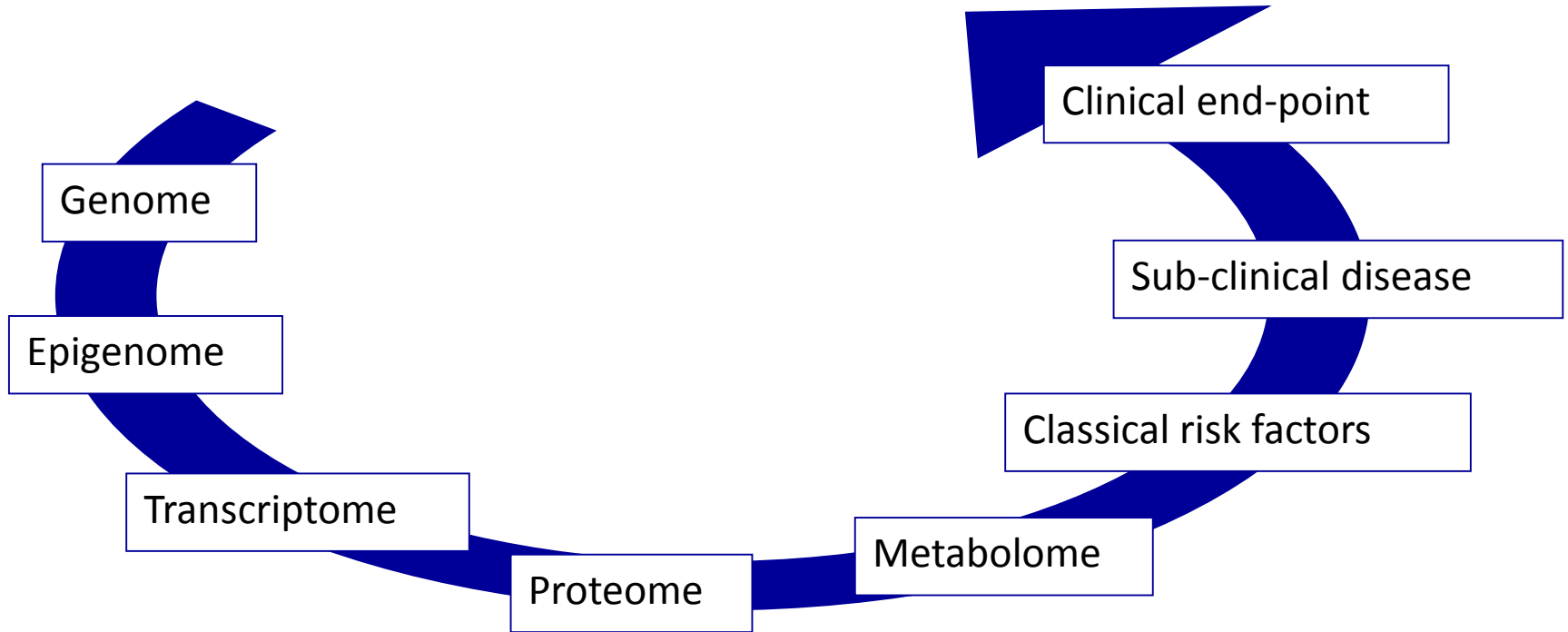


# An introduction to the epigenome

Bas Heijmans  
Biomedical Data Sciences  
Leiden University Medical Center  
The Netherlands  
[bas.heijmans@lumc.nl](mailto:bas.heijmans@lumc.nl)



# On offer for today

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

# The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC  
CCAGGGCCCCCAAGACACACAGA  
CGGCACAGCAGGGCTGGTTCAAG  
GGCTTTATTCCATCTCTCTCGGT  
GCAGGAGGCGGCGGGTGTGGGGC  
TGCCTGCGGGCTGCGTCTAGTTG  
CAGTAGTTCTCCAGCTGGTAGAG



