

Science senior editor Guy Riddihough taps experts
for their definition of epigenetics (6:01)

REVIEW ARTICLE

The Key Role of Epigenetics in Human Disease Prevention and Mitigation

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The NEW ENGLAND
JOURNAL of MEDICINE

Charlotte Darby

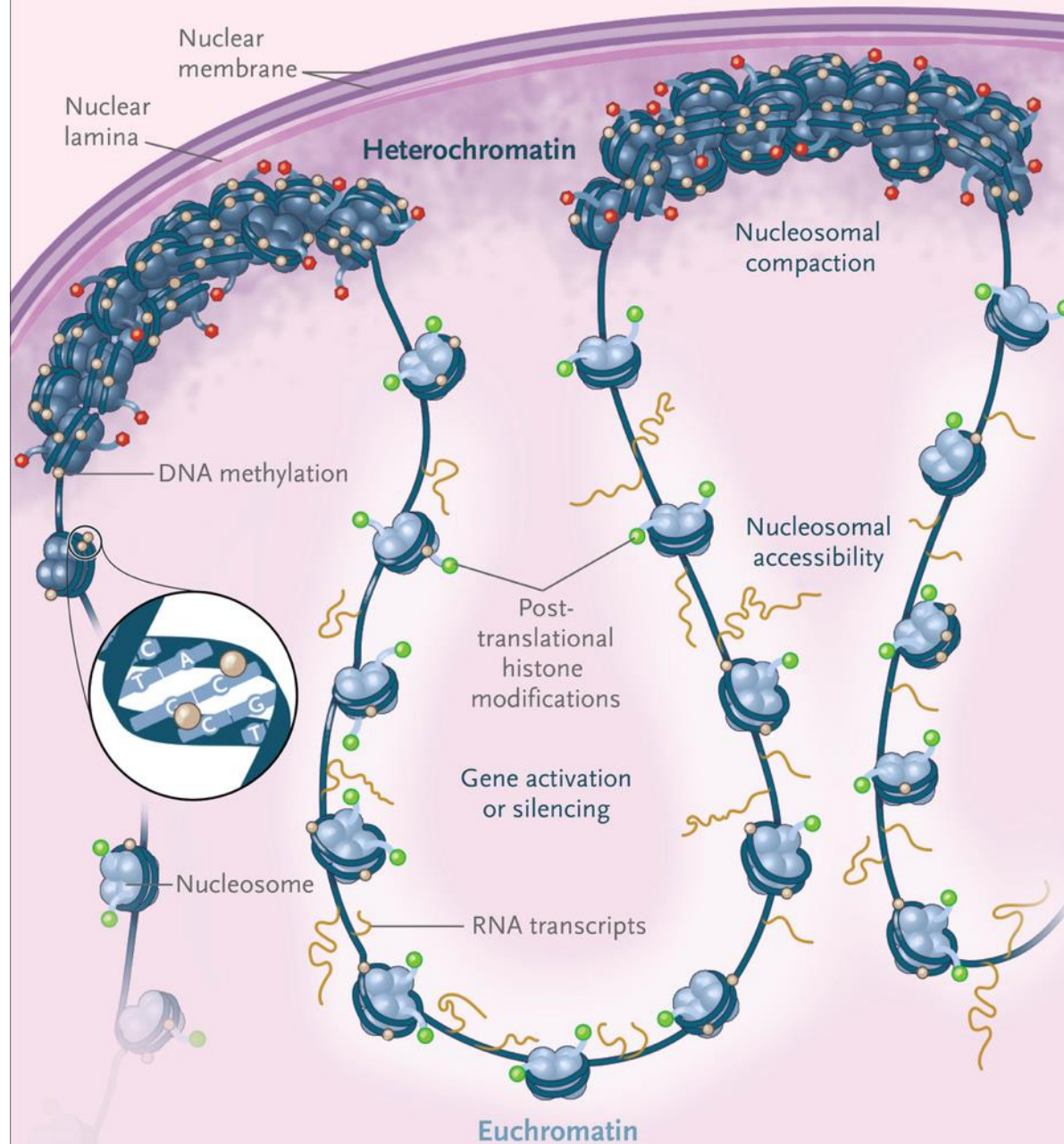
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Three forms of epigenetic information

