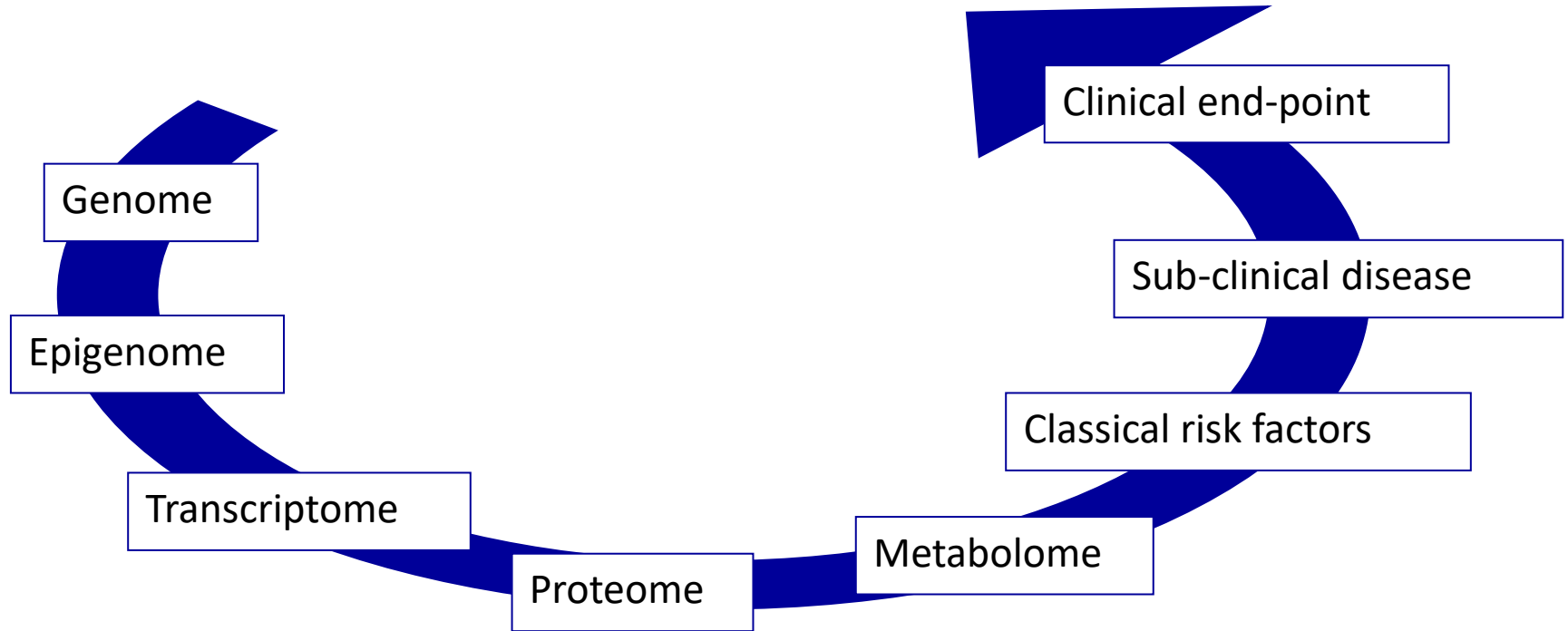


An introduction to the epigenome

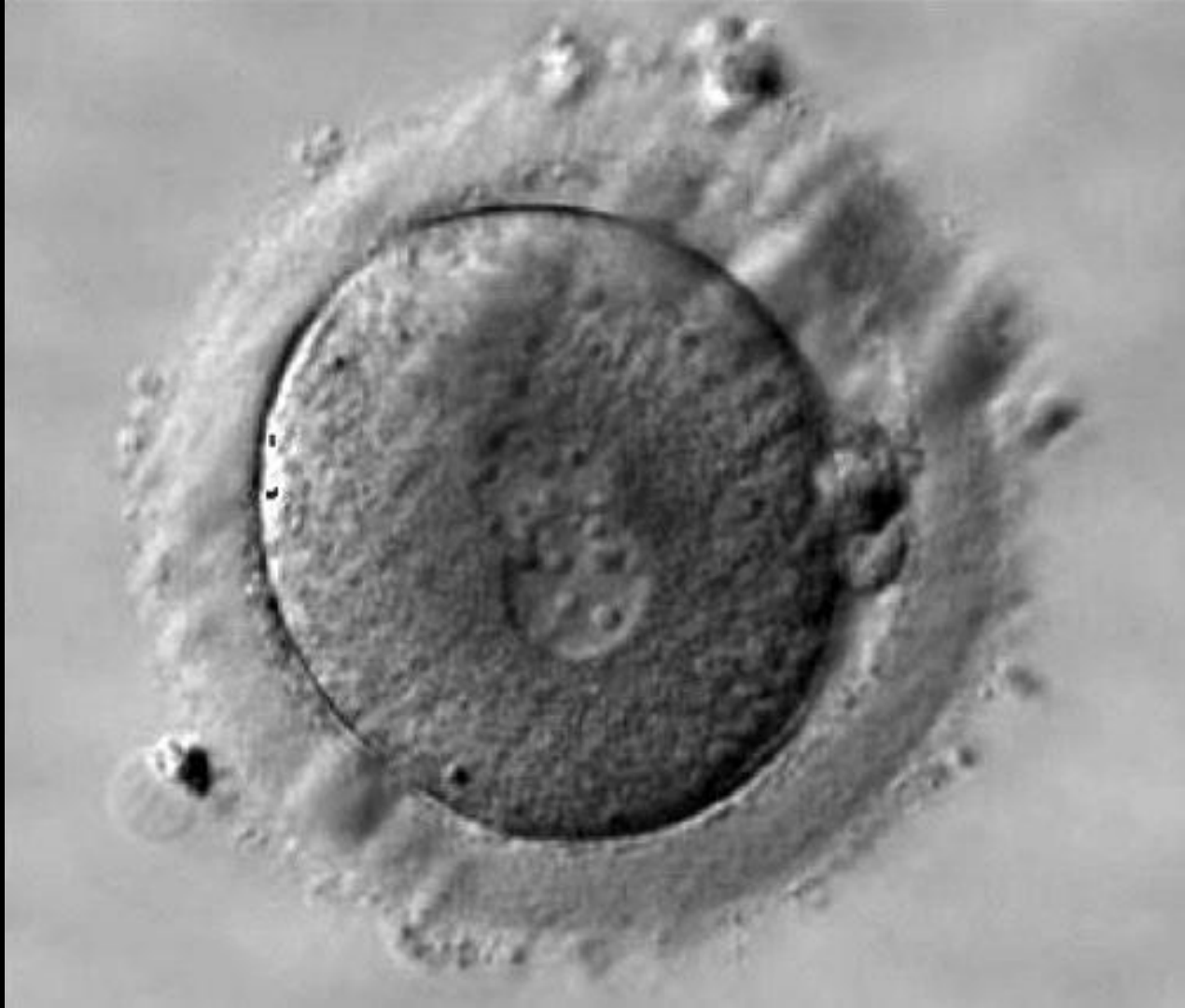
Bas Heijmans & Roderick Slieker
Biomedical Data Sciences & Cell and Chemical Biology
Leiden University Medical Center
The Netherlands
bas.heijmans@lumc.nl