# The genetic code is not enough

AGTGCCGGGAAGTGGGGCTTGGC  
CCAGGGCCCCCAAGACACACAGA  
CGGCACAGCAGGGCTGGTTCAAG  
GGCTTTATTCCATCTCTCTCGGT  
GCAGGAGGCGGGCGGGTGTGGGGC  
TGCCTGCGGGCTGCGTCTAGTTG  
CAGTAGTTCTCCAGCTGGTAGAG

A G T C



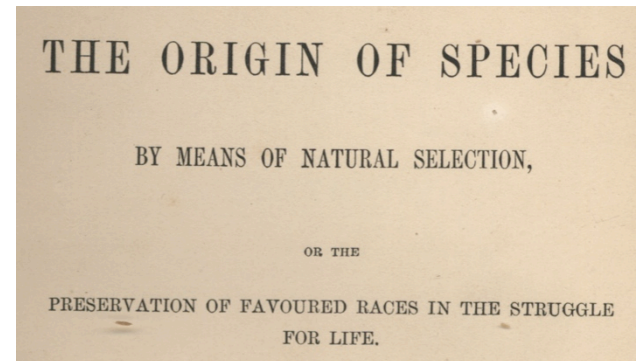
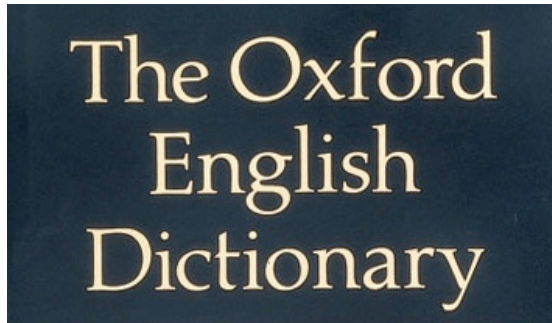
# The genetic code is not enough

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



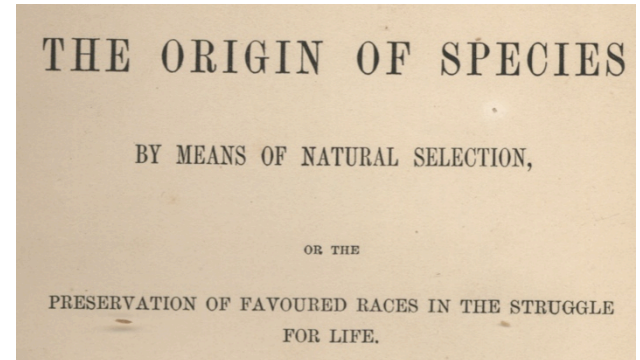
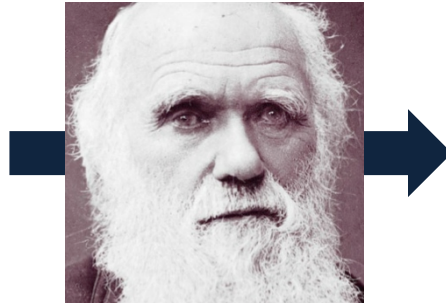
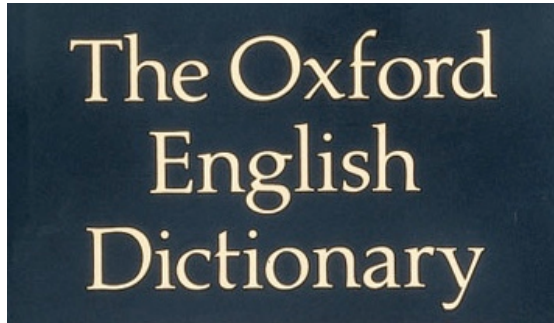
# The genetic code is not enough

