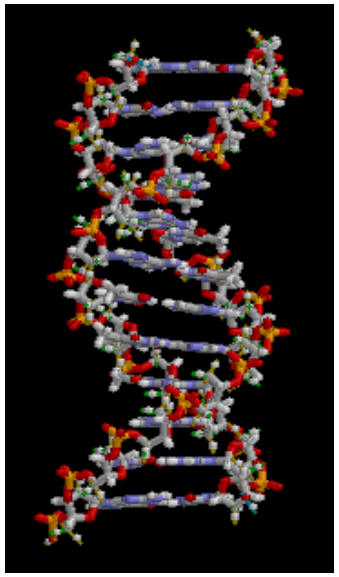
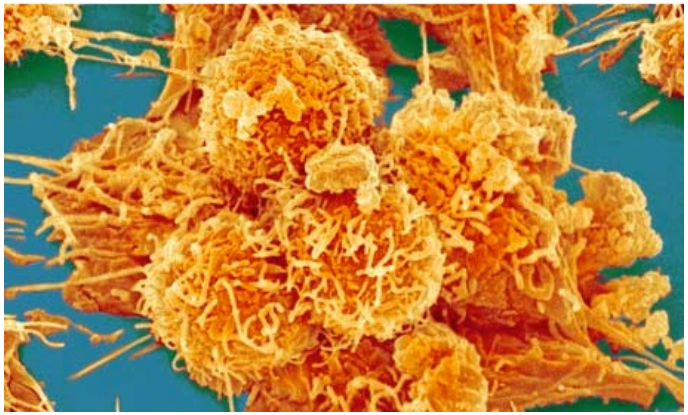
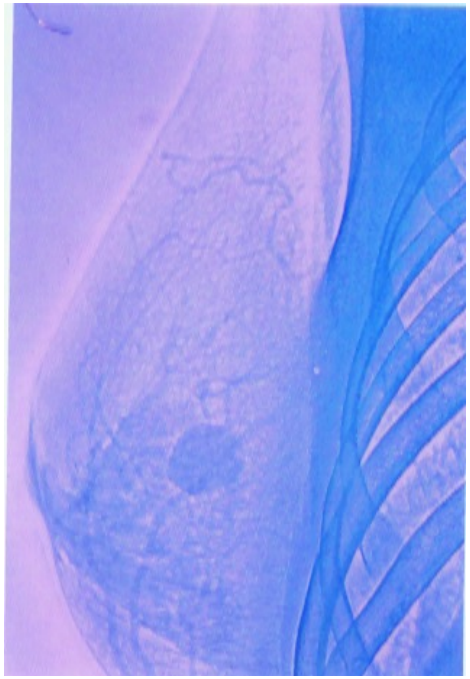


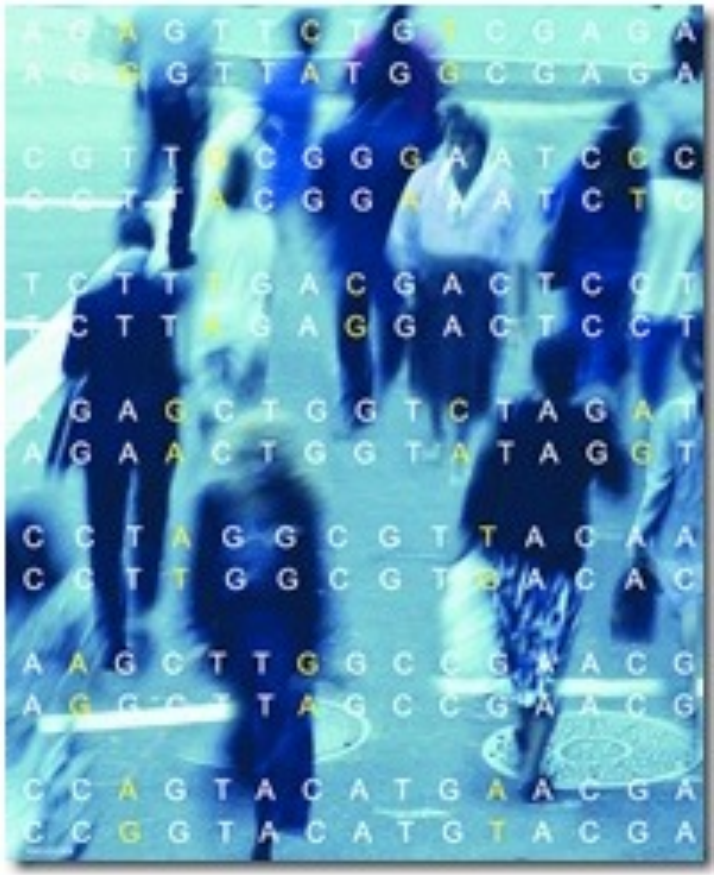
How genotype creates phenotype ??





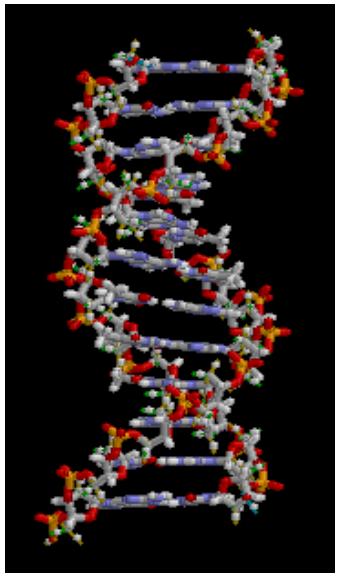
Mendelian genetics (mathematic abstractions) explain genes transmission but it sheds no light on how genes create cellular and organismic phenotypes.
Genotype embodied in DNA sequences creates phenotype through proteins.
We still possess an incomplete understanding of how genotype influences phenotype.

Γονιδια - Περιβαλλον

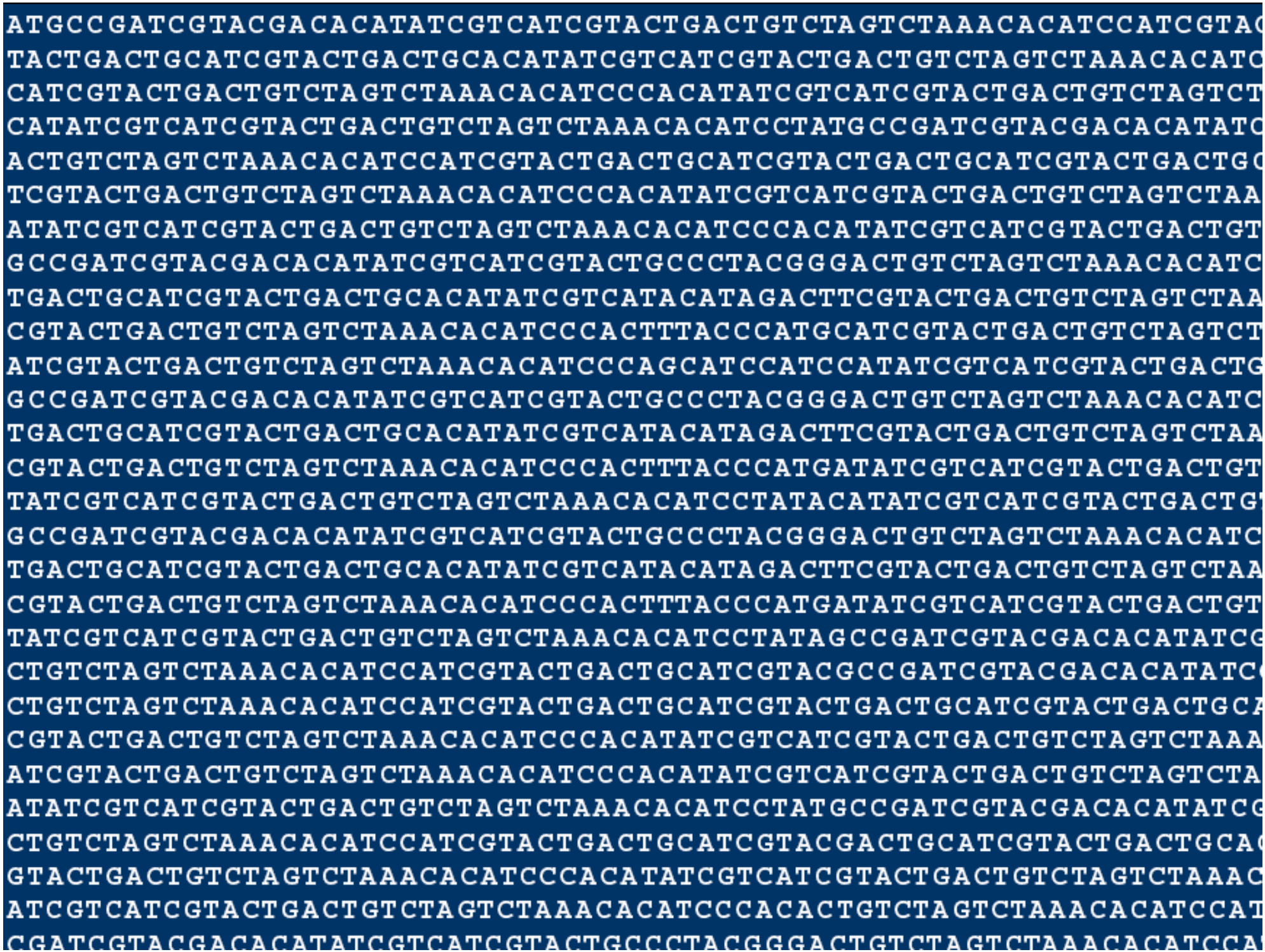


Η Γενετική Ασχολείται
με την
Συμπεριφορά γονιδίων
στα πλαίσια ενός κυττάρου
ή ενός οργανισμού

έκφραση των γονιδίων ενός οργανισμού +της επιρροής των περιβαλλοντικών παραγόντων +τις αλληλεπιδράσεις μεταξύ των δύο=φαινοτυπος.



DNA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CATCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCT
CATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATGCCGATCGTACGACACATATC
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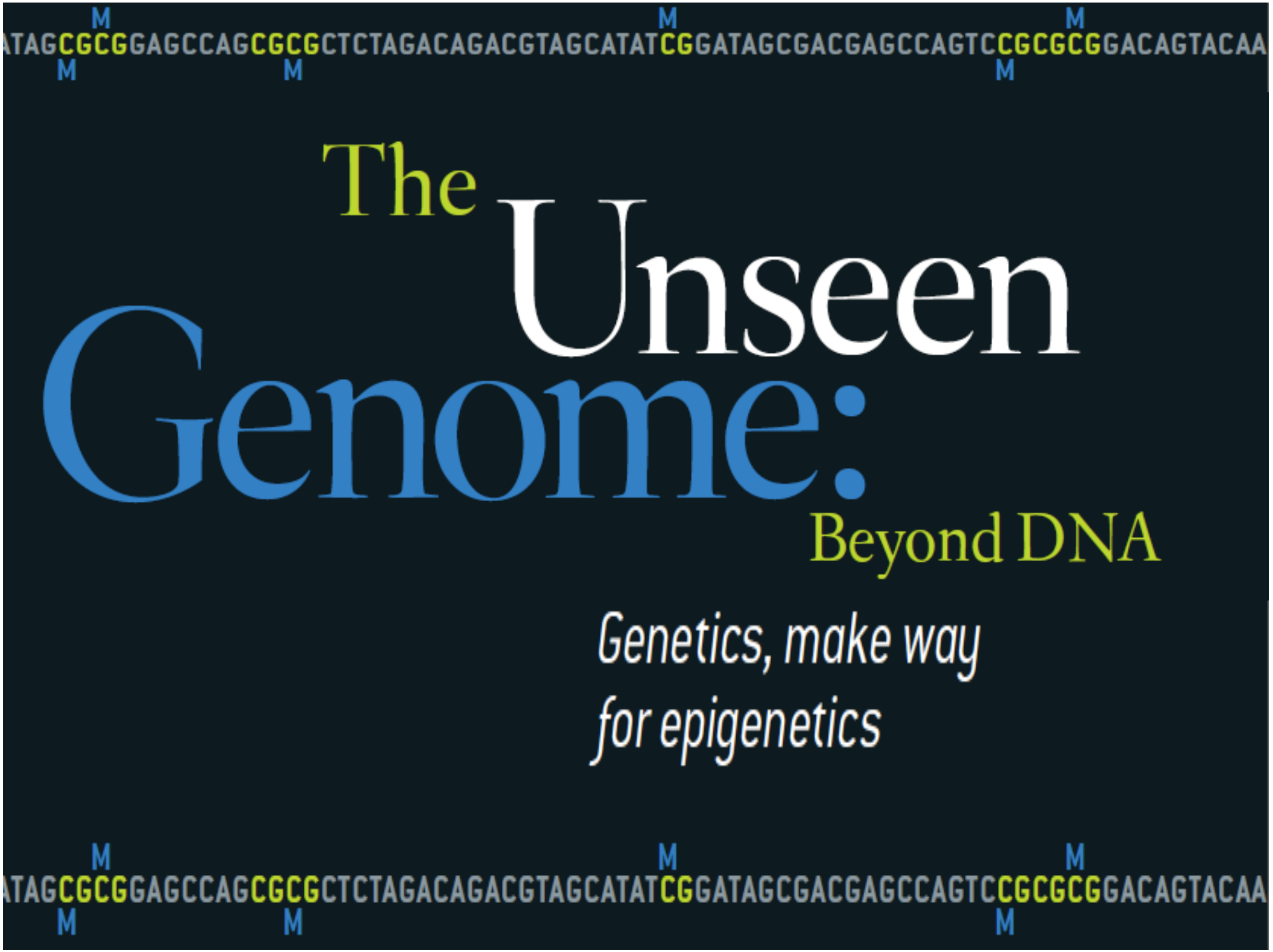
CGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCA

Why your DNA isn’t your destiny

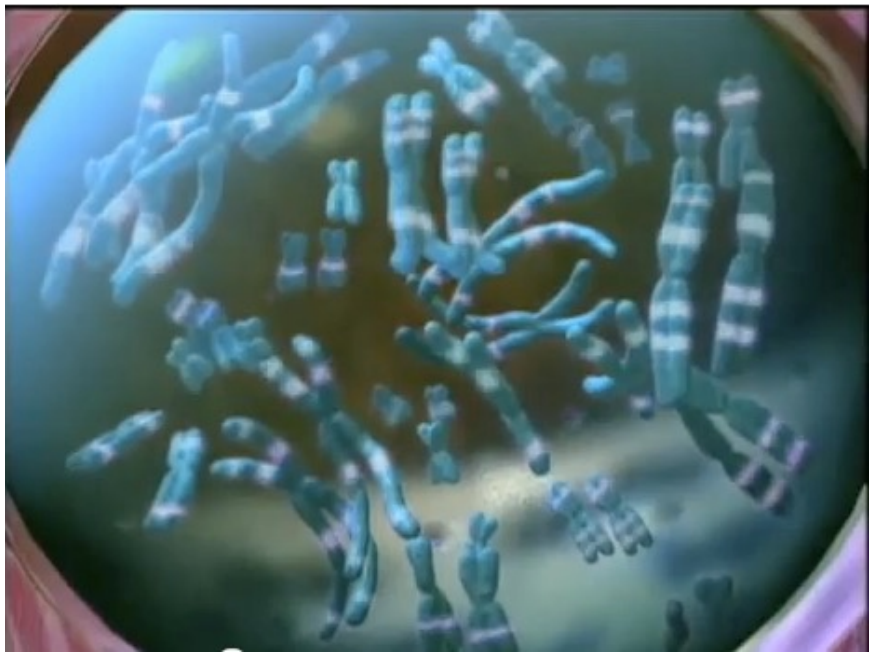

Excellent try, my dear Watson, but . . .
could you bring me a mirror, old boy?
SIMON '98


ATAGCGCGGAGCCAGCGCGCTCTAGACAGACGTAGCATATCGGATAGCGACGAGCCAGTCCGCGCGGACAGTACAA
The Unseen Genome:
Beyond DNA
Genetics, make way for epigenetics
ATAGCGCGGAGCCAGCGCGCTCTAGACAGACGTAGCATATCGGATAGCGACGAGCCAGTCCGCGCGGACAGTACAA

What Epigenetics is All About

turning genes on and off

Επιγενετικη



Η Epigenetics είναι η μελέτη ορισμένων ειδών χημικών αλλαγών που λειτουργούν σαν διακόπτες, που κλείνουν τα γονίδια η τα ανοίγουν και με αυτόν τον τρόπο αλλάζουν την έκφραση γονιδίων (δηλαδη κατα πόσον ένα γονίδιο δραστηριοποιειται για να «εκφραστη» σε πρωτεΐνη).