On offer

- The molecular basis of epigenetics
- The role of epigenetics in fundamental biology
- Epigenetics as integrator of environmental signals
- Epigenetics in disease mechanisms





20 hours after
fertilization



Day 3, 8 cells



The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC
CCAGGGCCCCCAAGACACACAGA
CGGCACAGCAGGGCTGGTTCAAG
GGCTTTATTCCATCTCTCTCGGT
GCAGGAGGCGGCGGGTGTGGGGC
TGCCTGCGGGCTGCGTCTAGTTG
CAGTAGTTCTCCAGCTGGTAGAG



The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC
CCAGGGCCCCCAAGACACACAGA
CGGCACAGCAGGGCTGGTTCAAG
GGCTTTATTCCATCTCTCTCGGT
GCAGGAGGGCGGCGGGTGTGGGGC
TGCTTGCGGGCTGCGTCTAGTTG
CAGTAGTTCTCCAGCTGGTAGAG

A G T C



The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC
CCAGGGCCCCCAAGACACACAGA
CGGCACAGCAGG**GCTGGTTCAAG**
GGCTTTATTCCATCTCTCTCGGT
GCAGGAGGCGGCGGGTGTGGGGC
TGCCTGCGGGCTGCGTCTAGTTG
CAGTAGTTCTCCAGCTGGTAGAG



The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC
CCAGGGCCCCCAAGACACACAGA
CGGCACAGCAGG**GCTGGTTCAAG**
GGCTTTATTCCATCTCTCTCGGT
GCAGGAGGCGGCGGGTGTGGGGC
TGCCTGCGGGCTGCGTCTAGTTG
CAGTAGTTCTCCAGCTGGTAGAG



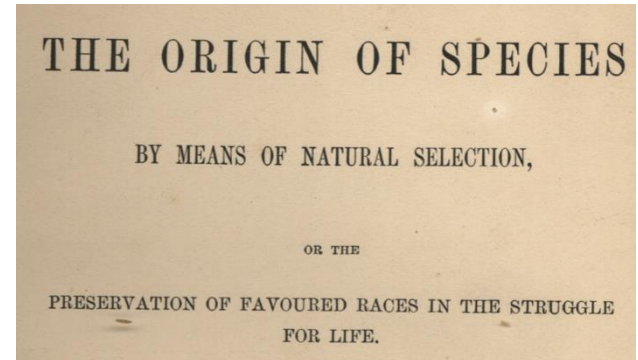
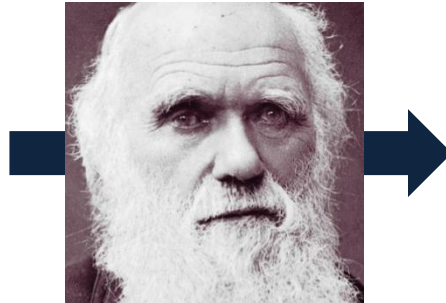
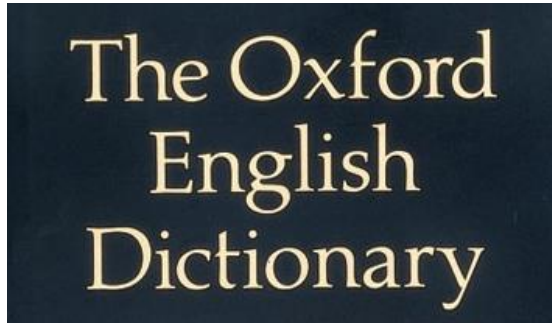
The Oxford
English
Dictionary



THE ORIGIN OF SPECIES
BY MEANS OF NATURAL SELECTION,
OR THE
PRESERVATION OF FAVOURED RACES IN THE STRUGGLE
FOR LIFE.

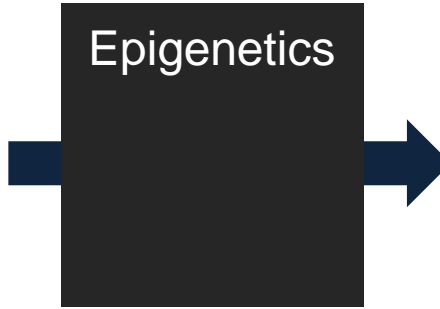
The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC
CCAGGGCCCCCAAGACACACAGA
CGGCACAGCAGG**GCTGGTTCAAG**
GGCTTTATTCCATCTCTCTCGGT
GCAGGAGGCGGCGGGTGTGGGGC
TGCCTGCGGGCTGCGTCTAGTTG
CAGTAGTTCTCCAGCTGGTAGAG



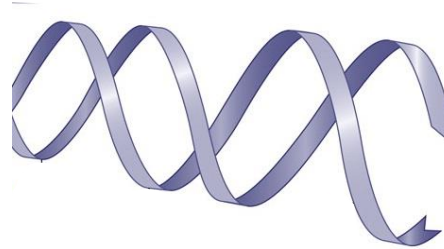
The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC
CCAGGGCCCCCAAGACACACAGA
CGGCACAGCAGG**GCTGGTTCAAG**
GGCTTTATTCCATCTCTCTCGGT
GCAGGAGGCGGCGGGTGTGGGGC
TGCCTGCGGGCTGCGTCTAGTTG
CAGTAGTTCTCCAGCTGGTAGAG

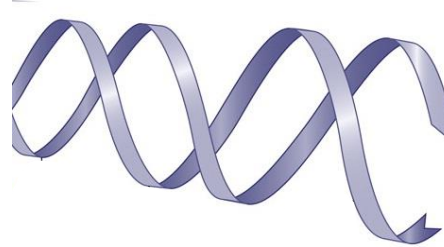
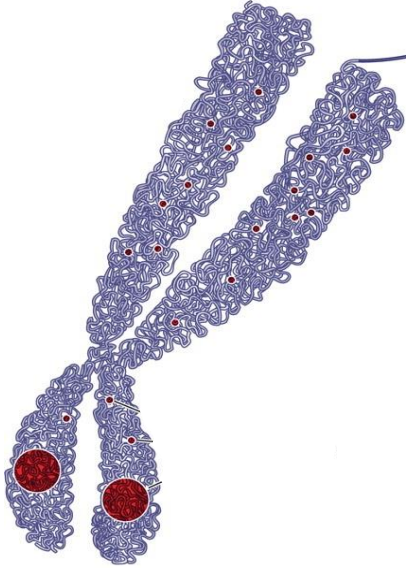


- Instructing the DNA where, when and how much to express a gene.
- Epigenetics provides variation & memory.