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



# The genetic code is not enough

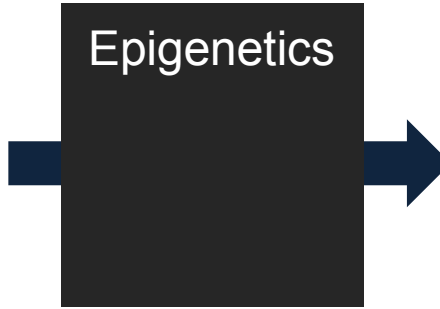
AGTGCCGGGAAGTGGGGCTTGGC  
CCAGGGCCCCCAAGACACACAGA  
CGGCACAGCAGG**GCTGGTTCAAG**  
**GGCTTTATTCCATCTCTCTCGGT**  
**GCAGGAGGCGGCGGGTGTGGGGC**  
**TGCCTGCGGGCTGCGTCTAGTTG**  
**CAGTAGTTCTCCAGCTGGTAGAG**





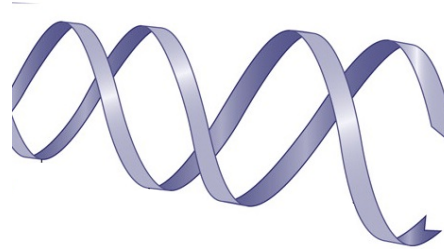
# The genetic code is not enough

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

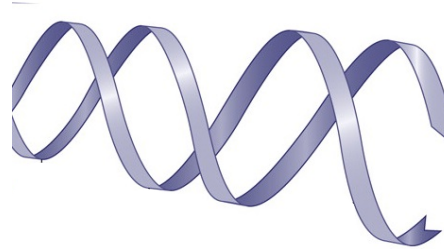
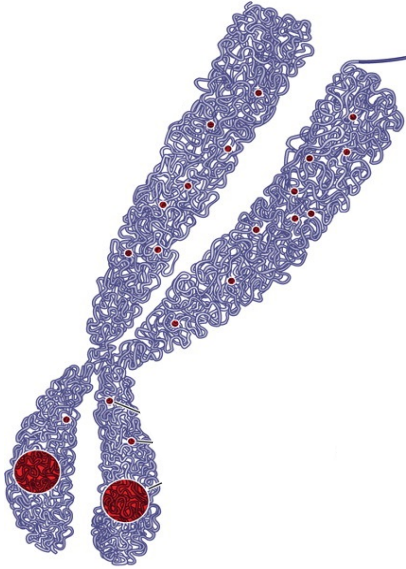


- Instructing the DNA where, when and how much to express a gene.
- Epigenetics provides variation & memory.

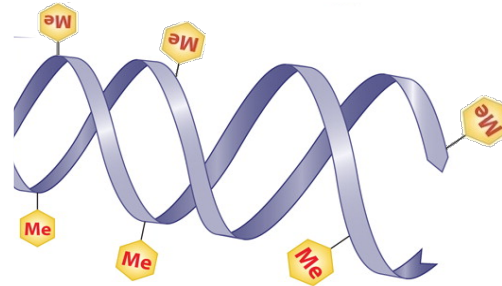
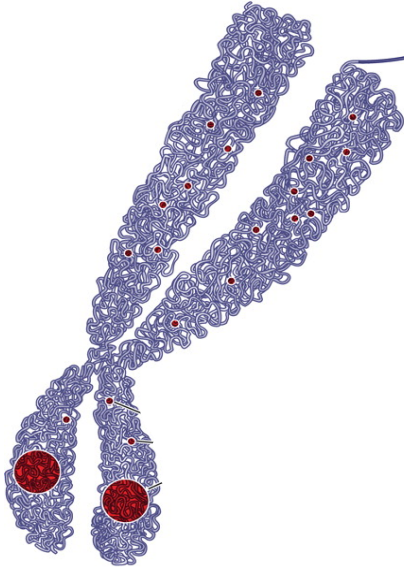
# Molecular dimmers on the DNA



