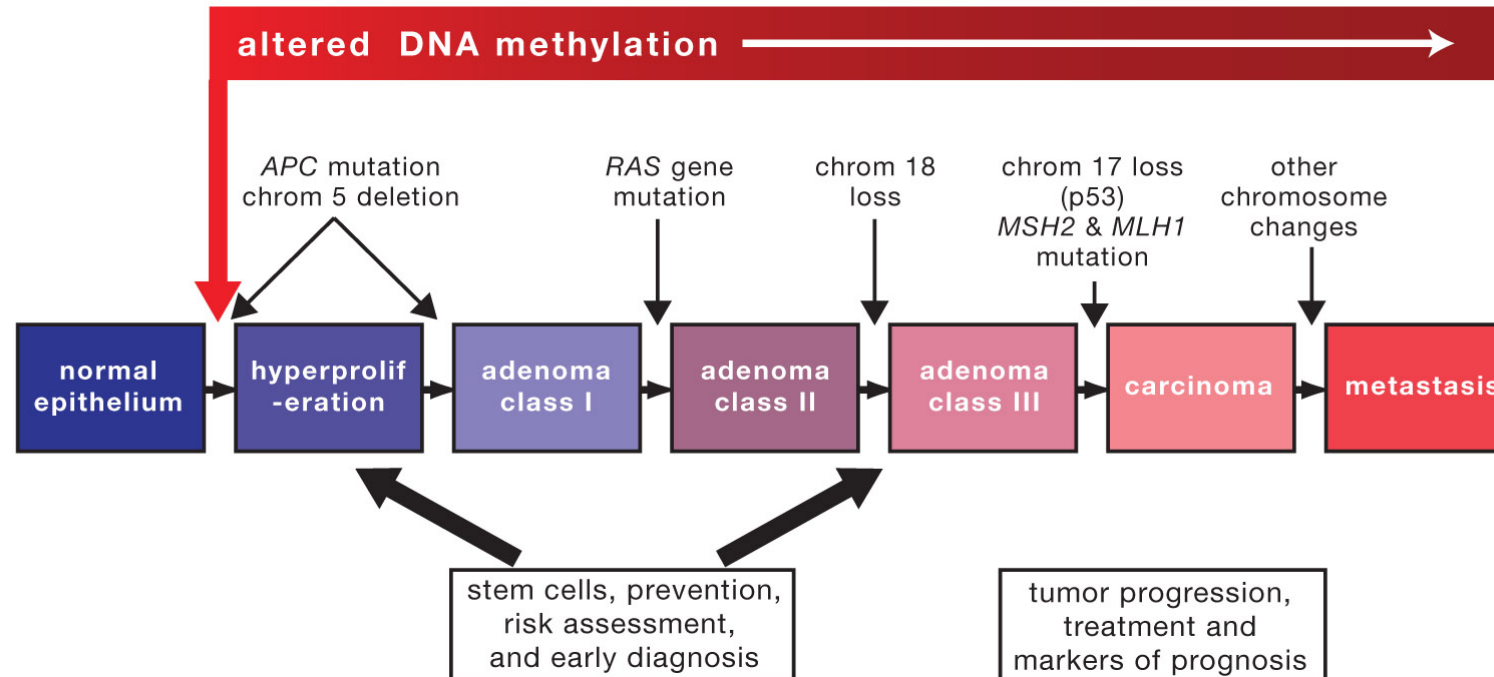
Probabilistic epigenetics

structure ----- function
gene ----- environment



Cancer is a disease of disturbed epigenetics

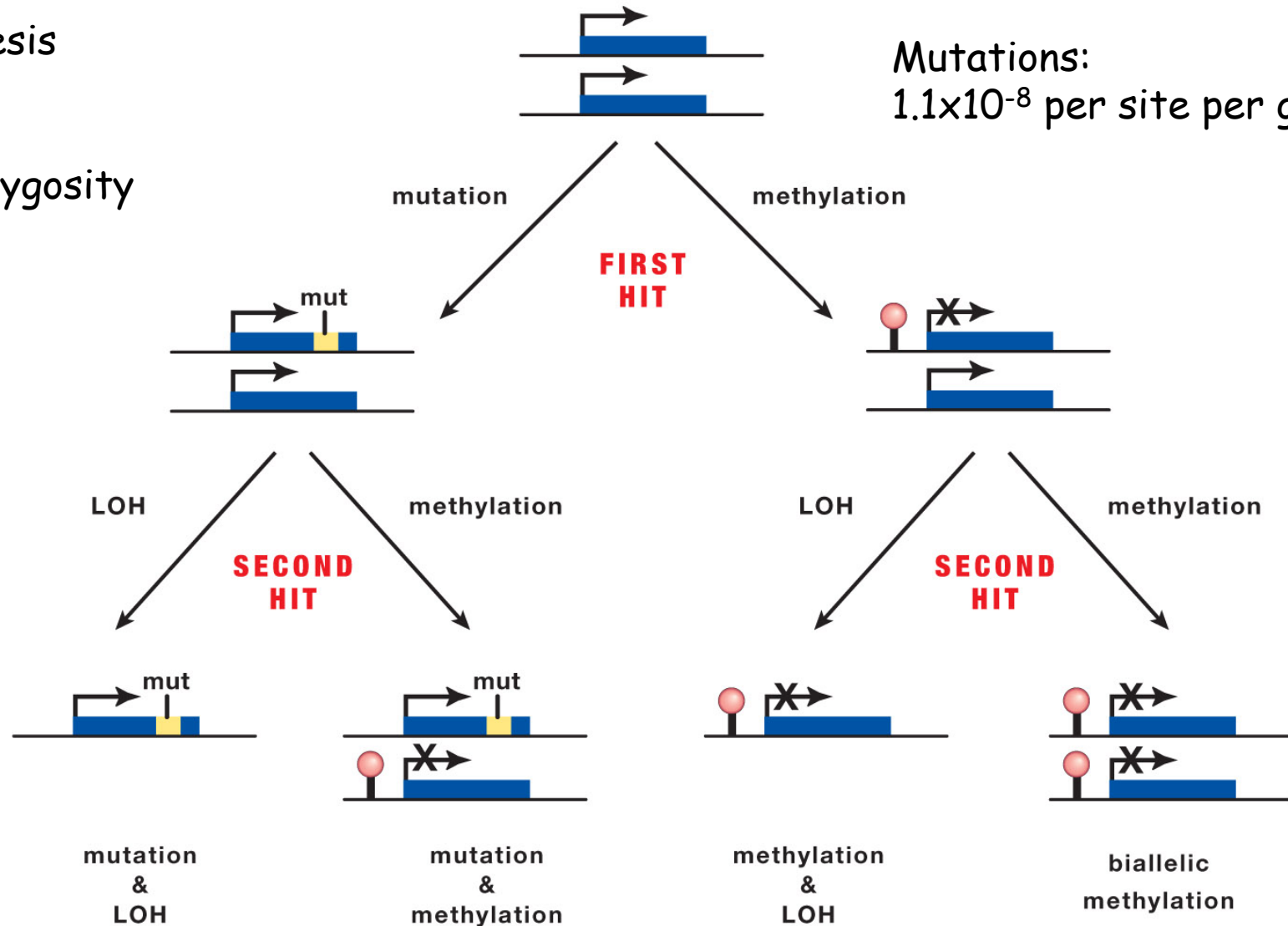
- Two critical events: LOI (Loss Of Imprinting) and silencing of genes associated with cancer (tumor-suppressor genes, genes involved in DNA repair, apoptosis etc.)
- Every phase in tumor initiation and progression is associated with specific epigenetic changes
- epigenetic changes specific for each type of cancer