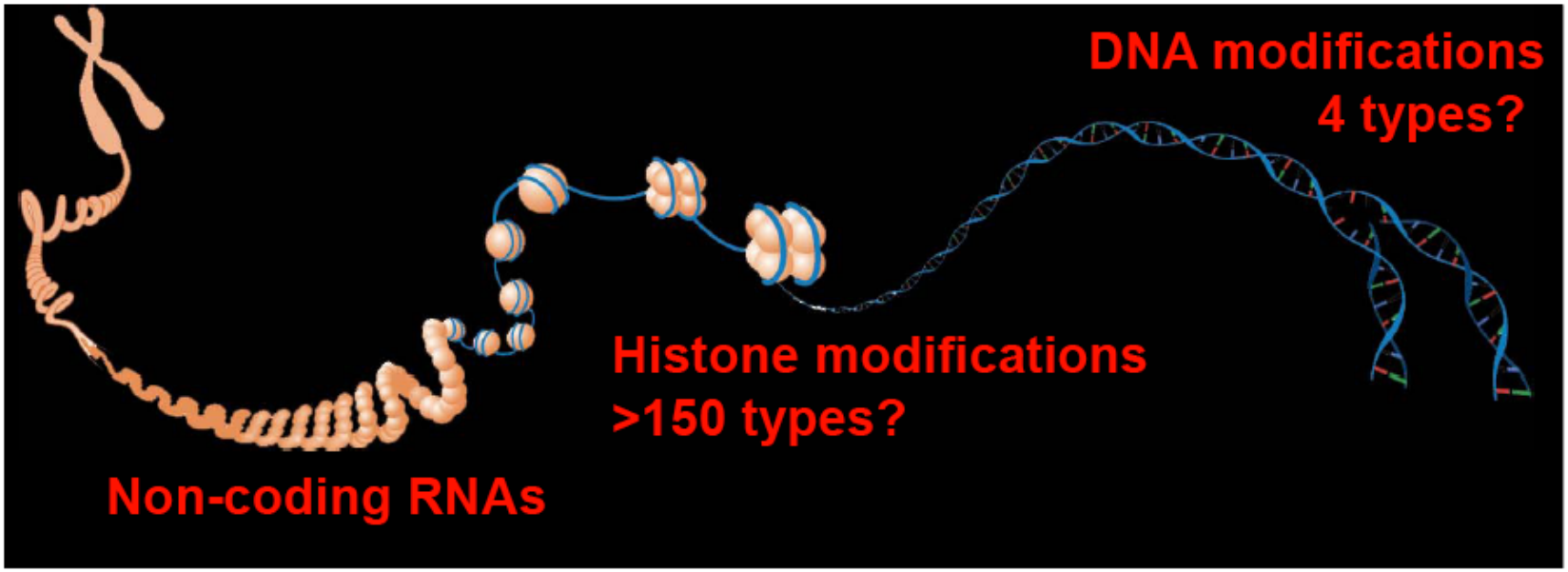
Definitions

- "Epi" – over, above, outer
- Epigenetics – stably heritable phenotype changes in a chromosome without alterations in the DNA sequence
  - Histone modifications
  - DNA methylation
- Epig*enomics* – refers to the study of the complete set of epigenetic alterations
- "Epigenetic code" – epigenetic features that maintain different phenotypes in different cells

Epigenetics and Epigenomics

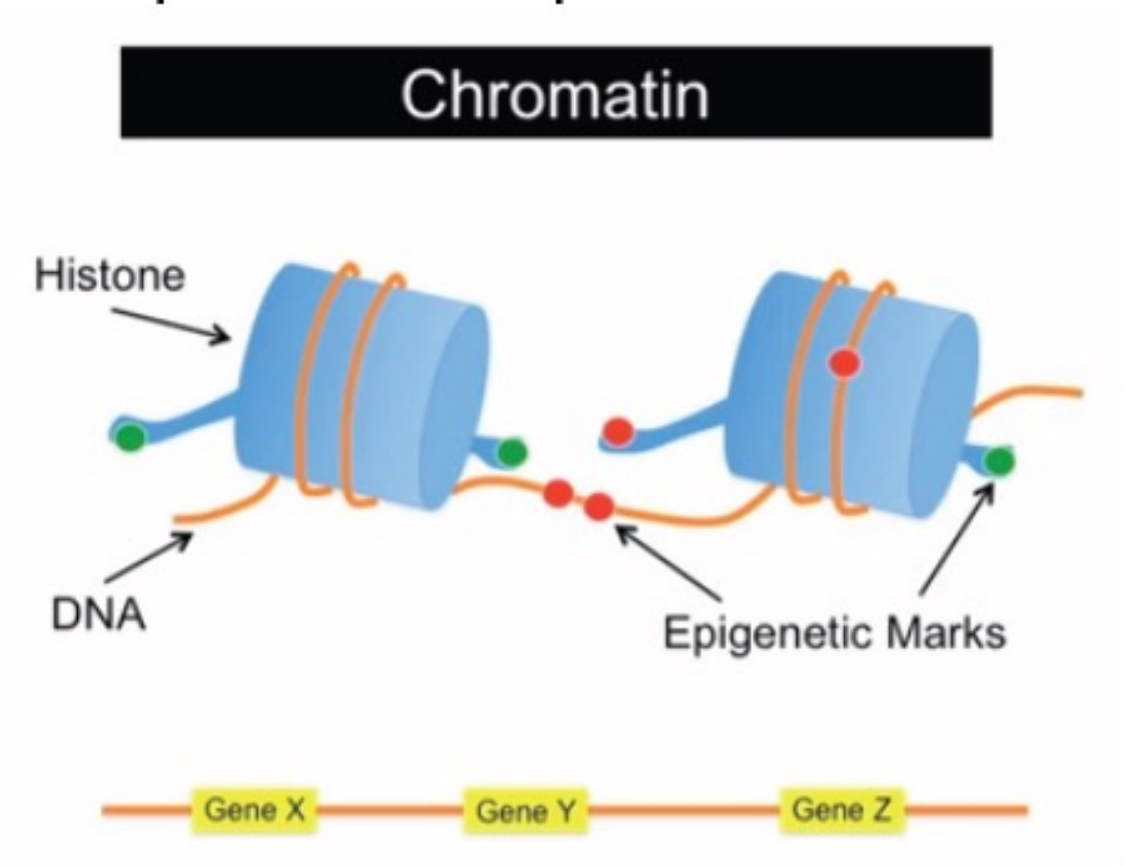
Epigenetics= the study of heritable or long lasting changes that are *not* caused by changes in the DNA sequence

Epigenome = all of the epigenetic marks for a cell type



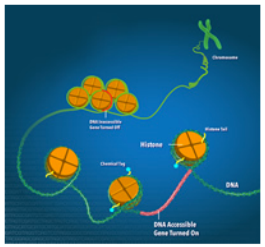
Epigenetic marks

Epigenetic marks – small chemical tags that sit on top of chromatin and help instruct it whether to open or to compact



https://www.genome.gov/27532724/
Search
Most Visited | χρυσή ευκαιρία | Getting Started | Latest Headlines | Tufts webmail | Countway | Image J Plugins | https://webmail.t... | https://mail.umc.... | Apple | Yahoo! | Google Maps | ciBit Δημοκριτειο...

Epigenomics



What is the epigenome?

The *epigenome* is a multitude of chemical compounds that can tell the *genome* what to do. The human genome is the complete assembly of DNA (deoxyribonucleic acid)-about 3 billion base pairs - that makes each individual unique. DNA holds the instructions for building the proteins that carry out a variety of functions in a cell. The epigenome is made up of chemical compounds and proteins that can attach to DNA and direct such actions as turning genes on or off, controlling the production of proteins in particular cells.

When epigenomic compounds attach to DNA and modify its function, they are said to have "marked" the genome. These marks do not change the sequence of the DNA. Rather, they change the way cells use the DNA's instructions. The marks are sometimes passed on from cell to cell as cells divide. They also can be passed down from one generation to the next.

What does the epigenome do?

A human being has trillions of cells, specialized for different functions in muscles, bones and the brain, and each of these cells carries essentially the same genome in its nucleus. The differences among cells are determined by how and when different sets of genes are turned on or off in various kinds of cells. Specialized cells in the eye turn on genes that make proteins that can detect light, while specialized cells in red blood cells make proteins that carry oxygen from the air to the rest of the body. The epigenome controls many of these changes to the genome.

What makes up the epigenome?

The epigenome is the set of chemical modifications to the DNA and DNA-associated proteins in the cell, which alter gene expression, and are heritable (via meiosis and mitosis). The modifications occur as a natural process of development and tissue differentiation, and can be altered in response to environmental exposures or disease.

The first type of mark, called DNA methylation, directly affects the DNA in a genome. In this process, proteins attach chemical tags called methyl groups to the bases of the DNA molecule in specific places. The methyl groups turn genes on or off by affecting interactions between the DNA and other proteins. In this way, cells can remember which genes are on or off.

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Epigenome:
The symphony in your cells

https://www.youtube.com/watch?v=W3Kg9w-srFk&feature=youtu.be

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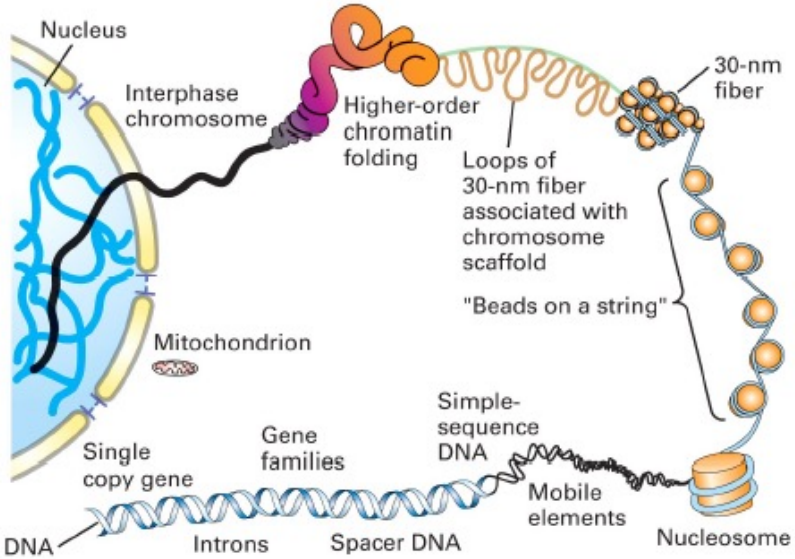


The dynamic epigenome and its implications

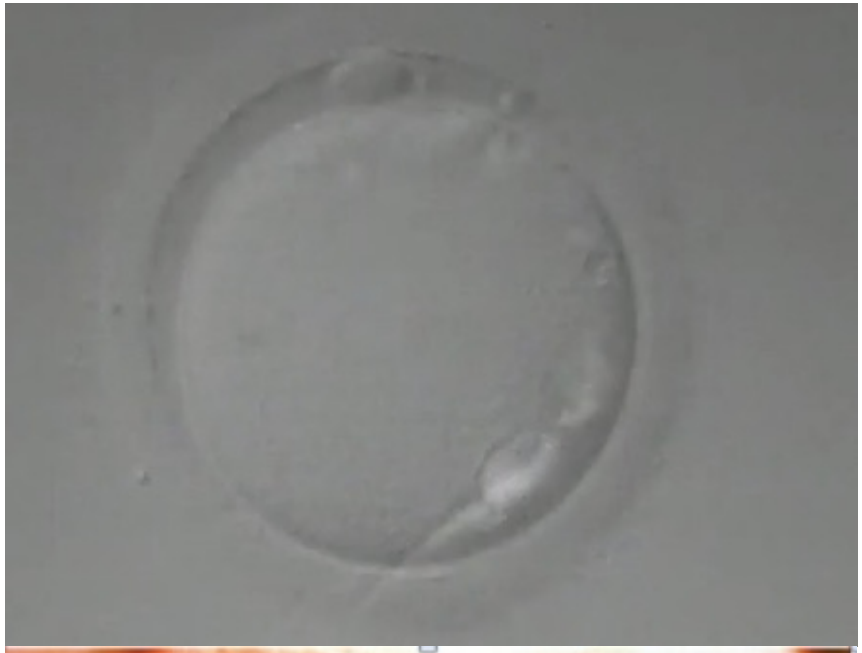
The programming of the genome is controlled by the epigenome

The epigenome is composed of two components:

1) the *chromatin* which is associated with the DNA and

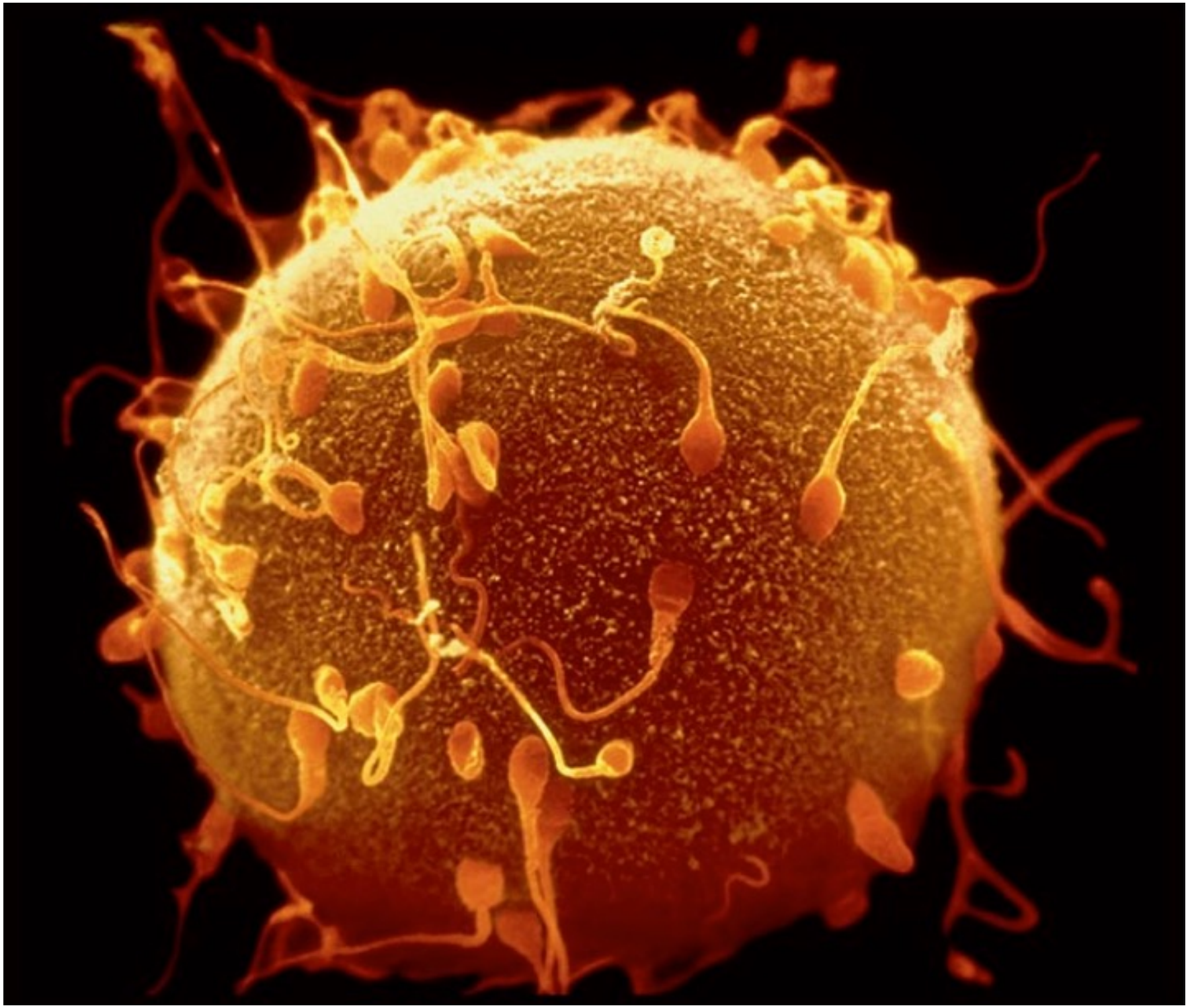
2) *DNA methylation* which is part of the covalent structure of the genome and is therefore a stable long-term signal

DNA methylation is an interface between the dynamic environment and the static genome

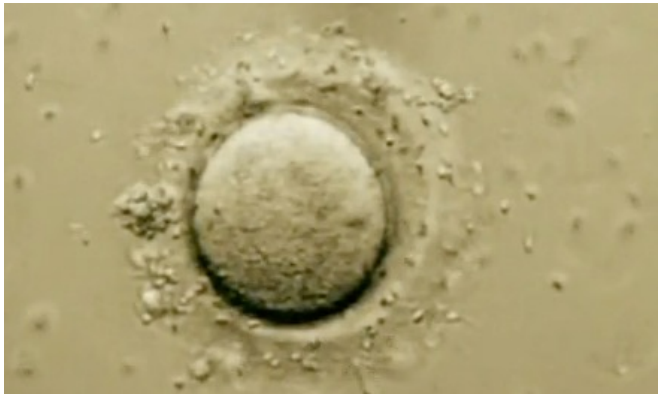


More dimensions…..

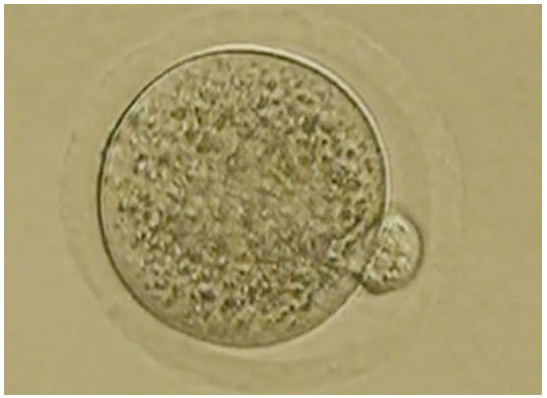
Timing..