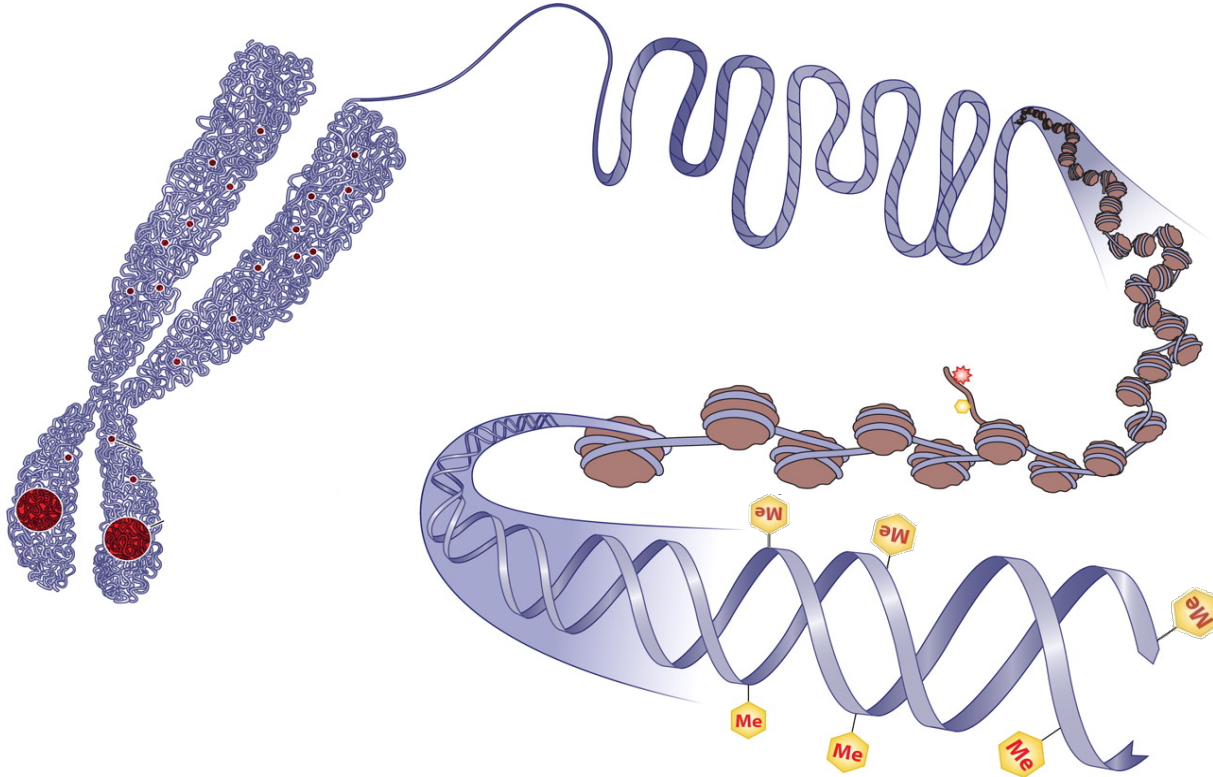
# Molecular dimmers on the DNA



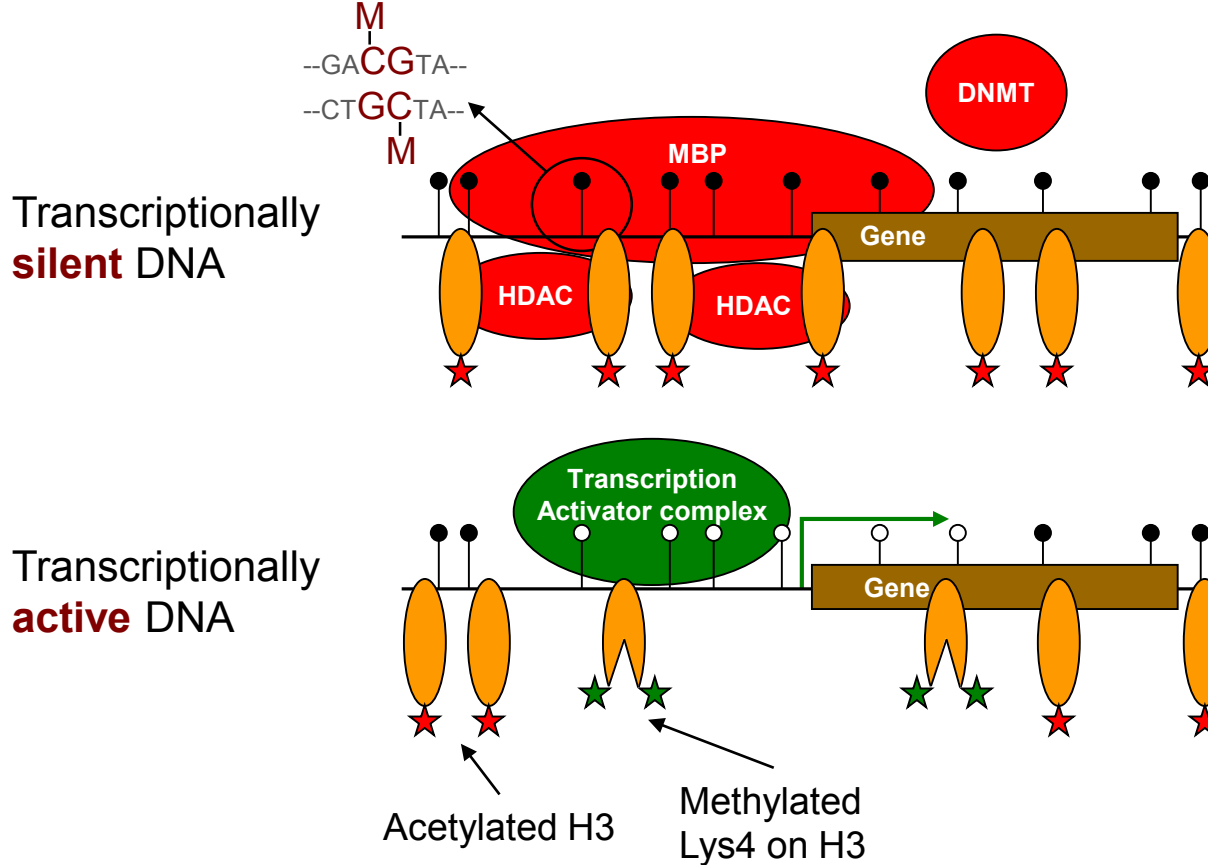
# Molecular dimmers on the DNA



# Molecular dimmers on the DNA



# The simplified (and outdated) text book view



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



20 hours after  
fertilization



Day 3, 8 cells





# 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 Epigenome Network of Excellence  
The focal point for the European

## Overview

What is the International Human Epigenome Consortium?

## Consortium goals

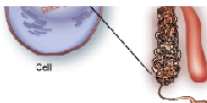
### Primary Goals

1. Coordinate the production of reference maps of

There is one human (reference) genome. How many epigenomes?



Epigenetics 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



years. To reach this goal, the consortium will use robust and validated technologies to generate:

- very high resolution maps of informative histone modifications

**ROADMAP epigenomics PROJECT**

SEARCH:

SCOPE PARTICIPANTS DATA PROTOCOLS QUALITY METRICS TOOLS PUBLICATIONS

OVERVIEW PROJECT DATA MAPPING CENTRES PROTOCOLS & STANDARDS PUBLICATIONS NEWS

**NIH Roadmap Epigenomics Mapping Consortium**

**VIEW/DOWNLOAD QUICK LINKS**

**UCSC Browser Mirrors**

- <http://www.genome.ucsc.edu>
- <http://genome.ucsc.edu/roadmap/>

**Data Repositories**

- [NCBI Epigenomics Gateway](#)
- [Epigenome Atlas](#)

