Epigenetics - part 1

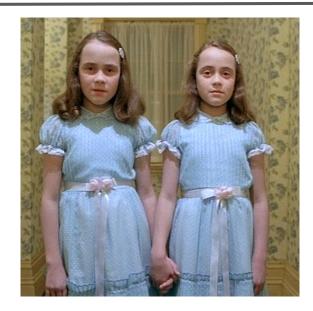


Nurture or nature?

Given the same sequence of DNA, should we expect the same phenotypic outcome?

Or put another way, can the results of experience be heritable (excepting mutagen exposure)?

Epigenetics - heritable changes of DNA, not involving sequence changes, that regulate gene expression





Levels of epigenetic regulation

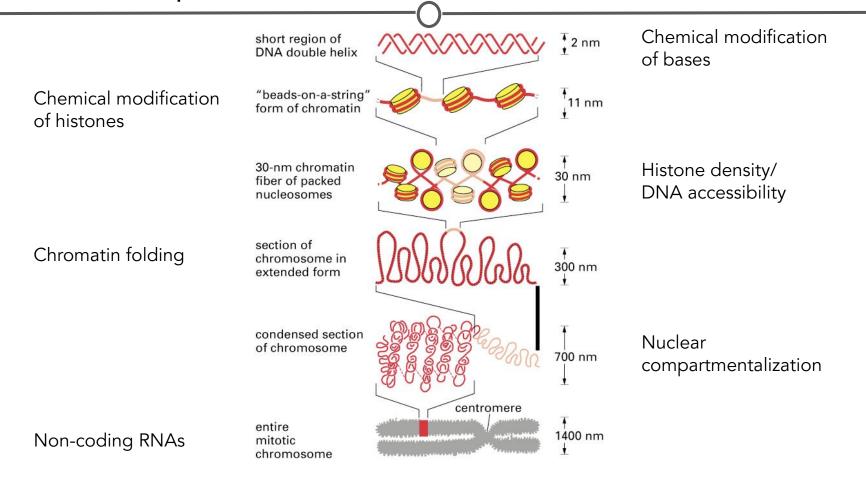


Figure 4–55. Molecular Biology of the Cell, 4th Edition.

Levels of epigenetic regulation

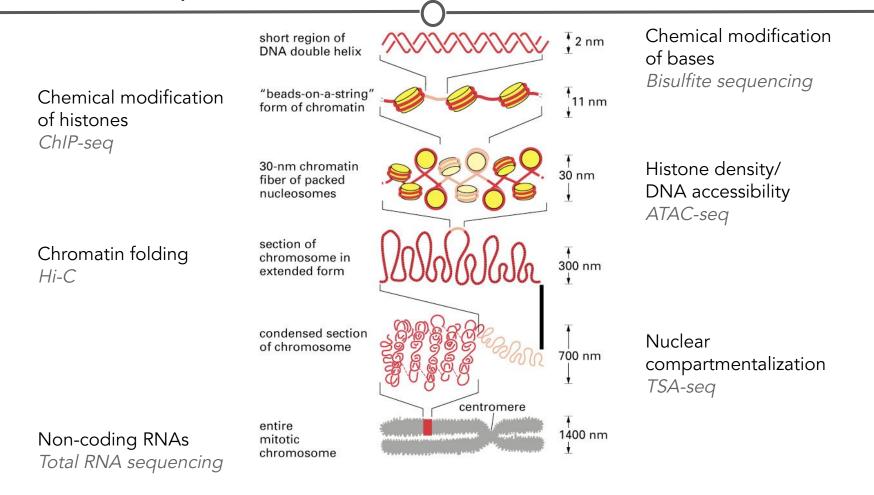


Figure 4–55. Molecular Biology of the Cell, 4th Edition.