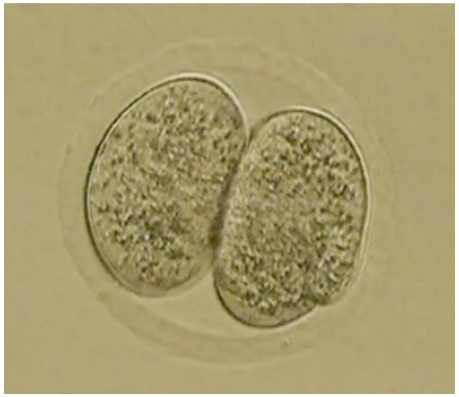


Γονιμοποίηση-Διαφοροποιηση



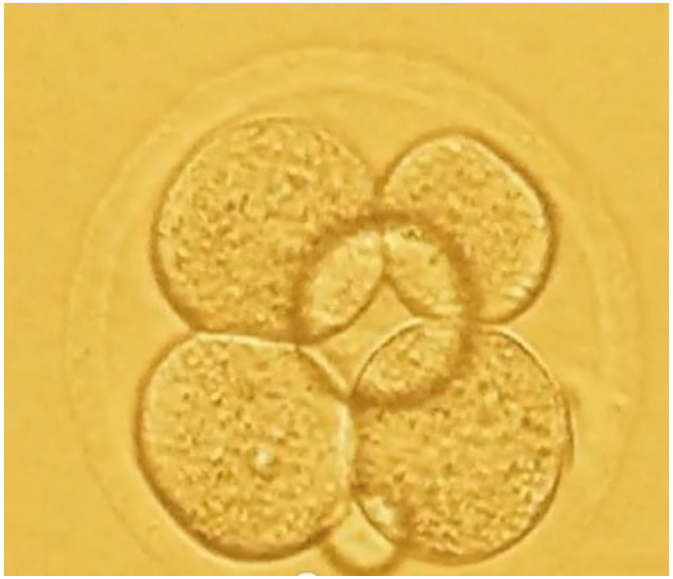
Γαμετες:
(ωαριο, σπερματοζωαριο)

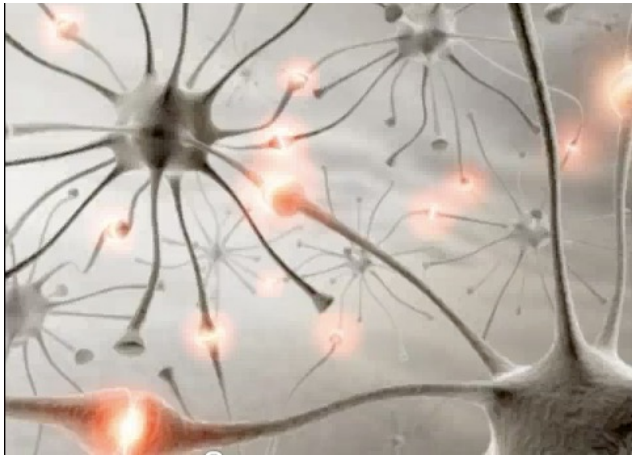


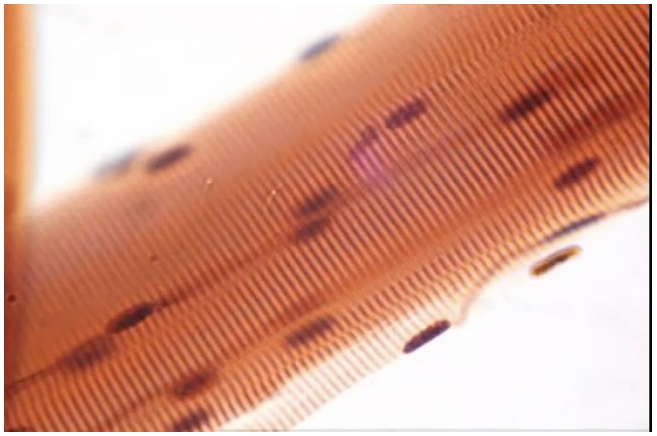


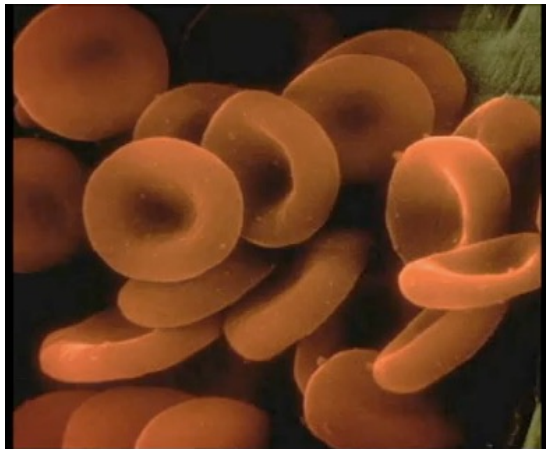
ενιαίο γονιμοποιημενο κύτταρο

Διαφοροποίηση









Development

Aging

twins

Μελετες επιδρασης περιβαλλοντος σε διδυμα

Beyond the Human Genome Project

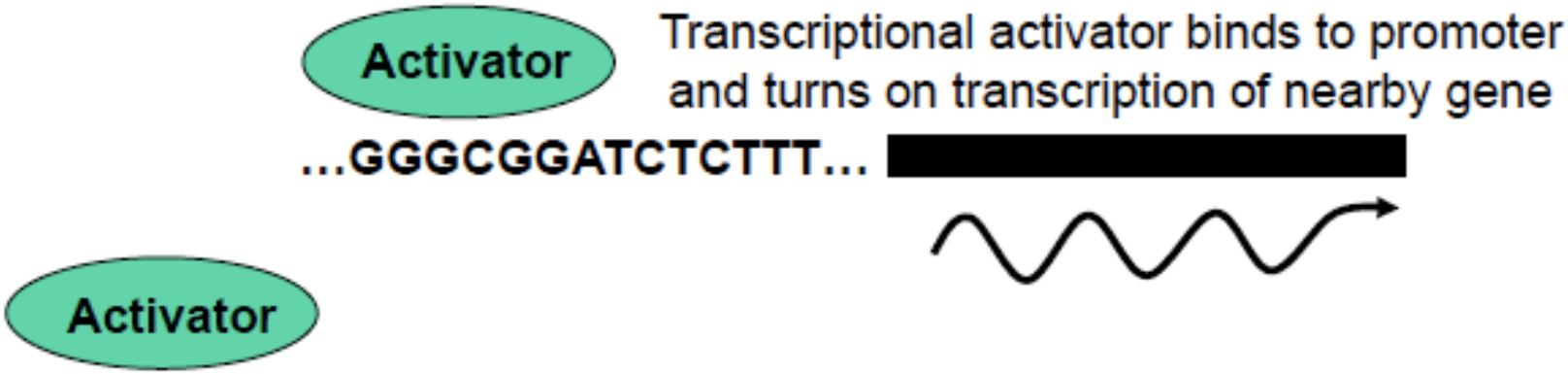
Human Genetic Variation

Genetic Variations

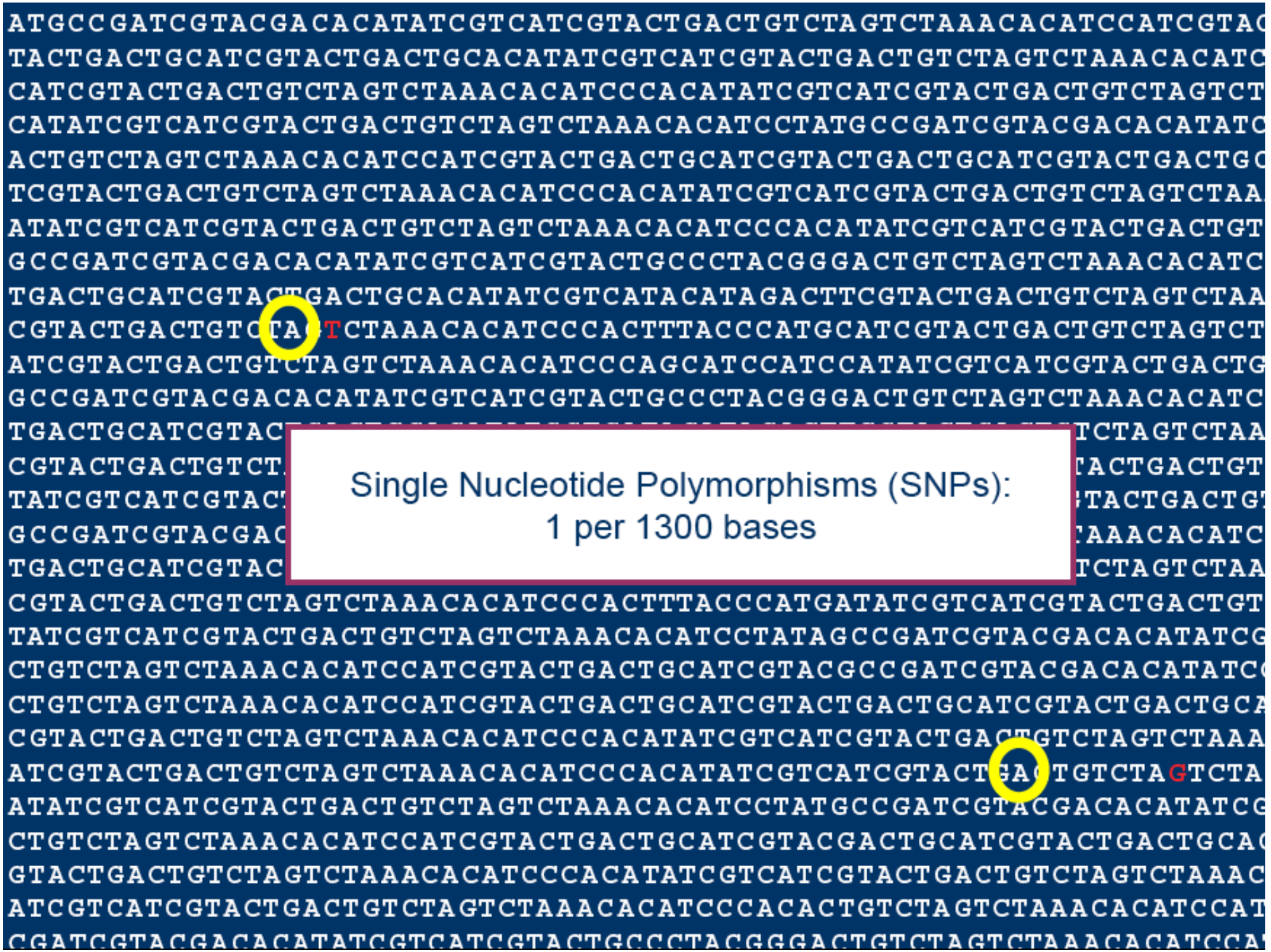
Mutations are likely to be rare and most mutations are neutral or deleterious, but in some instances the new alleles can be favored by natural selection.

Examination of DNA has shown genetic variation in both coding regions and in the non-coding intron region of genes.

Genetic variation in gene expression

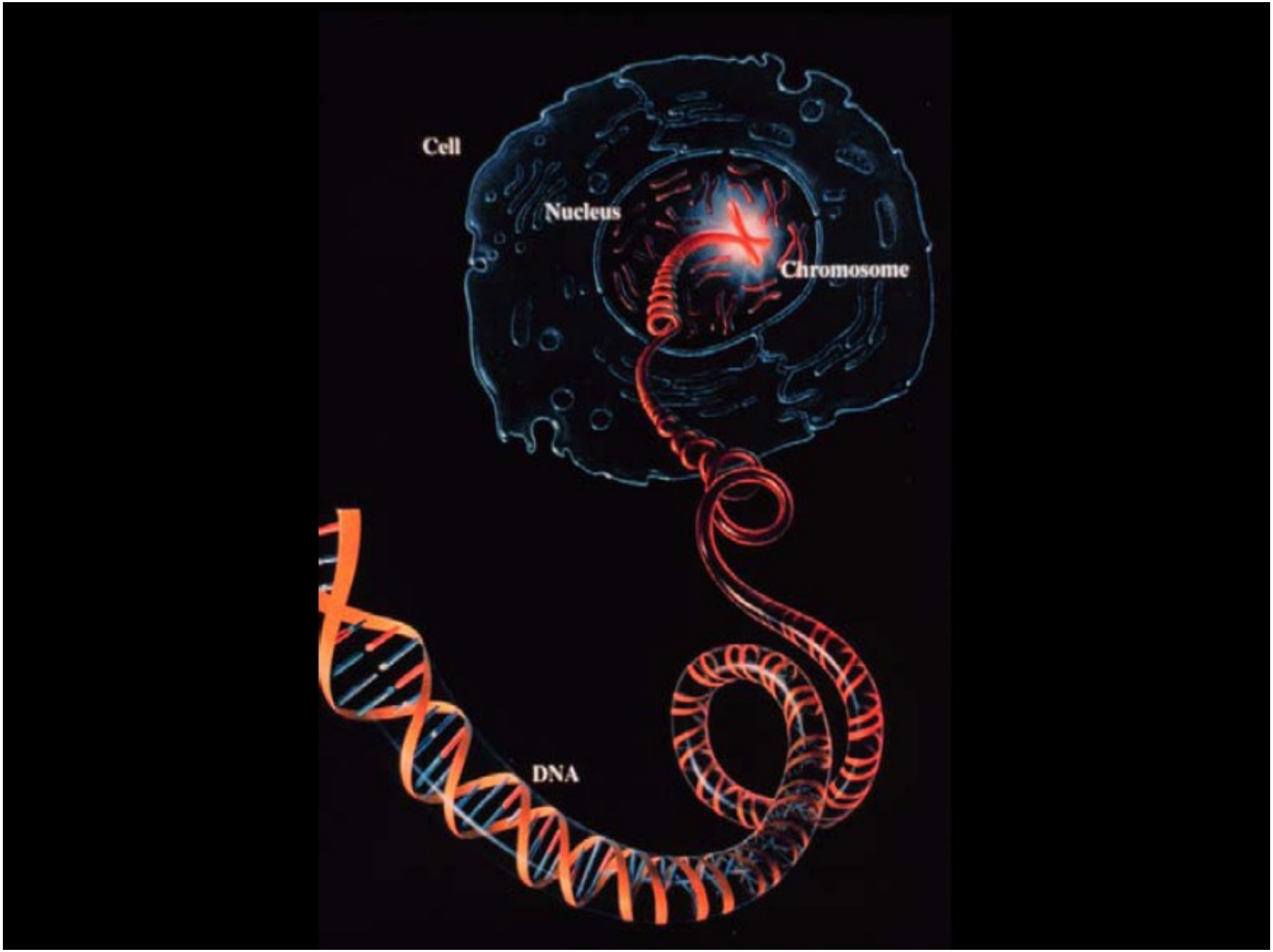


DNA sequence variant is inherited in all cell types and in offspring


Single Nucleotide Polymorphisms (SNPs):
1 per 1300 bases

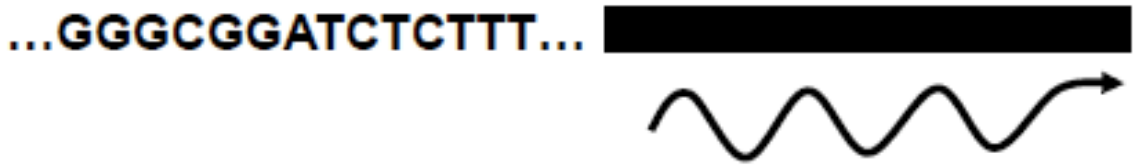
Common Variant Important in Risk of Common Disease

ApoE4	Alzheimer's disease
Factor V Leiden	Venous thrombosis
HFE	Hemachromatosis
PPARγ	Type 2 Diabetes
MTHFR 667T	Cardiovascular disease
CCR5	HIV resistance
HLA-DQα	Type 1 Diabetes



How Cells **Read** the Genome: From **DNA to Protein** , in the way in which **information** flows from **DNA to protein.**

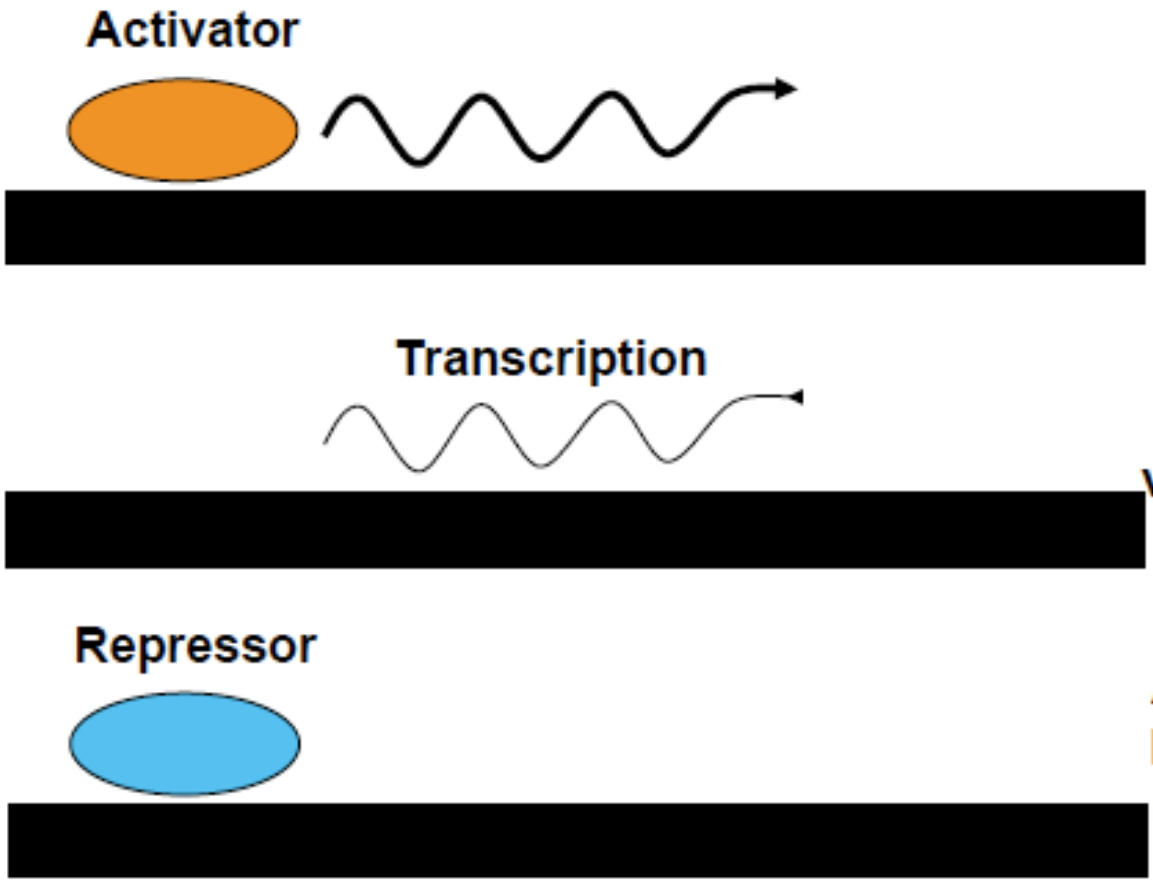
Epigenetic variation



Same DNA sequence can lead to active or inactive gene expression in different circumstances

The information is not coded in the DNA sequence, but can persist through DNA replication and be transmitted from "mother" to "daughter" cells

