

Decoding epigenome with integrative “omics” data analysis

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Presentation Outline

- **Introduction to Epigenetic codes**
- **Genome-wide Hairpin Bisulfite Sequencing**
 - **Application on embryonic stem cell renewal and differentiation**
- **Decoding brain epigenome with integrative “omics” data analysis**

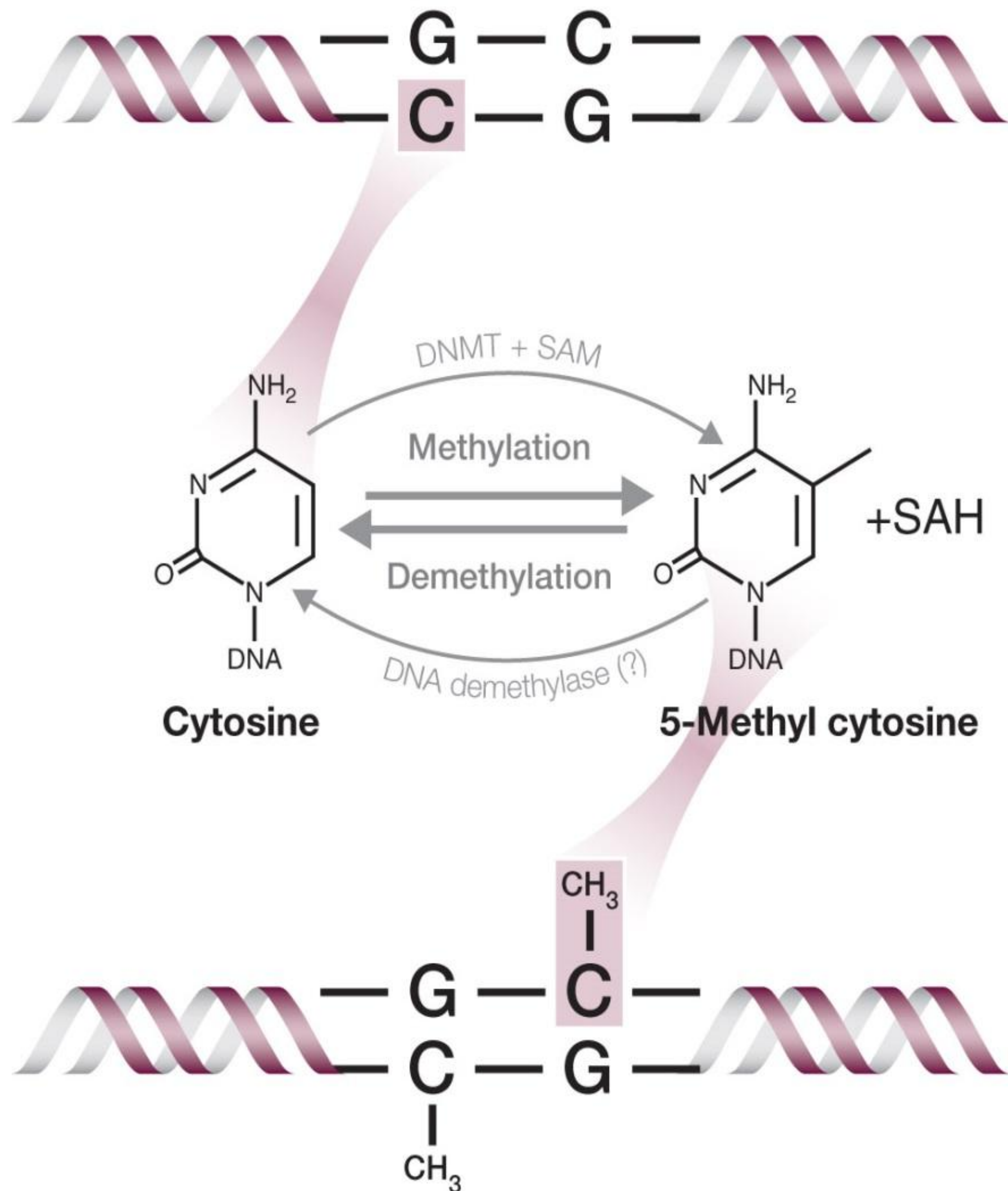
Epigenetics

Epigenetics is the study of heritable changes in gene activity that are **NOT** caused by changes in the DNA sequence.

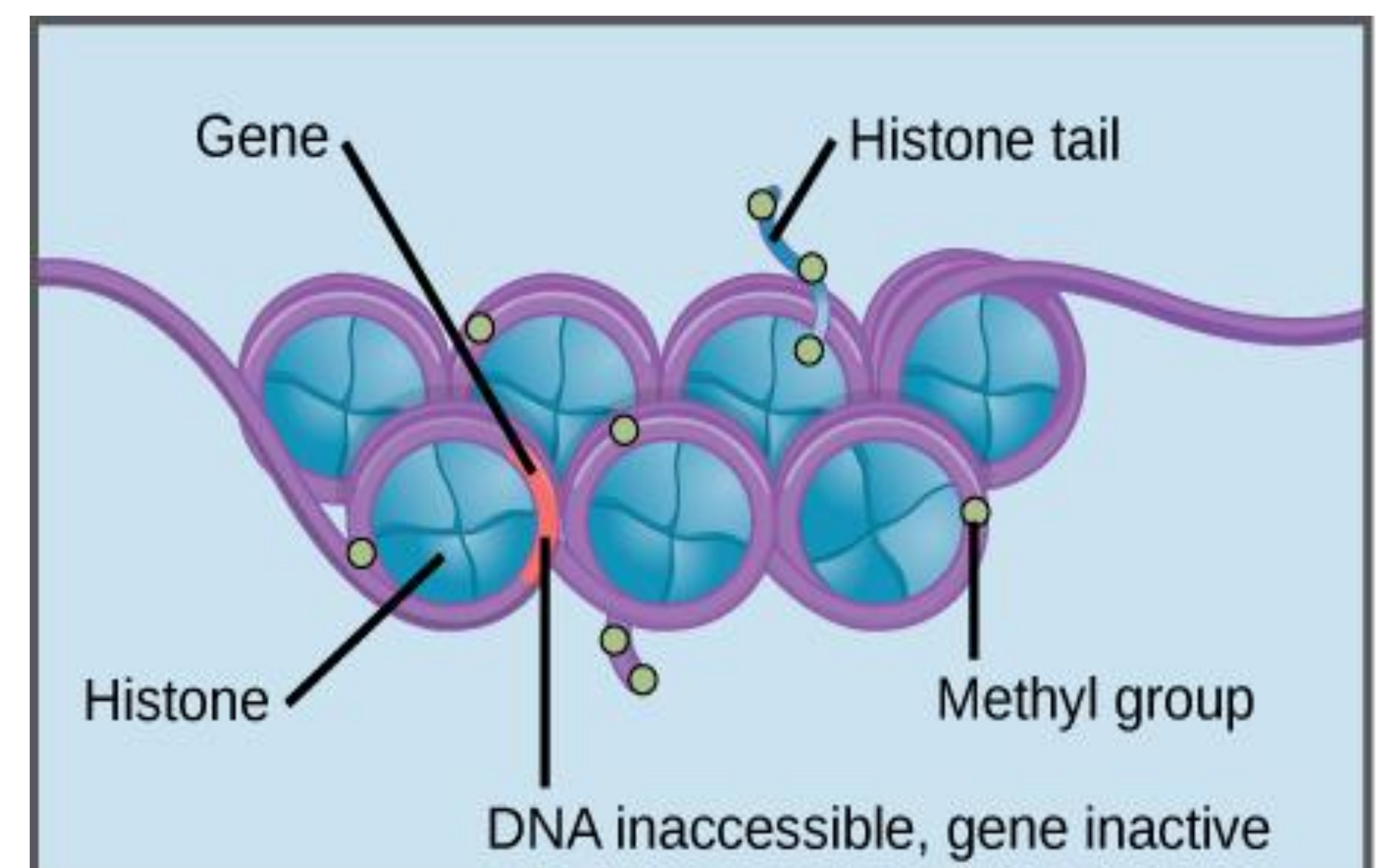
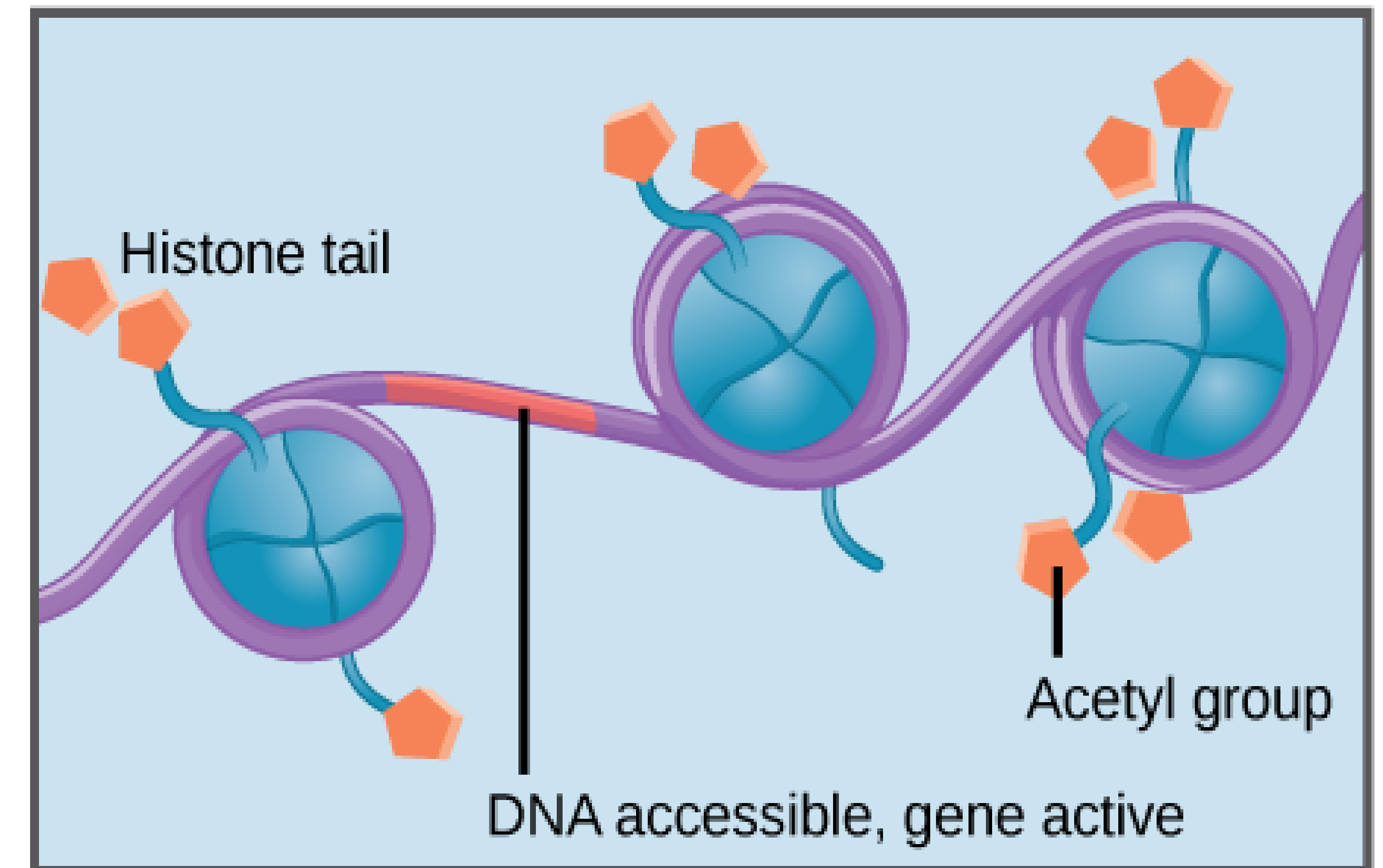
<http://en.wikipedia.org/wiki/>