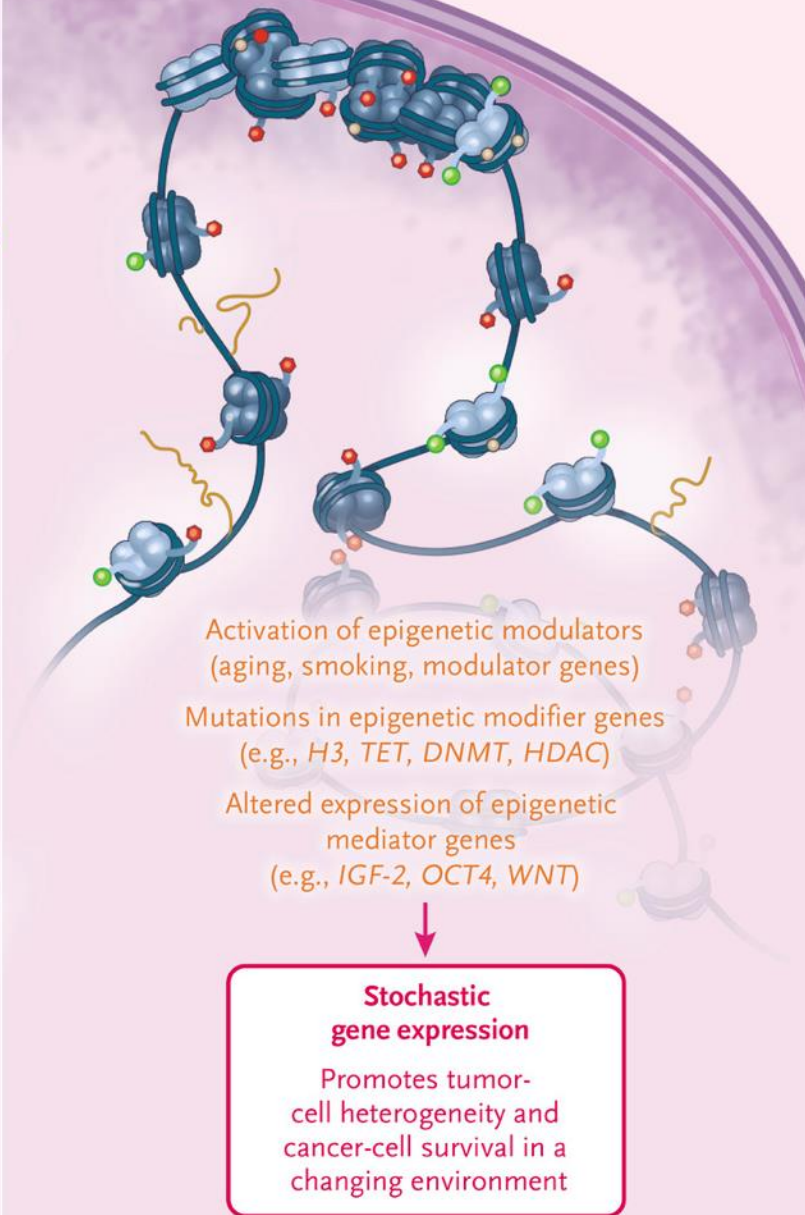
- DNA methylation
 - Maintained in DNA replication
 - Methylated = “off”
 - Stable even when a biological sample is preserved!
- Histone modification
 - Maintained in DNA replication...somehow?
- Chromatin structure
 - Tissue specificity