Transcriptional activators and repressors influence gene transcription



Same DNA sequence

Gene expression varies with presence of transcription factors

Active globin genes have transcriptional activators bound to promoters

Epigenetic variation

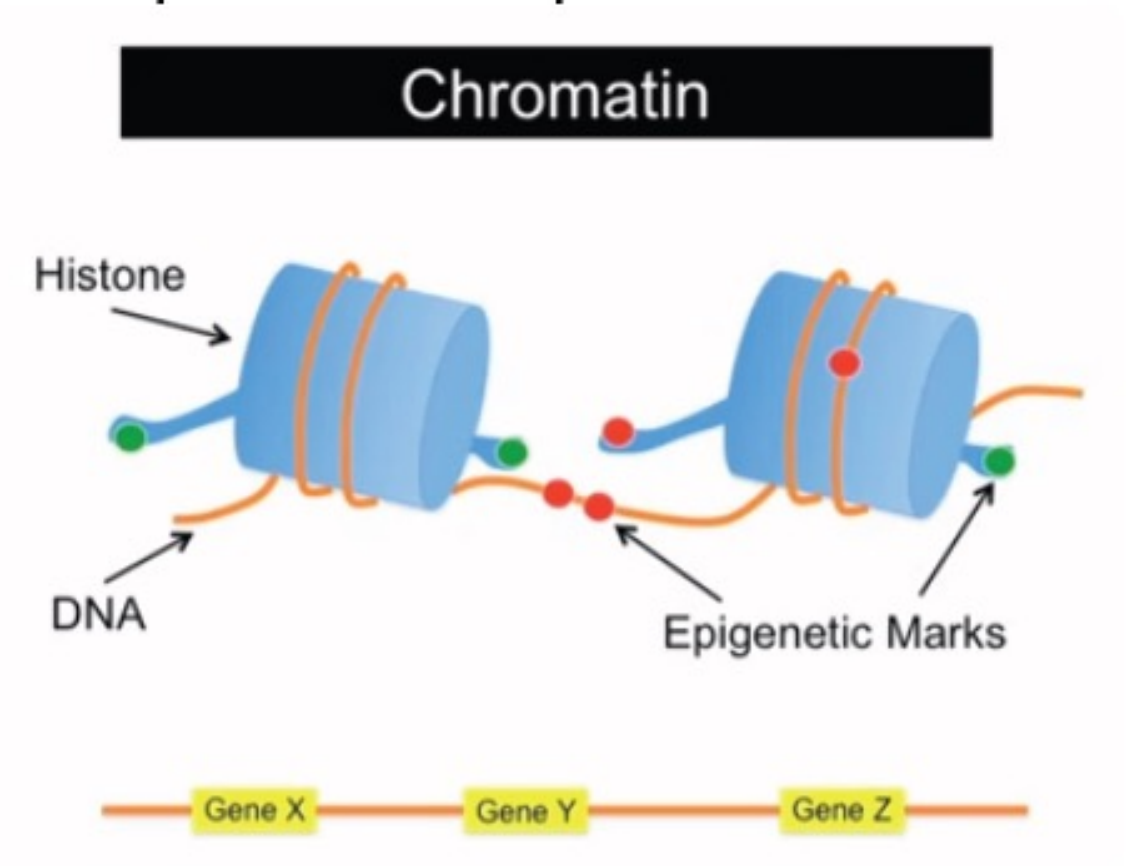
- Normal part of development
- Influenced by variation in:
  - Transcription factor binding
  - Histones and histone modifications
  - DNA modification - methylation
  - RNA from other genes
  - No doubt many other mechanisms
- Can have implications for disease

Epigenetics

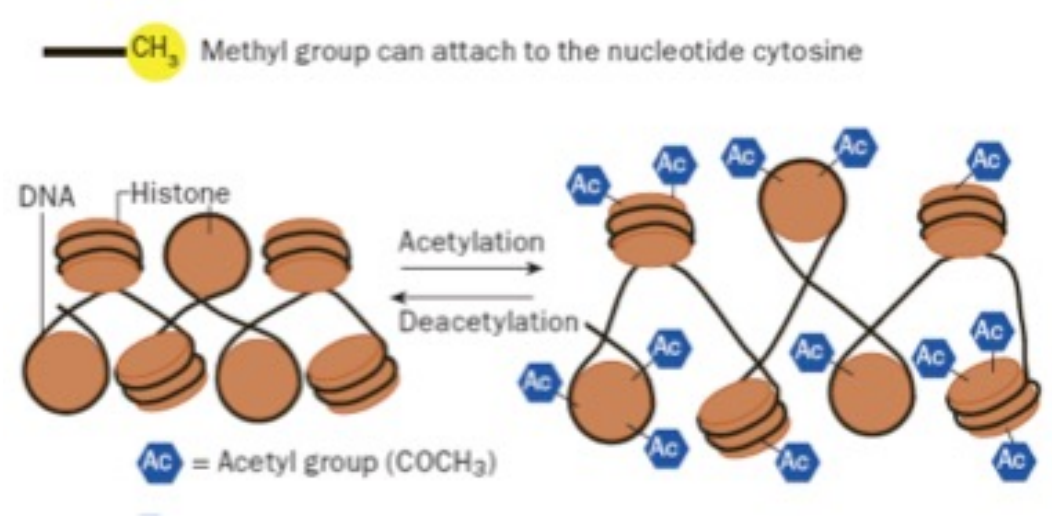
- Changes in gene expression & genome function that:
  - do not depend on the DNA code
  - are heritable/stable
    - From one generation of cells to the next (mitosis)
    - From one generation of individuals to the next (limited evidence in humans)
- Programming/Reprogramming of gene expression
  - Stable, but modifiable

Epigenetic marks

Epigenetic marks – small chemical tags that sit on top of chromatin and help instruct it whether to open or to compact



Η Μοριακη βάση της Επιγενετικης



Καποιες χημικές αλλαγές αλλάζουν την έκφραση γονιδίων χωρίς επιρροή στο γενετικού κώδικα. Παραδείγματος χάριν η επισύναψη των μεθυλικών ομάδων (methyl groups) στο DNA εμποδίζει την έκφραση γονιδίων. Ενω η προσθήκη των ακετυλικών ομάδων (acetyl groups) στις πρωτεΐνες που ονομαζονται histones χαλαρώνουν τη δομή των χρωμοσωμάτων, και ετσι καθιστουν τα συνιστομενα γονίδια να μεταγράφουν ευκολότερα.

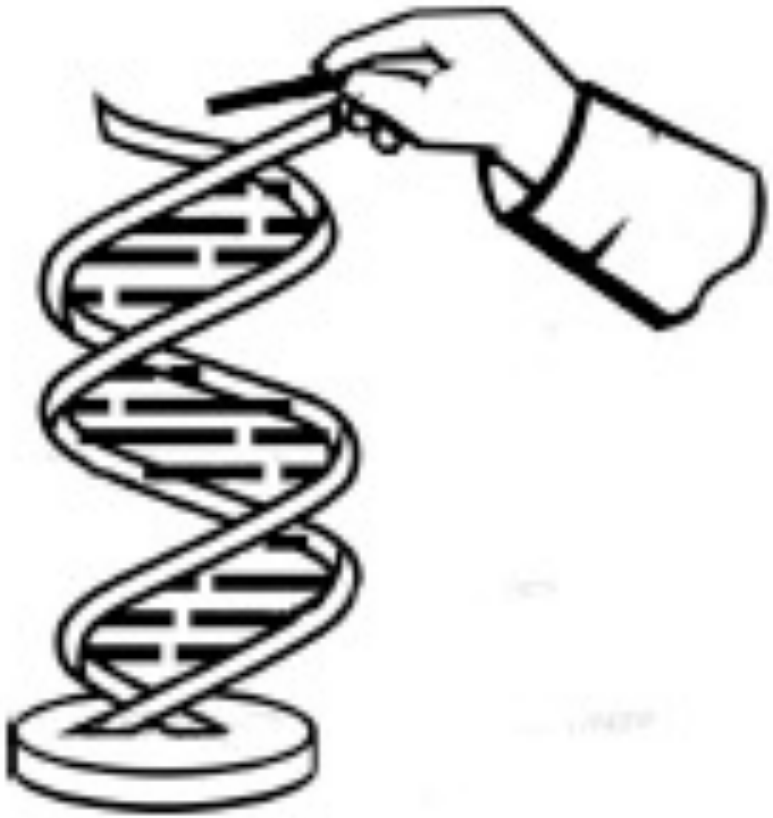
What makes up the epigenome?

The epigenome is the set of chemical modifications to the DNA and DNA-associated proteins in the cell, which alter gene expression, and are heritable (via meiosis and mitosis). The modifications occur as a natural process of development and tissue differentiation, and can be altered in response to environmental exposures or disease.

The first type of mark, called DNA methylation, directly affects the DNA in a genome. In this process, proteins attach chemical tags called methyl groups to the bases of the DNA molecule in specific places. The methyl groups turn genes on or off by affecting interactions between the DNA and other proteins. In this way, cells can remember which genes are on or off.

The second kind of mark, called histone modification, affects DNA indirectly. DNA in cells is wrapped around histone proteins, which form spool-like structures that enable DNA's very long molecules to be wound up neatly into chromosomes inside the cell nucleus. Proteins can attach a variety of chemical tags to histones. Other proteins in cells can detect these tags and determine whether that region of DNA should be used or ignored in that cell.

Chromatin Remodeling



Η Χρωματίνη είναι δυναμικό συστατικό του κυτταρικού κύκλου

Επιγενετικές αλλαγές στην οργάνωση της χρωματίνης ρυθμίζουν τη γονιδιακή έκφραση

Μηχανισμοι

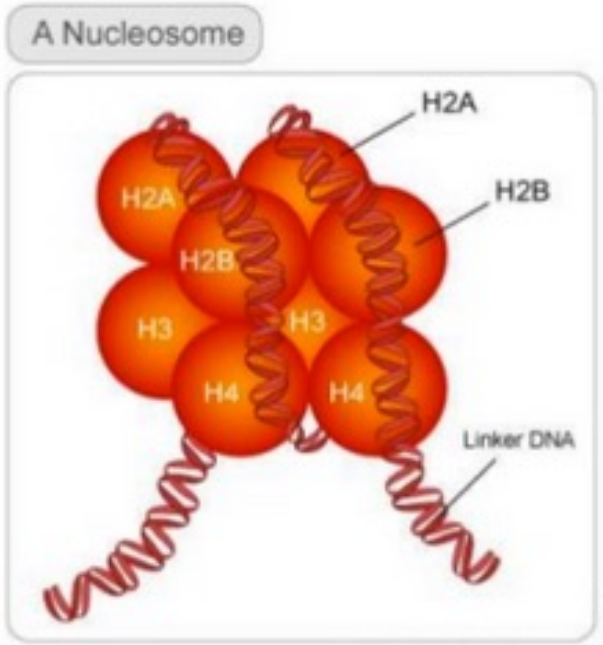
Σταδια ρυθμισης της έκφρασηςτων γονιδίων.

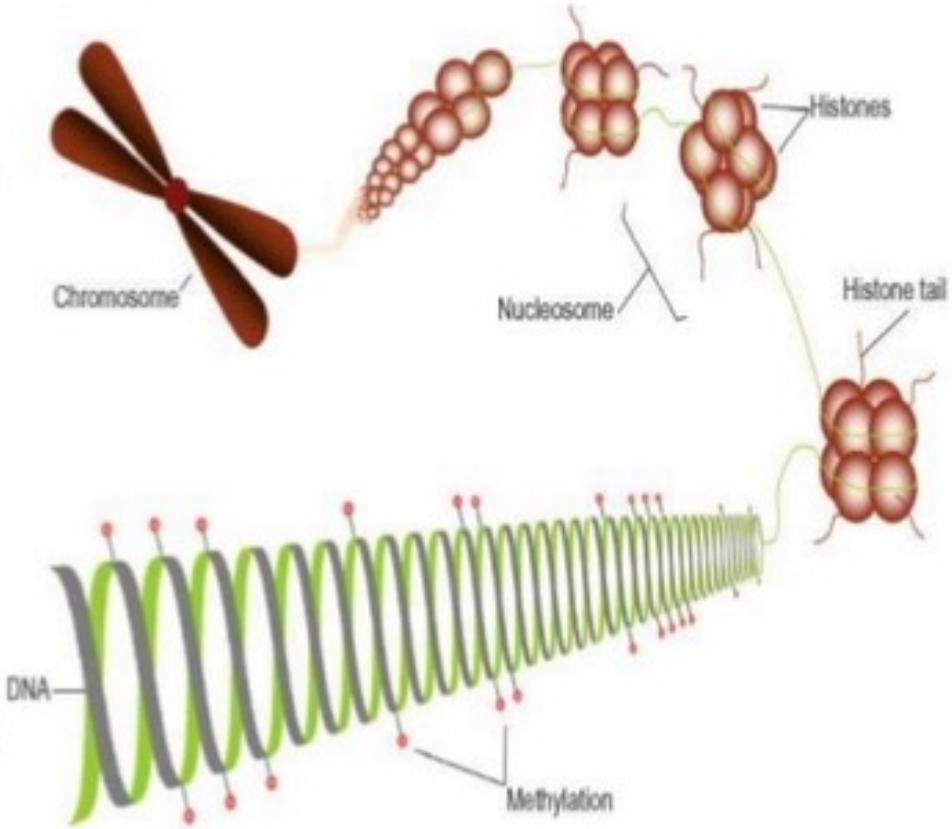
Μέσω της αναδιαμόρφωσης της χρωματίνης.

1. Chromatin remodelling
2.DNA methylation.

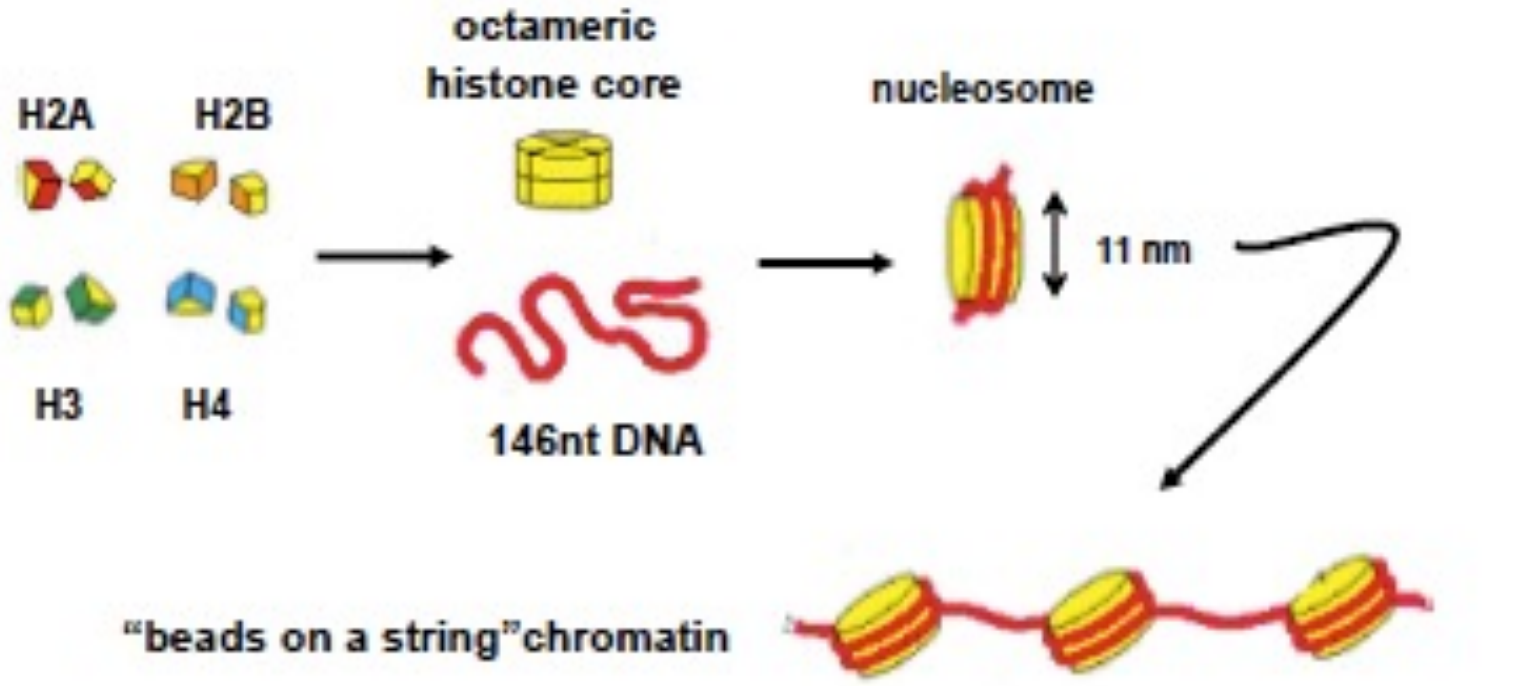
There are Eight Histone Proteins in Each Nucleosome

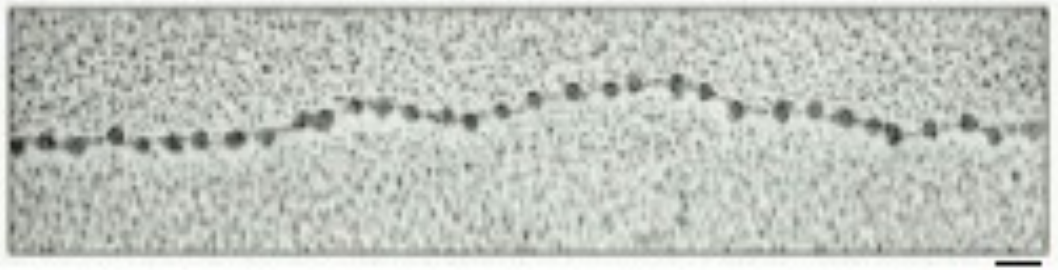
Histone 3 and 4 can be modified by methylation.