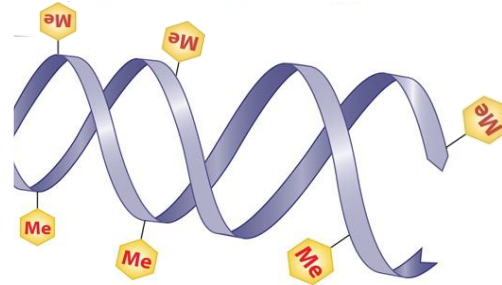
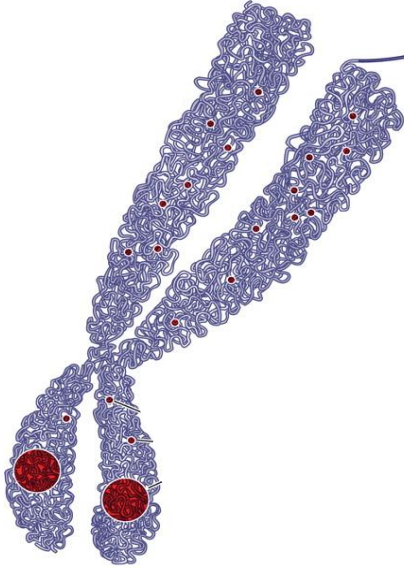
Molecular dimmers on the DNA