Epigenetic codes

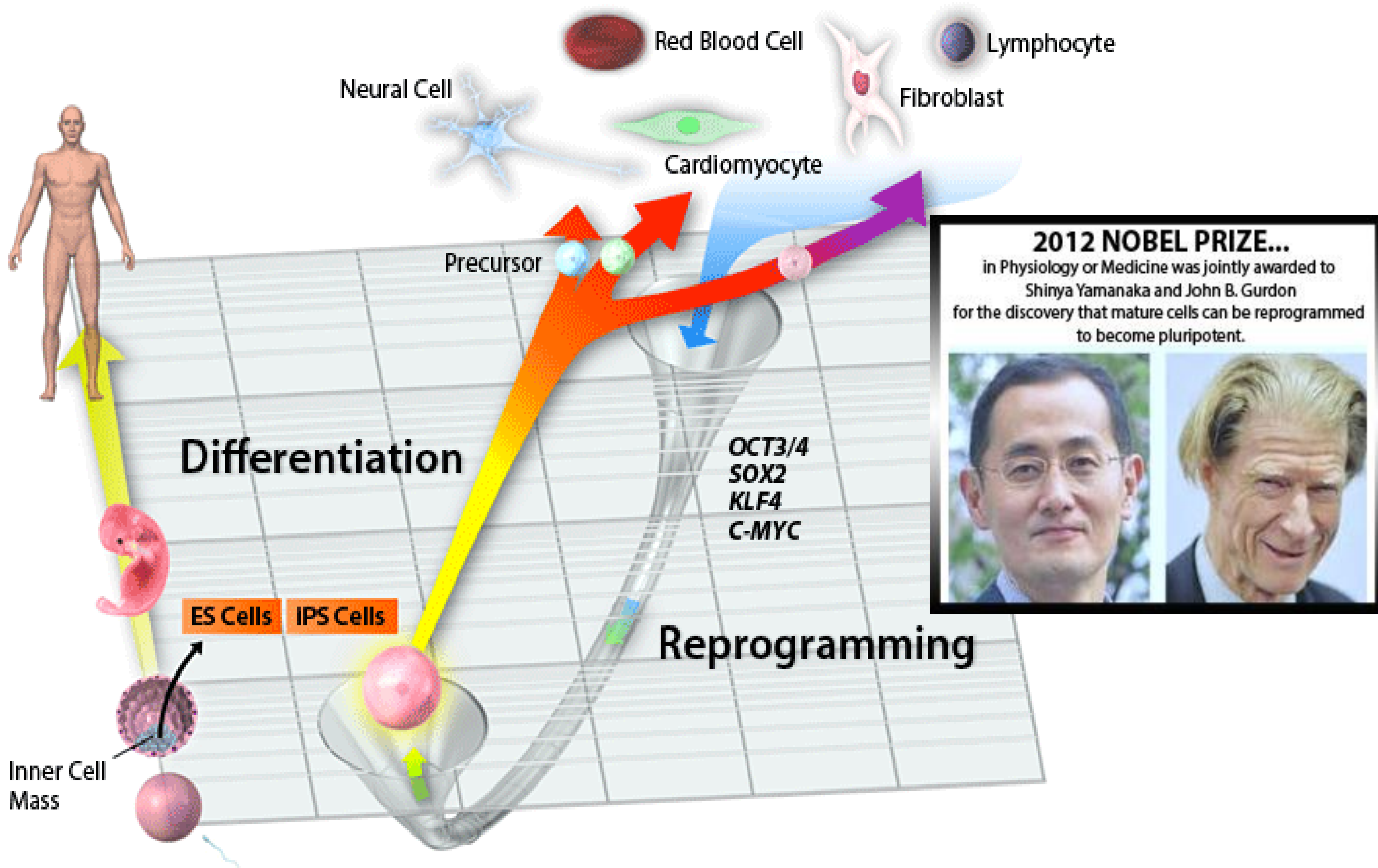
✓ DNA methylation



✓ Histone modifications



Methylation & iPSC Reprogramming



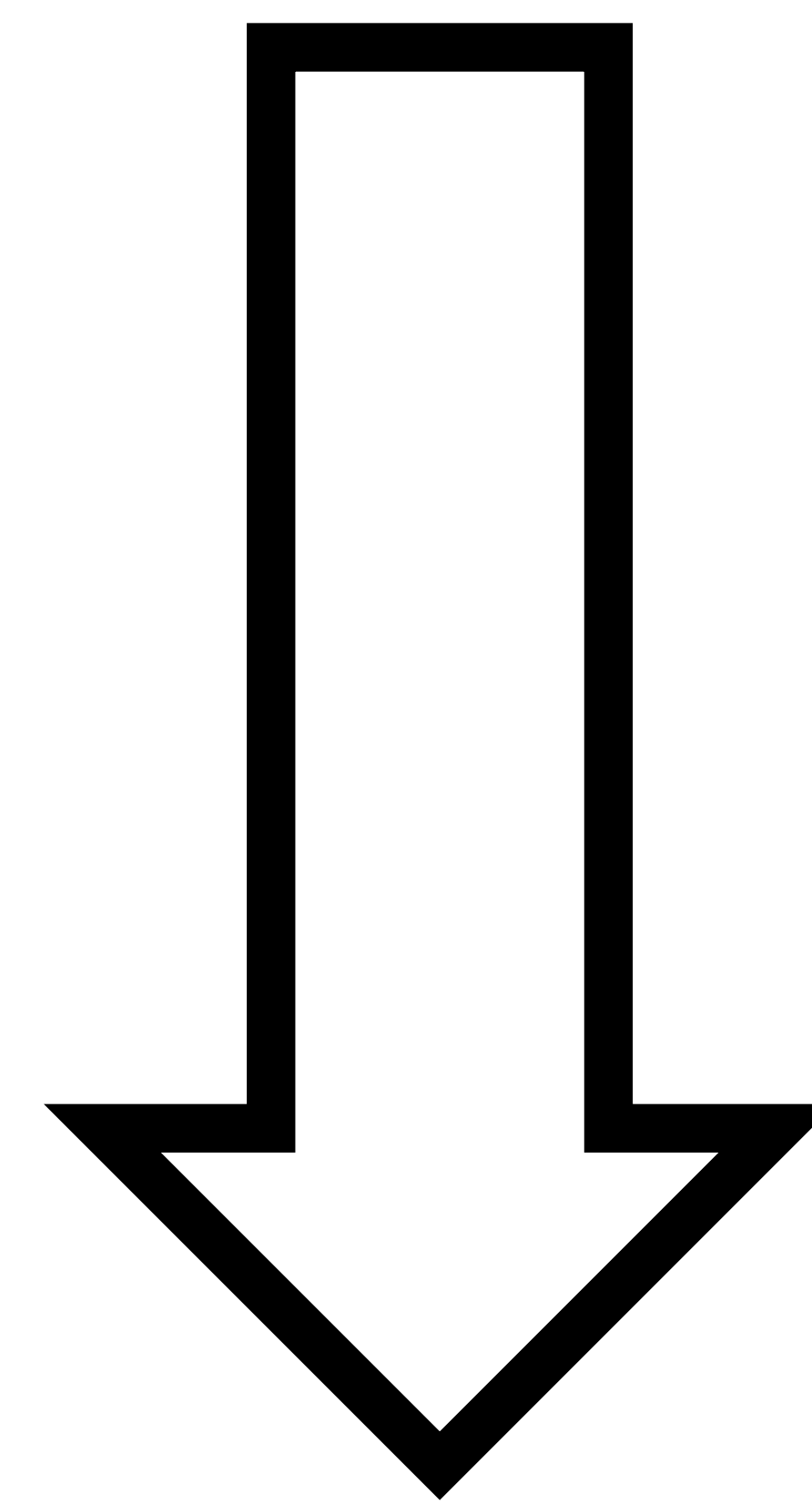
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Methylation Level *vs* Methylation Pattern