Hypermethylated promoters of tumor-suppressor genes

Knudson's hypothesis

- second hit
- loss of heterozygosity

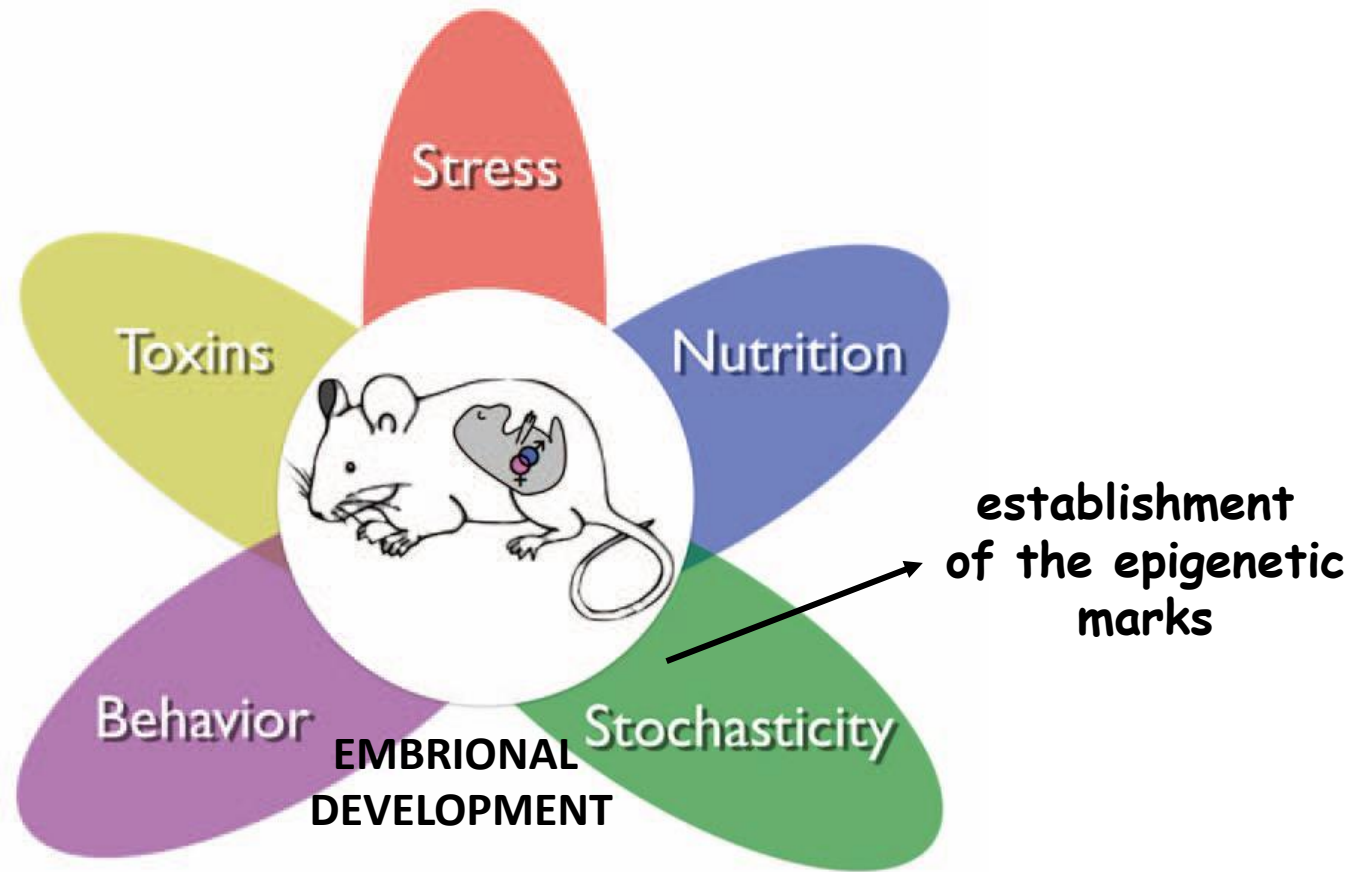


Interindividual epigenetic variability

- *Fraga et al. (2005) PNAS*: Epigenetic differences arise during the lifetime of monozygotic twins
- TwinsUK Registry at King's College London n= 13 000 twins