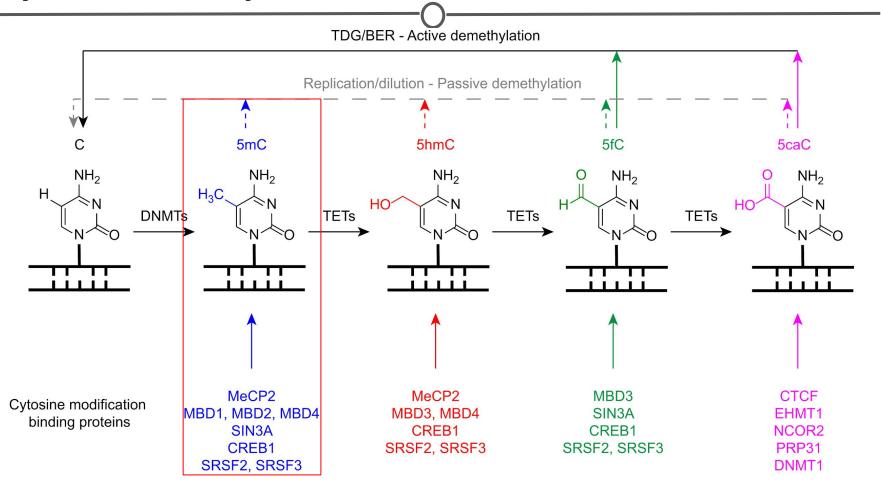
The epigenetic players

Out of ~25,000 coding genes, roughly 1000 are involved in epigenetic control

- DNA methylation:
 - DNA methylases/demethylases
- Histone modifications:
 - o methylases, demethylases, actylases, ubiquitinases, readers, ...
- Nucleosome positioning:
 - o Pioneer factors (Oct4, Sox2, Pou2, ...)
- Chromatin folding:
 - o CTCF, cohesin, YY1, topoisomerase, ...
- ncRNAs:
 - o Xist, piwiRNAs, IncRNAs, siRNAs, ...

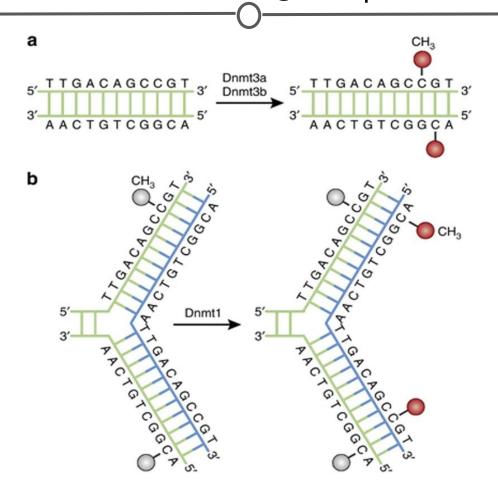
DNA methylation

Cytosine methylation



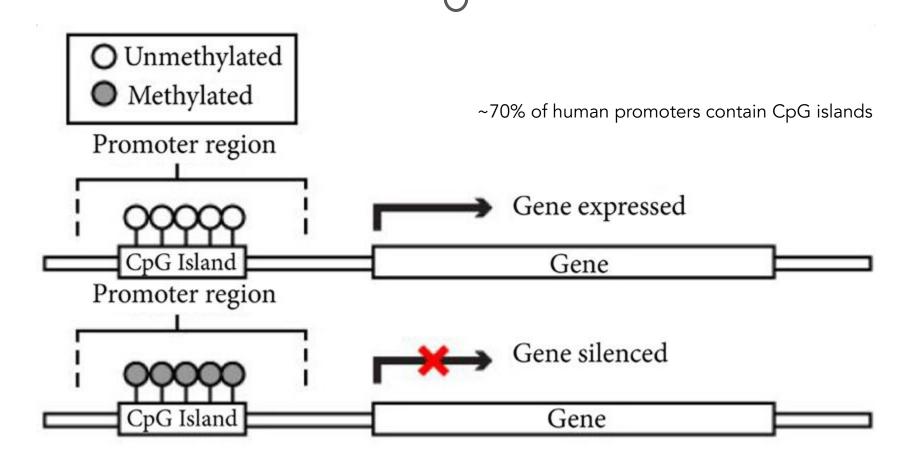
Chen K, Zhao BS, He C. Nucleic Acid Modifications in Regulation of Gene Expression. Cell Chem Biol. 2016 Jan 21;23(1):74-85. doi: 10.1016/j.chembiol.2015.11.007.