Δομική οργάνωση του νουκλεοσώματος

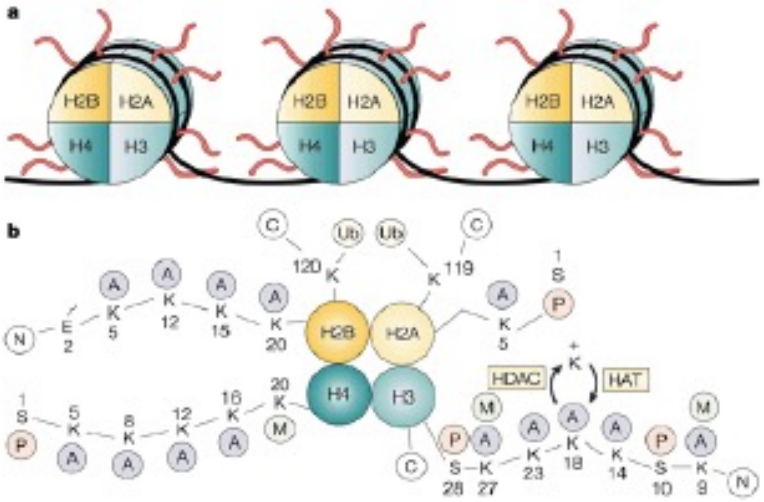


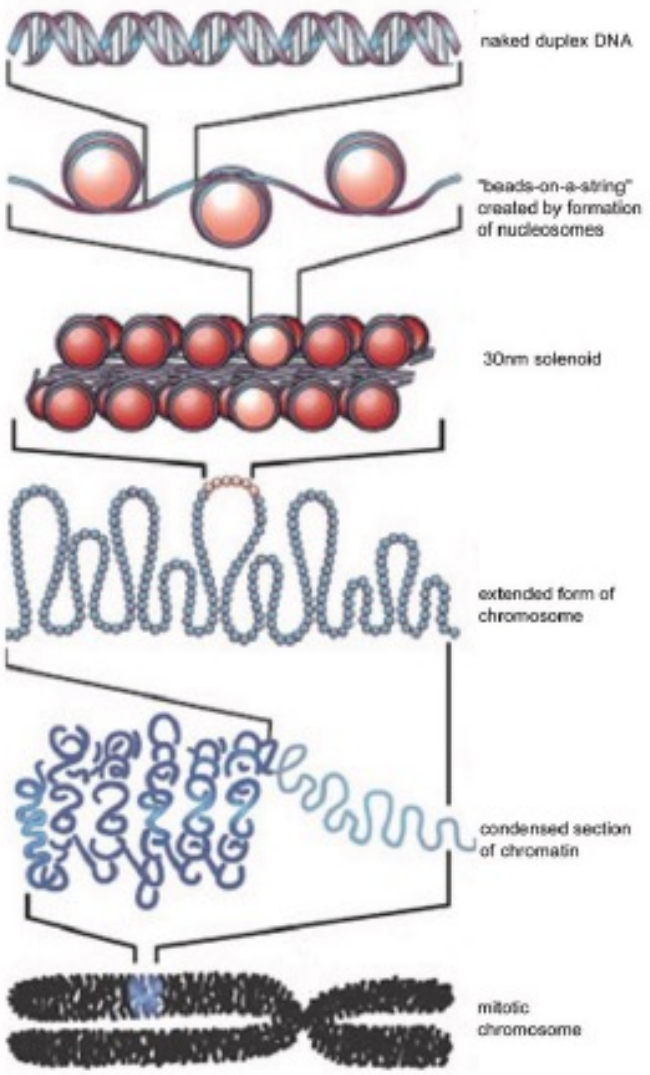


Adapted from the Molecular Biology of The Cell, Alberts *et al*, 4th Ed

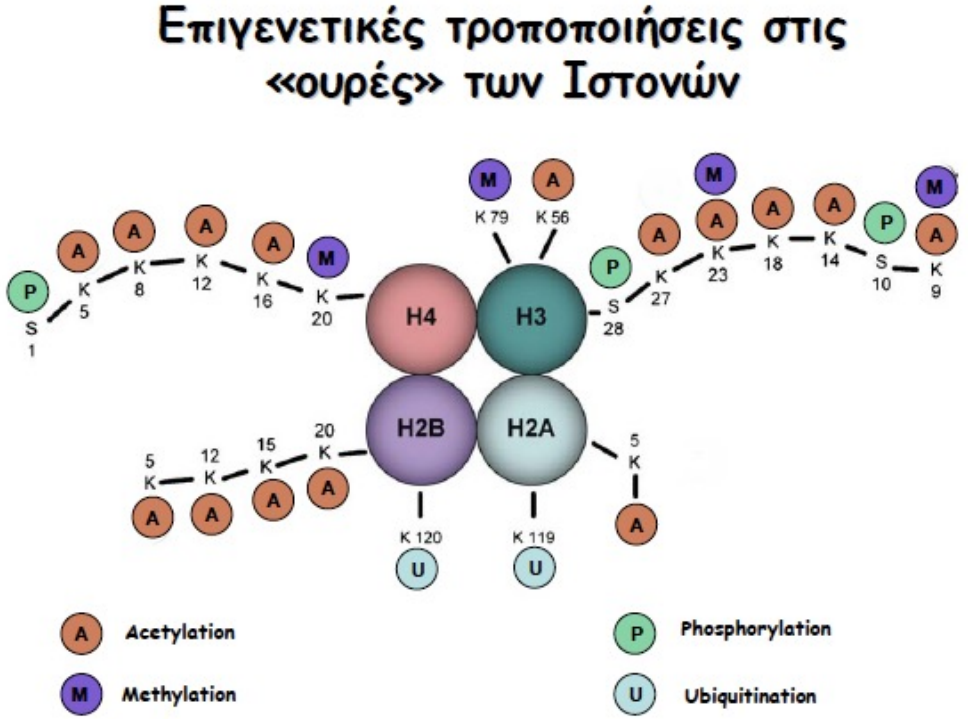
Definitions

- Histone: cluster of proteins
- Histone + DNA(146-7bp) = nucleosome





Modification of histones can influence gene transcription



Spencer and Davie, Gene 1999

Acetylation
methylation
ubiquitination
phosphorylation

Some modifications activate transcription

Some modifications repress transcription

Genome-wide surveys of modifications becoming available

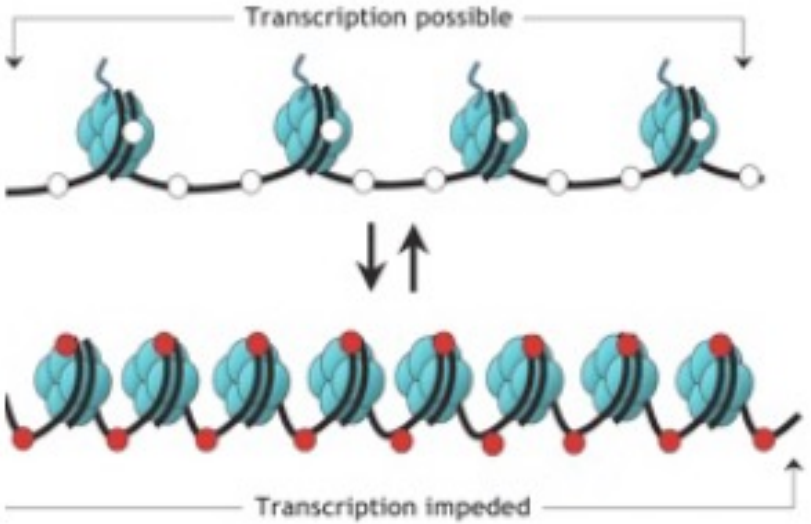
Chromatin structure can modify gene transcription

DNA packaged into nucleosomes (histones)

Nucleosome placement can alter transcription

"Open/active chromatin"

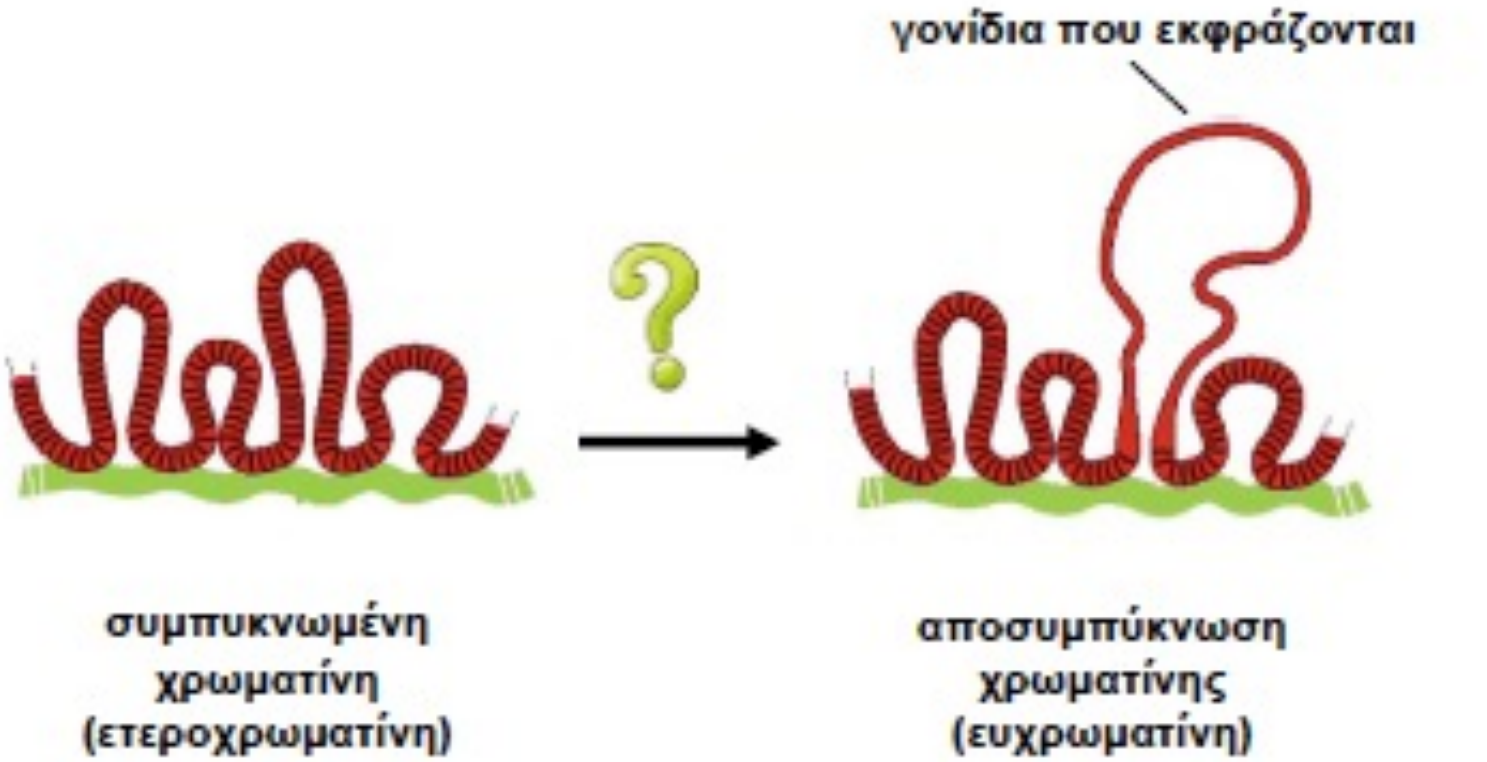
"Closed/inactive chromatin"



Active globin genes have "active" chromatin structure

Inactive or active chromatin structure can spread across regions ("domains")

Η χρωματίνη «αναπνέει»: Αναδιάπλαση της χρωματίνης κατά την έκφραση γονιδίων



Επιγενετικές τροποποιήσεις της χρωματίνης

- **Τροποποιήσεις Ιστονών**

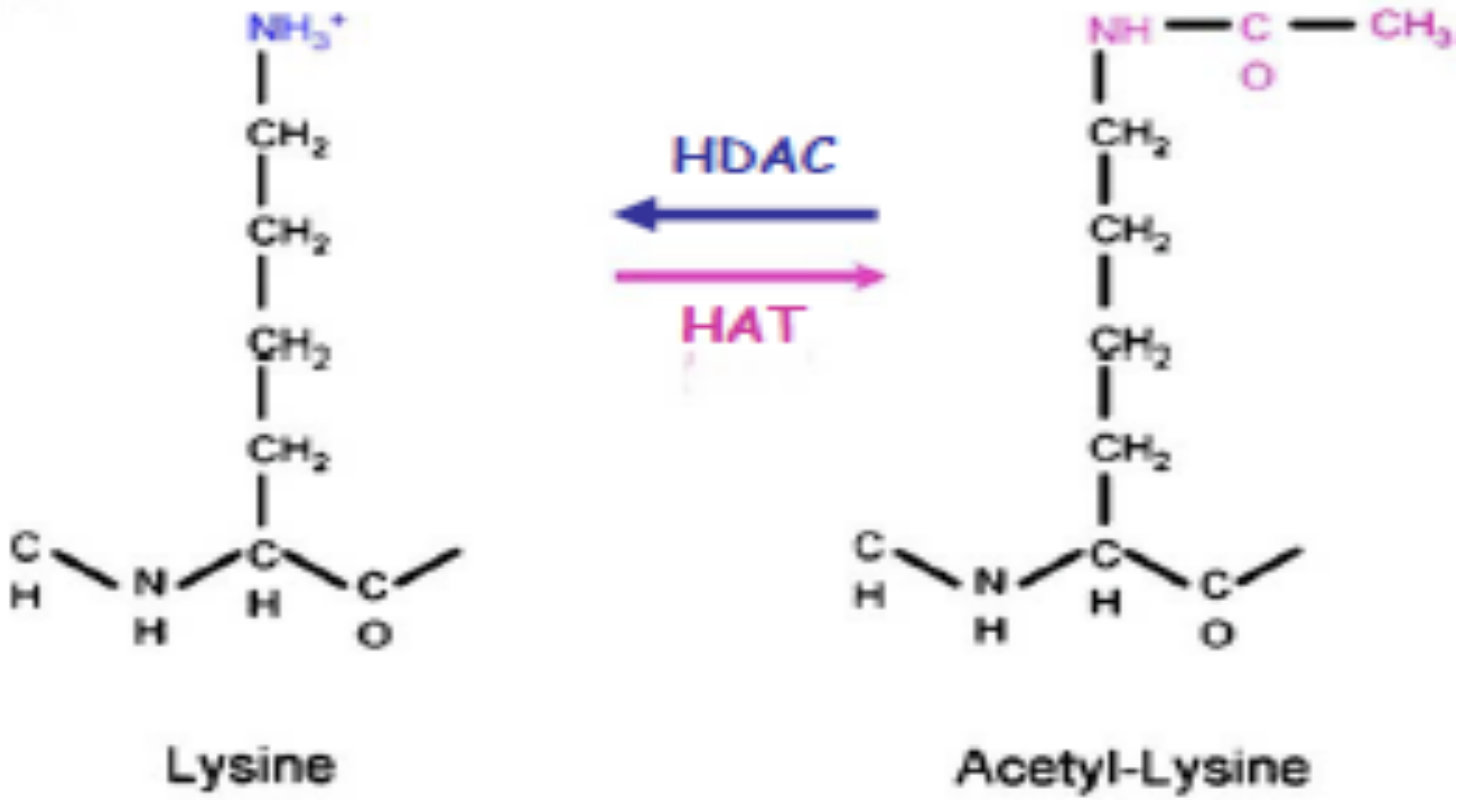
  Ακετυλίωση Ιστονών

  Μεθυλίωση Ιστονών

- Μεθυλίωση του DNA

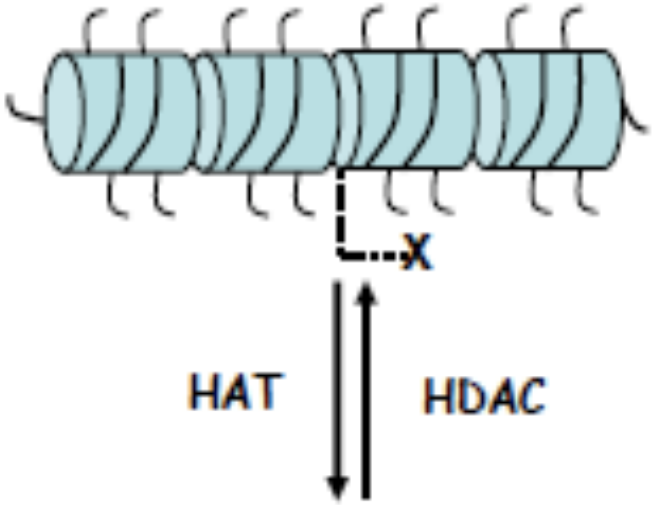
Ακετυλίωση Ιστονών

- **Μεταφορά ακετυλικής ομάδας σε αμινοξικό κατάλοιπο Λυσίνης ή Αργινίνης και δημιουργία ε-N-ακέτυλο-λυσίνης ή ε-N-ακέτυλο-αργινίνης**

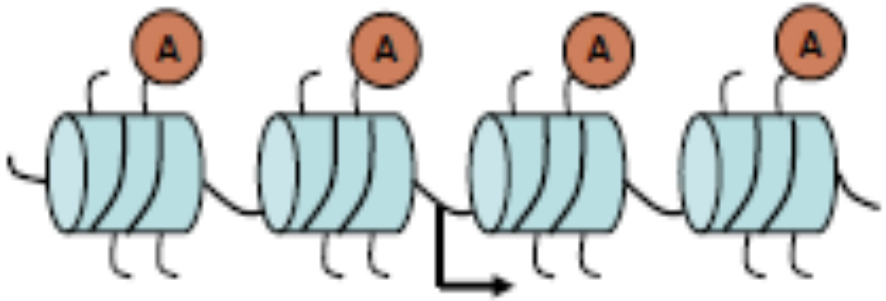


Ακετυλιώσεις Ιστονών διευκολύνουν τη χαλάρωση της δομής της χρωματίνης

συμπυκνωμένη χρωματίνη, δεν ευνοεί τη μεταγραφή

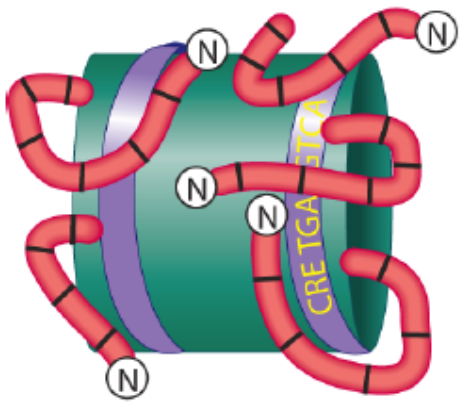


χαλαρή χρωματίνη, επιτρέπει τη μεταγραφή



Histone acetylation controls chromatin structure and gene expression

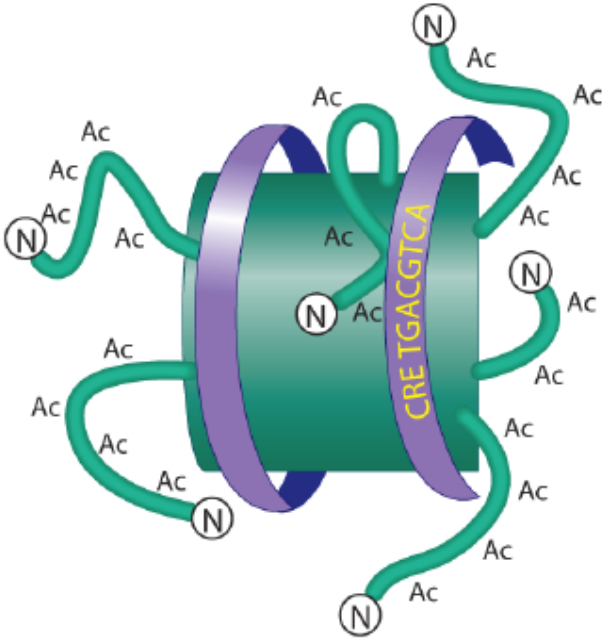
COMPRESSED CHROMATIN



Histone Acetyltransferase
HAT (e.g. CBP)