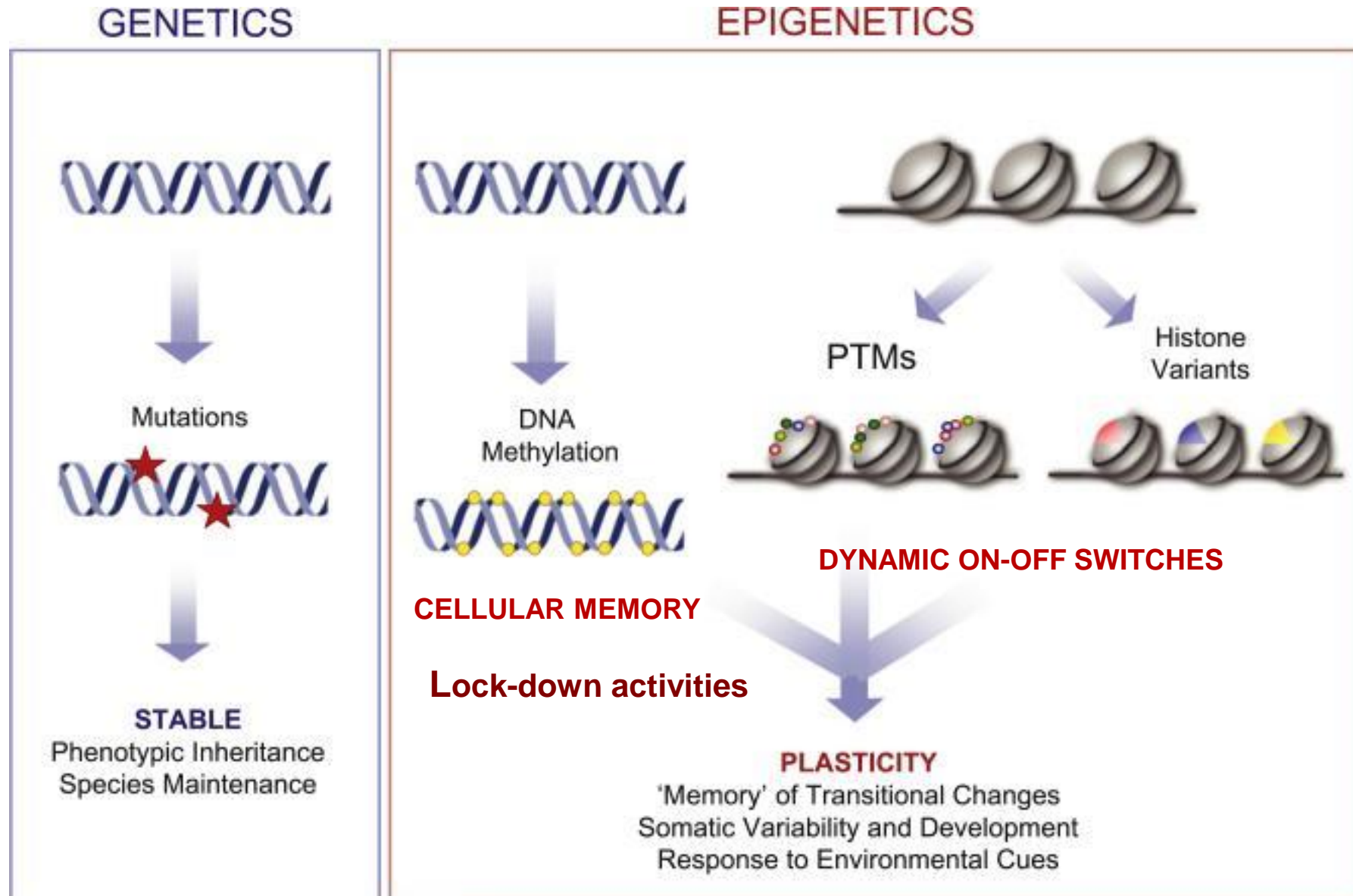


- intra-pair difference proportional to the degree of intra-pair lifestyle dissimilarity: age and environment largely influence epigenetic information
- **important contribution of the epigenotype to the phenotypic manifestation of the inherited genotype**