**NEWS**

27 [Discover How Links to Gene Regulation](#)  
MAY

6 [Epigenome effort makes its mark](#)

**BLUEPRINT epigenome**

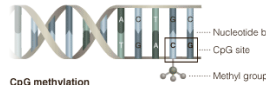
Home Contact

Search

Insightful epigenetics BLUEPRINTs of innate immunity and hematopoiesis

## 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

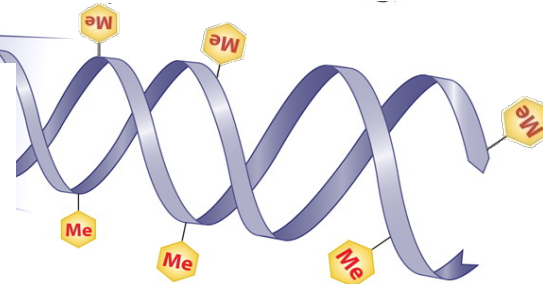
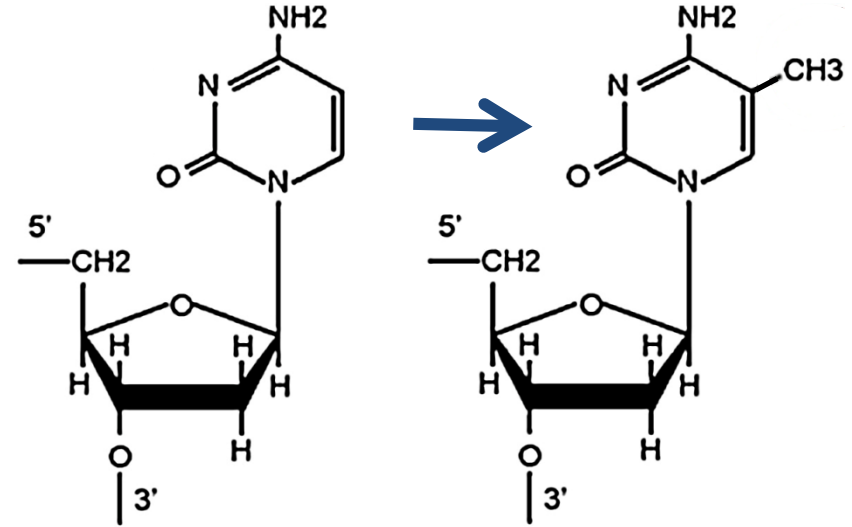
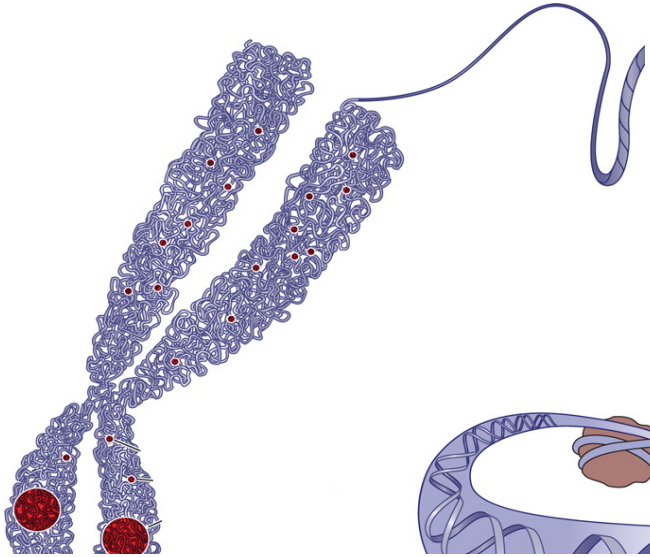
0 to 20%  
20 to 80%  
80 to 100% of CpG sites