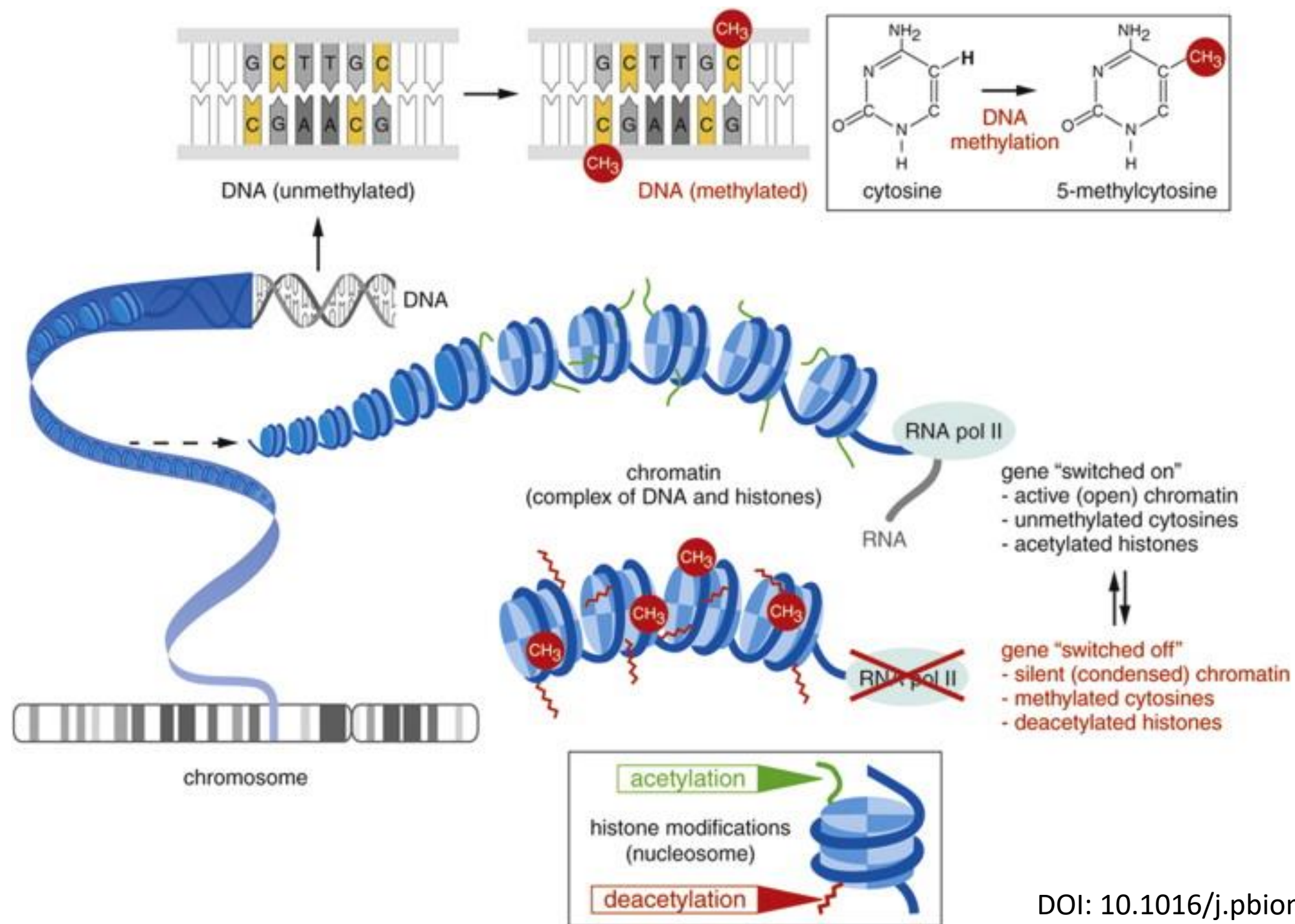
“An epigenetic system should be heritable, self-perpetuating, and reversible.” Riddihough and Zahn, Science (2010)