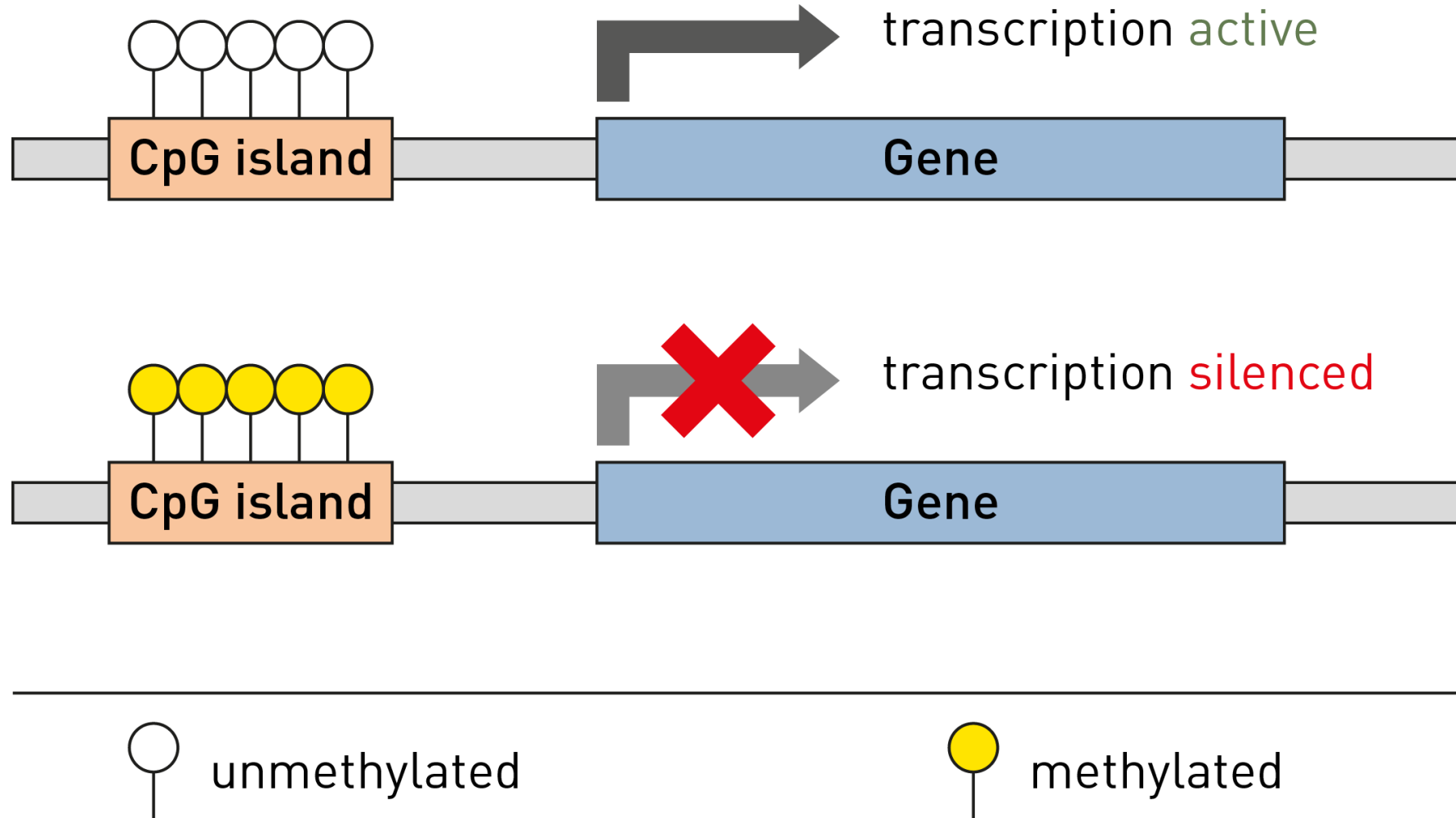


- environmental factors can influence epigenetic information in embryonal and early neonatal development
- can have long-term phenotypic results (including development of various complex diseases in adult life)
- the primary mechanism is the epigenetic inheritance through development of cellular lineages (mitotic divisions) - CELLULAR MEMORY

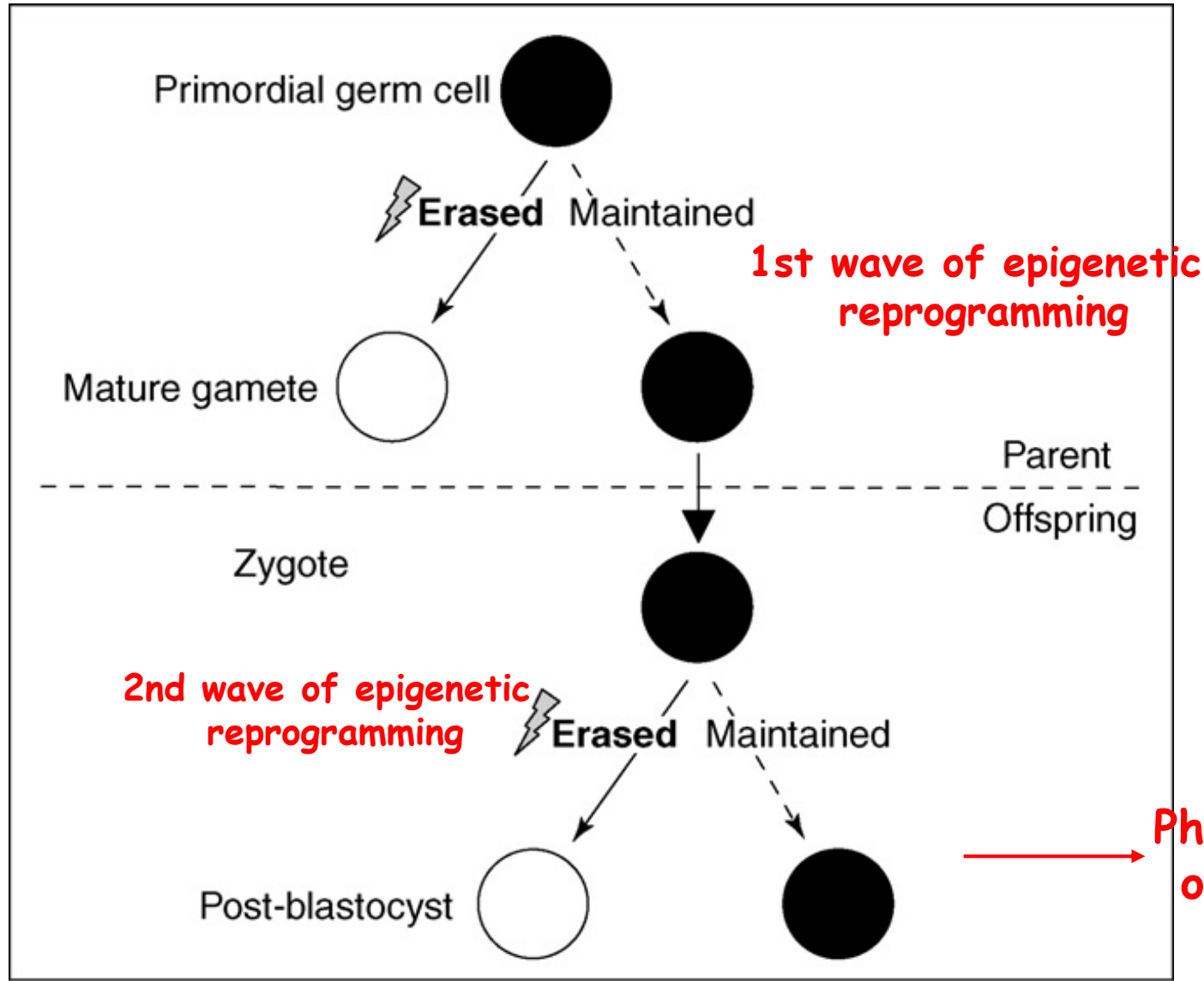
Stability versus plasticity of the epigenetic code