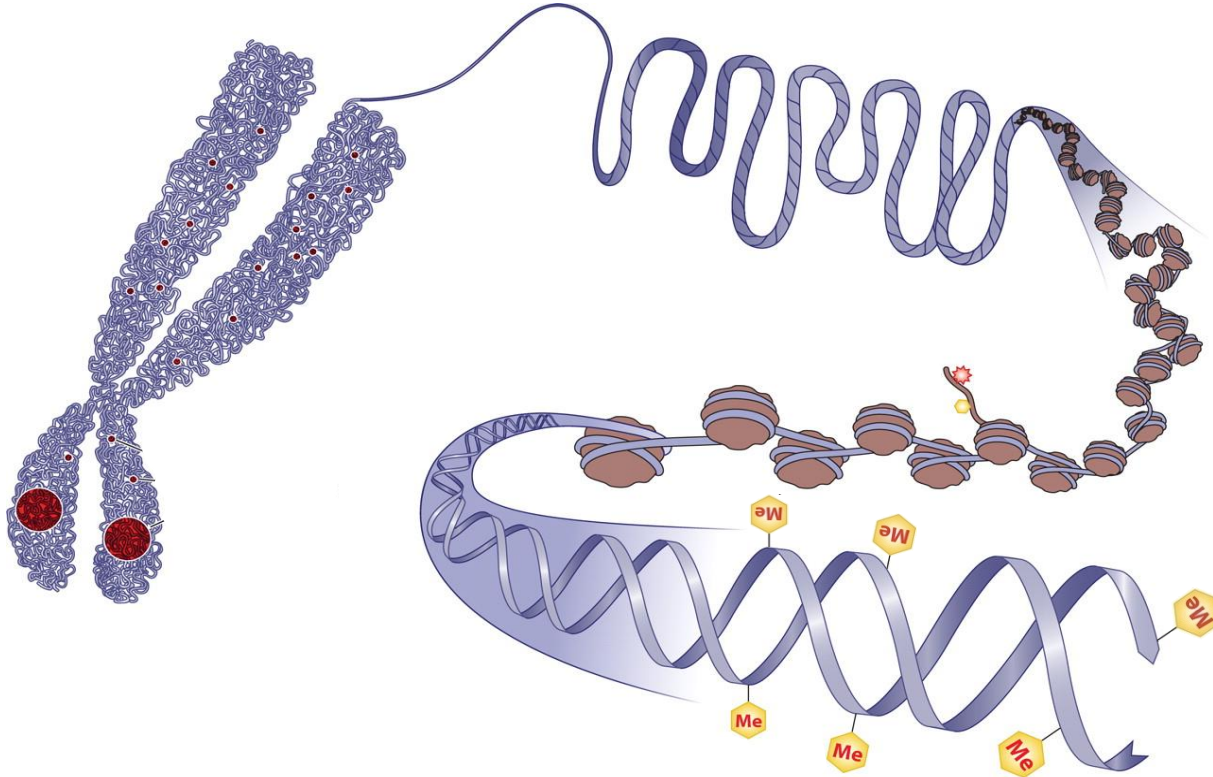
Molecular dimmers on the DNA



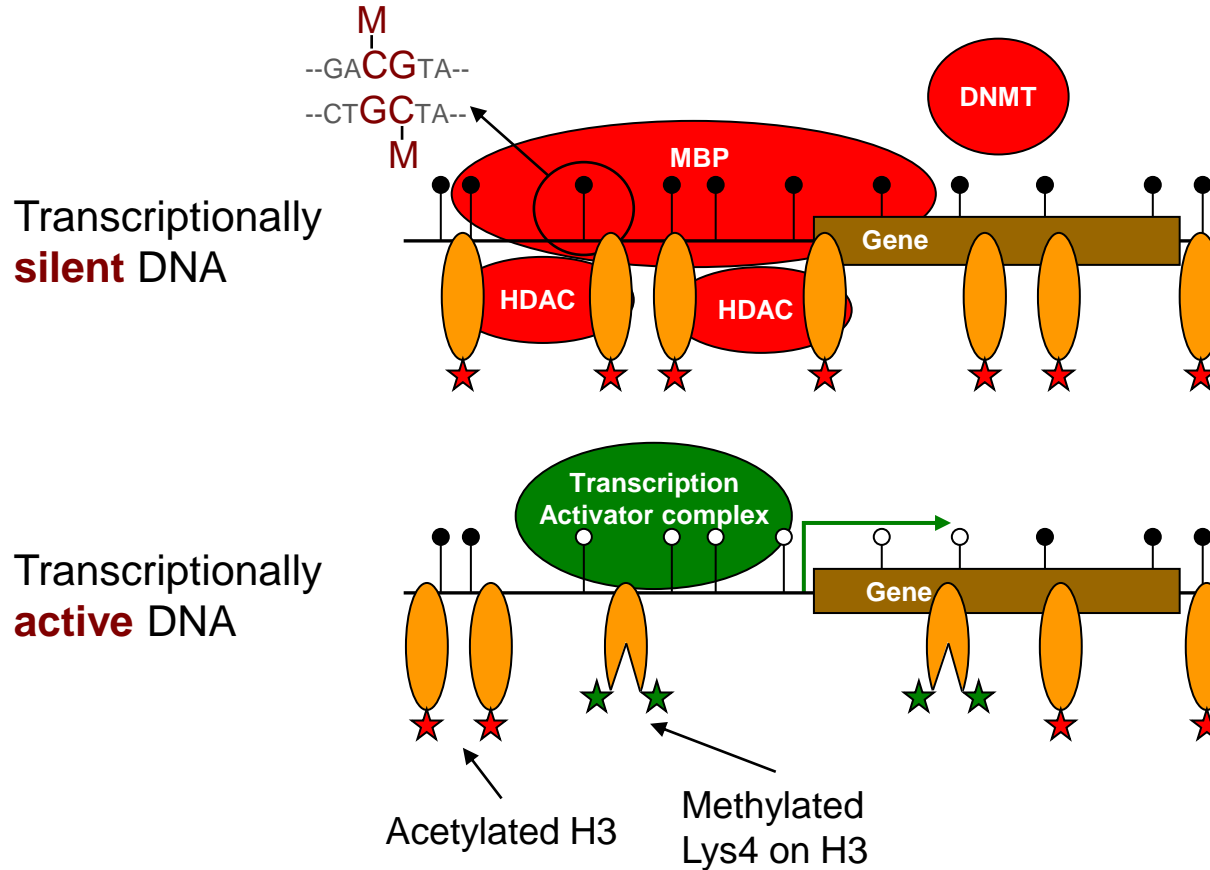
Molecular dimmers on the DNA



Molecular dimmers on the DNA

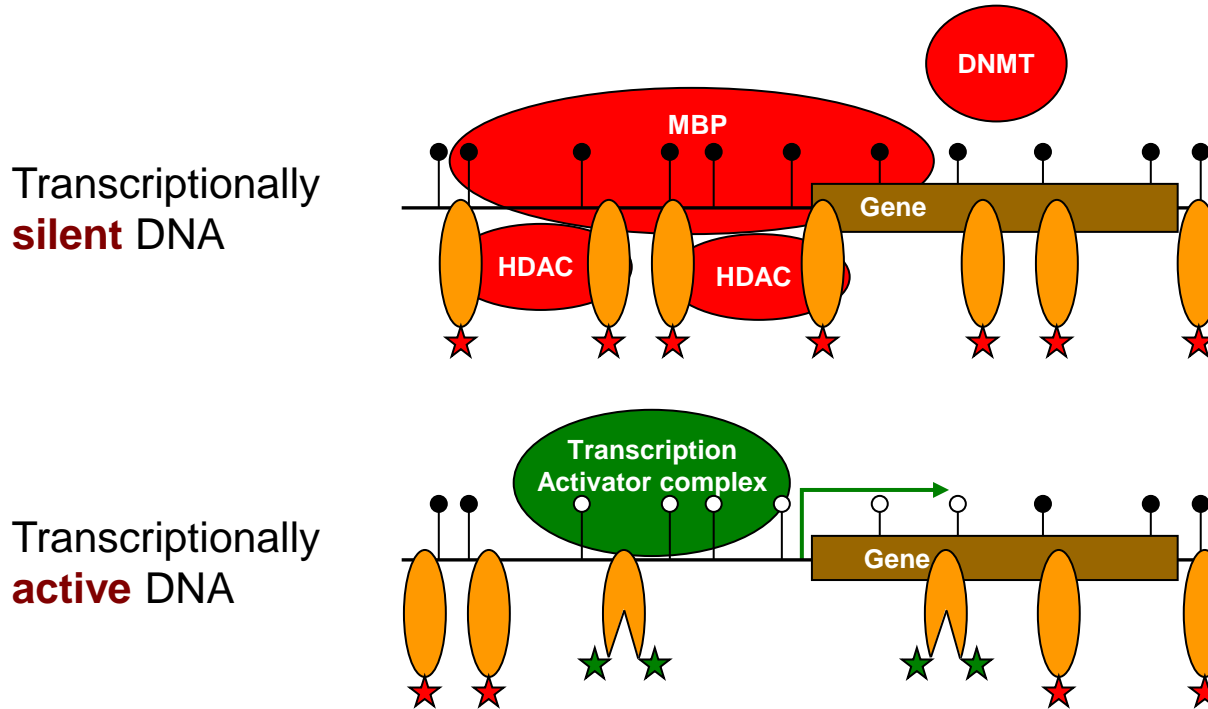


The simplified (and outdated) textbook view



Disclaimer: The order of events (cause and consequence) is not known

The simplified (and outdated) textbook view



But Bonder, Luijk et al. *Nat Genet* 2017:

- 70% negative, 30% positive correlation.
- Not necessarily in promoter.

Epigenetic mechanisms

1. Control gene expression
(by changes in the accessibility of DNA and recruiting regulatory factors like transcription factors and chromatin modifiers).
2. Stable, long-term, but in principle reversible.
3. Transmitted during cell division, particularly mitosis.

Epigenome: the whole of epigenetics marks in a cell.

Epigenome Projects



International Human Epigenome Consortium

[Home](#) [Areas of focus](#) [Standard Operating Procedures](#) [Tools / Useful Information](#) [Policies and Guidelines](#) [IHEC Structure](#) [Outreach and Training](#) [Feedback](#) [Intranet](#)

Links



The focal point for the European epigenetics research community



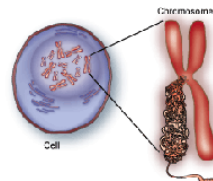
Centre of Excellence funded by The Danish National Research Foundation.



Overview

What is the International Human Epigenome Consortium?