### 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

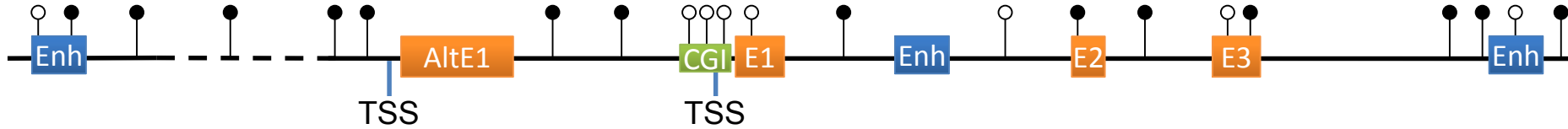
# Focus on DNA methylation



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

\* Controls, stabilizes or reflects gene expression.

# Significance methylation depends on genomic context

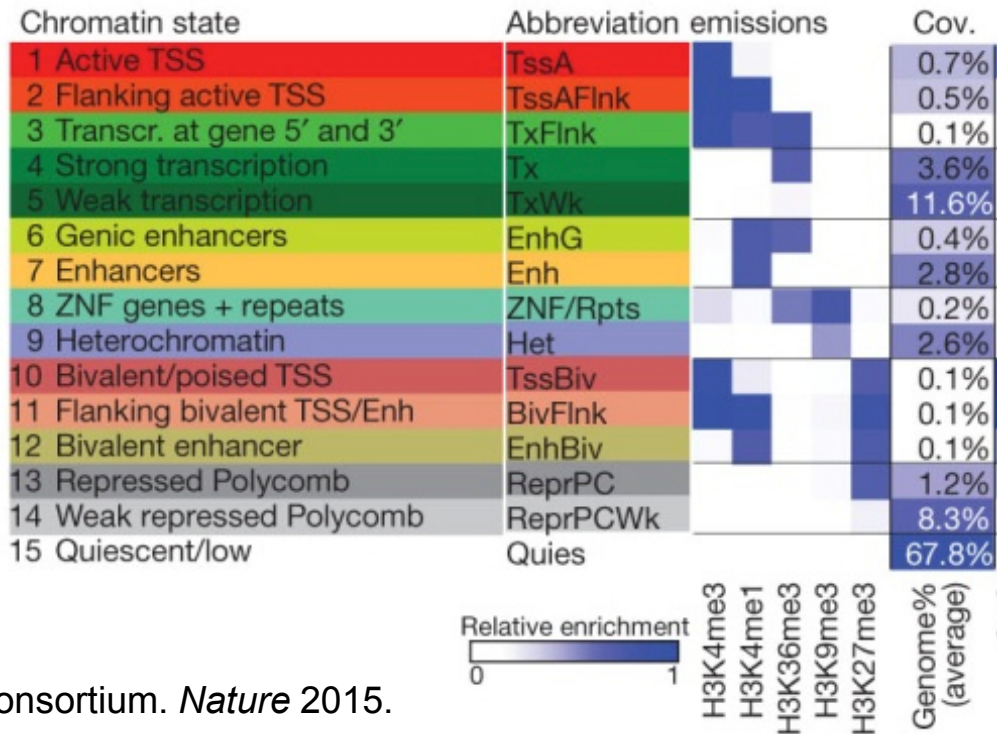


→ Genomic annotation is essential when interpreting DNA methylation data



# 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.

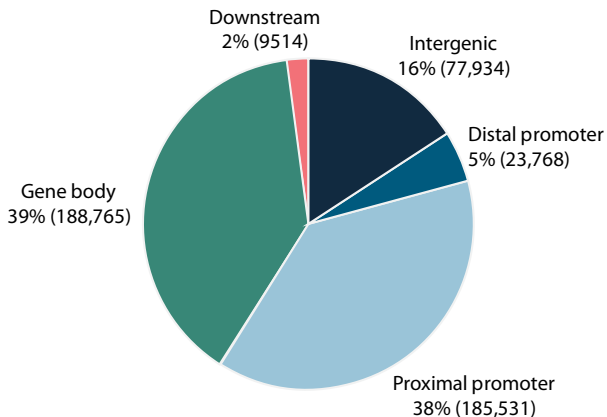




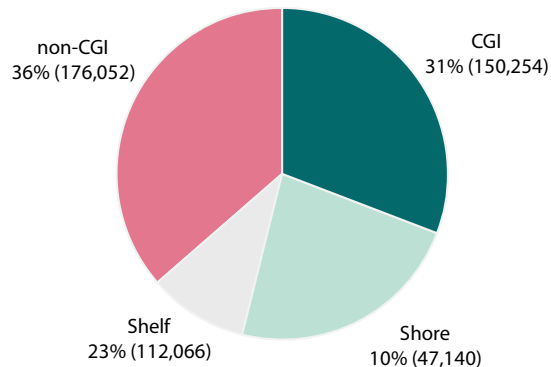
# Illumina 450k DNA methylation array

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

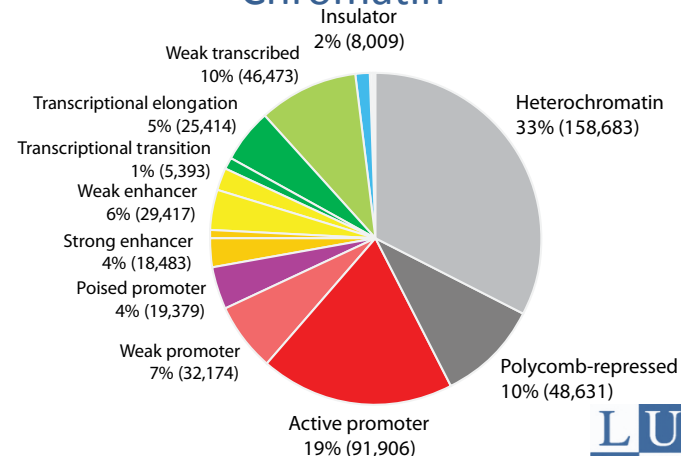