Sequence read: —^mCG—^mCG—CG—CG—

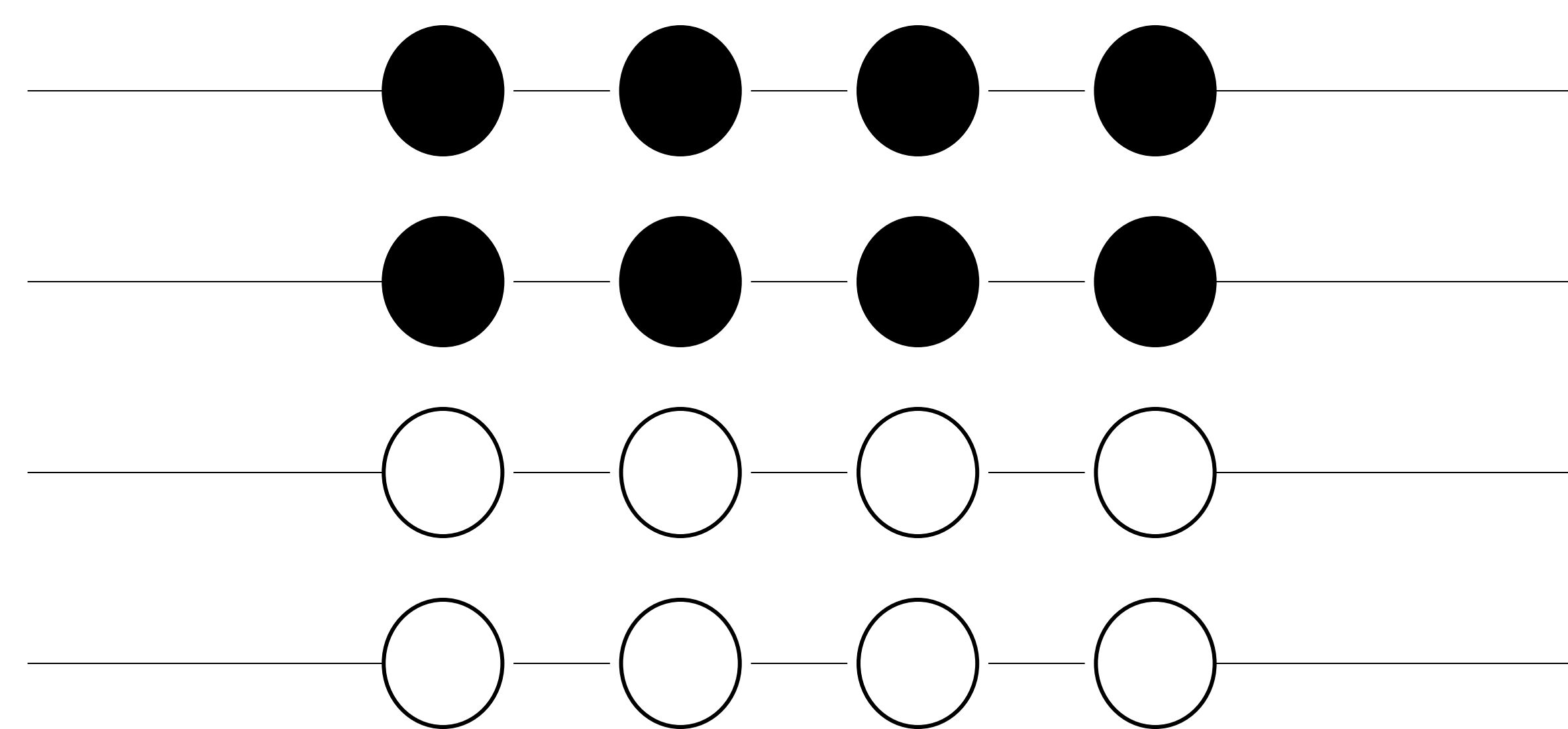
Methylation level = 50%



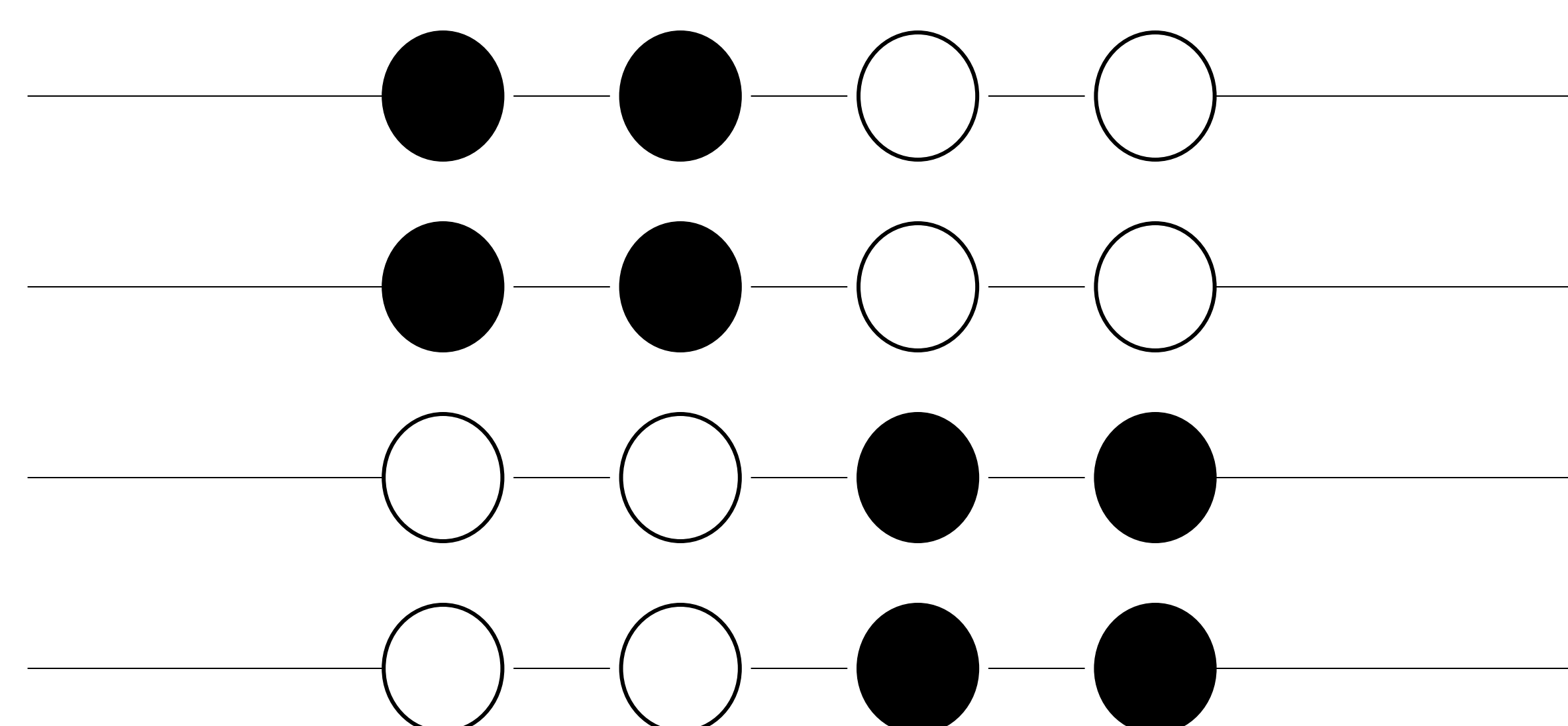
● : methylated ^mCG
○ : unmethylated CG

Sequence read: —●—●—○—○—