A Normal Cells



B Cancer Cells



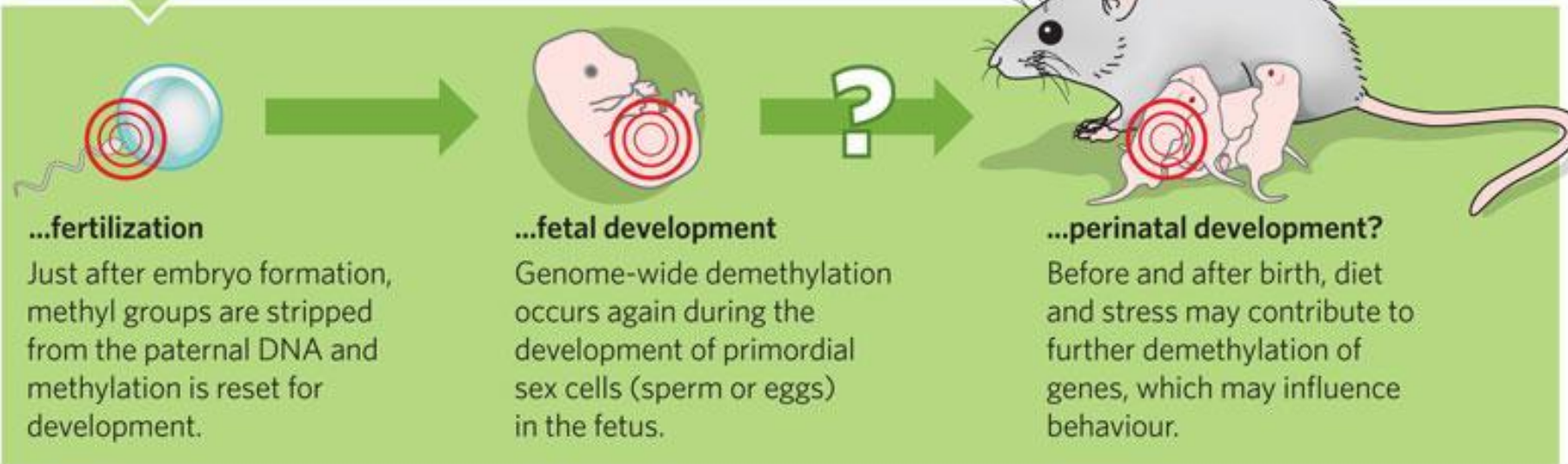
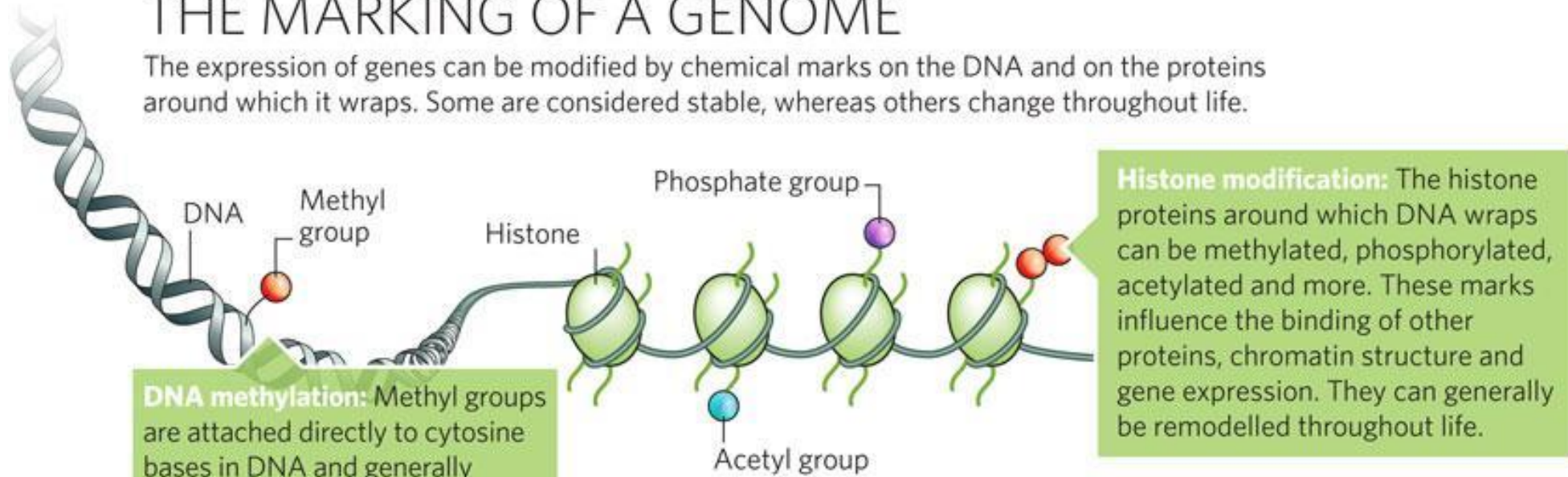


The environment can change epigenetic information

- Intergenerational phenotypic effects caused by environment of male ancestor (epigenetic changes in gametes) or prenatal environment of mother