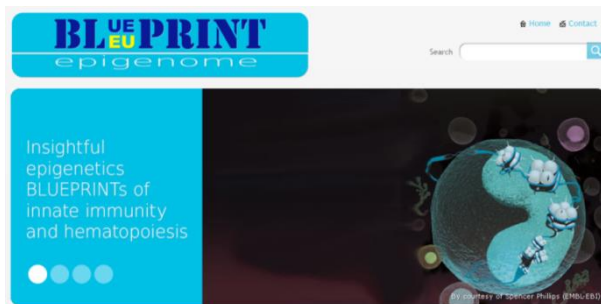
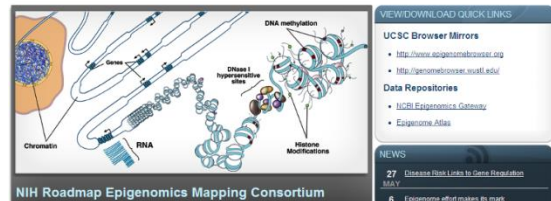
The deciphering of the human genome sequence has helped our understanding of biological processes in health and diseases. However, the way in which the genomic information is organized within the cell, through epigenetic processes, is known to play a major role in regulating gene expression and in controlling specific cellular functions. Epigenetic processes go beyond DNA-stored information and are essential for packaging and interpreting the genome, are fundamental to normal



Consortium goals

Primary Goals

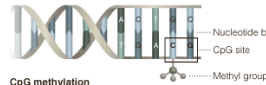
1. Coordinate the production of reference maps of human epigenomes for key cellular states relevant to health and diseases. To have a substantial coverage of the human epigenome, the IHEC sets the ambitious goal to decipher at least 1000 epigenomes within the next 7-10 years. To reach this goal, the consortium will use robust and validated technologies to generate:
 - very high resolution maps of informative histone modifications



**There is one human reference genome.
What is the theoretical number of
reference epigenomes?**

Mapping the Epigenome

DNA contains the genetic blueprint for all human cells, but the reading and execution of the blueprint inside each cell is controlled in part by chemical markers attached to the DNA. Scientists have begun to map some of these epigenetic markers, including CpG methylation.



CpG methylation

DNA is a code written with four letters: **A, T, C and G**, each standing for one nucleotide.

In CpG methylation, a small marker called a methyl group attaches to the DNA at a CpG site, where a **C** and a **G** nucleotide sit next to each other.

Chromosome 22
Of the 23 pairs of chromosomes in the human genome, 22 is the second smallest, containing only about 2 percent of DNA in the genome.

Gray and white bands on the circular chart correspond to these bands on the chromosome.

Reading the chart

The outer ring represents 35 million base pairs in chromosome 22. Orange marks highlight areas of the chromosome that were tested for CpG methylation in a pilot study by the Human Epigenome Project.

Measuring CpG methylation

Bar charts indicate the average amount of CpG methylation found within the tested areas. Each chart covers 100,000 base pairs. Some charts have been shifted, shown with connecting lines.

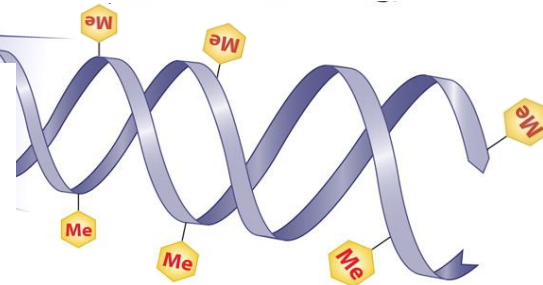
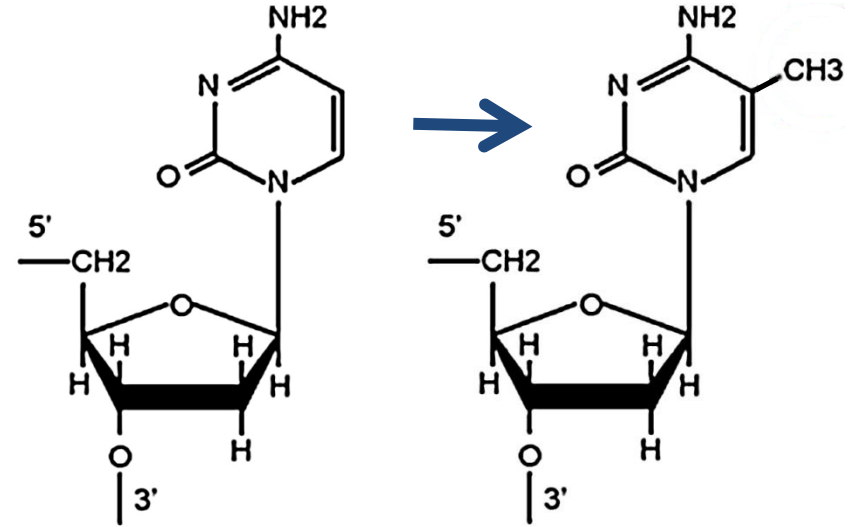
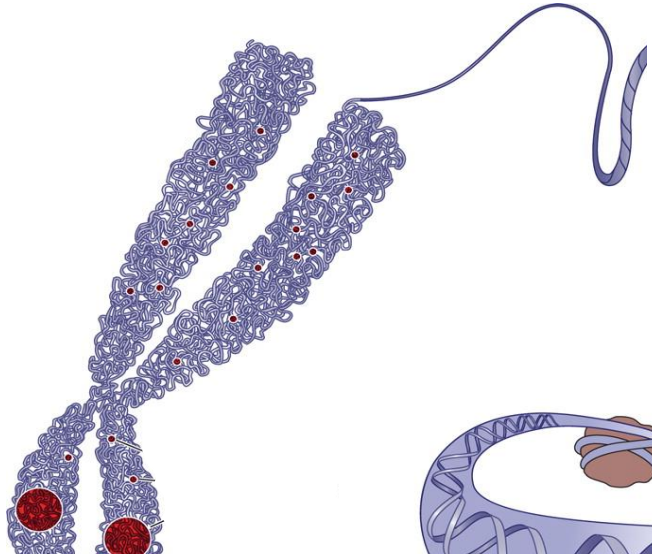
AMOUNT OF METHYLATION
0 to 20%
20 to 80%
80 to 100% of CpG sites

Variation among tissues

Each concentric ring of bar charts represents a different tissue, from muscle cells to sperm cells. Methylation levels that are significantly above or below the average level across all of the tissues are highlighted, indicating possible cell-specific differences.