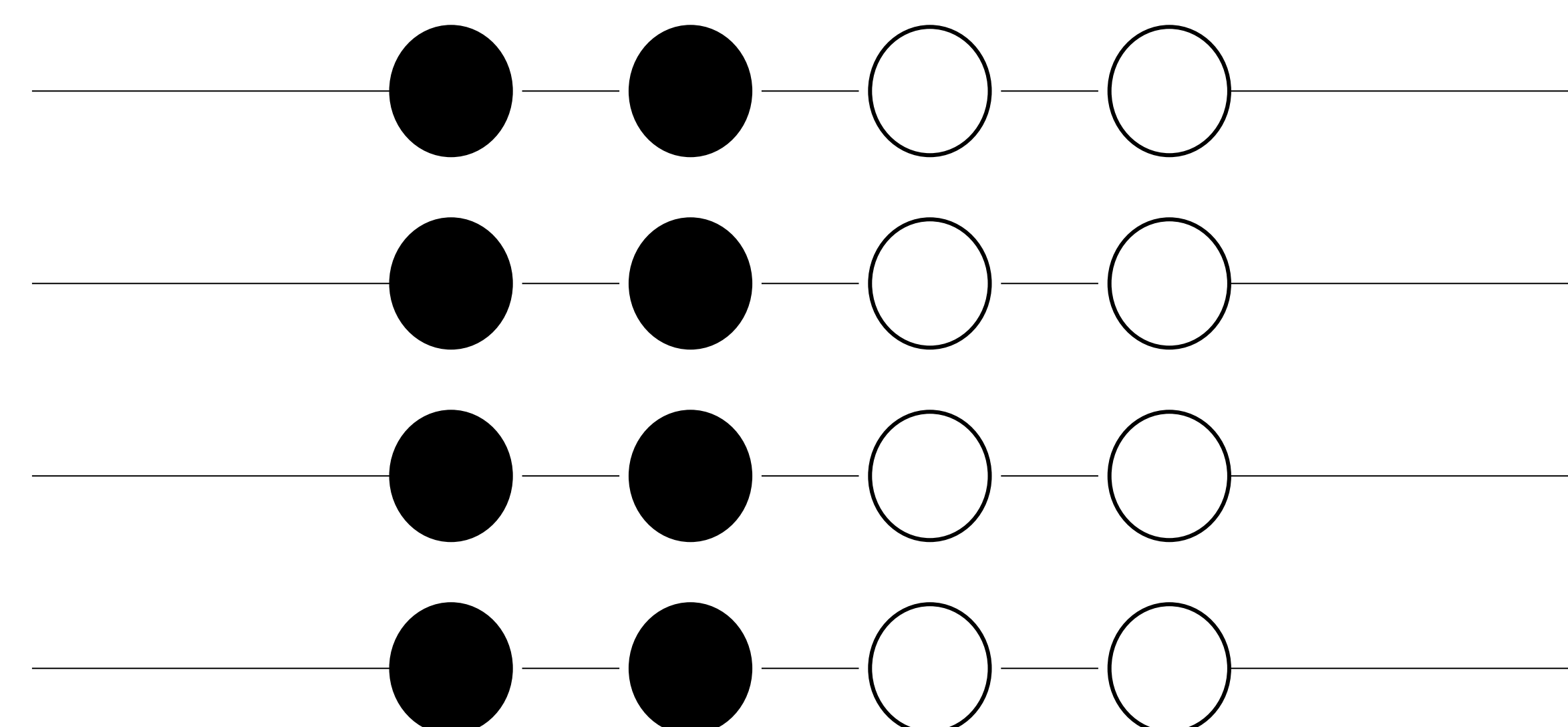
Pattern 1:



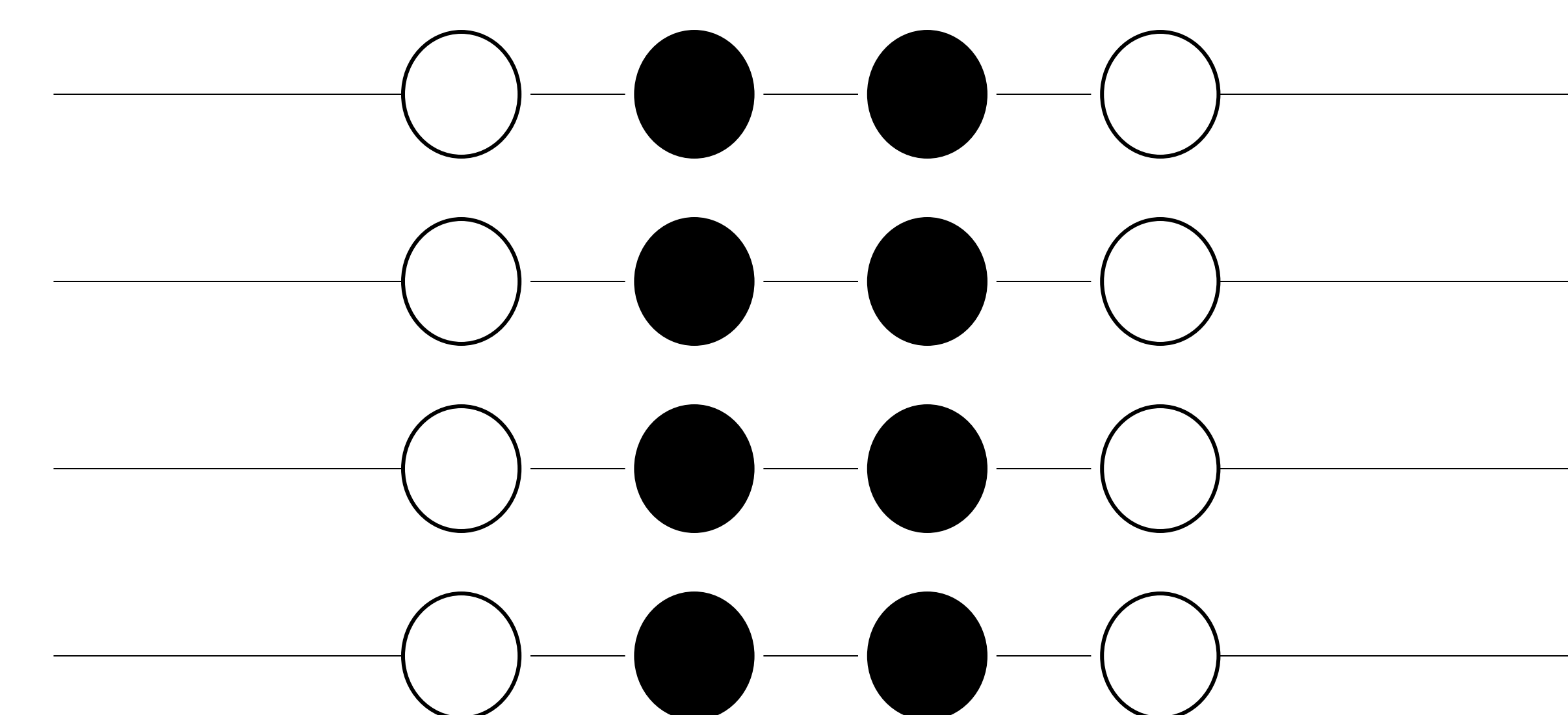
Pattern 2:



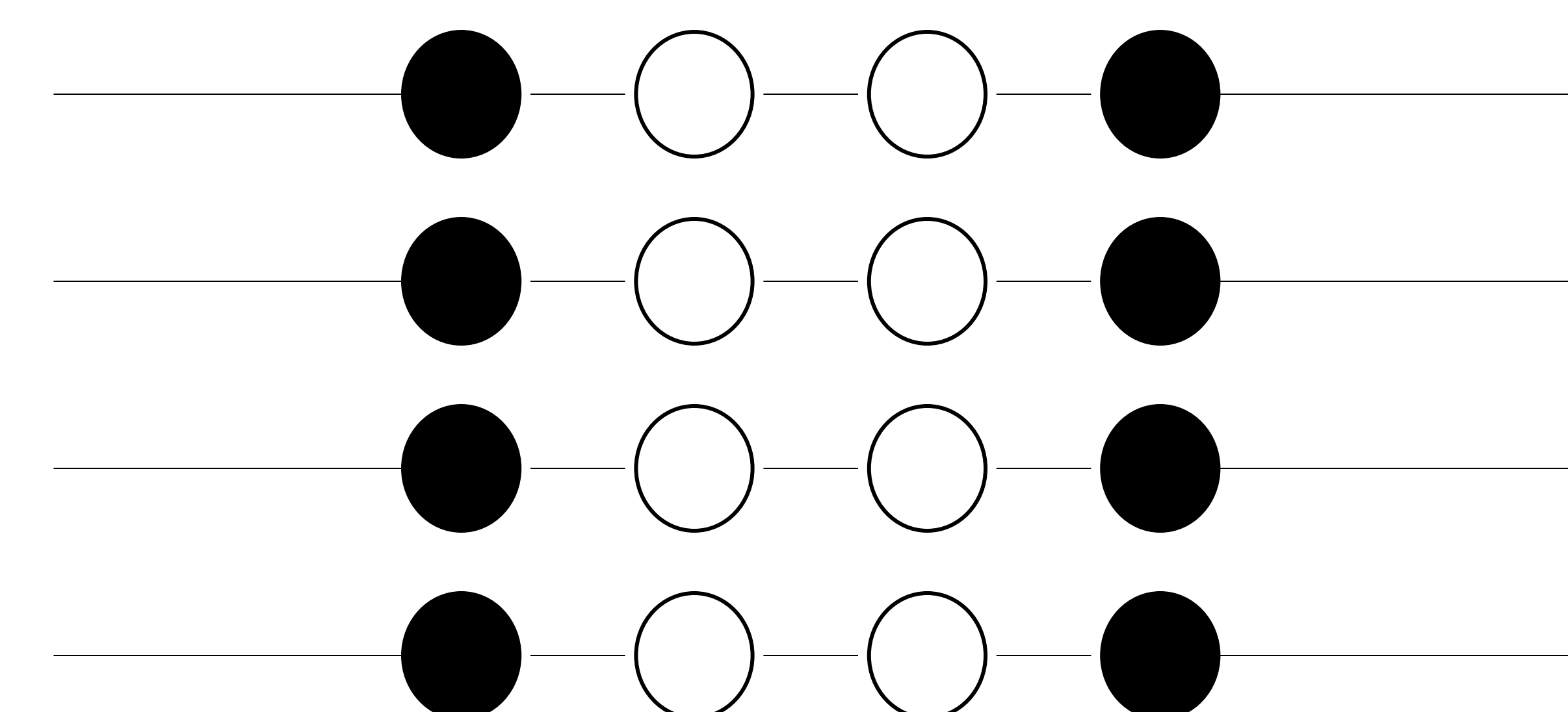
Pattern 3:



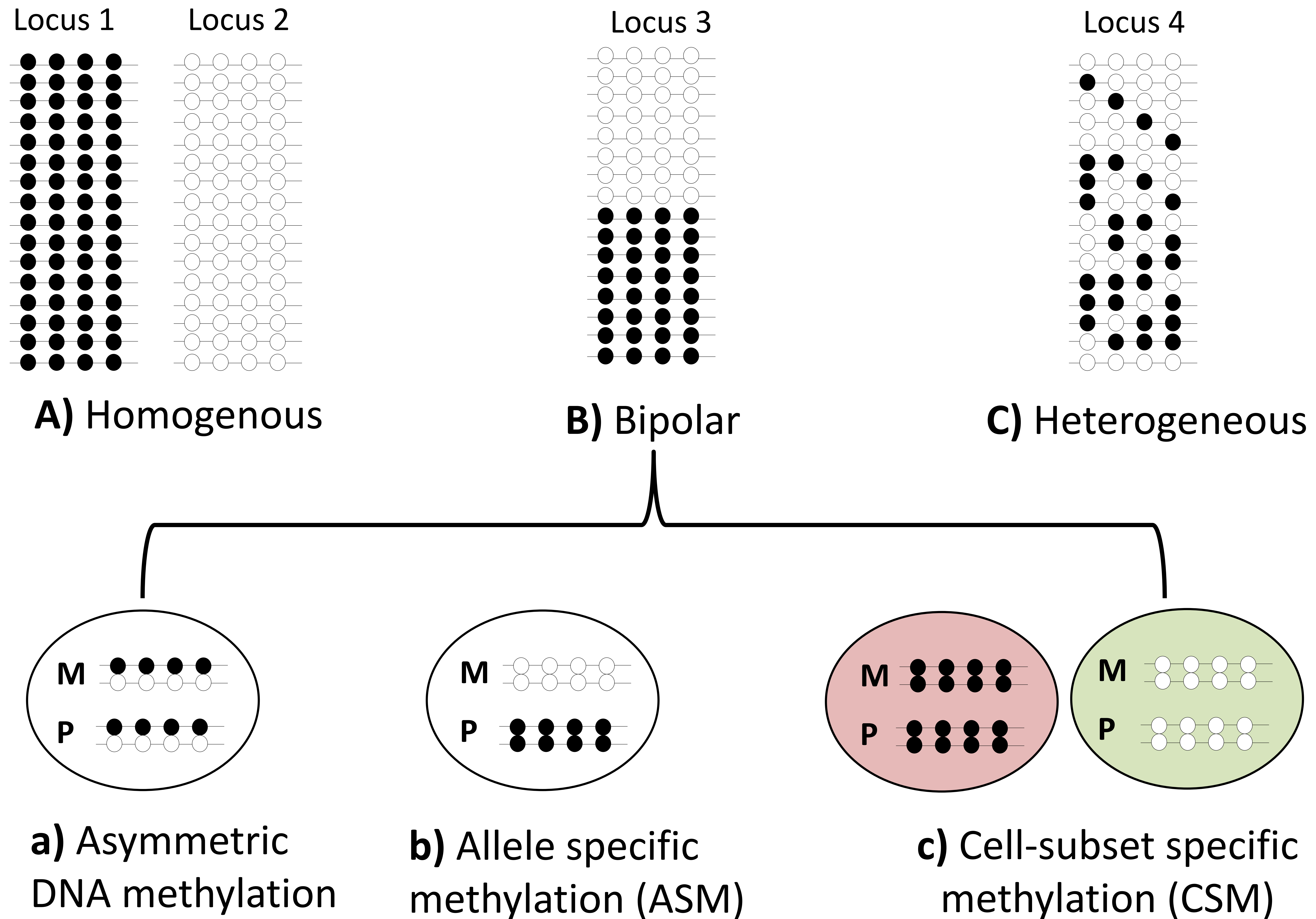
Pattern 4:



Pattern 5:

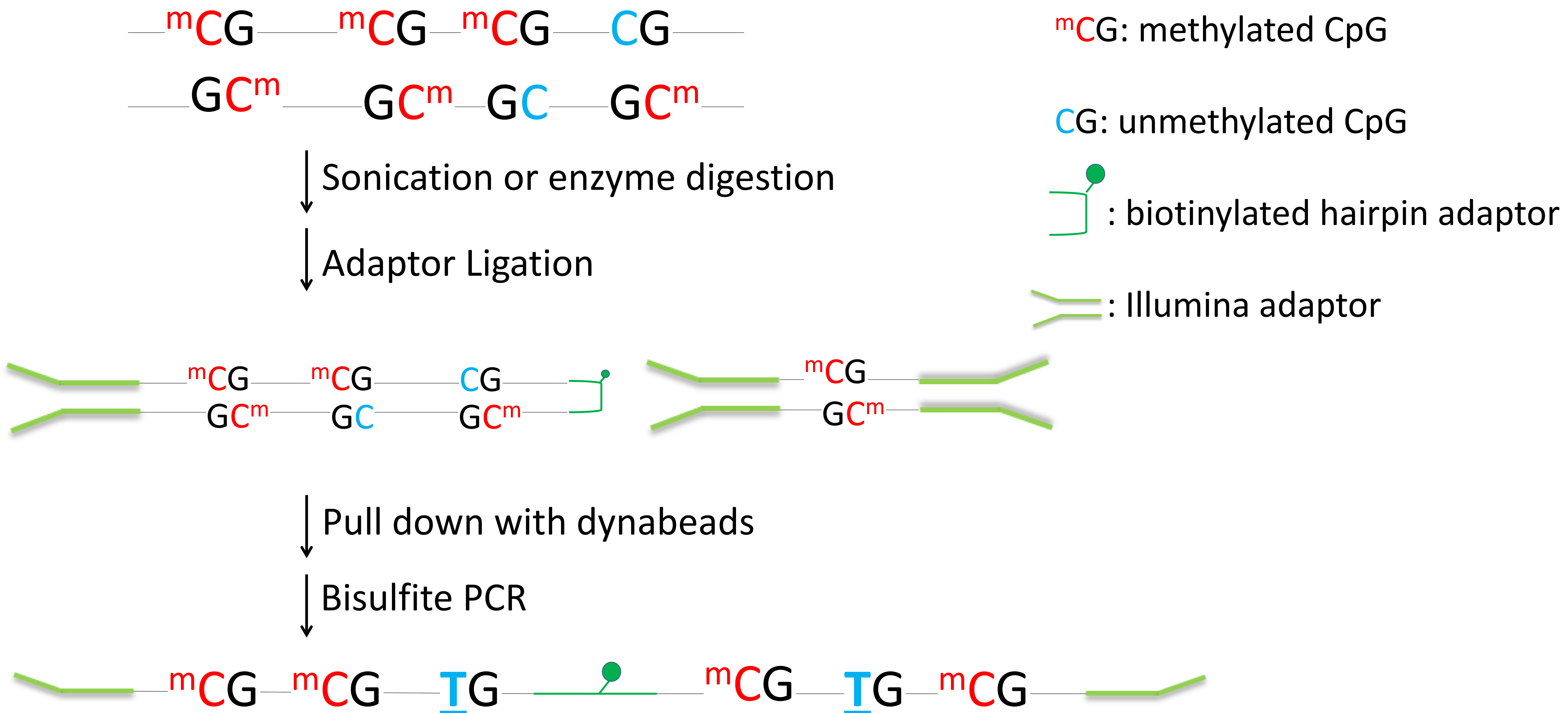


Epigenetic Heterogeneity

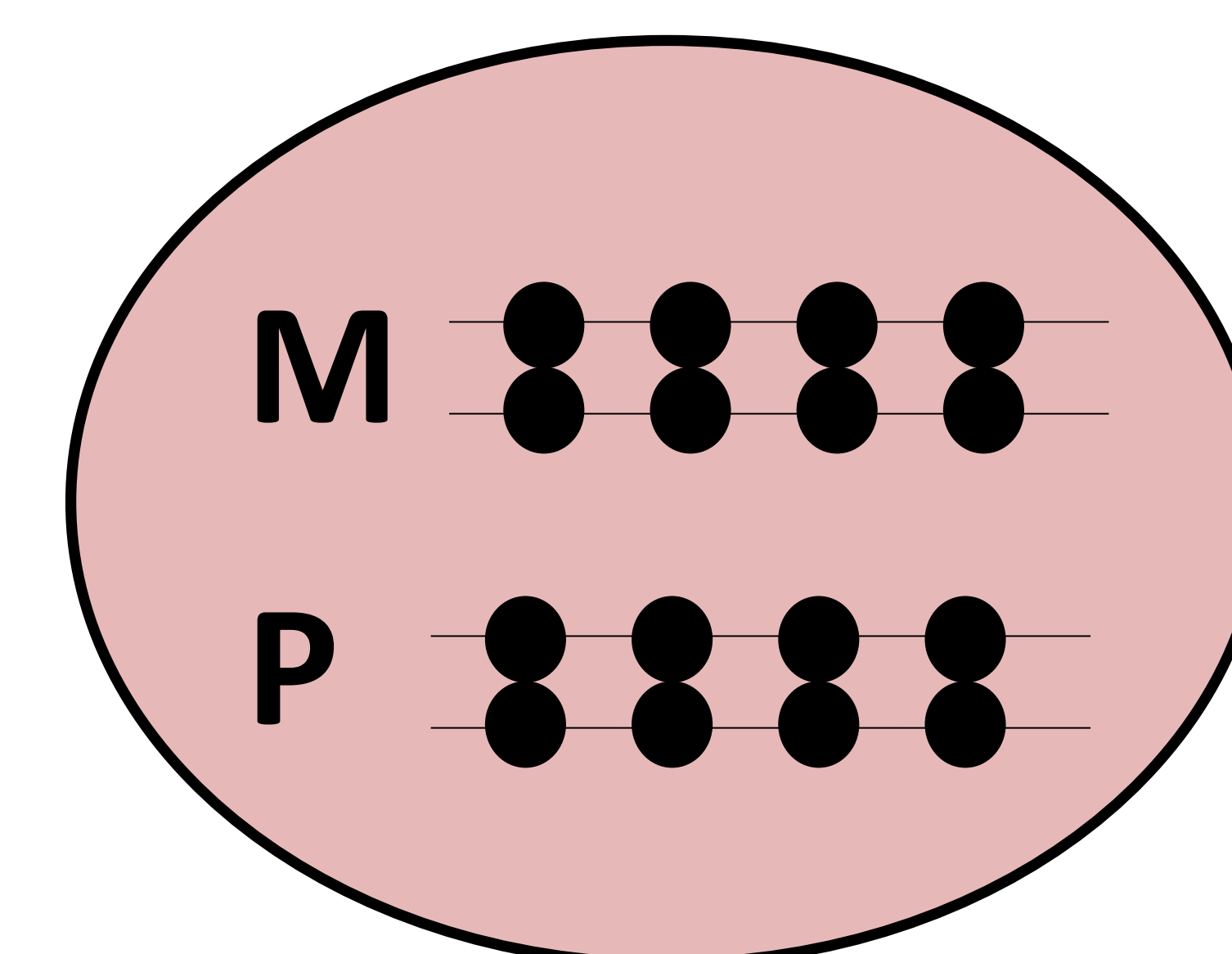
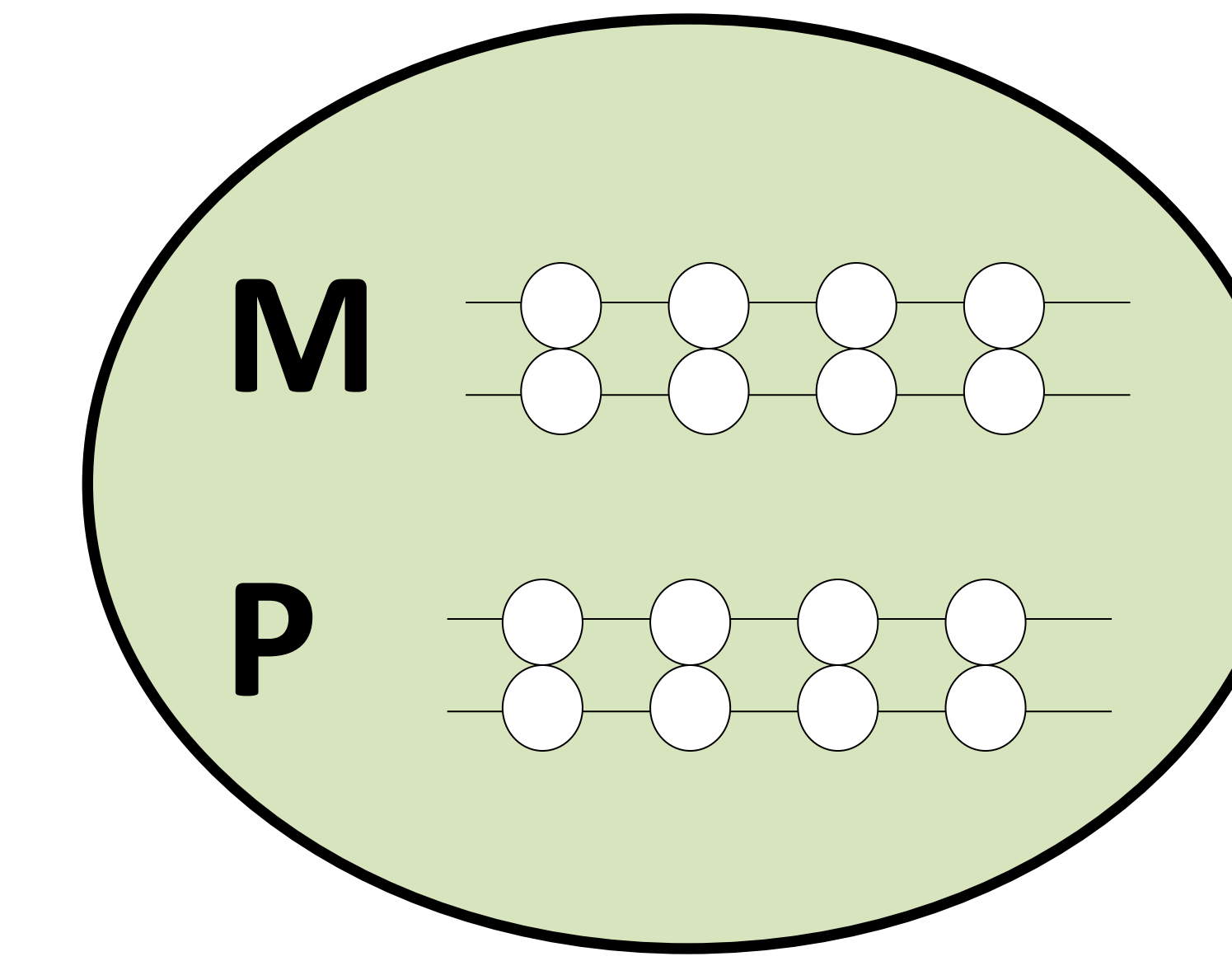
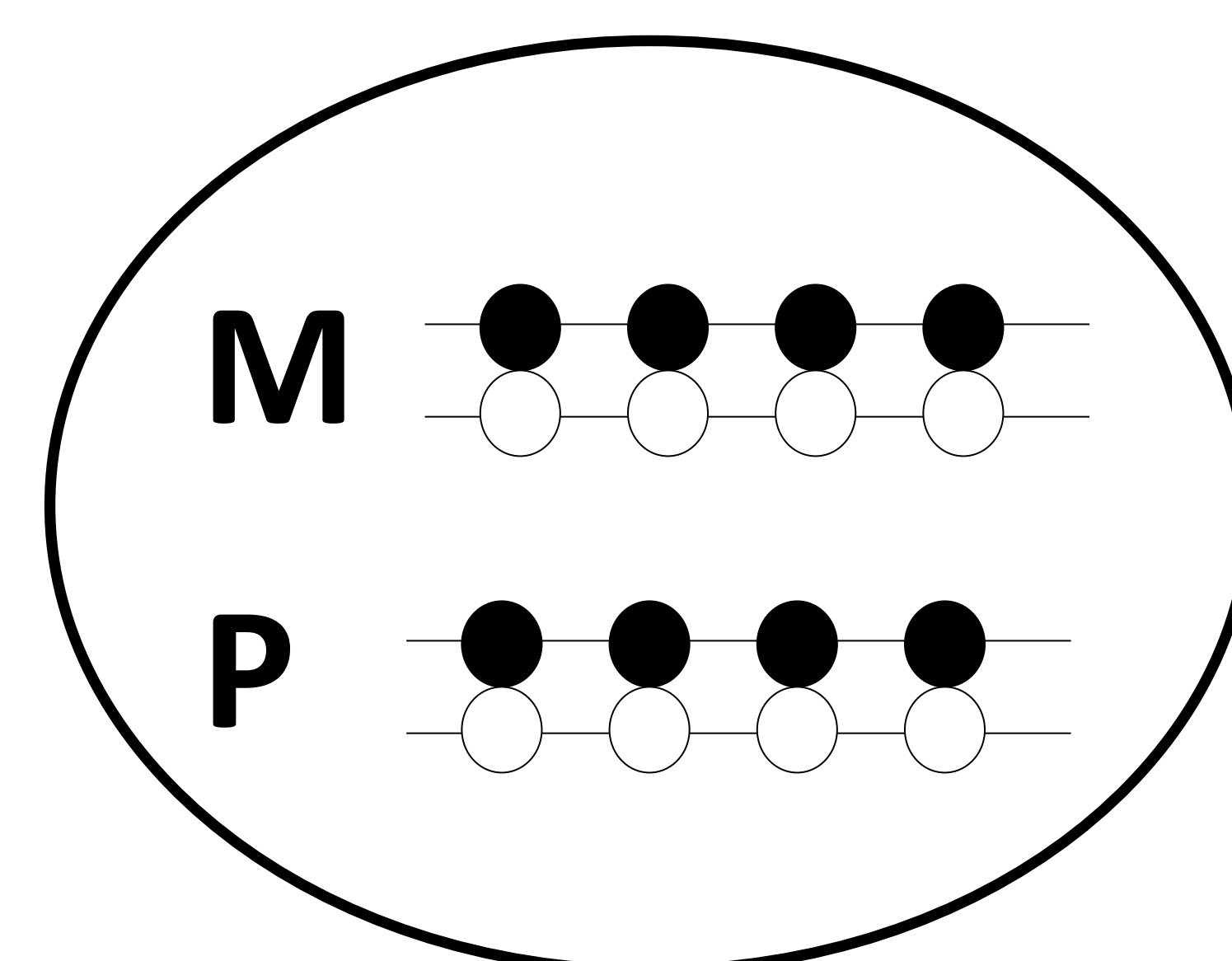