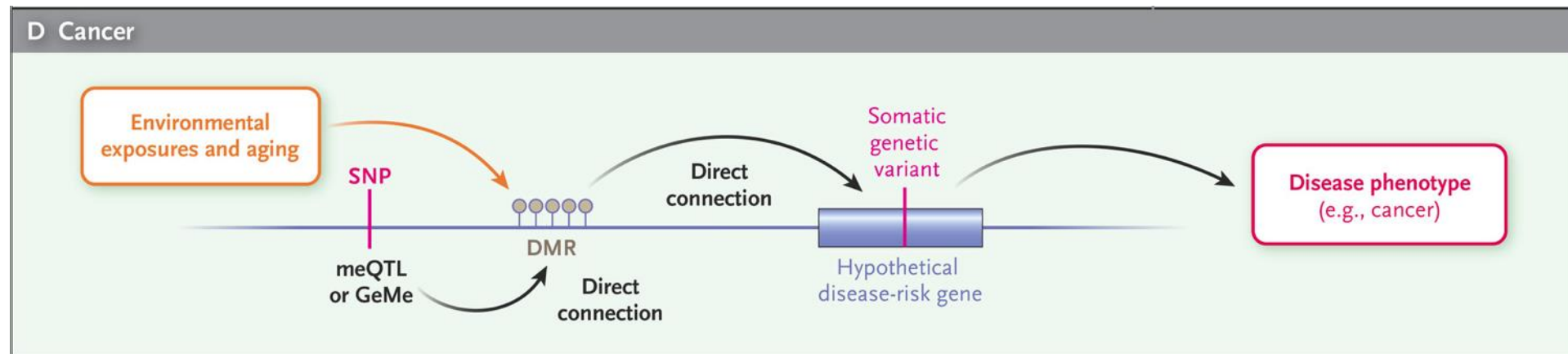
THE MARKING OF A GENOME

The expression of genes can be modified by chemical marks on the DNA and on the proteins around which it wraps. Some are considered stable, whereas others change throughout life.



“It has been known since the 1980s that most or all tumors are associated with widespread losses and some gains of DNA methylation throughout the genome.”

“My colleagues and I, as well as others, have argued that cancers are in fact more alike than different and that the central feature of cancer is a disrupted and unstable epigenome, usually but not always caused by mutations and often preceded by epigenetic changes to the normal tissues themselves as a result of age and injury. These changes lead to epigenetic instability, erosion of defined chromatin regions, and variability of gene expression, resulting in tumor-cell heterogeneity. Moreover, mutations specifically driving metastasis have not been identified in cancer, yet epigenetic changes in large areas of the genome have been shown to drive metastasis.”