Histo e De ylase

EXPANDED CHROMATIN



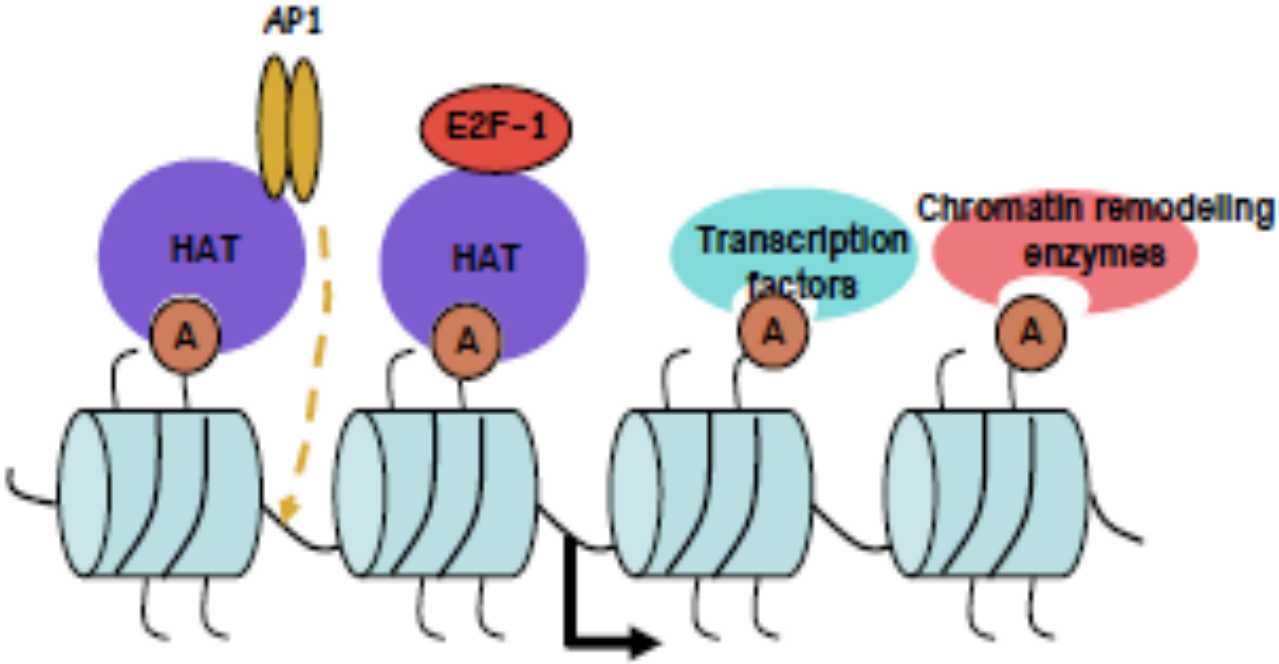
Less histone acetylation

Decreased gene expression

More histone acetylation

Increased gene expression

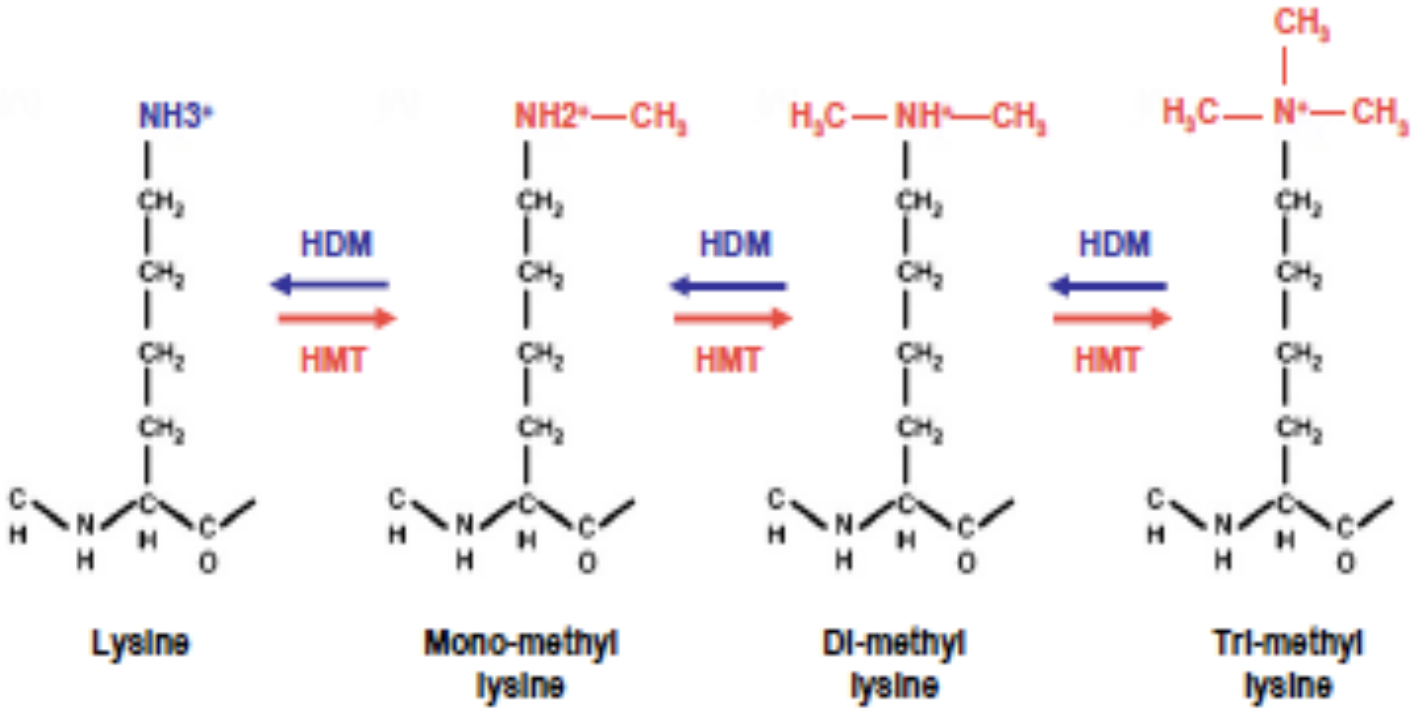
Ακετυλιώσεις Ιστονών στην περιοχή του υποκινητή διευκολύνουν την προσέλκυση παραγόντων ρυθμιστικών της μεταγραφής



Μεθυλίωση Ιστονών

2

- Τροποποίηση αμινοξικών καταλοίπων Λυσίνης ή Αργινίνης με προσθήκη ενός, δύο ή τριών μεθυλικών ομάδων



Μεθυλίωση Ιστονών

- Μεθυλιώσεις Ιστονών αλλάζουν τις αλληλεπιδράσεις του νουκλεοσώματος με πρωτεΐνες οι οποίες προσδένονται σε Ιστόνες

- Μεθυλιώσεις Ιστονών σχετίζονται με ενεργοποίηση ή καταστολή της μεταγραφής, ανάλογα με το αμινοξικό κατάλοιπο

- Οι Histone Methyltransferases (HMTs) μεθυλιώνουν αμινοξικά κατάλοιπα Ιστονών

- Οι Histone Demethylases (HDMs) απομεθυλιώνουν αμινοξικά κατάλοιπα Ιστονών

Ο ρόλος της Μεθυλίωσης Ιστονών

Μεθυλίωση της H3-K9: απενεργοποίηση της έκφρασης γονιδίων

- Η πρωτεΐνη HP1 προσδένεται στη μεθυλιωμένη H3-K9 μέσω του chromodomain
- Αλληλεπιδράσεις μεταξύ των chromoshadow domains των HP1 οδηγούν σε συμπύκνωση της χρωματίνης
- Η συμπυκνωμένη χρωματίνη δεν είναι προσβάσιμη σε μεταγραφικούς παράγοντες και RNA πολυμεράση -> καταστολή της γονιδιακής έκφρασης

Μεθυλίωση της H3-K4 ενεργοποιεί την έκφραση γονιδίων

- Πρόσδεση μεταγραφικών παραγόντων στην μεθυλιωμένη K4

Επιγενετικές τροποποιήσεις της χρωματίνης

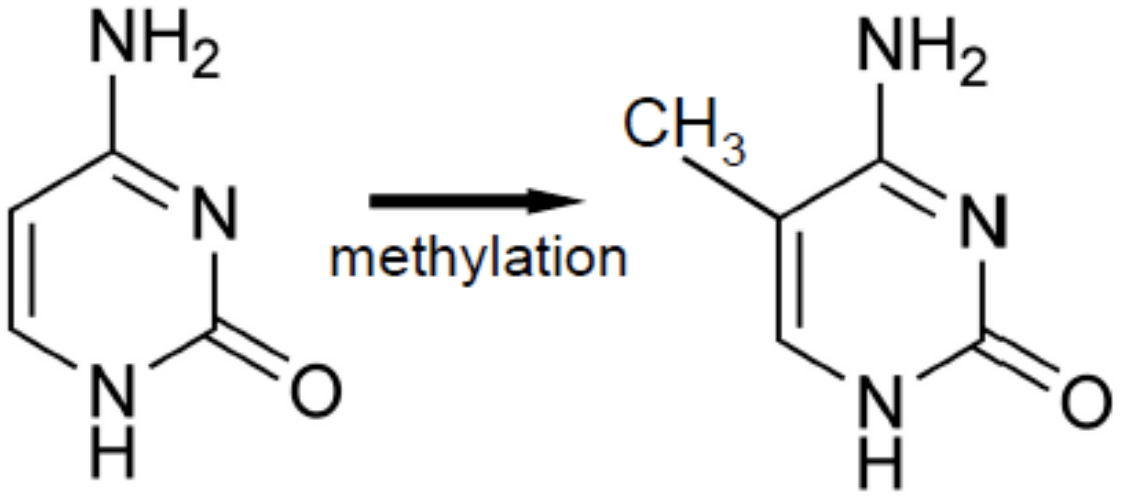
- Τροποποιήσεις Ιστονών

  Ακετυλίωση Ιστονών

  Μεθυλίωση Ιστονών

- Μεθυλίωση του DNA

Methylation of DNA can modify gene transcription



cytosine

5-methylcytosine

Methylation of DNA can modify gene transcription

Transcription, no methylation

Methylation, no transcription

Methylation preferentially of C followed by G ("CpG")

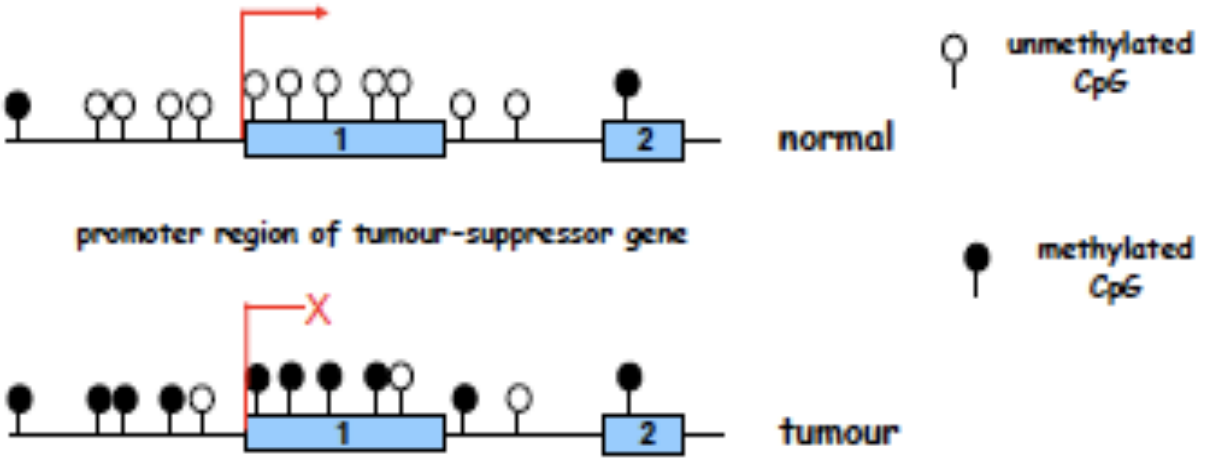
Methylation usually associated with gene silencing

Mechanism of silencing not clear

Over- or under-expression of methylases changes gene expression

Επιγενετικές τροποποιήσεις και καρκίνος

- Η υπερμεθυλίωση υποκινητών αποτελεί μηχανισμό απενεργοποίησης ογκοκατασταλτικών γονιδίων



DNA Methylation Modifiers

- Aging (cell, individual)
- Micronutrients (e.g., folate deficiency)
- Chemotherapy other drugs
- Inflammation
- Environmental Pollutants

Methylation's mark on inheritance

Epigenetic changes to the genome can have heritable effects. An epigenome-wide study of wild plants identifies shared patterns of such modifications and their associations with genetic information. SEE ARTICLE P.193

STEVEN EICHTEN & JUSTIN BOREVITZ

We have long known that genes carry the blueprint of inherited instructions that are passed from individuals to their offspring. More recent developments have shown that the make-up of an individual's epigenome — chemical and structural modifications to the genome that do not change the DNA sequence — may also contribute to this instruction set. One chemical modification, DNA methylation, is thought to target certain genetic elements, but it remains unclear what proportion of these marks is completely separate from genetic information. Reporting on page 193 of this issue, Schmitz *et al.*[1] begin to disentangle *de novo* methylation from that linked to variation in DNA sequence by studying the genome and epigenome of the model plant *Arabidopsis thaliana**.

The addition of a methyl group to cytosine residues in DNA is one of the most common epigenetic modifications in both plants and animals. Such methylation is frequently seen in repetitive sequences, is known to repress the movement of transposable genetic elements and, in some cases, can inhibit gene expression. There are three classes of methylation marks in plants: CG, CHG and CHH, in which C is methylated cytosine and H is any nucleotide residue other than guanine (G). These methylation classes differ in their mechanisms of establishment, maintenance and inheritance; and they have distinct roles in genomic regulation, thereby leading to differing effects on the characteristics — or phenotype — of an organism[2]. Previous analyses of genome-wide methylation profiles have identified many regions of variable DNA methylation in several plant systems[3,4].

"Schmitz and colleagues' study is an example of how association studies that include the epigenome can help to uncover additional sources of heritability."

*This article and the paper under discussion[1] were published online on 6 March 2013.

ses to the population level by studying genotypically distinct wild *A. thaliana* individuals collected from around the Northern Hemisphere. The authors obtained whole-genome DNA sequences for 217 individual plants, and, of these, whole-genome methylation profiles for 152 and gene-transcript profiles for 144 plants. From these data, they identified hundreds of thousands of sites at which a single nucleotide was methylated in some of the individuals (single methylation polymorphisms, or SMPs) and tens of thousands of differentially methylated regions (DMRs). More than 30% of these DMRs were directly associated with local sites of DNA-sequence variation. These associations define regions at which the genetic and epigenetic variants are inherited together. The authors also demonstrate that, as expected, many of these sites of association correlate with differential gene expression.

Using statistical tests that are designed to uncover associations between epigenetic variation and phenotype, Schmitz *et al.* were able to identify quantitative-trait loci (genomic regions that control trait variation) that were associated with differential methylation of all three classes. Furthermore, their examination of loci for which methylation was present across the samples led to the discovery that some genes have co-opted epigenetic regulatory mechanisms that were thought to target only transposable elements and repeat sequences. Many of these genes are important for the generation of gametes (sperm and egg cells or, in plants, pollen and ovules). It seems that DNA methylation prevents the expression of these genes during the vegetative phase of

Specific epigenetic processes

1. Imprinting (e.g. Angelman syndrome – maternally lost genes on chr15, paternally silenced)
2. Gene silencing
3. X chromosome inactivation
4. Paramutation (interaction between alleles at a single locus, e.g. maize)
5. Bookmarking (transmitting cellular pattern of expression during mitosis to the daughter cell)
6. Reprogramming
7. Transvection (interaction of alleles on diff. homologous chromosomes)
8. Maternal effects
9. Progress of carcinogenesis
10. Regulation of histone modifications and heterochromatin

Is the epigenome inherited?

The genome is passed from parents to their offspring and from cells, when they divide, to their next generation. Much of the epigenome is reset when parents pass their genomes to their offspring; however, under some circumstances, some of the chemical tags on the DNA and histones of eggs and sperm may be passed on to the next generation. When cells divide, often much of the epigenome is passed on to the next generation of cells, helping the cells remain specialized.

Changes during mitosis

- Fidelity of “transcription” of DNA methylation varies between 97-99.9%
- De-novo methylation: 3-5% mitosis
- Much more dynamic compared to DNA sequence!

Lots of ways of altering gene expression
besides DNA sequence changes

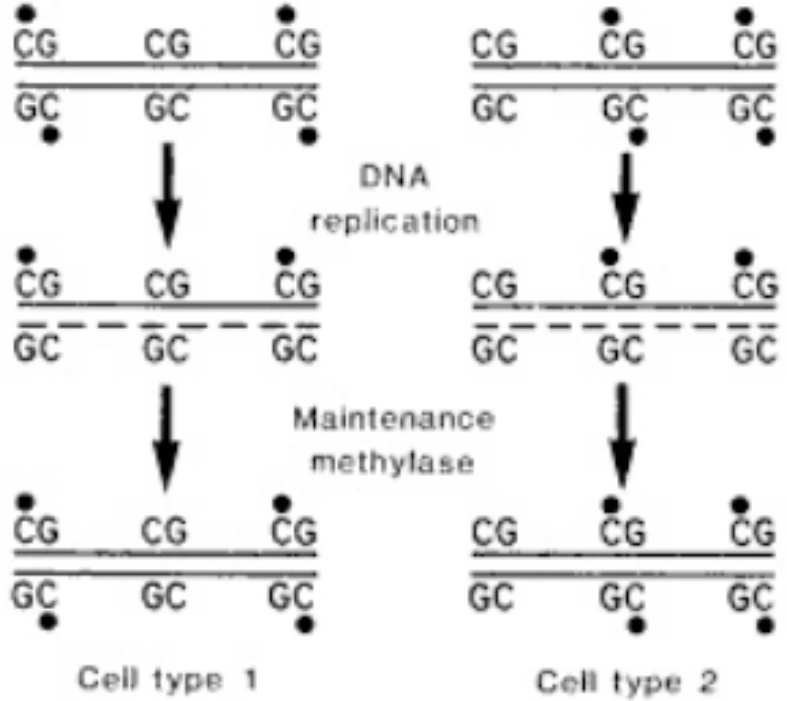
What happens during replication?