DNA methylation



Model for transgenerational inheritance of methylation marks



Probability of passing on the epiallele to the next generation is not 100%

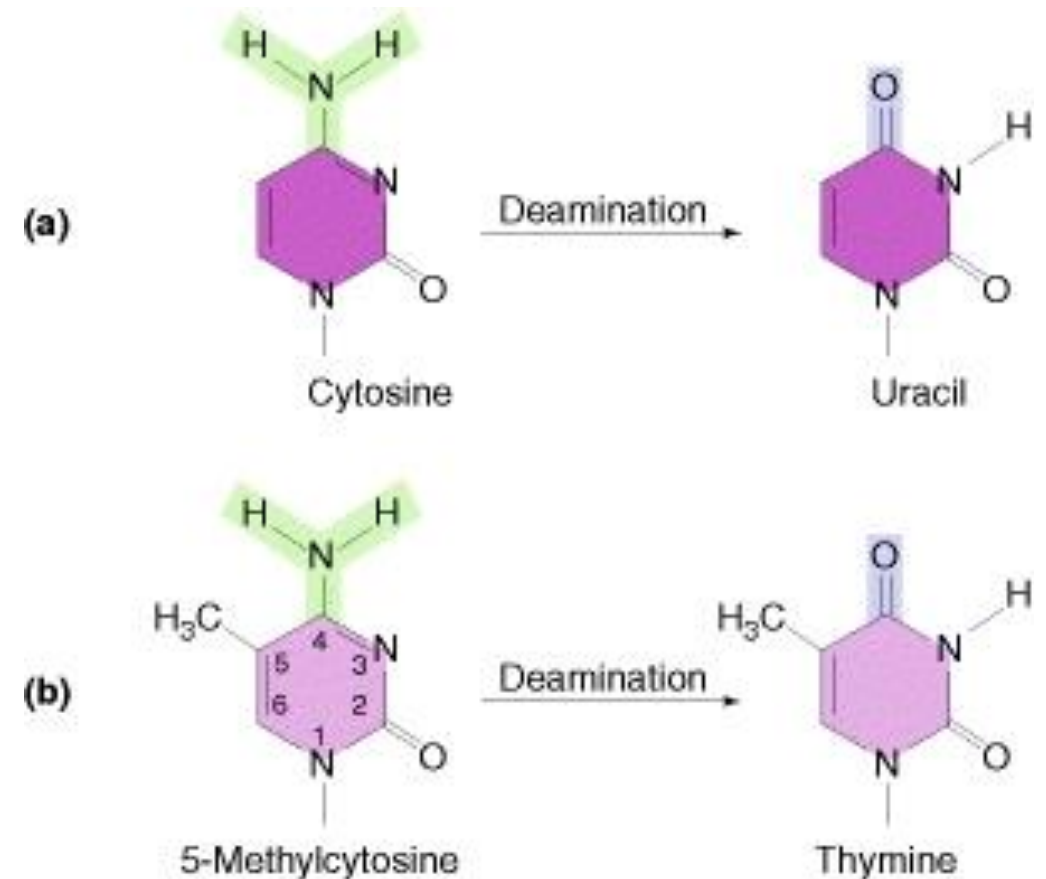
Phenotypes associated with epialleles are inherited in non-Mendelian manner

DNA methylation is the epigenetic mechanism involved in transgenerational epigenetic inheritance

- mouse studies - DNA methylation status (meDIP) through phases of morula, gastrula etc.
- **around 100 promoters** (imprinted genes are not included)
escape epigenetic reprogramming of the methylation marks
- potential loci which participate in epigenetic transgenerational inheritance

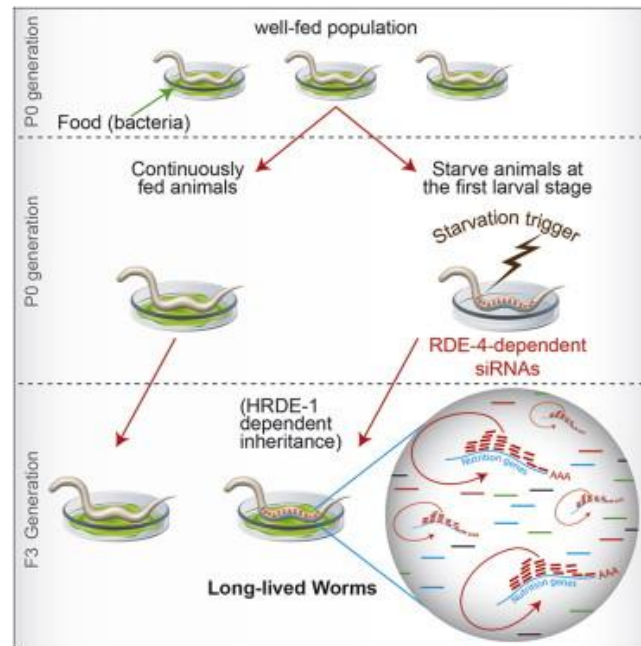
Mutagenity of cytosine methylation

- spontaneous deamination $C \rightarrow U$, repaired by uracil DNA glycosylase
- $C \rightarrow T$ transition after deamination of 5-methylcytosine is transmitted to new cells by DNA replication
- 1/3 of all point mutations is $C \rightarrow T$ transition in CpG dinucleotides
- the most common event in *single cause* genetic disease