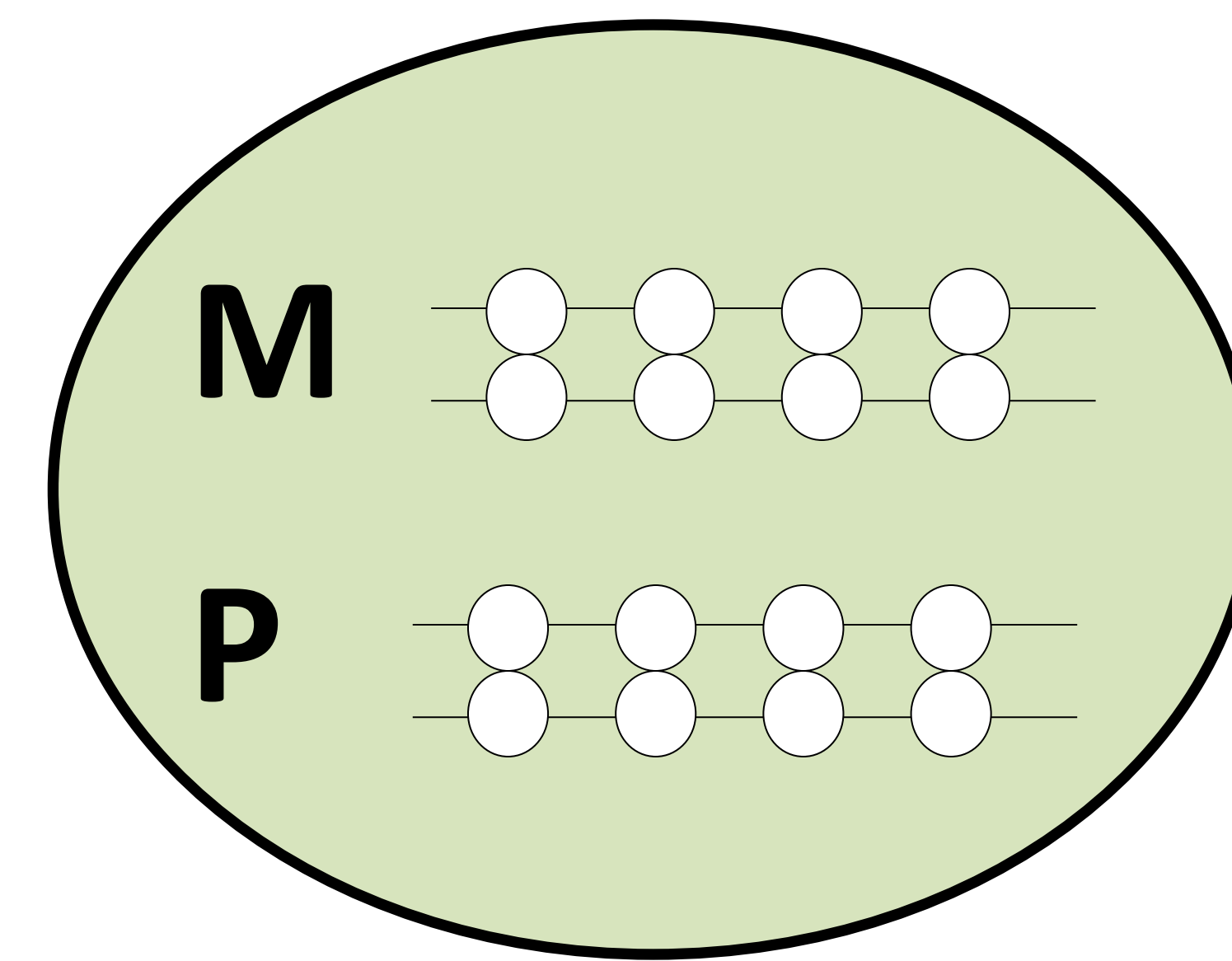
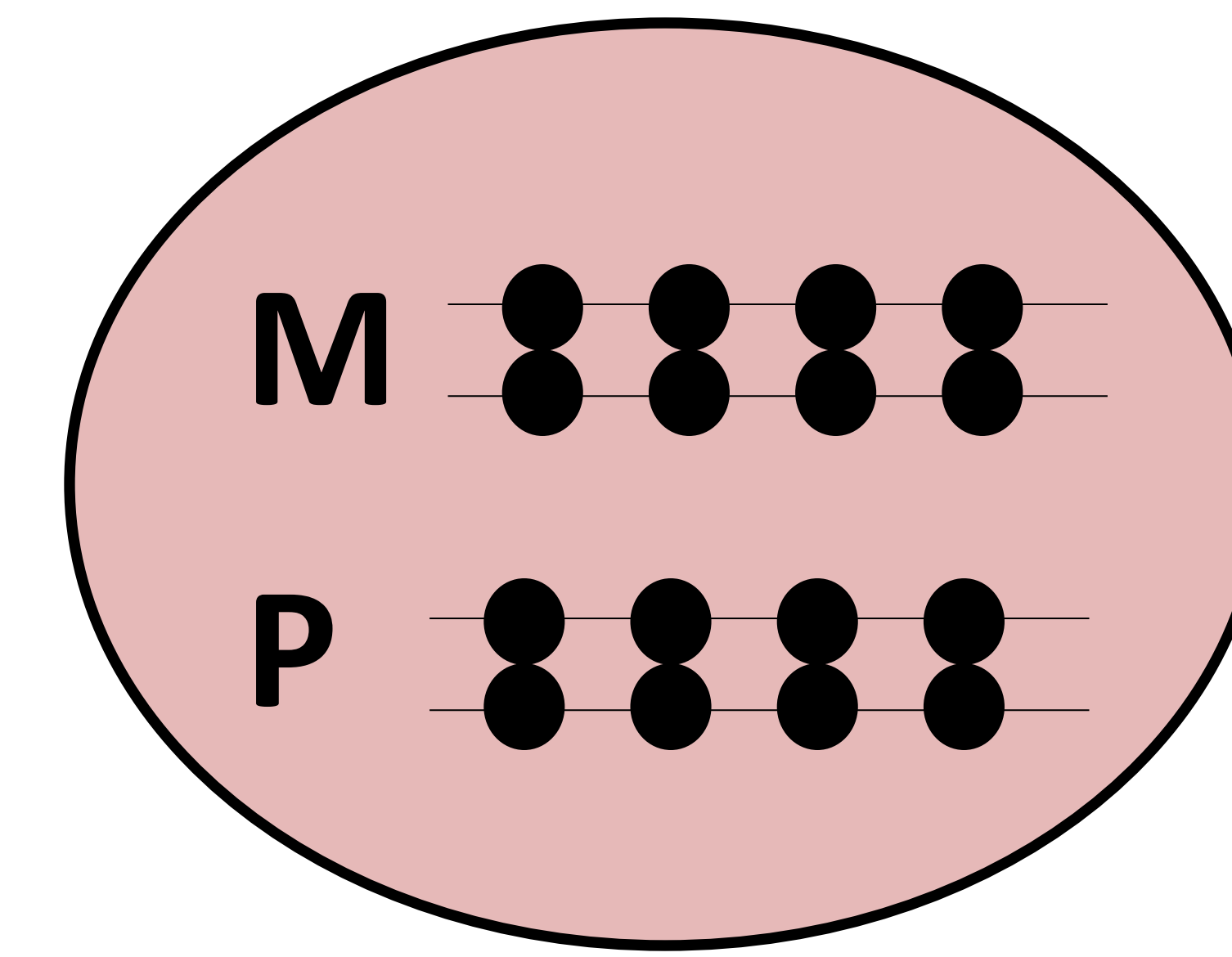
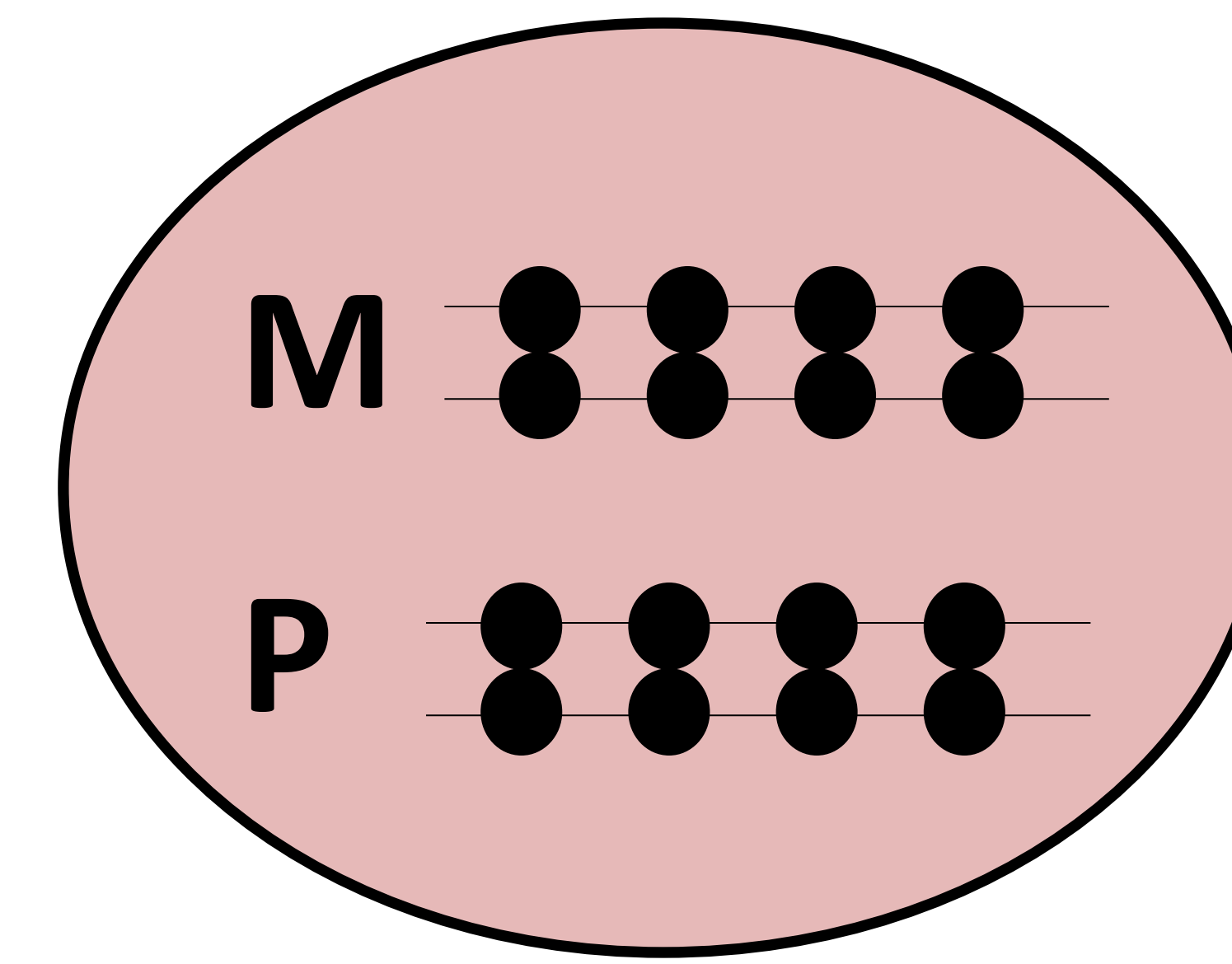
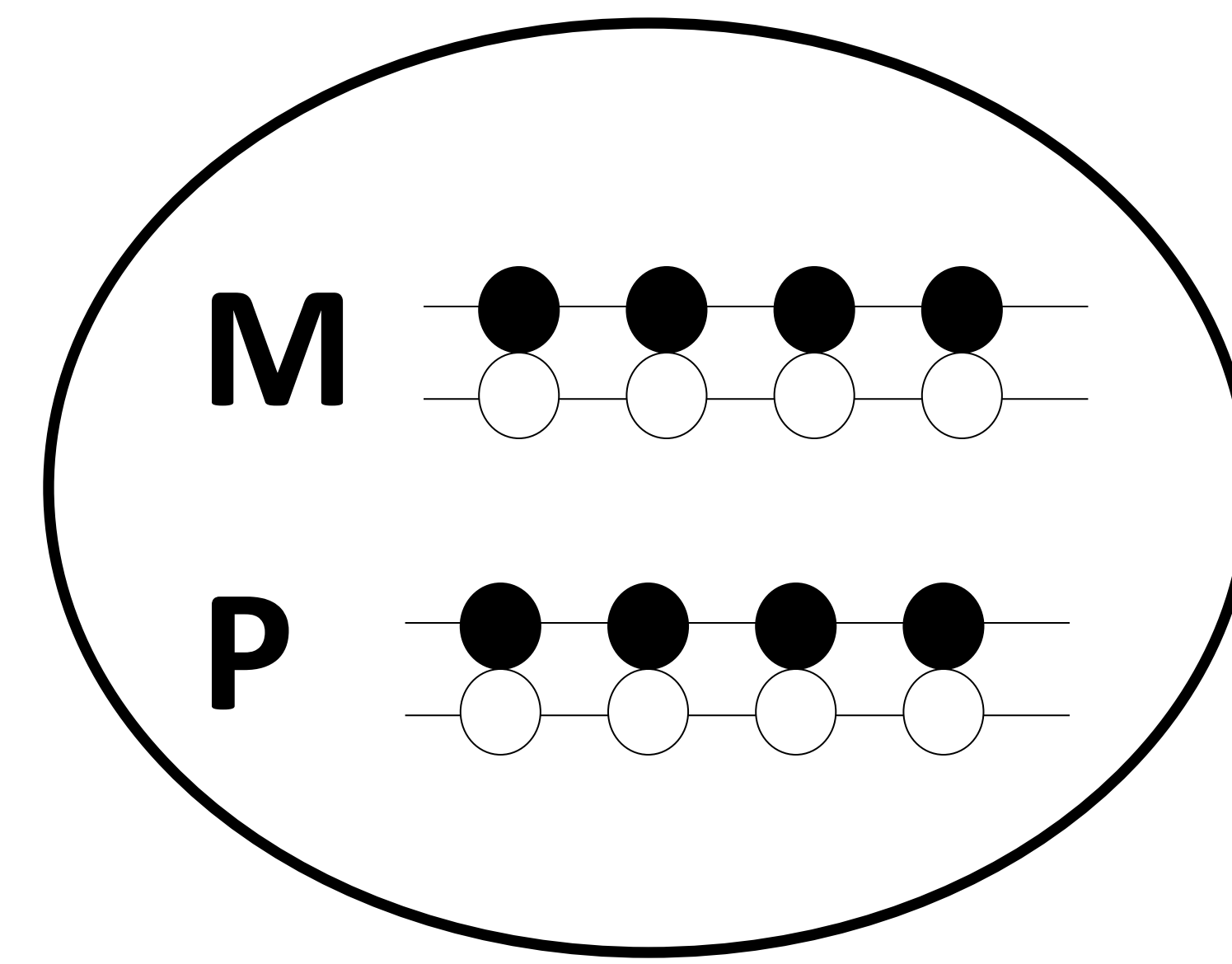
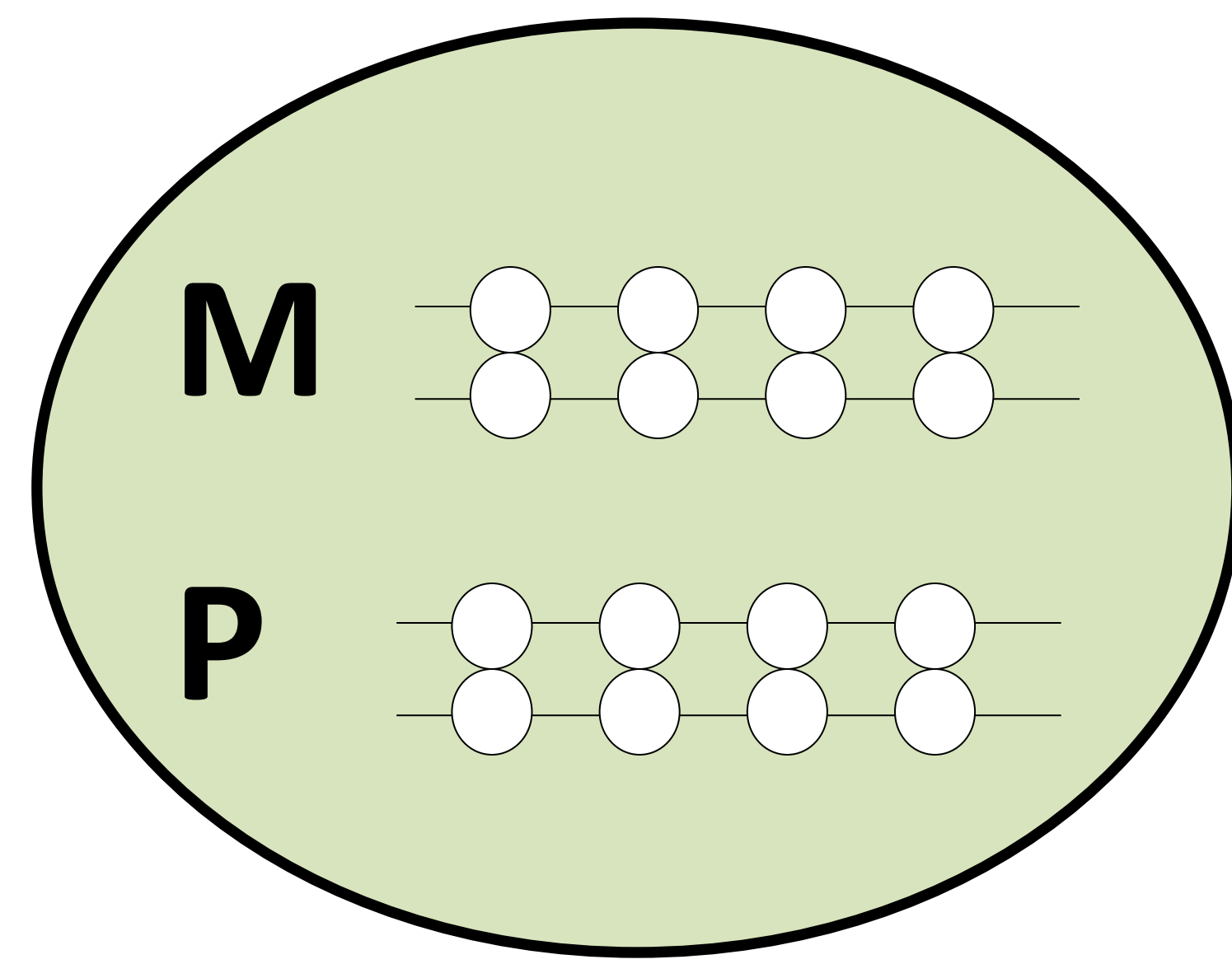