Methylation patterns are maintained through replication

Semiconservative replication leads to hemimethylated DNA

Methylase recognizes hemimethylated DNA and restores methylation

Other epigenetic modifications can also persist through replication



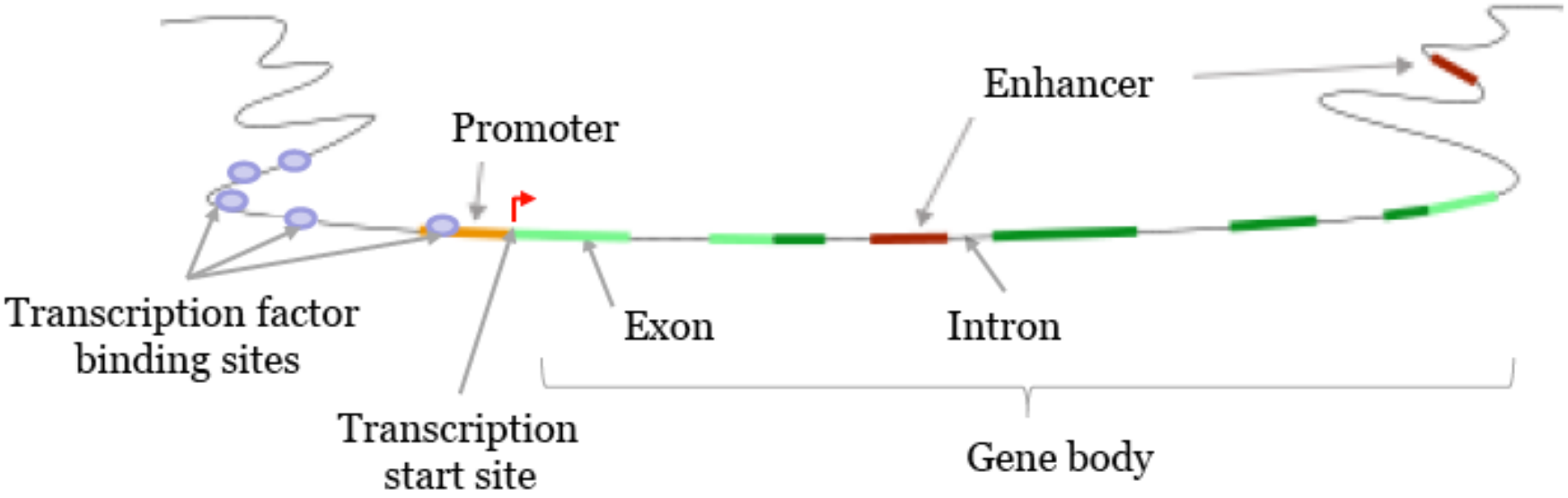
Razin and Riggs, Science 1980

Studies linking early life exposures to changes in DNA methylation using animal models

Early life exposure	Animal model	Epigenetic change	Disease association
Maternal nutrition			
Low Protein	Rat, Mouse, Pig	↑ and ↓ DNA methylation, ↑ and ↓ histone acetylation and histone methylation	Obesity
Calorie restriction	Sheep, Rat	↓ DNA methylation, ↑ histone acetylation and ↓ histone methylation	Obesity, Diabetes
Periconceptional restriction B_{12}, folate, methionine	Sheep	Altered DNA methylation	Obesity
High fat	Macaque, Mouse	↑ and ↓ DNA methylation, ↑ and ↓ histone acetylation and ↑ and ↓ histone methylation	Obesity
Surgical models			
IUGR (uterine artery ligation)	Rat	Altered DNA methylation, ↓ histone acetylation	Diabetes
Environmental toxin			
Arsenic	Mouse	↓ DNA methylation	Diabetes
Paternal effect			
Low protein	Mouse	↑ DNA methylation	Obesity
Neonatal diet			
Leptin treatment	Rat	↑ DNA methylation	Obesity
Extendin-4	Rat	Hyperacetylation	Diabetes
Reversal with folic acid			
Methyl supplementation	A^{vy} mouse	↑ DNA methylation	Obesity
Genistein supplementation +FA	A^{vy} mouse	↑ DNA methylation	Obesity
Protein restriction + FA	Rat	Prevented or reversed hypomethylation	Obesity

Seki Y et al. *Endocrinology* 2012

The component parts of a gene



Maternal diet and aging alter the epigenetic control of a promoter–enhancer interaction at the *Hnf4a* gene in rat pancreatic islets

Ionel Sandovici[a,b,1], Noel H. Smith[c,1], Marloes Dekker Nitert[d], Matthew Ackers-Johnson[c], Santiago Uribe-Lewis[e], Yoko Ito[e], R. Huw Jones[c], Victor E. Marquez[f], William Cairns[g], Mohammed Tadayyon[g], Laura P. O'Neill[h], Adele Murrell[e], Charlotte Ling[d], Miguel Constância[a,b,1,2], and Susan E. Ozanne[c,1,2]

Evidence from human studies

ORIGINAL ARTICLE

Epigenetic Gene Promoter Methylation at Birth Is Associated With Child's Later Adiposity

Keith M. Godfrey,[1,2,3] Allan Sheppard,[4,5] Peter D. Gluckman,[4,6] Karen A. Lillycrop,[1] Graham C. Burdge,[1] Cameron McLean,[4,5] Joanne Rodford,[1,3] Joanne L. Slater-Jefferies,[1] Emma Garratt,[1,3] Sarah R. Crozier,[2] B. Starling Emerald,[6] Catharine R. Gale,[2] Hazel M. Inskip,[2] Cyrus Cooper,[2,3] and Mark A. Hanson[1,3]

OPEN ACCESS Freely available online PLoS one

DNA Methylation Patterns in Cord Blood DNA and Body Size in Childhood

Caroline L. Relton[1], Alexandra Groom[1*], Beate St. Pourcain[2], Adrian E. Sayers[3], Daniel C. Swan[4], Nicholas D. Embleton[5,6], Mark S. Pearce[6], Susan M. Ring[7], Kate Northstone[2], Jon H. Tobias[3], Joseph Trakalo[8], Andy R. Ness[9], Seif O. Shaheen[10], George Davey Smith[2]

ORIGINAL ARTICLE

Postnatal Growth and DNA Methylation Are Associated With Differential Gene Expression of the *TACSTD2* Gene and Childhood Fat Mass

Alexandra Groom,[1] Catherine Potter,[1] Daniel C. Swan,[2] Ghazaleh Fatemifar,[3] David M. Evans,[3] Susan M. Ring,[4] Valerie Turcot,[5] Mark S. Pearce,[6] Nicholas D. Embleton,[6,7] George Davey Smith,[8] John C. Mathers,[8] and Caroline L. Relton[1]

OPEN ACCESS Freely available online PLoS one

Genetic and Non-Genetic Influences during Pregnancy on Infant Global and Site Specific DNA Methylation: Role for Folate Gene Variants and Vitamin B_{12}

Jill A. McKay[1*], Alexandra Groom[2], Catherine Potter[2], Lisa J. Coneyworth[3], Dianne Ford[3], John C. Mathers[1], Caroline L. Relton[2]

OPEN ACCESS Freely available online PLoS one

Prenatal Famine and Genetic Variation Are Independently and Additively Associated with DNA Methylation at Regulatory Loci within *IGF2/H19*

Elmar W. Tobi[1], P. Eline Slagboom[1,2], Jenny van Dongen[1,4], Dennis Kremer[1], Aryeh D. Stein[5], Hein Putter[2], Bastiaan T. Heijmans[1,2,*], L. H. Lumey[6,*]

What is imprinting?

The human genome contains two copies of every gene-one copy inherited from the mother and one from the father. For a small number of genes, only the copy from the mother gets switched on; for others, only the copy from the father is turned on. This pattern is called imprinting. The epigenome distinguishes between the two copies of an imprinted gene and determines which is switched on.

Some diseases are caused by abnormal imprinting. They include Beckwith-Wiedemann syndrome, a disorder associated with body overgrowth and increased risk of cancer; Prader-Willi syndrome, associated with poor muscle tone and constant hunger, leading to obesity; and Angelman syndrome, which leads to intellectual disability, as well motion difficulties.

Can the epigenome change?

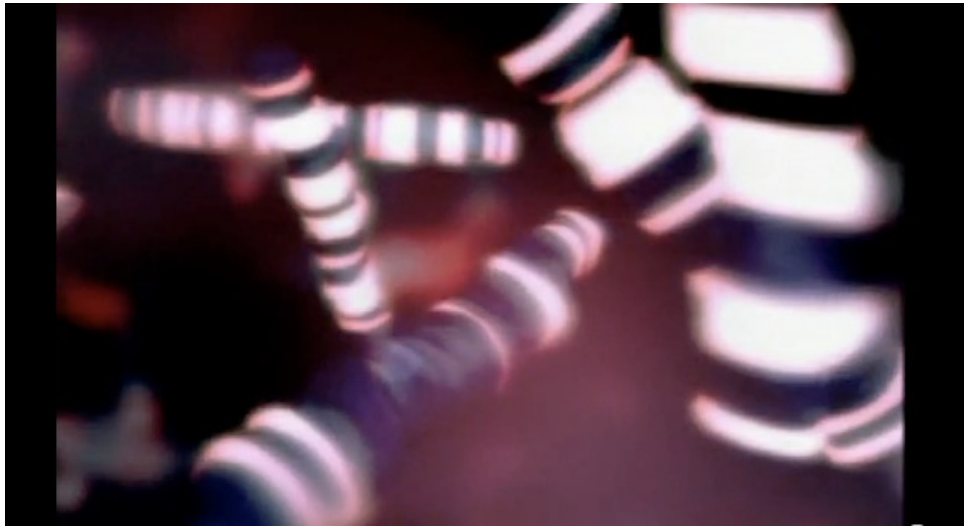
Although all cells in the body contain essentially the same genome, the DNA marked by chemical tags on the DNA and histones gets rearranged when cells become specialized. The epigenome can also change throughout a person's lifetime.

What makes the epigenome change?

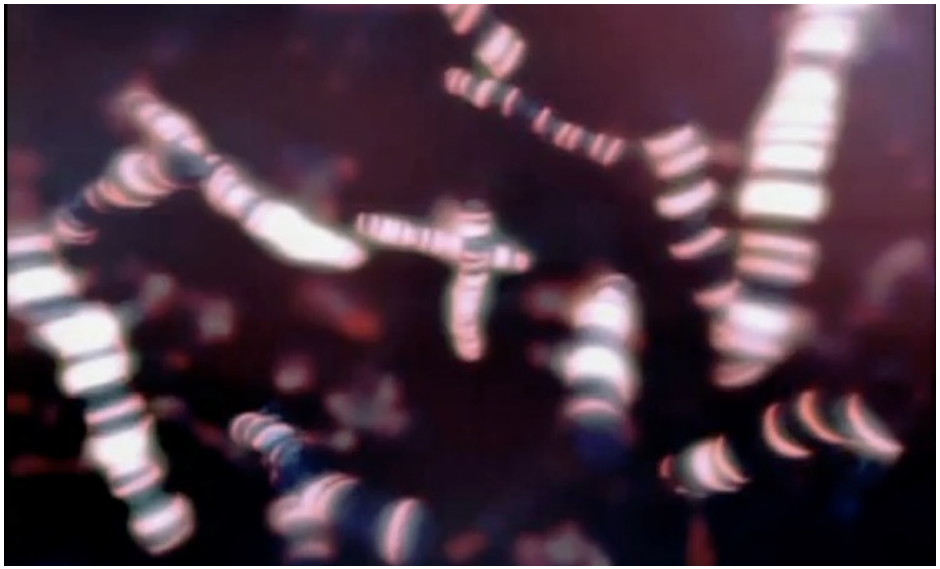
Lifestyle and environmental factors (such as smoking, diet and infectious disease) can expose a person to pressures that prompt chemical responses. These responses, in turn, often lead to changes in the epigenome, some of which can be damaging. However, the ability of the epigenome to adjust to the pressures of life appears to be required for normal human health. Some human diseases are caused by malfunctions in the proteins that "read" and "write" epigenomic marks.