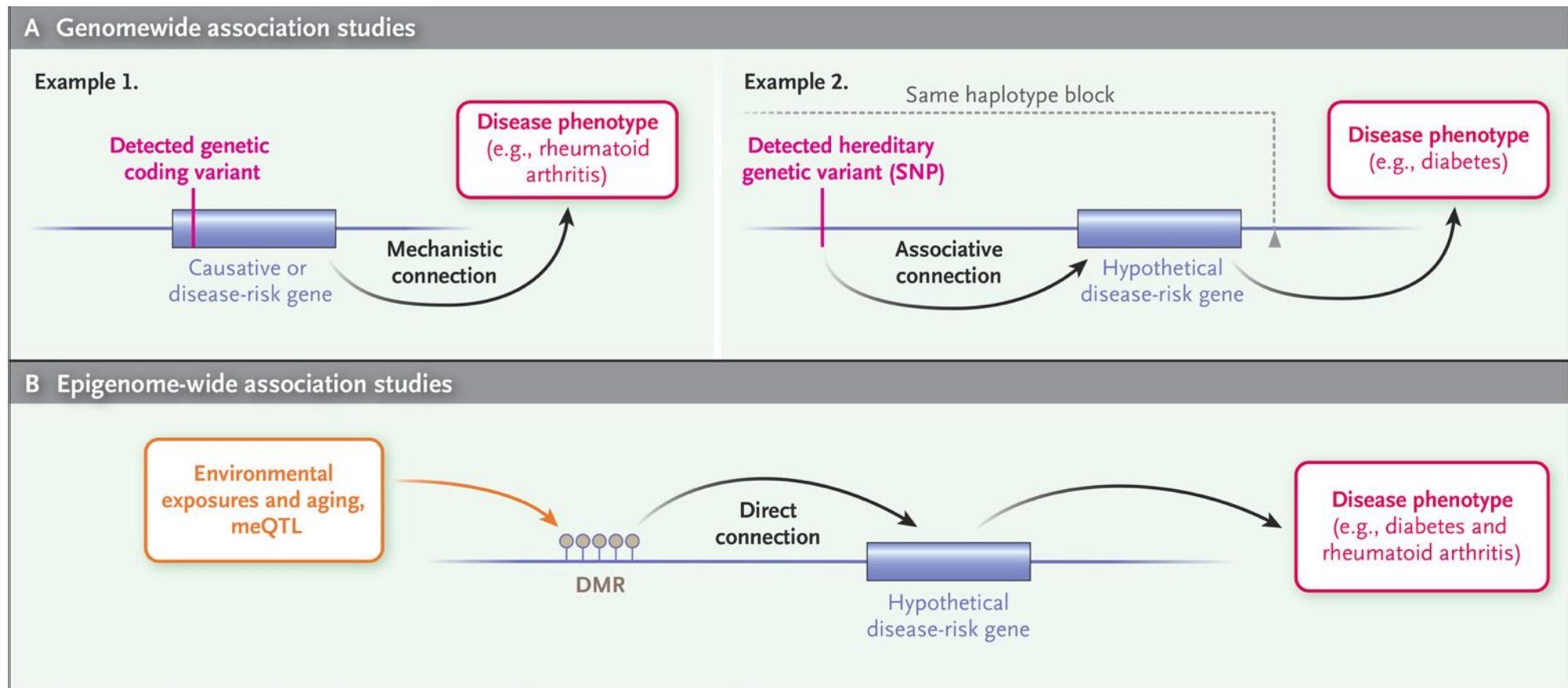


Epigenetic changes in cancer

- Modifiers
 - Gene products modify the epigenome
- Mediators
 - Targets of epigenetic modifiers
- Modulators
 - Influence the modifiers
- May relate to metastasis
- “Diagnosis and prognosis” potential