Diverse methylation patterns reflect distinct epigenetic events. Each line represents a sequence read or a DNA strand; open circle represents unmethylated cytosine; filled circle represents methylated cytosine; “M” and “P” indicate maternal and paternal alleles.

Genome-wide Hairpin Bisulfite Sequencing



SSM, CSM and Hairpin Bisulfite Sequencing



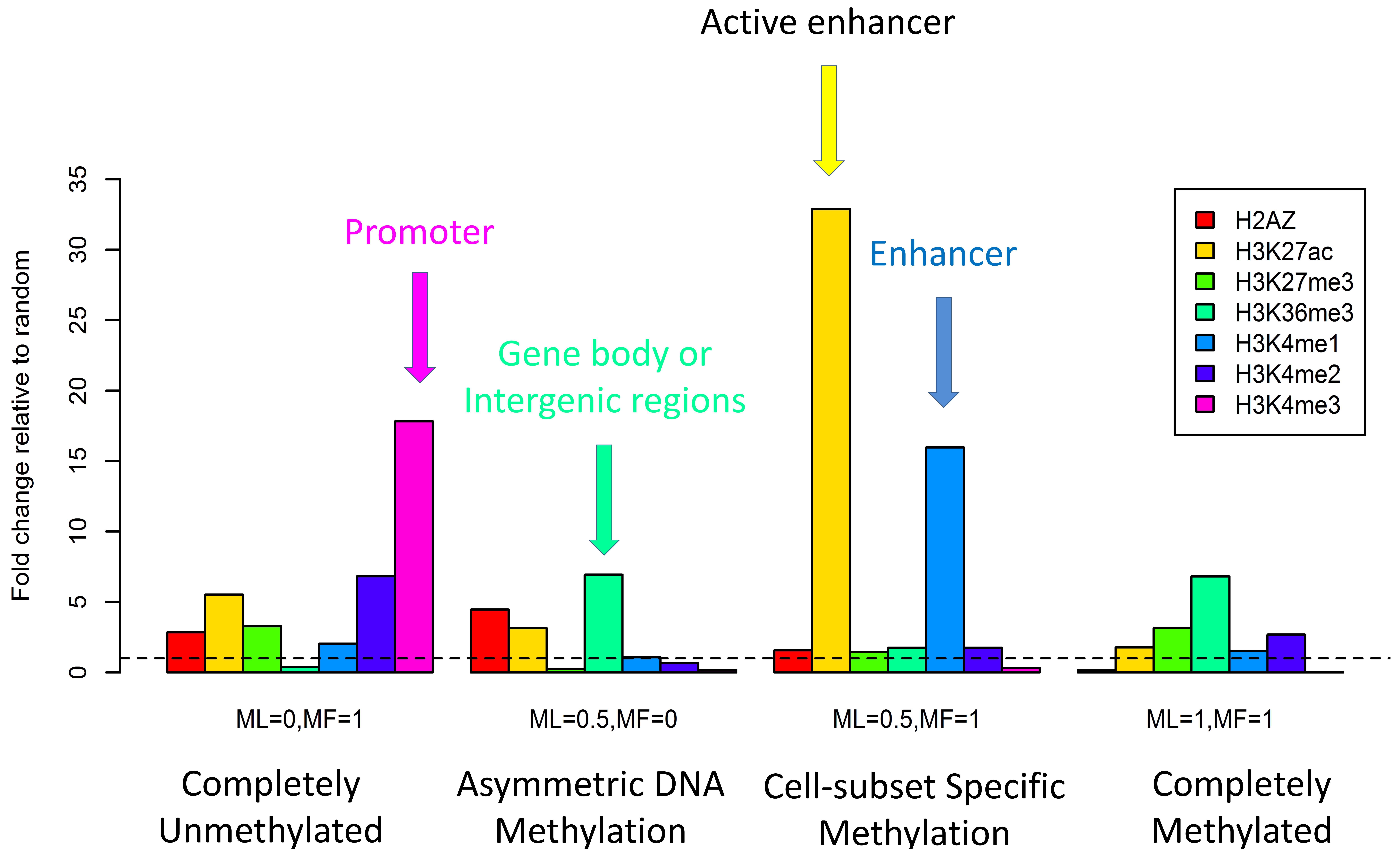
Completely Unmethylated

Asymmetric DNA Methylation

Cell-subset Specific Methylation

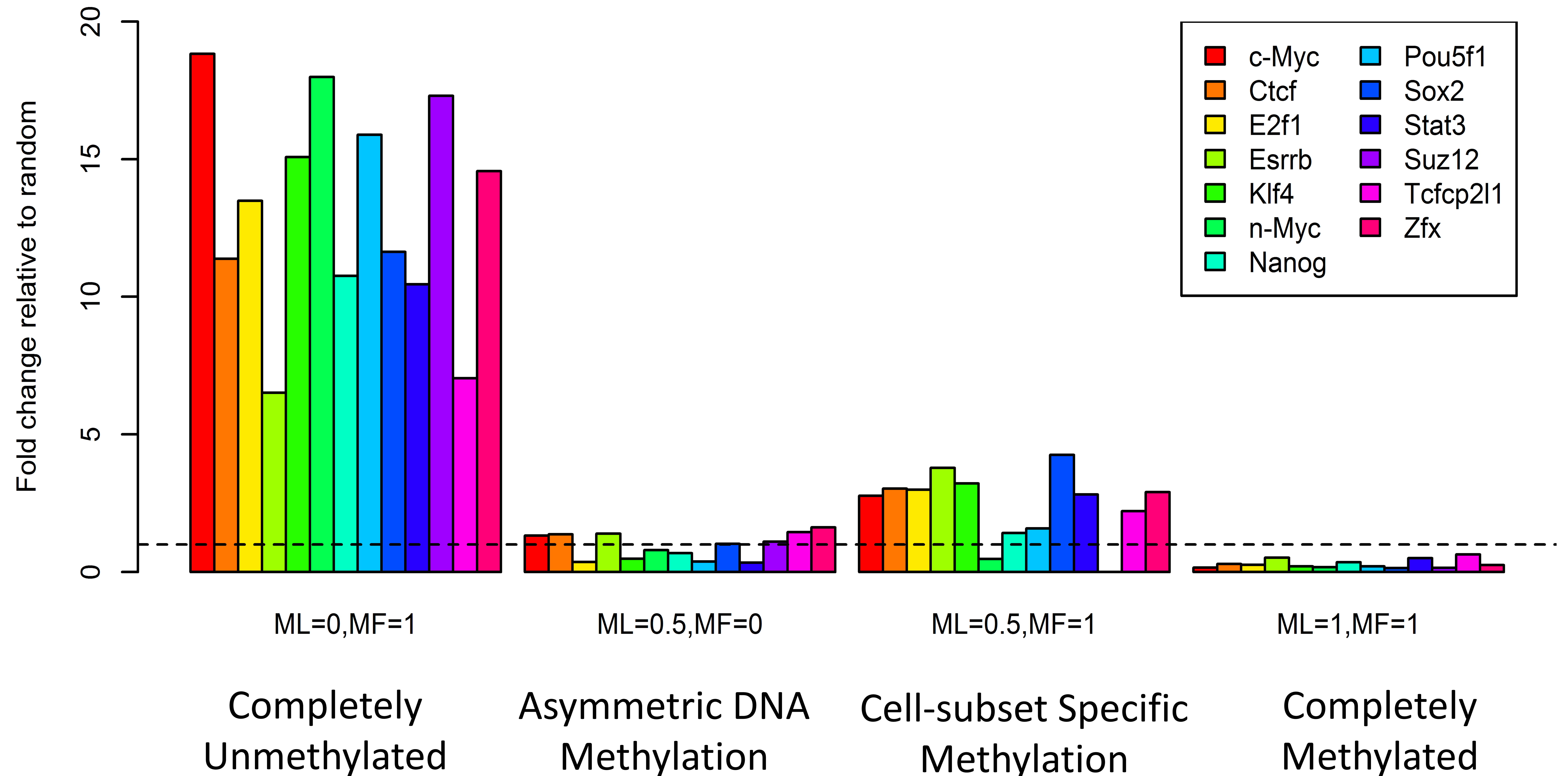
Completely Methylated

SSM, CSM and Histone Modifications



- 1) Strand specific methylated CpG sites enriched in gene body with H3K36me3 marks
- 2) Cell specific methylated CpG sites enriched in active enhancers with H3K27ac and H3K4me1 marks

SSM, CSM and TF Bindings



- 1) Strand specific methylated CpG sites depleted from TF binding sites
- 2) Cell specific methylated CpG sites enriched in a number of TF binding sites

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Epigenetic dynamics of developing brain

Genomic DNA methylation pattern from a mixed cell population



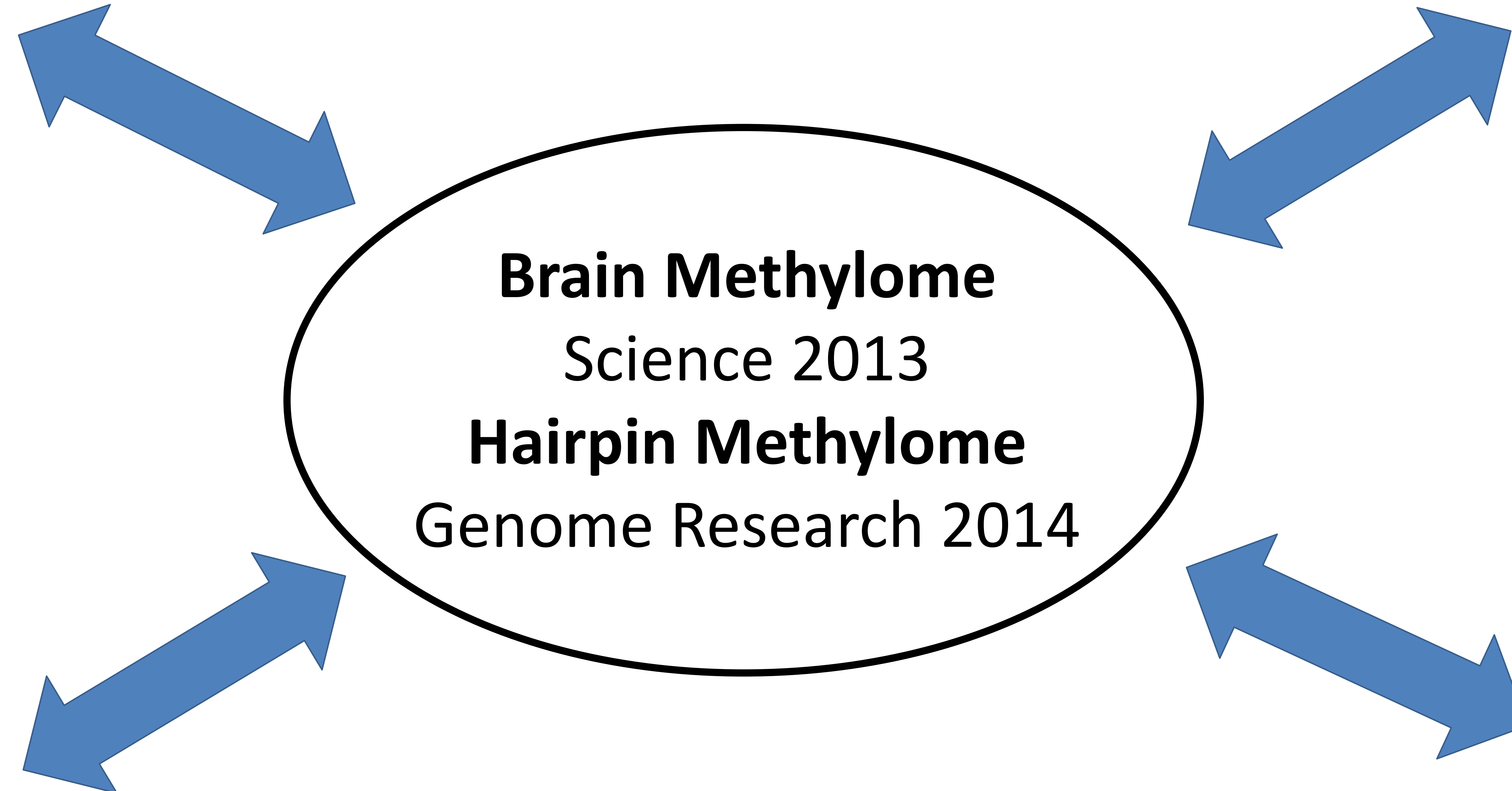
Ongoing Research

Enhancer maps

Xie et al, Cell 2012
Nord et al, Cell 2013
Zhu et al, Cell 2013
Andersson et al, Nature 2014

TF binding maps

Encode Project, Nature 2012



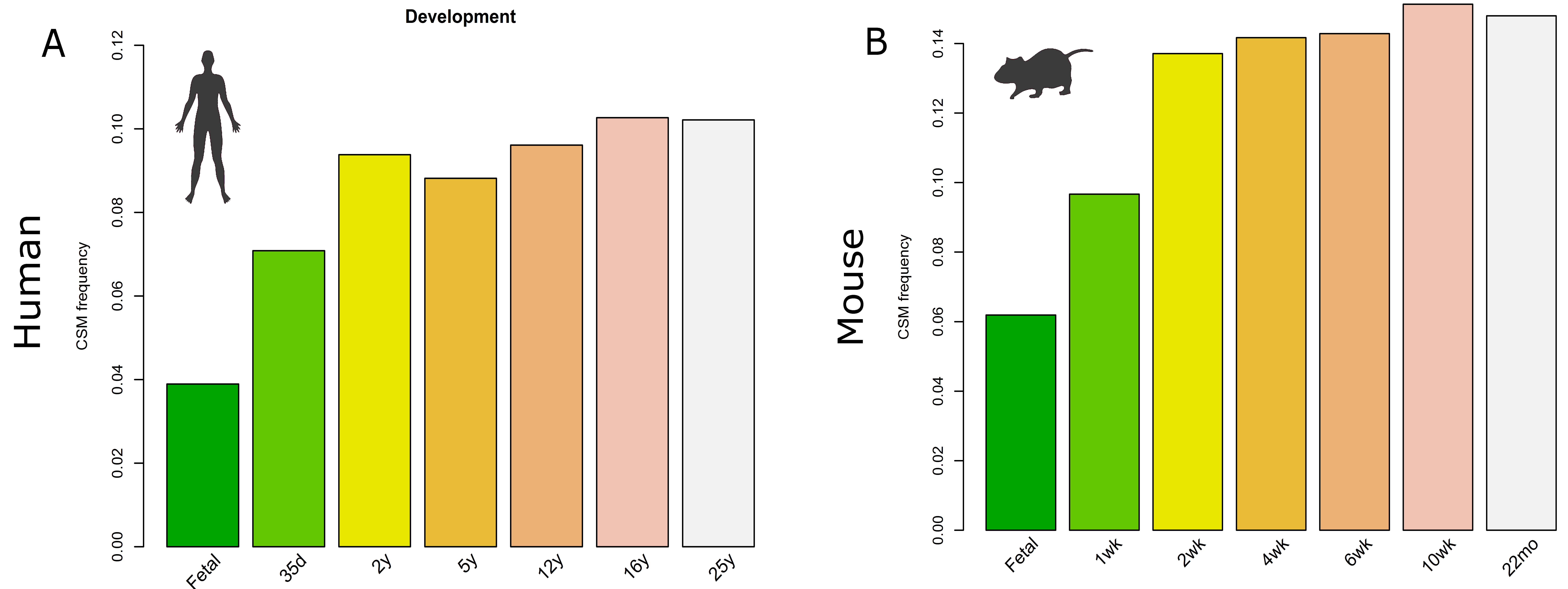
Transcriptome

ALLEN Brain Atlas, Cell 2013
Mazi et al, MSB 2013

Genetic mutations

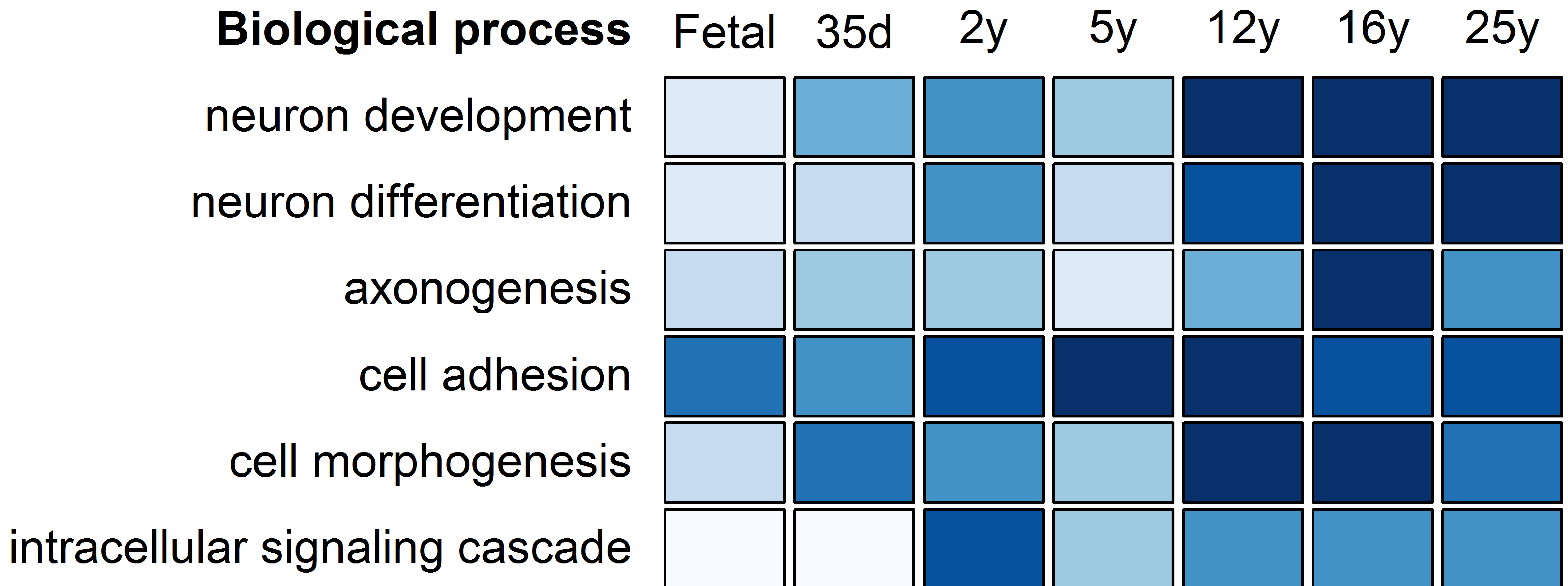
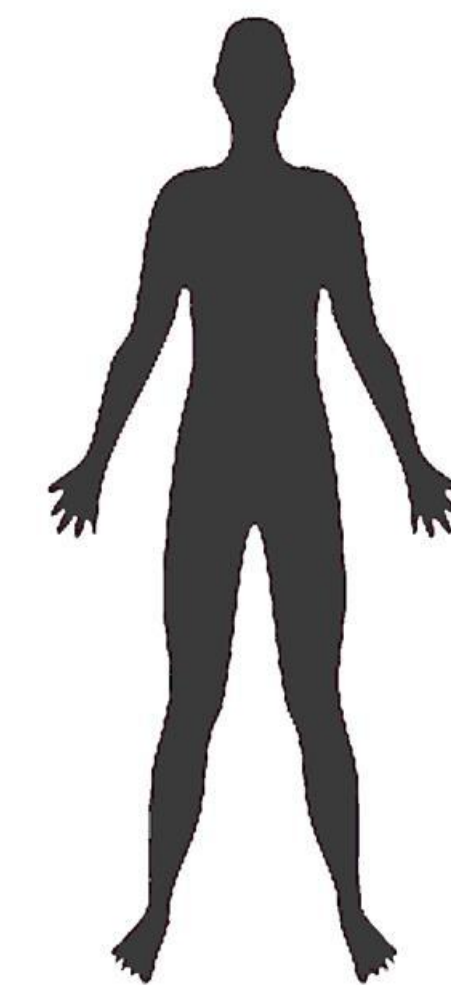
Khurana et al, Science 2013
Human Gene Mutation Database
GWAS catalogue