## Genic



## CpG island



## Chromatin



# Principle methylation array

x 485,000 (out of 28M)

...CCTGGTAC<sup>M?</sup>GTCTAGC<sup>M?</sup>CGTAATTAGCT<sup>M?</sup>CGATTCC<sup>M?</sup>GGT...

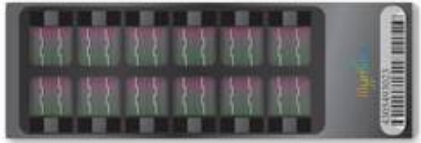
Bisulfite conversion

unmethylated

methylated

...UUTGGT<sup>U</sup>GTUTAG...

...UUTGGT<sup>CG</sup>TUTAG...



unmeth signal

meth signal

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

# 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?**

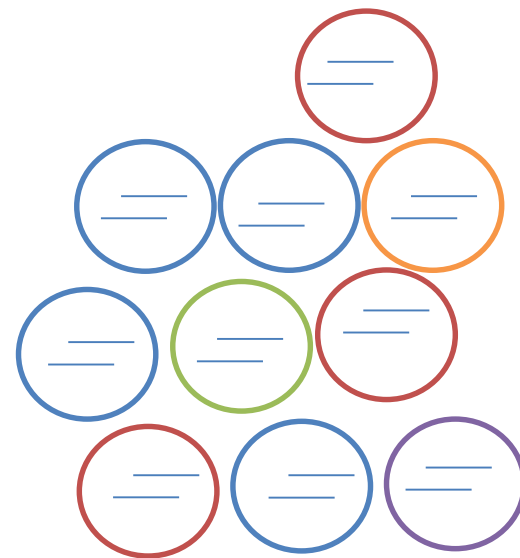
|

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

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

|

**M?**



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



# Amazing DISCOVERIES