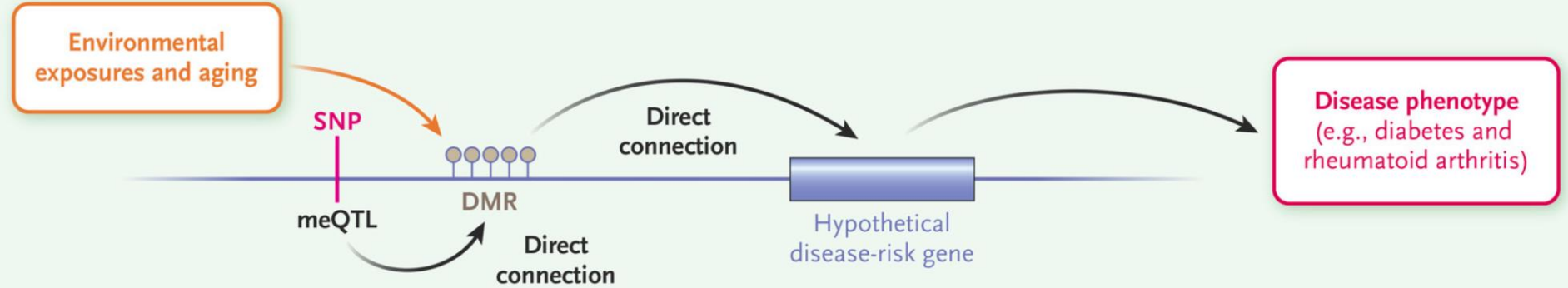
Epigenetic epidemiology

- Epigenome-wide association study

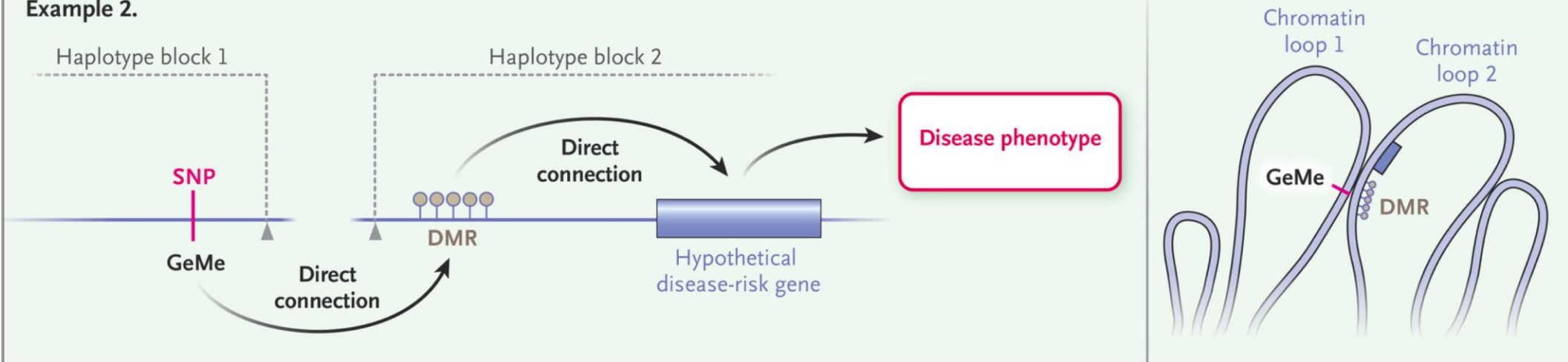


C Integrated genomewide and epigenome-wide association studies

Example 1.



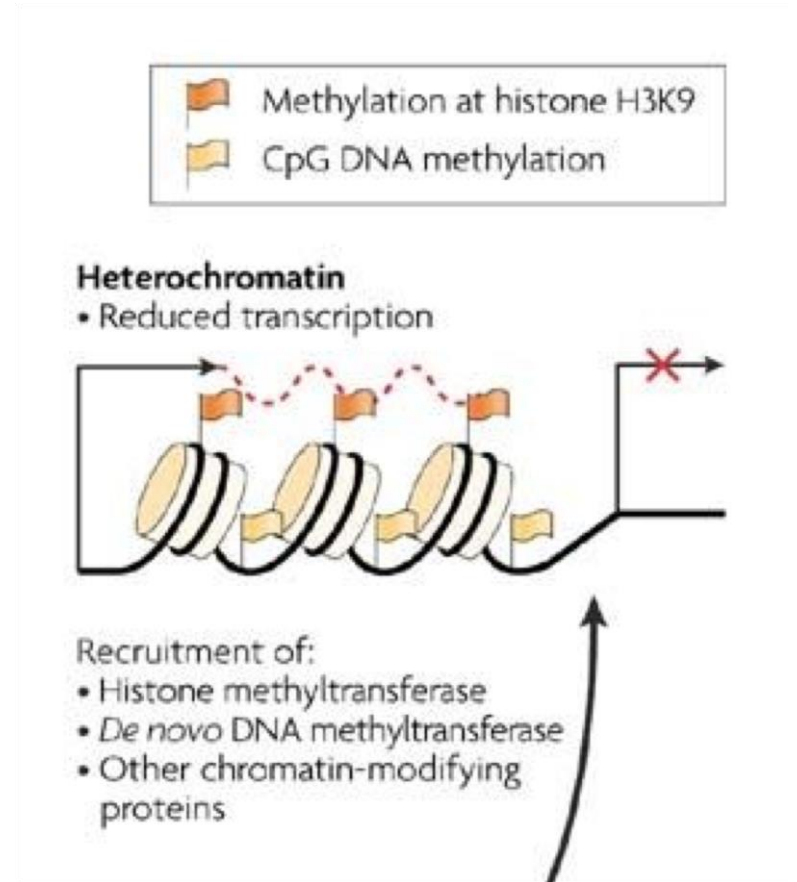
Example 2.



“Changes in DNA methylation might occur at a DMR that is in turn regulated by genetic variants identified in genomewide association studies.”

Why does DNA methylation exist?

- Defense against transposable elements
- “Faster” adaptation than mutation
- Multicellularity



Transposable elements and the epigenetic regulation of the genome. Slotkin and Martienssen, Nat Rev Genet (2007)

Inheritance of traits that does not involve a change in the DNA sequence...

PERSPECTIVE

Epigenetics in the Extreme: Prions and the Inheritance of Environmentally Acquired Traits

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“Here, we discuss an extreme case of epigenetic inheritance with a mechanism that is not based on heritable changes in nucleic acid. Instead, it is based on robust self-propagating changes in the folding of certain proteins known as prions.”