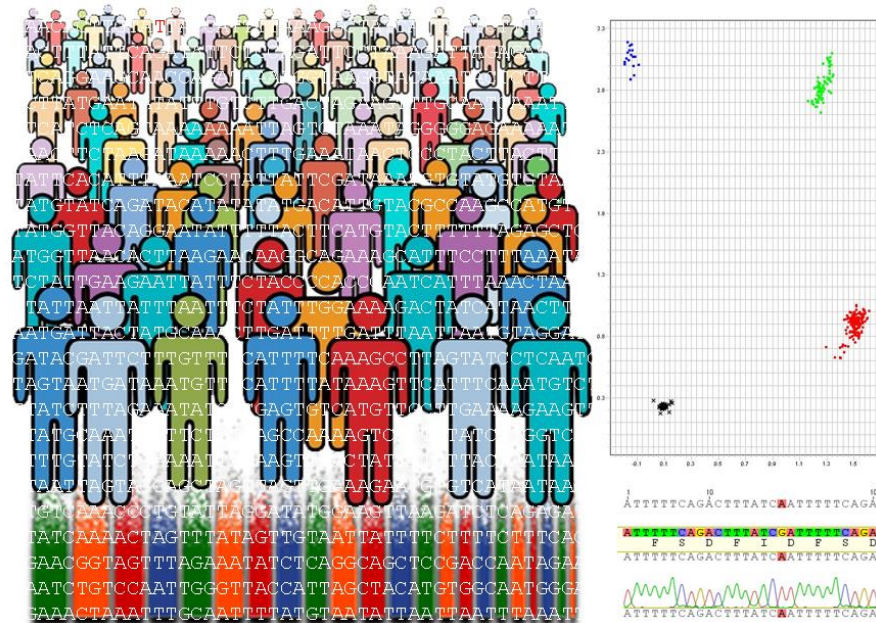


Non-coding RNAs - an important epigenetic mechanism involved in transgenerational inheritance

- In sperm and oocytes - many classes of non-coding RNAs (lnc RNAs, micro-RNAs, endo si-RNAs, piwiRNAs)
- Involved in gene silencing
- Non coding RNAs in gametes can provide zygote with necessary information to survive until two-cell phase when transcription begins
- In *C. elegans* and plants - small ncRNAs can be transported from cell to cell



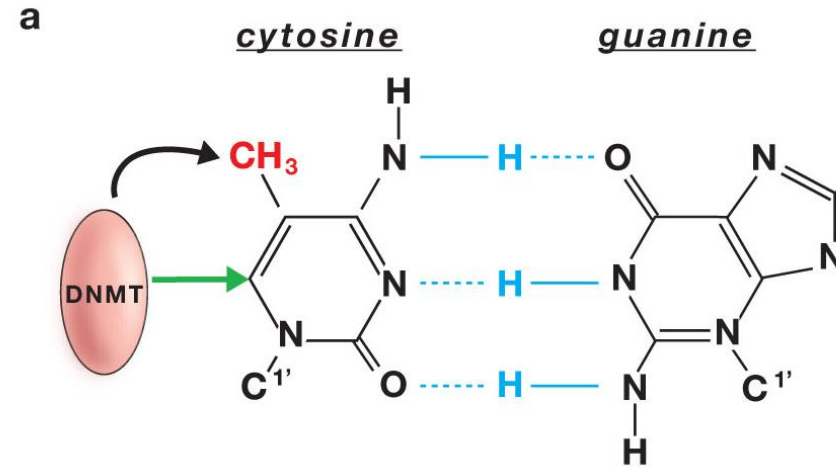
Epigenetic variability and epigenetic transgenerational inheritance as an additional source for evolution



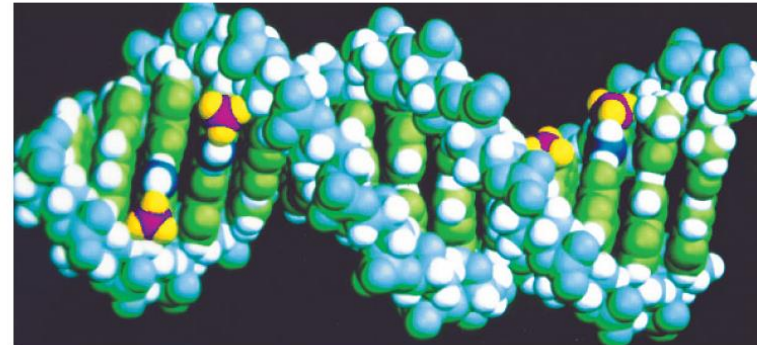
- Epigenetic variants can be important means of adaptive evolution in the face of environmental change without a permanent alteration in the DNA sequence

DNA methylation

- CpG methylation in genome of mammals
- mechanism of cell memory: CpG dinucleotides are complementary in two strands of DNA molecule – symmetric methylation
- **Dnmt 1 (maintenance DNA methyltransferase)** – maintain the pattern of DNA methylation

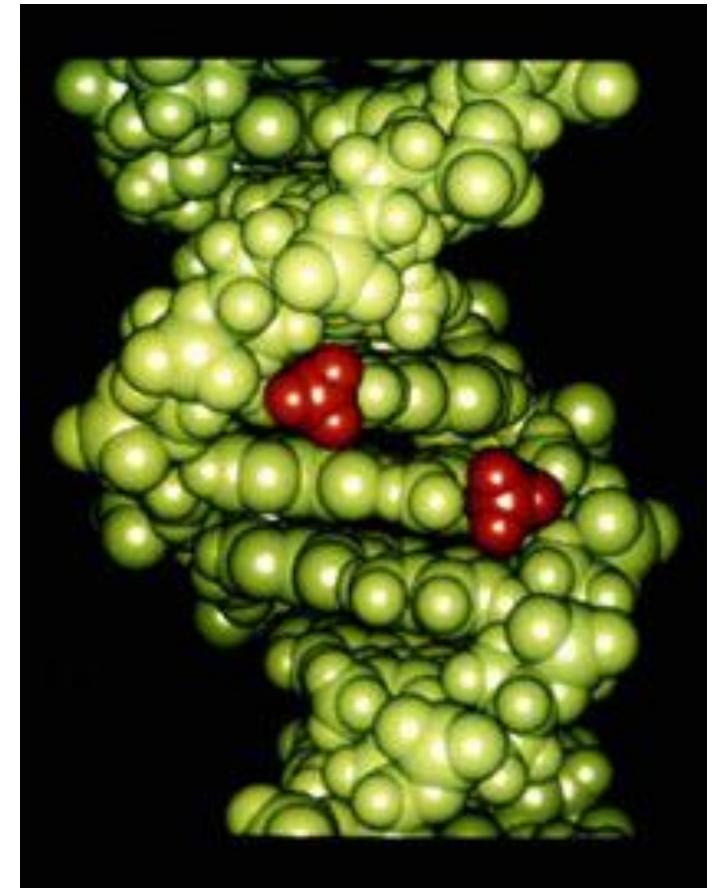


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DNA methylation roles in the mammalian genome:

- regulation of gene expression
- chromatin compaction
- keeping genome stability
- control of homologous recombination of repetitive sequences
- defence mechanism against foreign DN
- X-chromosome inactivation in mammalian females
- genome imprinting



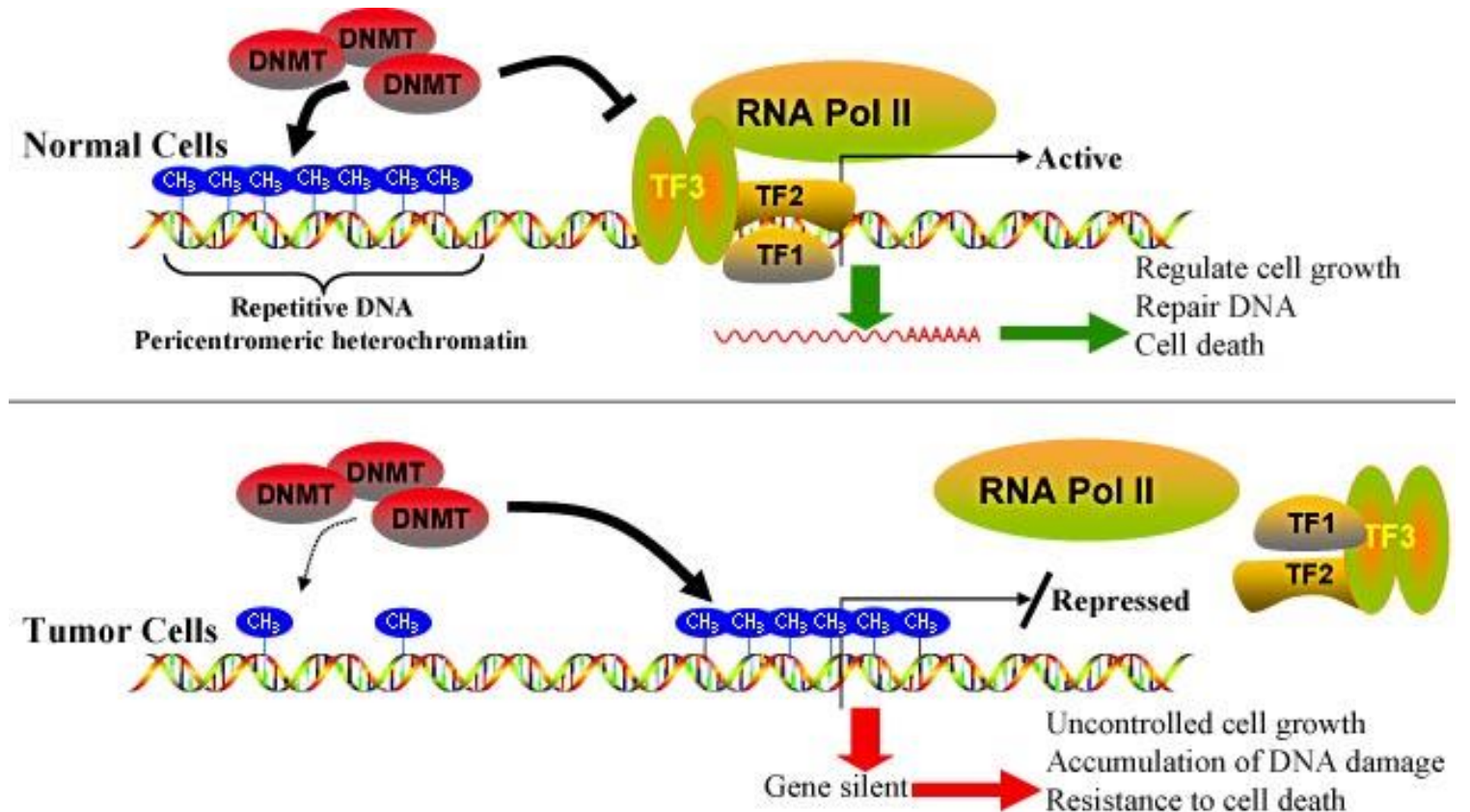
Pattern of DNA methylation in mammalian genome

- Bimodale distribution of 5-mC:
 - 1) Global genome hypermethylation (70%) – repetitive sequences (satellite DNA, intergenic spacers and gene exons)
 - 2) Unmethylated 5' end of genes, promoters (TSS*), **CpG islands**, first gene exons

*TSS = transcription start site

Aberrant DNA methylation

- Normal cells: global hypermethylation and non-metabolism of gene promoters
- Cancer cells: global hypomethylation (recurring DNA) and germ promoter hypermethylation
- Global hypomethylation: enhanced transcriptional transcription, increased warfare mutations, and increased frequency of mitotic recombination
- Silencing the tumor suppressor p16INK4a gene allows rapid tumor cell growth




RESEARCH

Open Access



Increased DNA methylation variability in rheumatoid arthritis-discordant monozygotic twins

Amy P. Webster^{1,2*} , Darren Plant³, Simone Ecker², Flore Zufferey⁴, Jordana T. Bell⁴, Andrew Feber^{2,5}, Dirk S. Paul⁶, Stephan Beck², Anne Barton^{1,3}, Frances M. K. Williams^{4†} and Jane Worthington^{1,3*†}