Maintenance of 5mC through replication

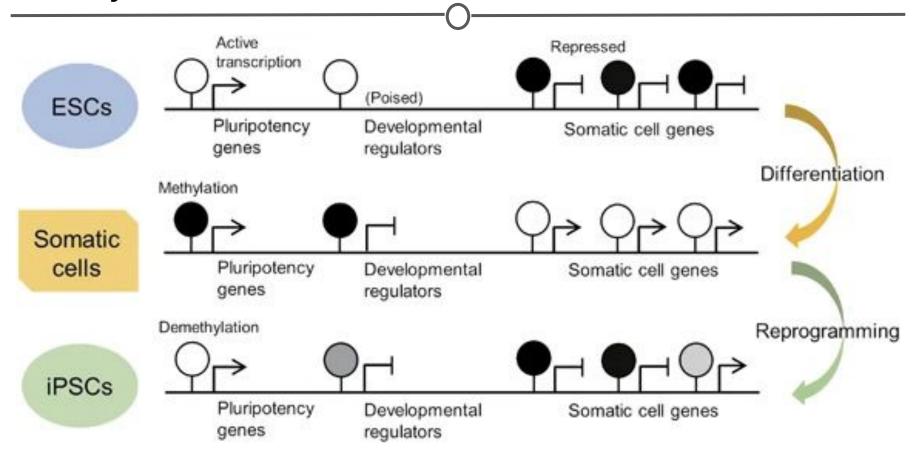


Effects of DNA methylation

CpG islands and gene regulation

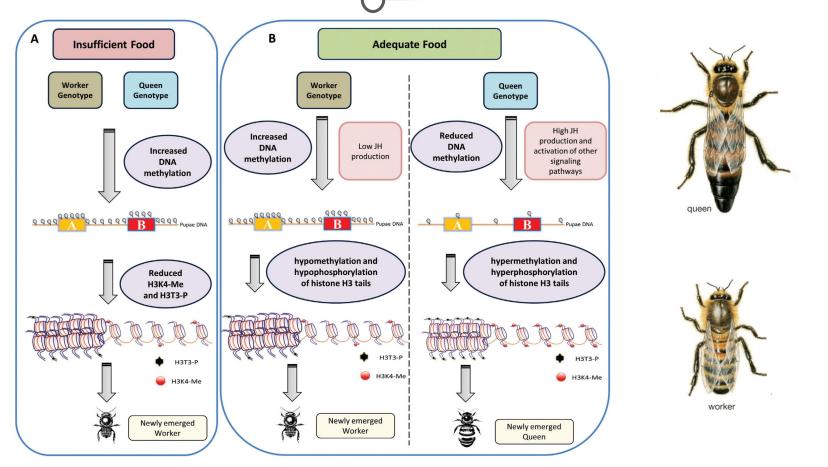


Methylation reinforces differentiation



Kim M, Costello J. DNA methylation: an epigenetic mark of cellular memory. Exp Mol Med. 2017 Apr 28;49(4):e322.

Environmental cues and methylation



Cardoso-Júnior Carlos A.M., Fujimura Patrícia Tieme, Santos-Júnior Célio Dias, Borges Naiara Araújo, Ueira-Vieira Carlos, Hartfelder Klaus et al . Epigenetic modifications and their relation to caste and sex determination and adult division of labor in the stingless bee Melipona scutellaris. Genet. Mol. Biol. 2017 Mar; 40(1): 61-68.

Suppression of transposable elements (TEs)

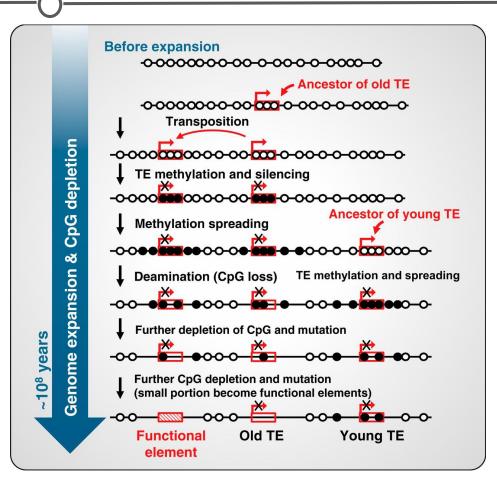
TEs are mobile repetitive sequences that can replicate and integrate into the genome

Two classes:

Class 1 - RNA intermediate

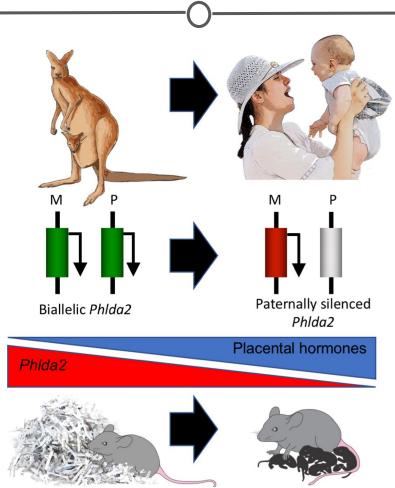
Class 2 - DNA intermediate

Make up ~45% of the human genome



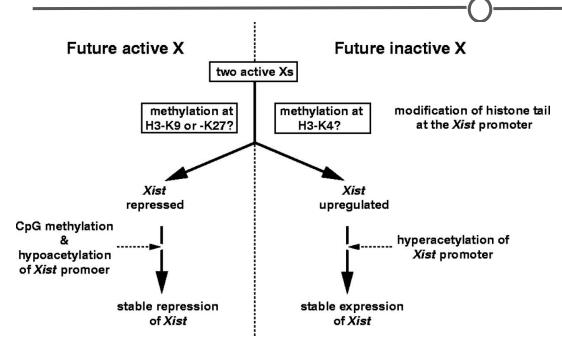
Wanding Zhou, Gangning Liang, Peter L. Molloy, Peter A. Jones. DNA methylation enables transposable element-driven genome expansion. Proceedings of the National Academy of Sciences Aug 2020, 117 (32) 19359-19366

Genetic imprinting



Creeth HDJ, McNamara GI, Tunster SJ, Boque-Sastre R, Allen B, Sumption L, Eddy JB, Isles AR, John RM. Maternal care boosted by paternal imprinting in mammals. PLoS Biol. 2018 Jul 31;16(7):e2006599.

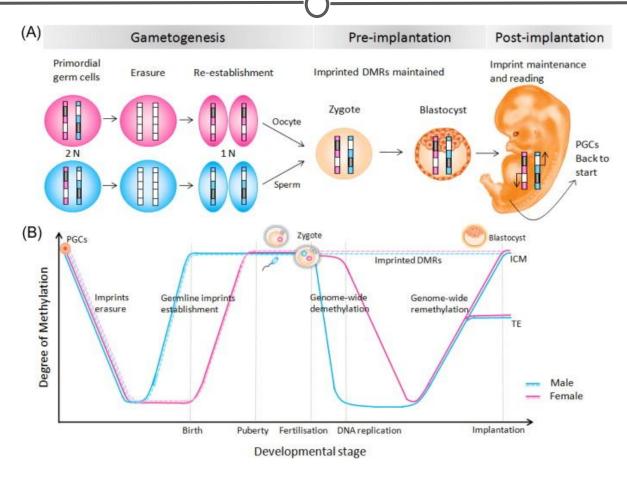
X chromosome inactivation





Sado T, Okano M, Li E, Sasaki H. De novo DNA methylation is dispensable for the initiation and propagation of X chromosome inactivation. Development. 2004 Mar;131(5):975-82.

Methylome erasure



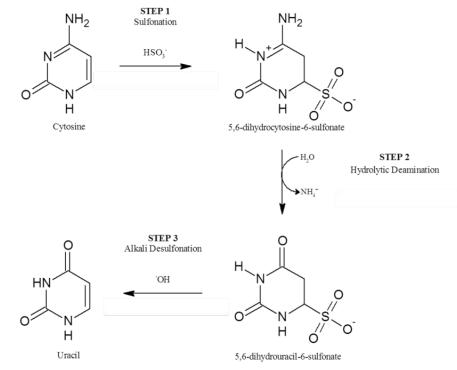
Ishida, Miho & Moore, Gudrun. (2012). The role of Imprinted genes in humans. Molecular Aspects of Medicine. 34. 10.1016/j.mam.2012.06.009.

Assaying DNA methylation

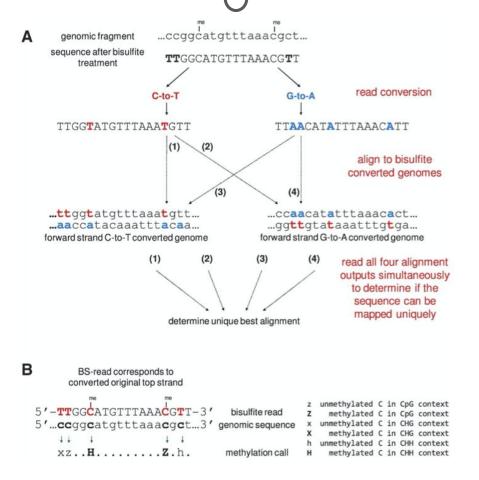
Bisulfite treatment

 Sodium bisulfite treatment of DNA causes unmethylated Cytosines to become Uracils