20% or more above average
20% or more below average

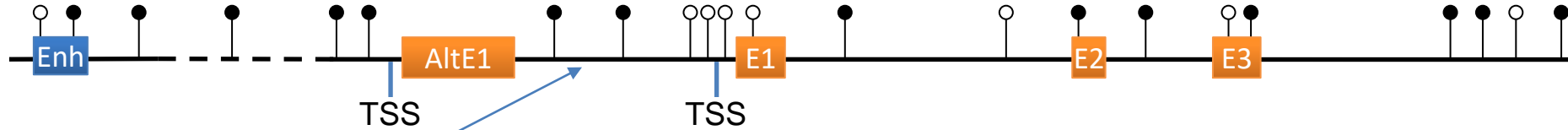
Focus on DNA methylation



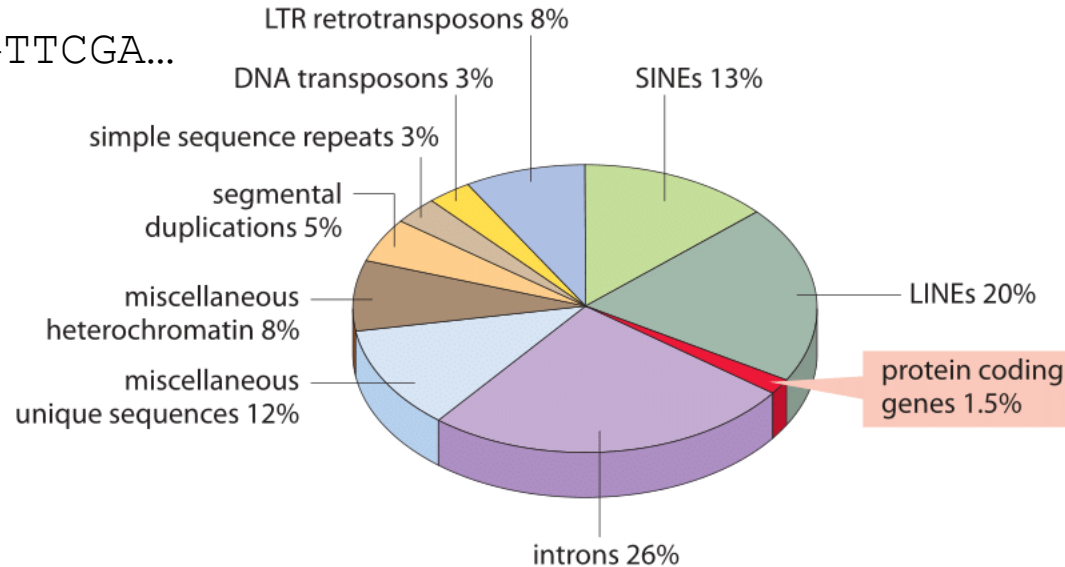
- Signals altered genomic regulation.*
- Standard biomaterial and storage.
- High-throughput profiling.

* Controls, stabilizes or reflects gene expression.