Epigenetic dynamics of developing brain



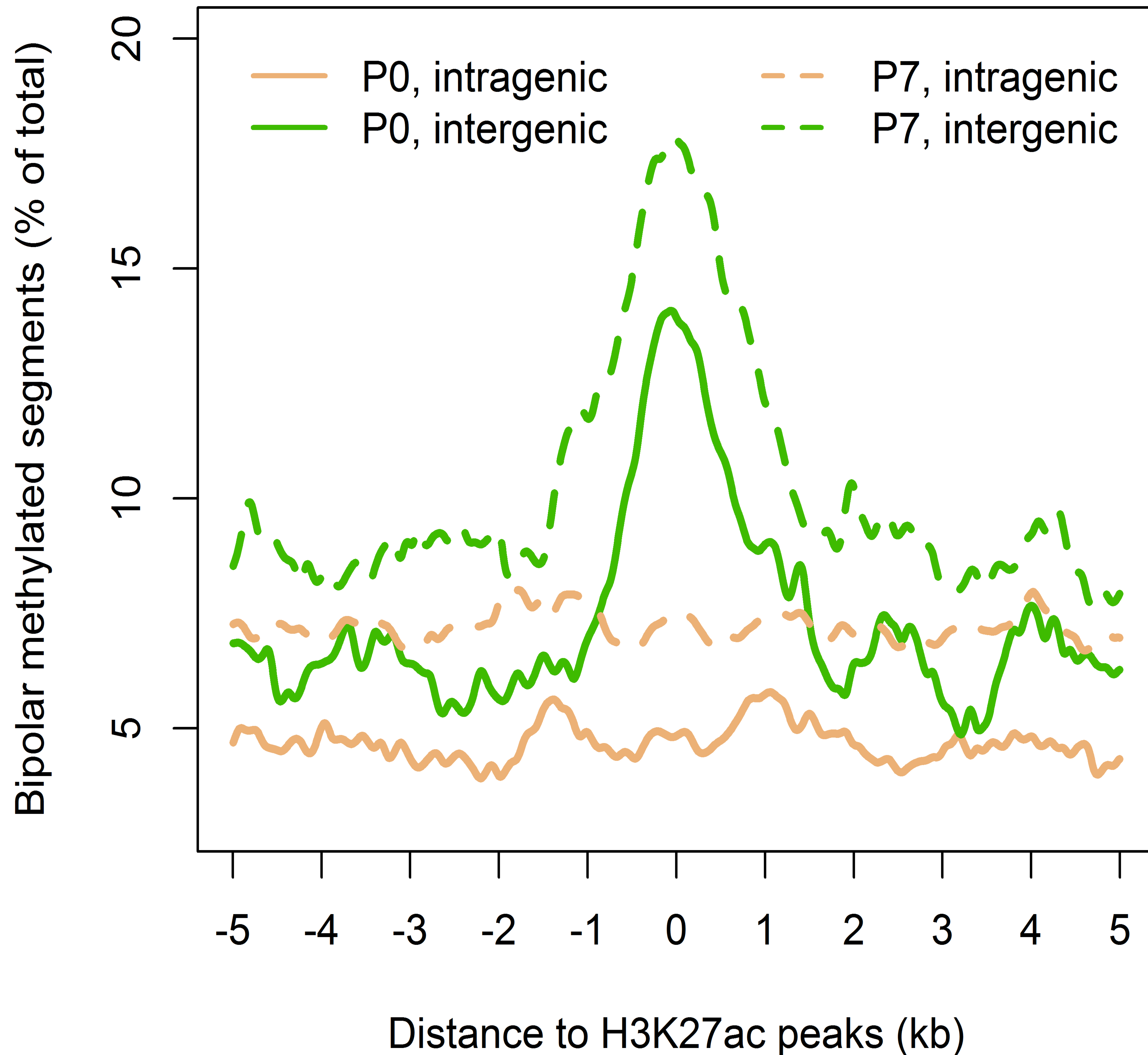
CSM frequencies increase dramatically at early stages of brain development.

GO enrichment for CSM associated genes

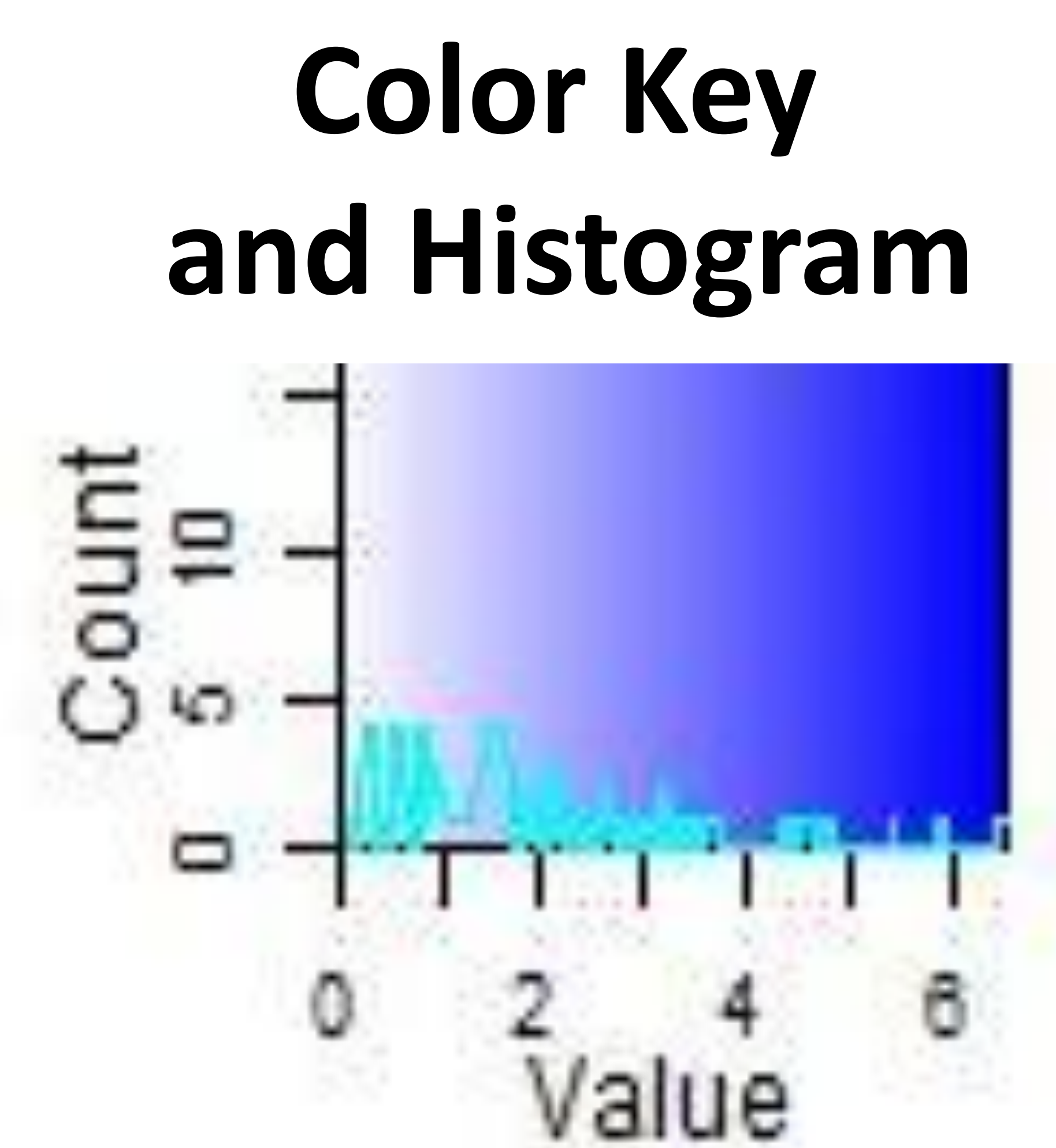
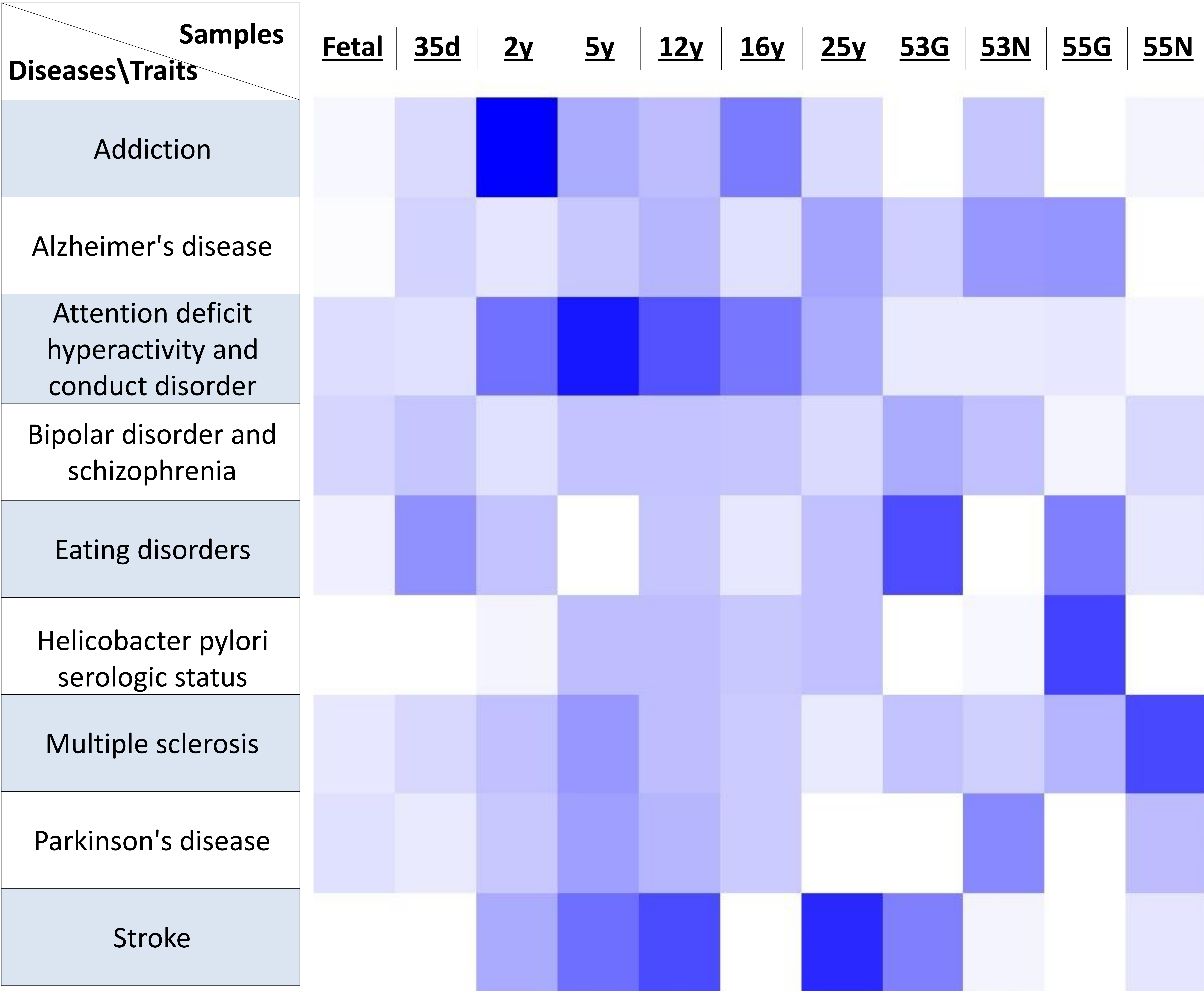


The CSM associated genes are enriched for function related to brain development.

CSM and Histone Modifications



Disease-associated genetic variations in CSM regions



Summary

- The combination of hairpin bisulfite sequencing and computational approach assist in the distinction of cell-subset specific methylation from allele-specific and asymmetric DNA methylation;
- Mammalian brain development is accompanied with a dramatic increase in the number of cell-subset specific methylated loci;
- Cell-subset specific methylation is highly correlated with histone marks for active enhancers and enriched in transcription factor binding;
- Genetic variations associated with neurological disorders are enriched in brain cell-subset specific methylated regions

Acknowledgements

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