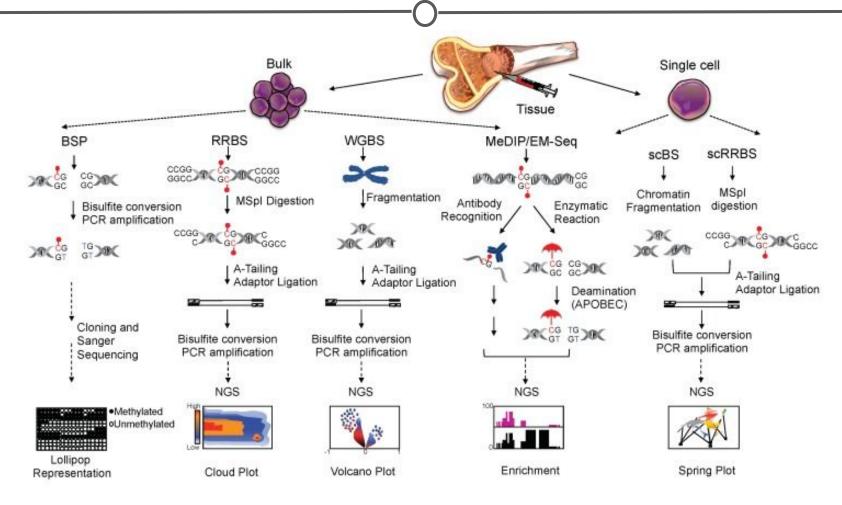
Methylated CpGs are unaffected



Bisulfite sequencing and mapping

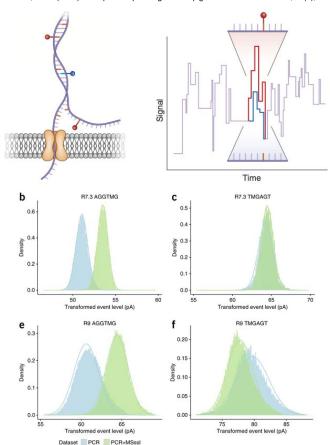


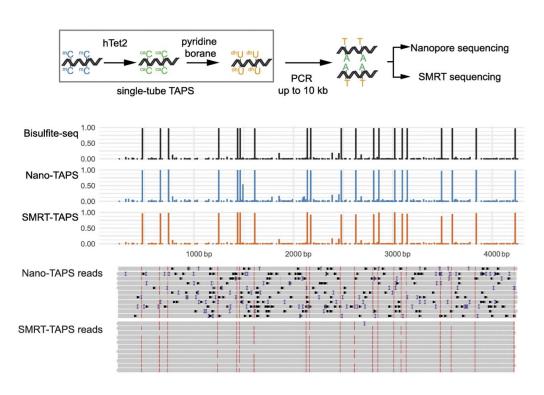
Additional methylation assays



Direct sequencing of methylation

Schatz, M. C. (2017). Nanopore sequencing meets epigenetics. Nature Methods, 14(4), 347-348.



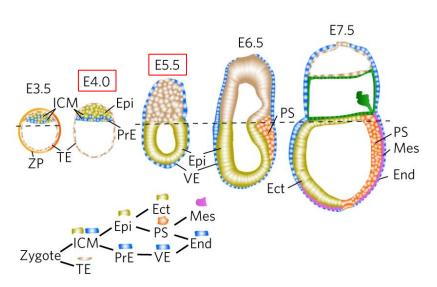


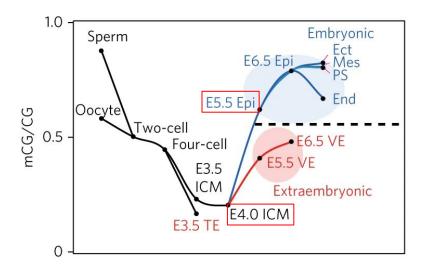
Liu, Y., Cheng, J., Siejka-Zielińska, P., Weldon, C., Roberts, H., Lopopolo, M., Magri, A., D'Arienzo, V., Harris, J. M., McKeating, J. A., & Song, C.-X. (2020). Accurate targeted long-read DNA methylation and hydroxymethylation sequencing with TAPS. *Genome Biology*, *21*(1), 54.

Simpson, J. T., Workman, R. E., Zuzarte, P. C., David, M., Dursi, L. J., & Timp, W. (2017). Detecting DNA cytosine methylation using nanopore sequencing. *Nature Methods*, *14*(4), 407–410.

Assignment data

Overview of early development (E3.5-E7.5)





Zhang Y, Xiang Y, Yin Q, Du Z, Peng X, Wang Q, Fidalgo M, Xia W, Li Y, Zhao ZA, Zhang W, Ma J, Xu F, Wang J, Li L, Xie W. Dynamic epigenomic landscapes during early lineage specification in mouse embryos. Nat Genet. 2018 Jan;50(1):96-105.