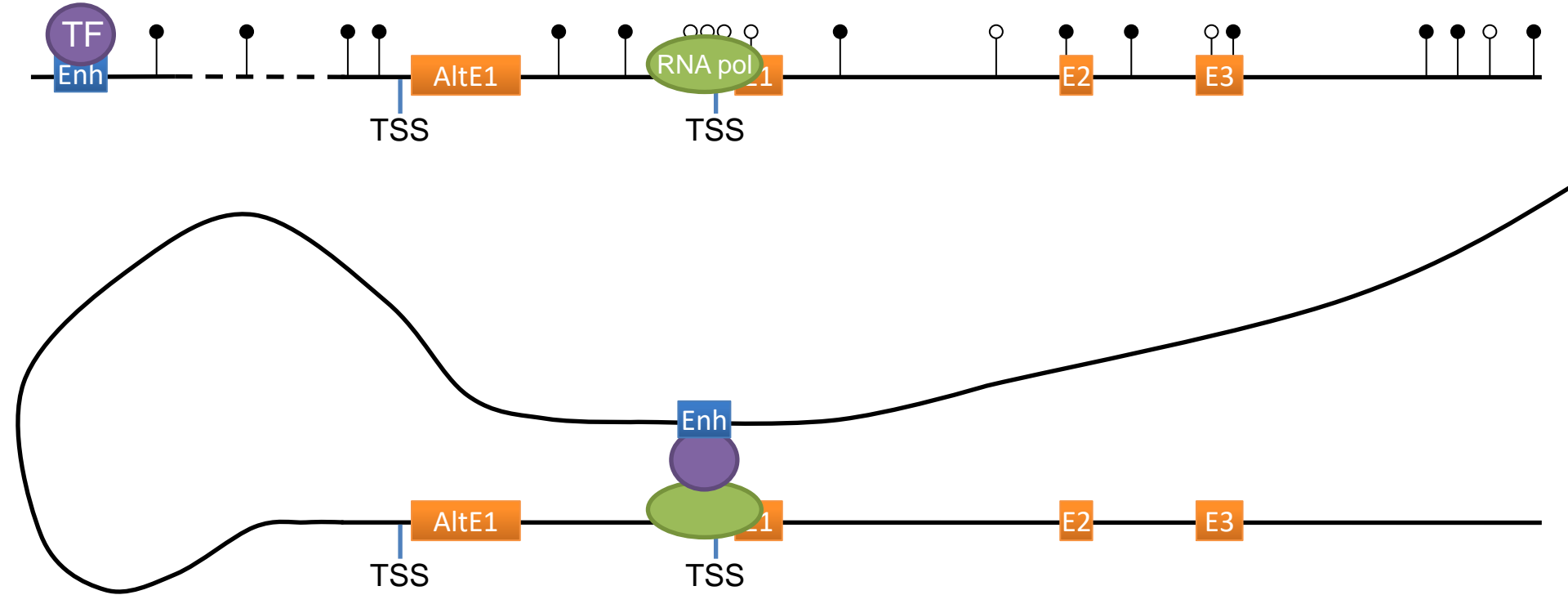
Significance depends on context



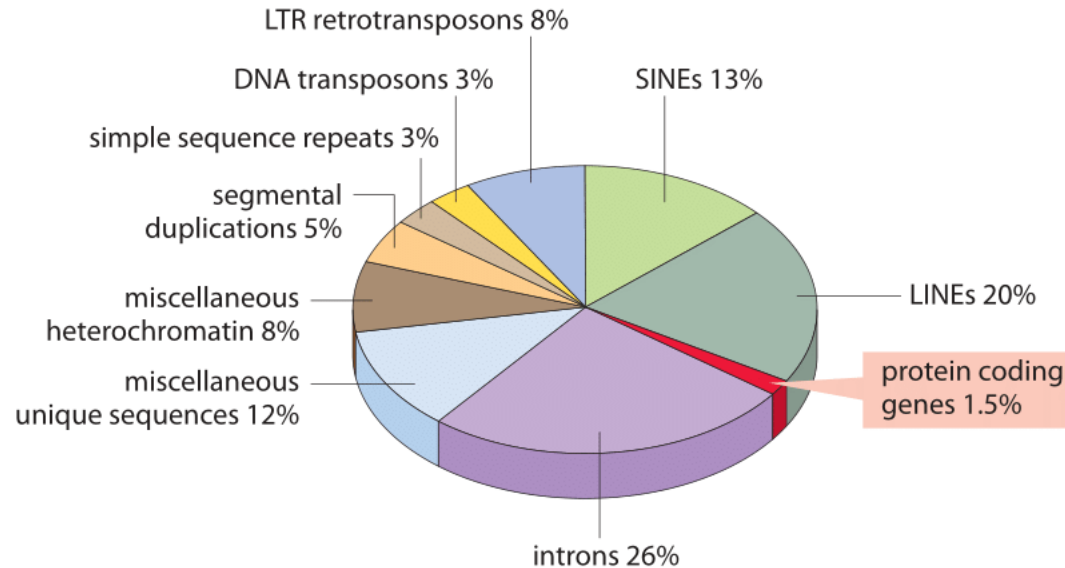
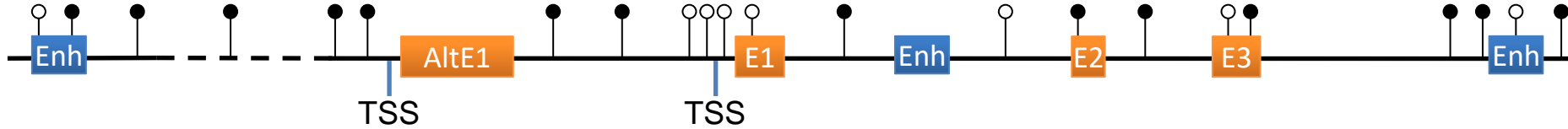
...AAGCAATGGTTCGA...