Clinical example – rheumatoid arthritis (RA)

- prevalence ~ 1% population
- joints - synovium inflammation, bony erosions
other tissues – kidneys, eyes, cardiovascular
- seropositive (circulating citrullinated Ig & seronegative disease: HLA-DRB1
- Genetic risk: ~ 30 – 50% heritability, 20-30% MZ twin concordance



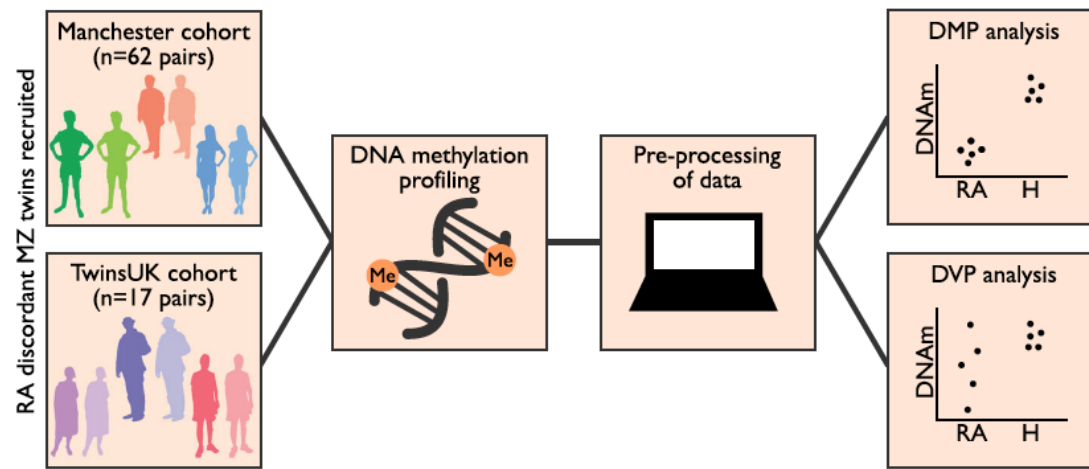


Fig. 1 Overview of study design. Rheumatoid arthritis-discordant twin pairs were recruited from the RA twins study in Manchester and TwinsUK in London, and genome-wide DNA methylation was investigated in the context of both differentially methylated positions and differentially variable positions

hypervariable enrichment in RA in 3'UTR, gene bodies and non-CPG island associated region

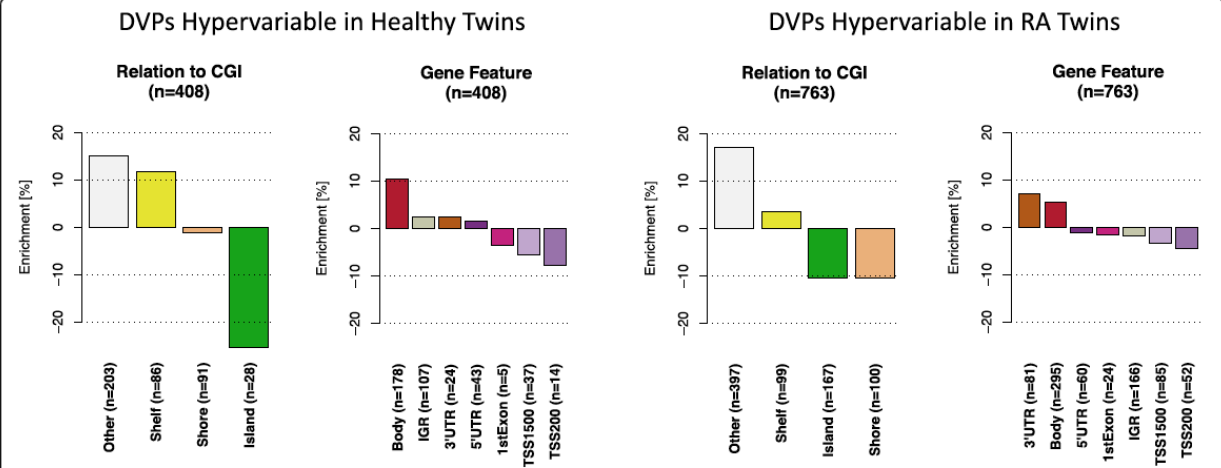


Fig. 3 Feature enrichment for RA-associated differentially variable positions which are hypervariable in healthy and RA-affected twins respectively. Differentially variable positions which are hypervariable in the healthy twins were enriched in CpG island shelves and non-CpG island-associated regions, and in the bodies of genes. Meanwhile, differentially variable positions enriched in RA-affected twins were enriched in 3'UTRs of genes, gene bodies and non-CpG island-associated regions

Thank you for listening and thanks to Prof Vladka Zoldos

REVIEWS

 DISEASE MECHANISMS

Epigenetic modulators, modifiers and mediators in cancer aetiology and progression

Andrew P. Feinberg¹, Michael A. Koldobskiy¹ and Anita Göndör²

Review

Cell
PRESS

Emerging patterns of epigenomic variation

Aleksandar Milosavljevic

Edwards et al. *Epigenetics & Chromatin* (2017) 10:23
DOI 10.1186/s13072-017-0130-8


Epigenetics & Chromatin

REVIEW

Open Access



DNA methylation and DNA methyltransferases

John R. Edwards¹, Olya Yarychkivska², Mathieu Boulard² and Timothy H. Bestor^{2*} 

Van Baak et al. *Genome Biology* (2018) 19:2
DOI 10.1186/s13059-017-1374-0

Genome Biology

RESEARCH

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Epigenetic supersimilarity of monozygotic twin pairs



REVIEW

EPIGENETICS

Epigenetics and aging

Sangita Pal^{1,2} and Jessica K. Tyler^{1*}

Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease

Andrew P. Feinberg¹ and Rafael A. Irizarry