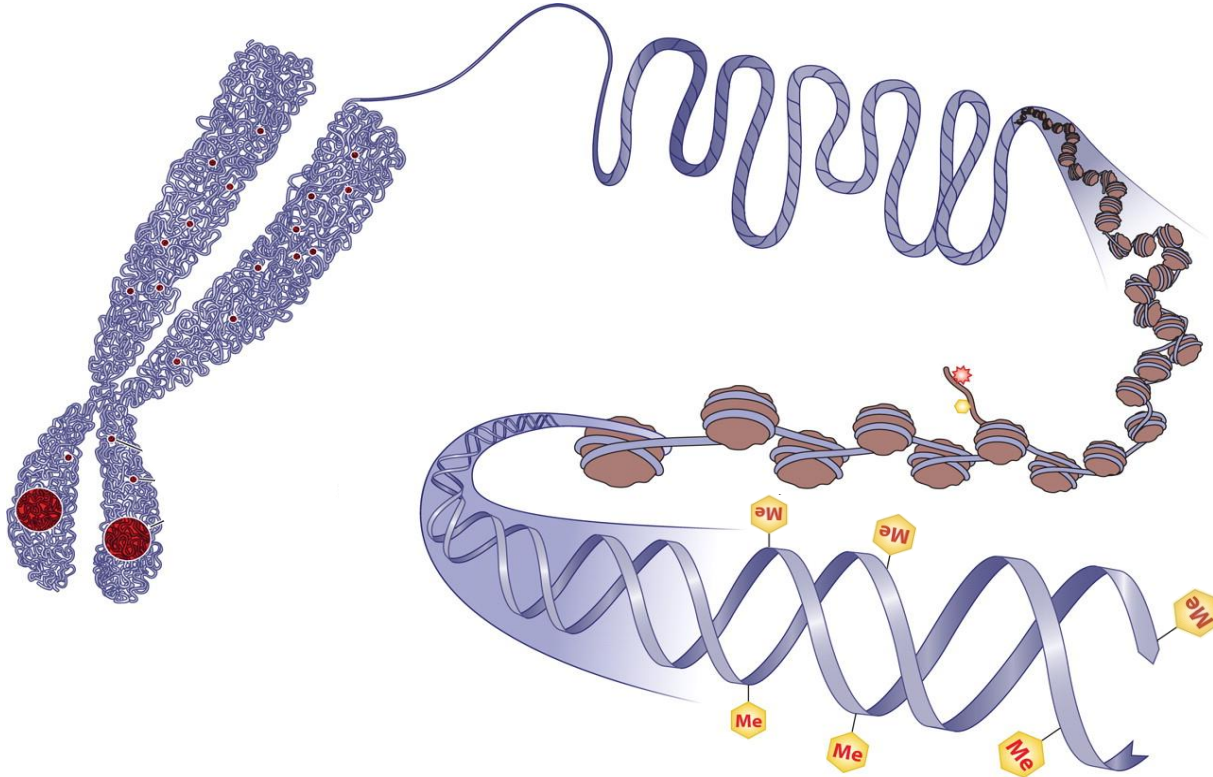
Significance depends on context



Significance depends on context

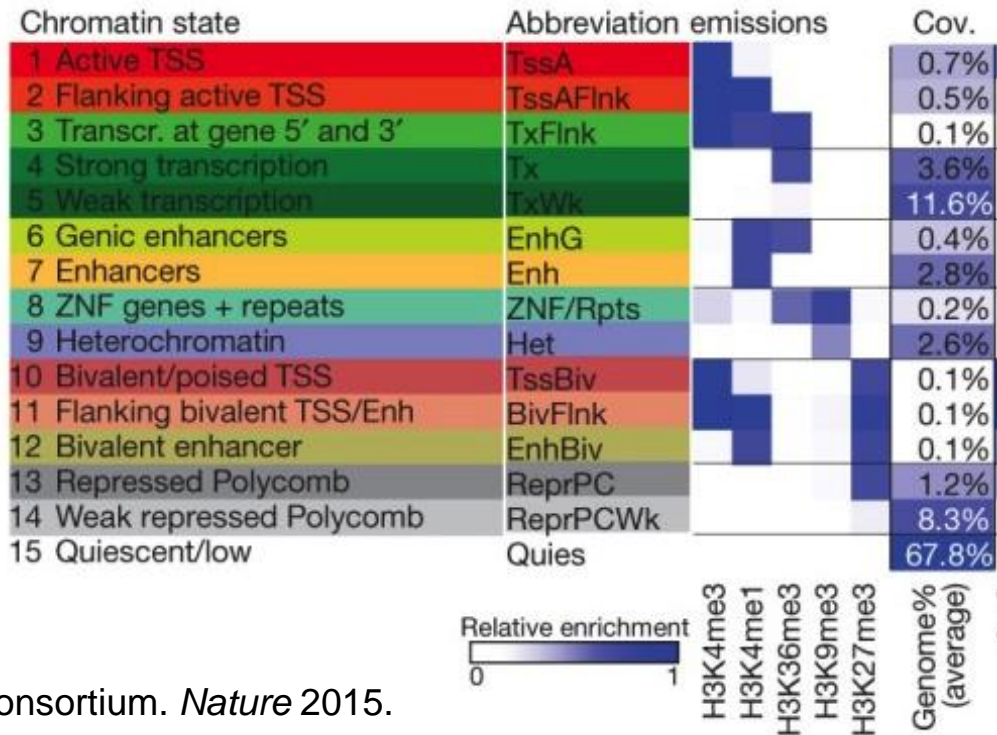


Molecular dimmers on the DNA



Reference epigenomes inform on biological function

Chromatin states (or segmentation)



Practical

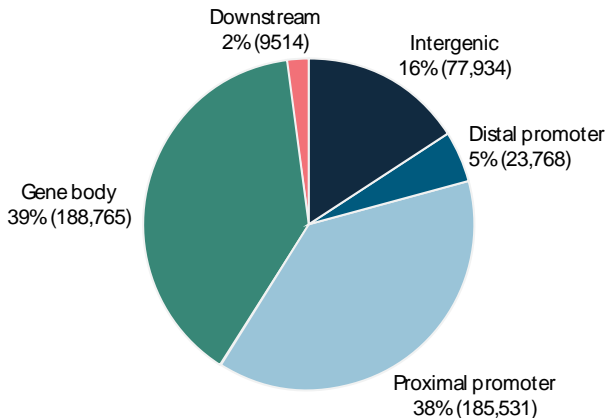
- Characterizing DNA methylation differences between tissues.
- Genome-wide methylation of close to 500 thousand CpG sites.



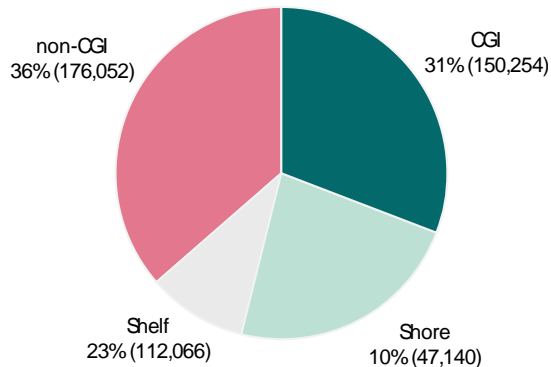
Illumina 450k DNA methylation array

- Genome-wide: ~483,000 CpGs (<2%) but many annotations
- Affordable: ~200 euro per sample
- Fast: >1000 samples a week
- Data: relatively easy to manage (amount and complexity)

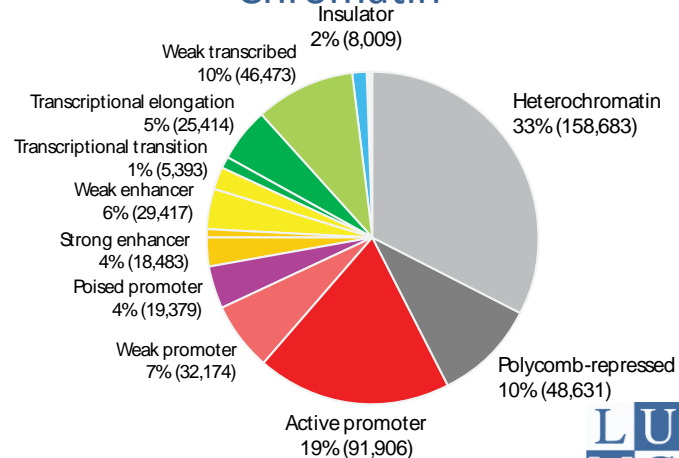
Genic



CpG island



Chromatin



Principle methylation array

...CCTGGTAC^{M?}CGTCTAGC^{M?}CGTAATTAGCT^{M?}CGATTCC^{M?}CGGT...

x 485,000 (out of 28M)
X 850,000

Bisulfite conversion

unmethylated

methylated

...TTTGGT^TGTUTAG...

...TTTGGT^{CG}TTTAG...



unmeth signal

meth signal

$$\beta\text{-value} = \text{meth} / (\text{meth} + \text{unmeth})$$

New

Possible DNA methylation levels of one CpG site



- A DNA molecule?
- A cell?

M?

|

...CCTGGTAC**CG**TCTAG...

|

...GGACCAT**GC**AGATC...

|

M?

M?

|

...CCTGGTAC**CG**TCTAG...

|

...GGACCAT**GC**AGATC...

|

M?

M?

|

...CCTGGTAC**CG**TCTAG...

|

...GGACCAT**GC**AGATC...

|

M?

Possible DNA methylation levels of one CpG site



- A DNA molecule?
- A cell?
- A blood sample?
- A muscle biopsy?

M?

|

...CCTGGTAC**CG**TCTAG...

...GGACCAT**GC**AGATC...

|

M?

M?

|

...CCTGGTAC**CG**TCTAG...

...GGACCAT**GC**AGATC...

|

M?

M?

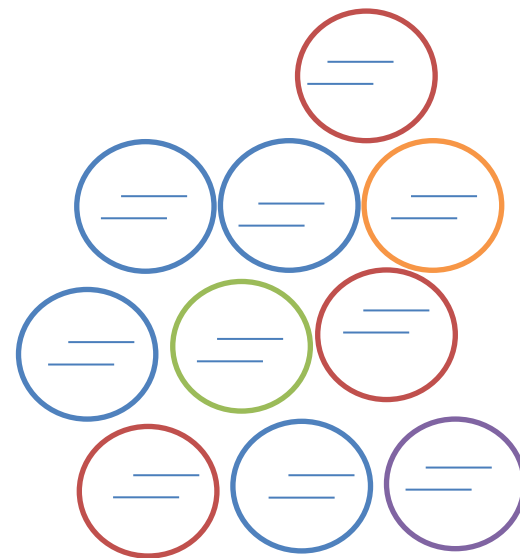
|

...CCTGGTAC**CG**TCTAG...

...GGACCAT**GC**AGATC...

|

M?



$$4*1 + 3*0 + 1*0.5 + 1*1 + 1*1$$



Amazing DISCOVERIES