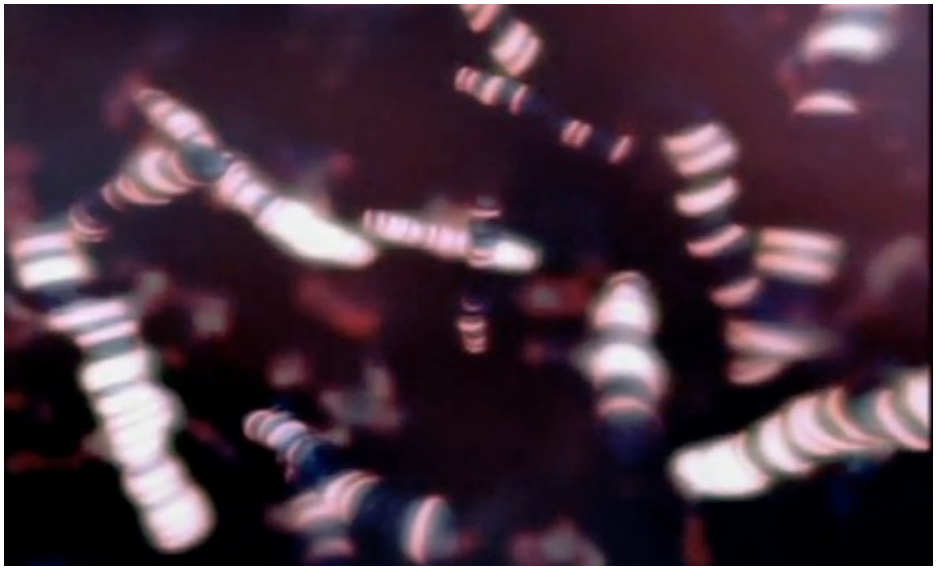
The dynamic epigenome

Waterland RA. *Nutr Rev* 2008

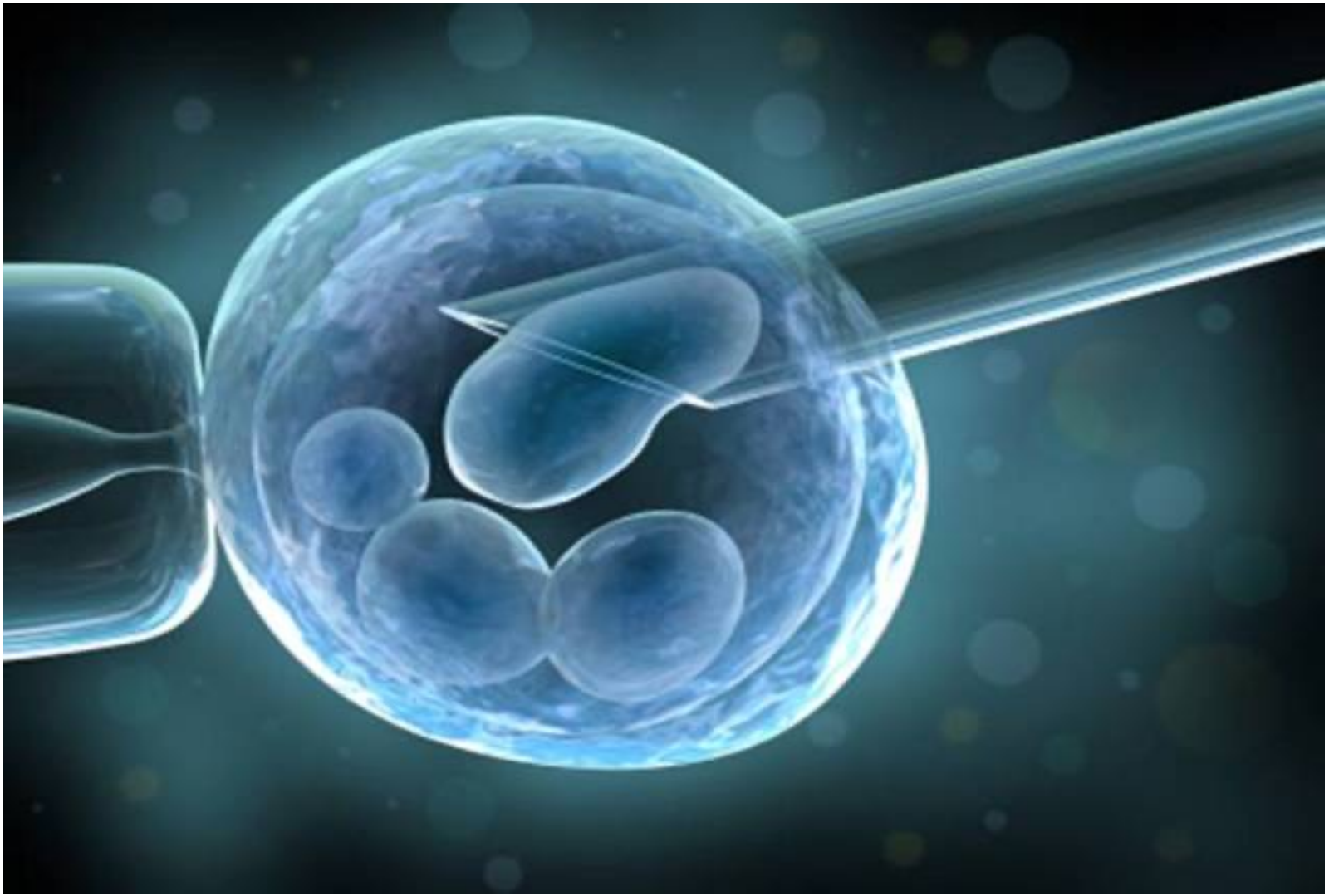


Switch On/Off

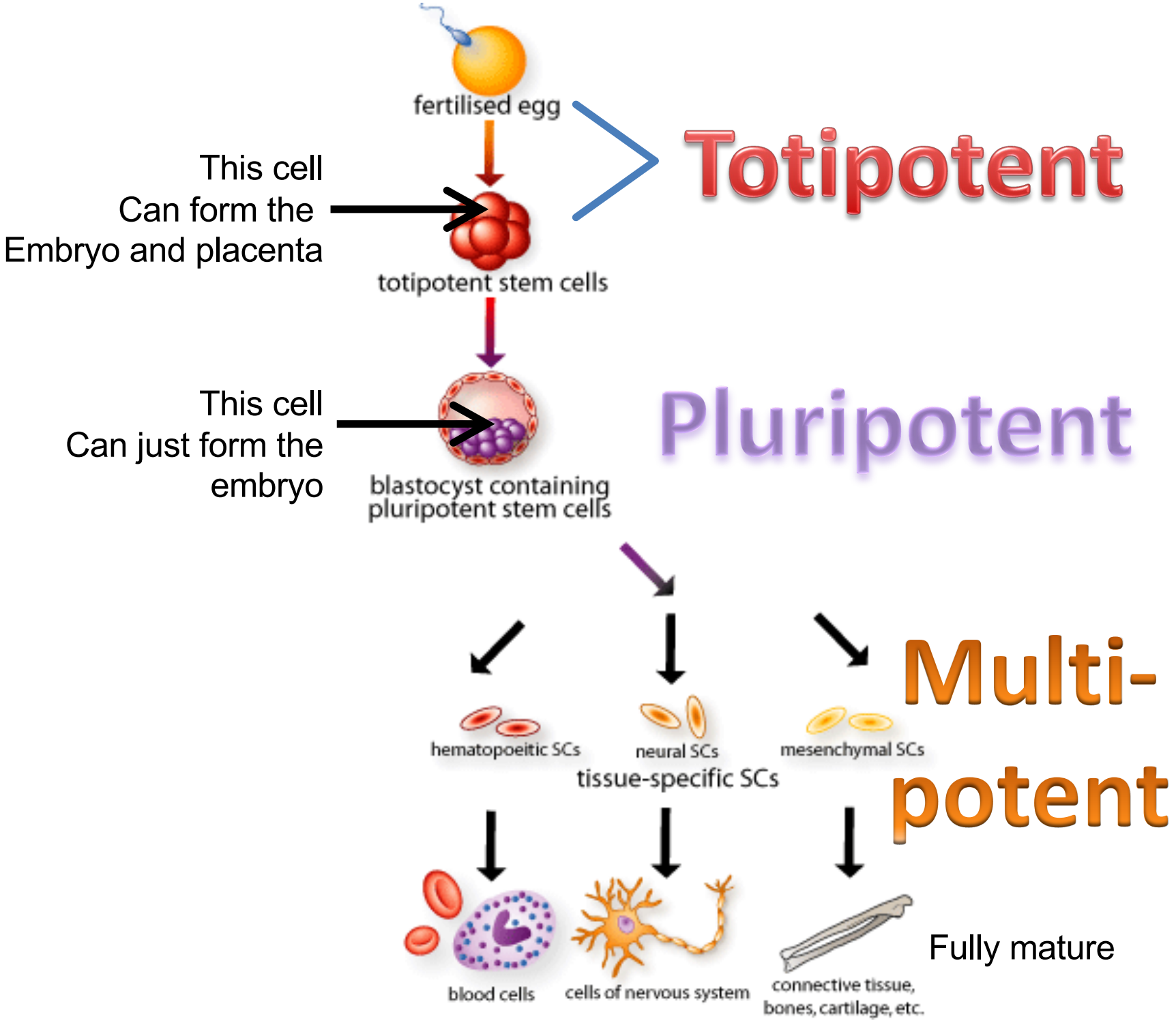




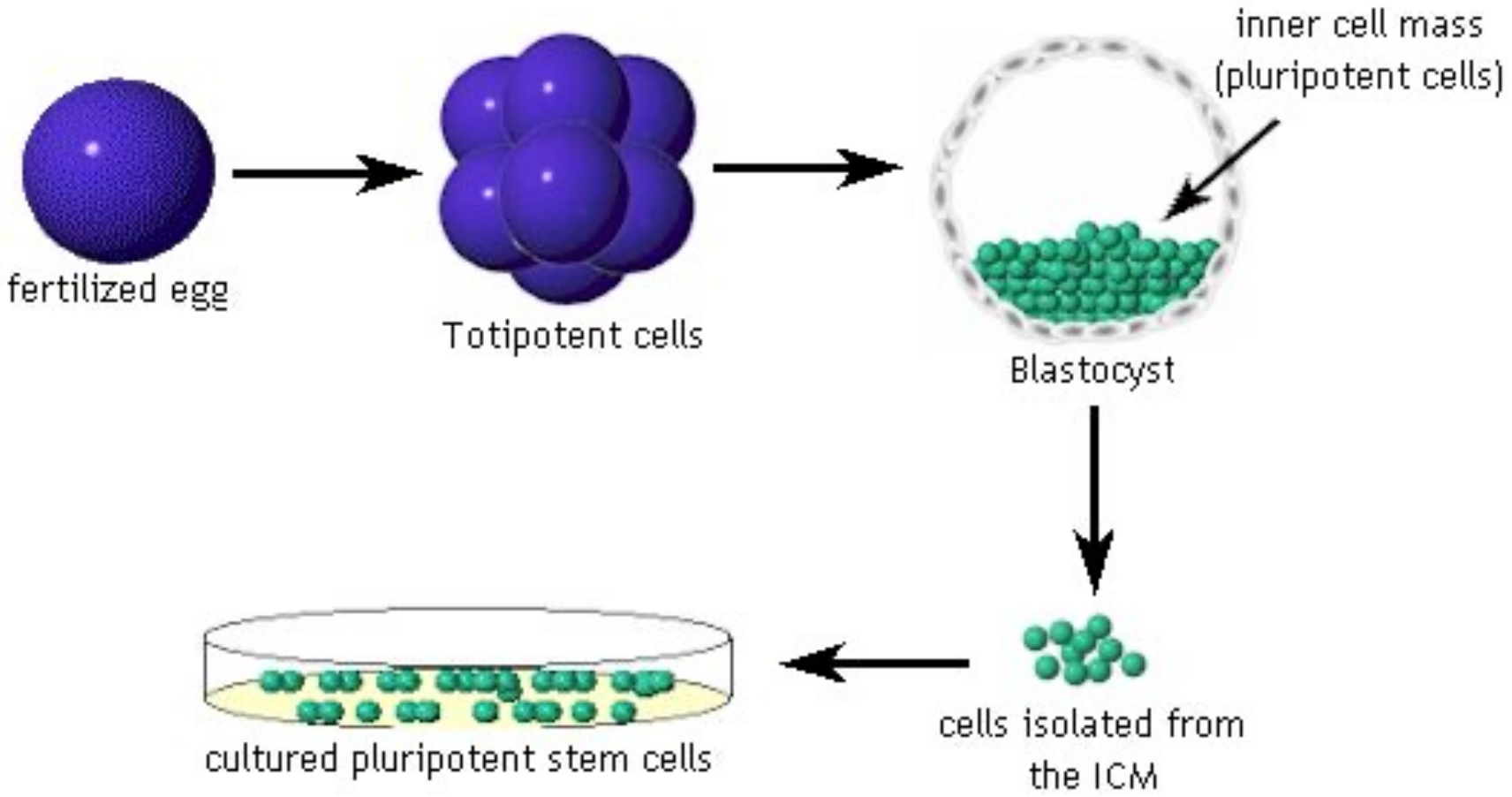
Embryonic Stem Cells



Mainly from IVF

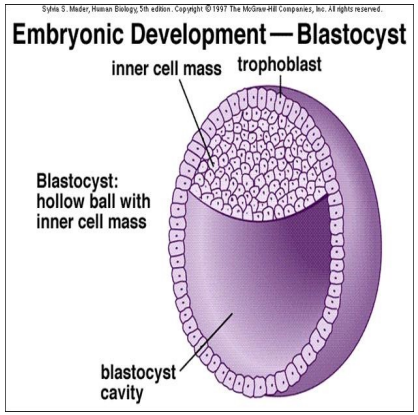

fertilised egg
This cell
Can form the
Embryo and placenta
totipotent stem cells
Totipotent
This cell
Can just form the
embryo
blastocyst containing
pluripotent stem cells
Pluripotent
hematopoeitic SCs
neural SCs
mesenchymal SCs
tissue-specific SCs
Multi-
potent
blood cells
cells of nervous system
connective tissue,
bones, cartilage, etc.
Fully mature

Blastocyst Diagram

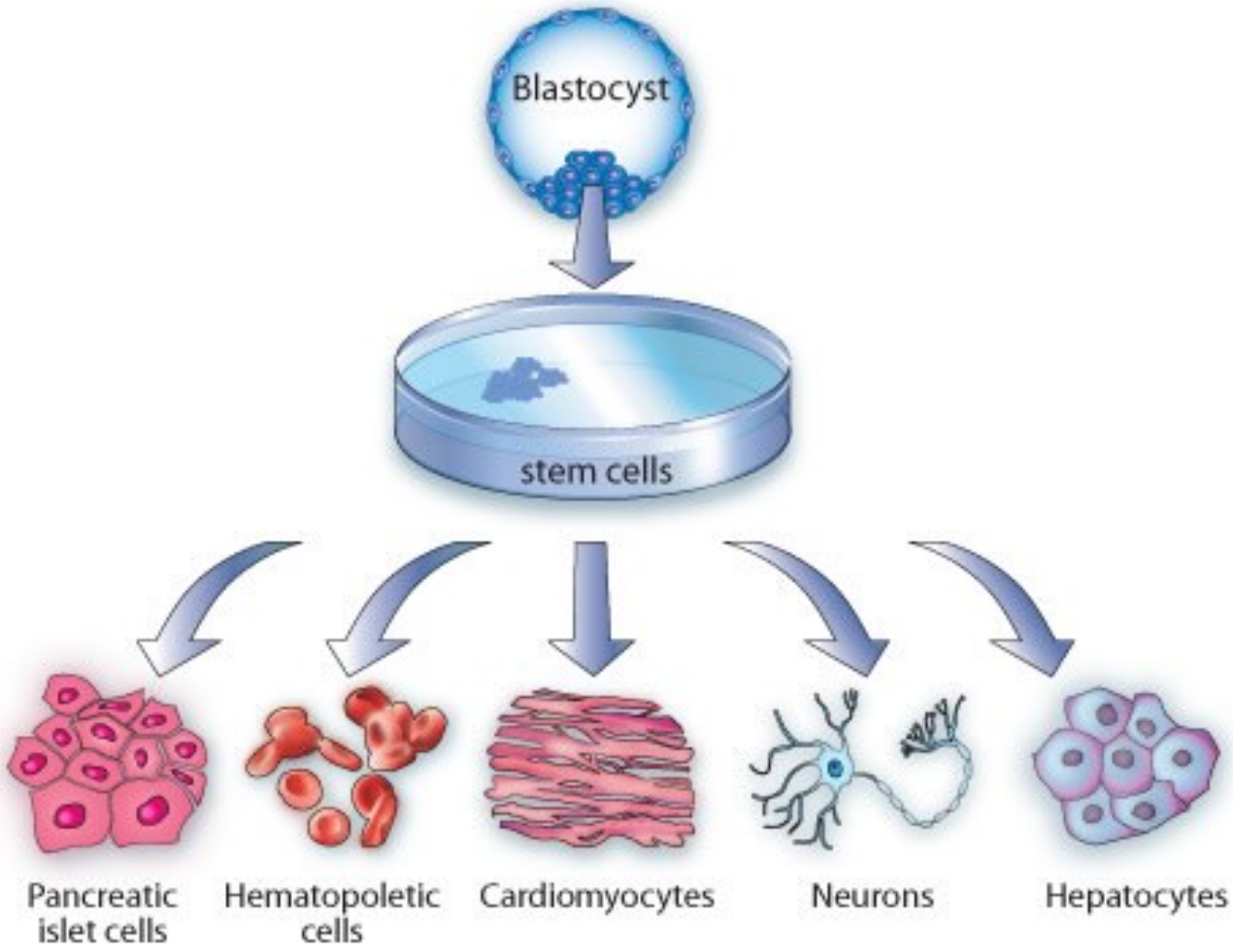


Embryonic Stem Cells

- The zygote contains "totipotent" stem cells which can develop into any cell including those that make up the human embryo
- Once the zygote has developed into a blastocyst, the inner cell mass will contain embryonic stem cells
  - Pluripotent -> limited capabilities but can still further create several specialized cell types



Pluripotent Stem Cells – more potential to become any type of cell



Multipotent stem cells

- Multipotent stem cells – limited in what the cells can become

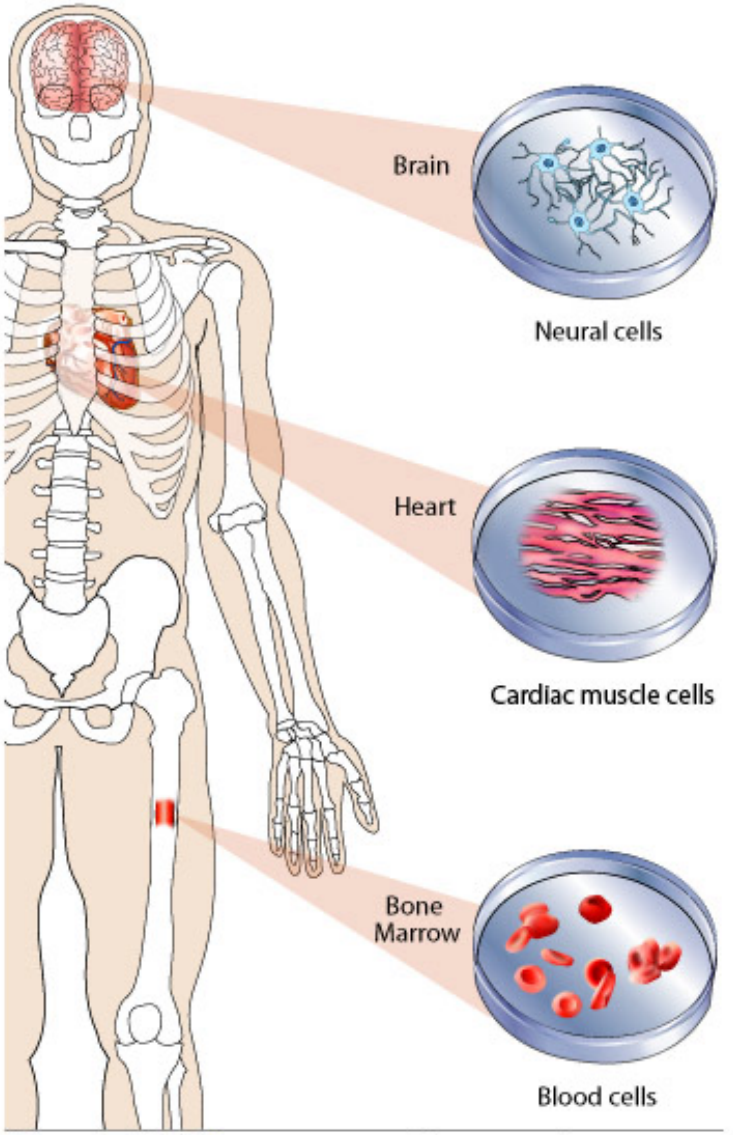


Illustration by Cell Imaging Core of the Center for Reproductive Sciences.

Adult Stem Cells

An undifferentiated cells found among specialized or differentiated cells in a tissue or organ after birth

- Skin
- Fat Cells
- Bone marrow
- Brain
- Many other organs & tissues

Tissue-specific stem cells

Tissue	Stem cell	Differentiated progeny
Blood	HSC	All lineages of blood cells
Brain	NSC	Neurons, glia
Intestine	ISC	Intestinal epithelium
Skin	Bulge cell	Hair, sebaceous gland, epidermis
Muscle	Satellite cell	Myoblasts, myofibers
Germline	Germ cell	Oocyte, sperm
Liver	Oval cell	Hepatocyte, bile duct
Heart	Cardiac progenitor	Cardiomyocytes, smooth muscle,
Blood vessels	EPC	Endothelium
Lung	BASC	Alveoli, pneumocytes
Kidney	?	Renal tubule
Pancreas	?	Exocrine/endocrine cells
Fat	?	adipocytes

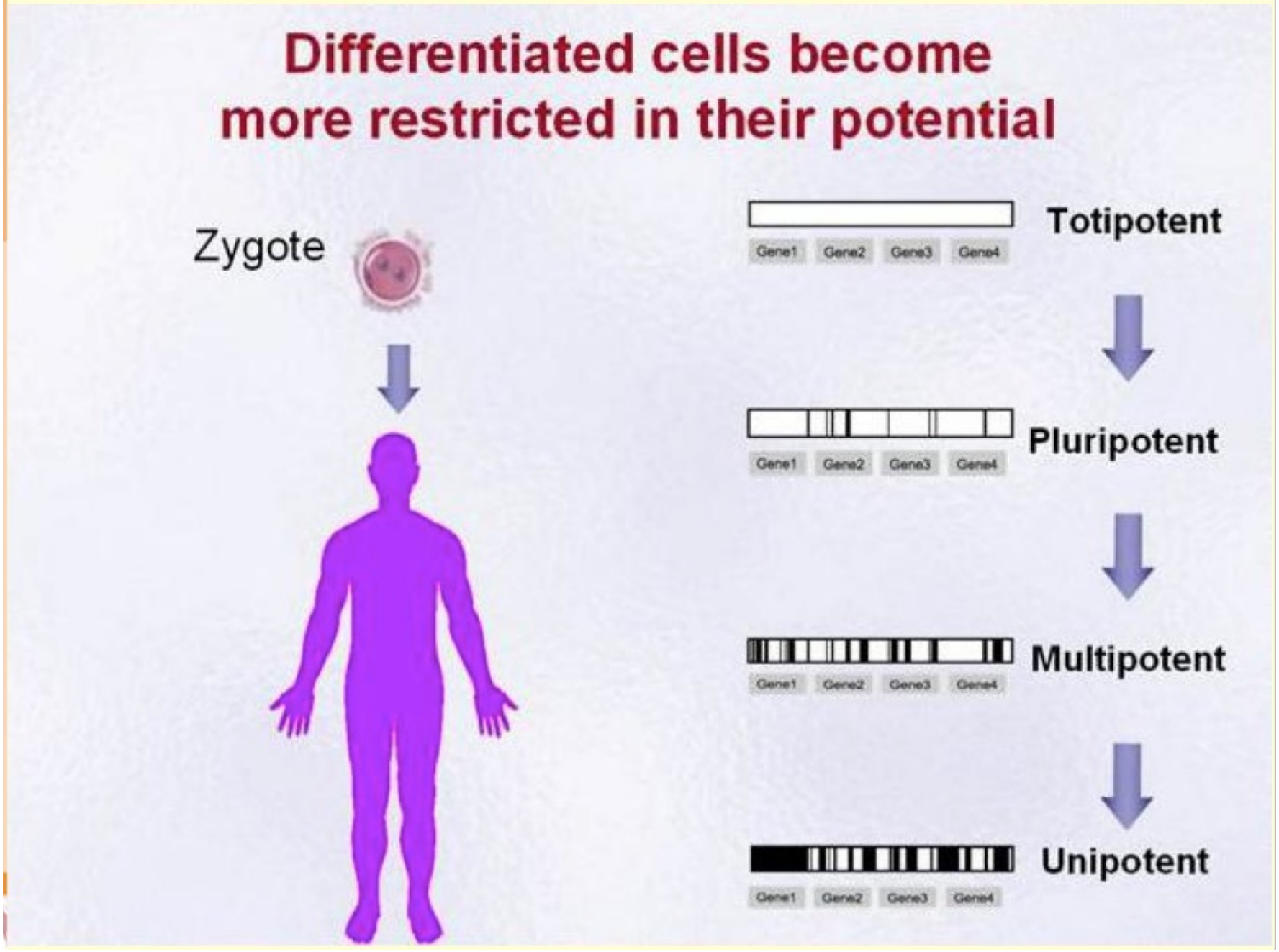
Methylated DNA from Zygote to Adult

ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGAT
GTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACC
AGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTAACA
TAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGATGTT
TTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACCAGT
AGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTTTATTAT
AGGACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCAT
GATGTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATG
ACCAGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTA
ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATACAGCACCATACCATGAT

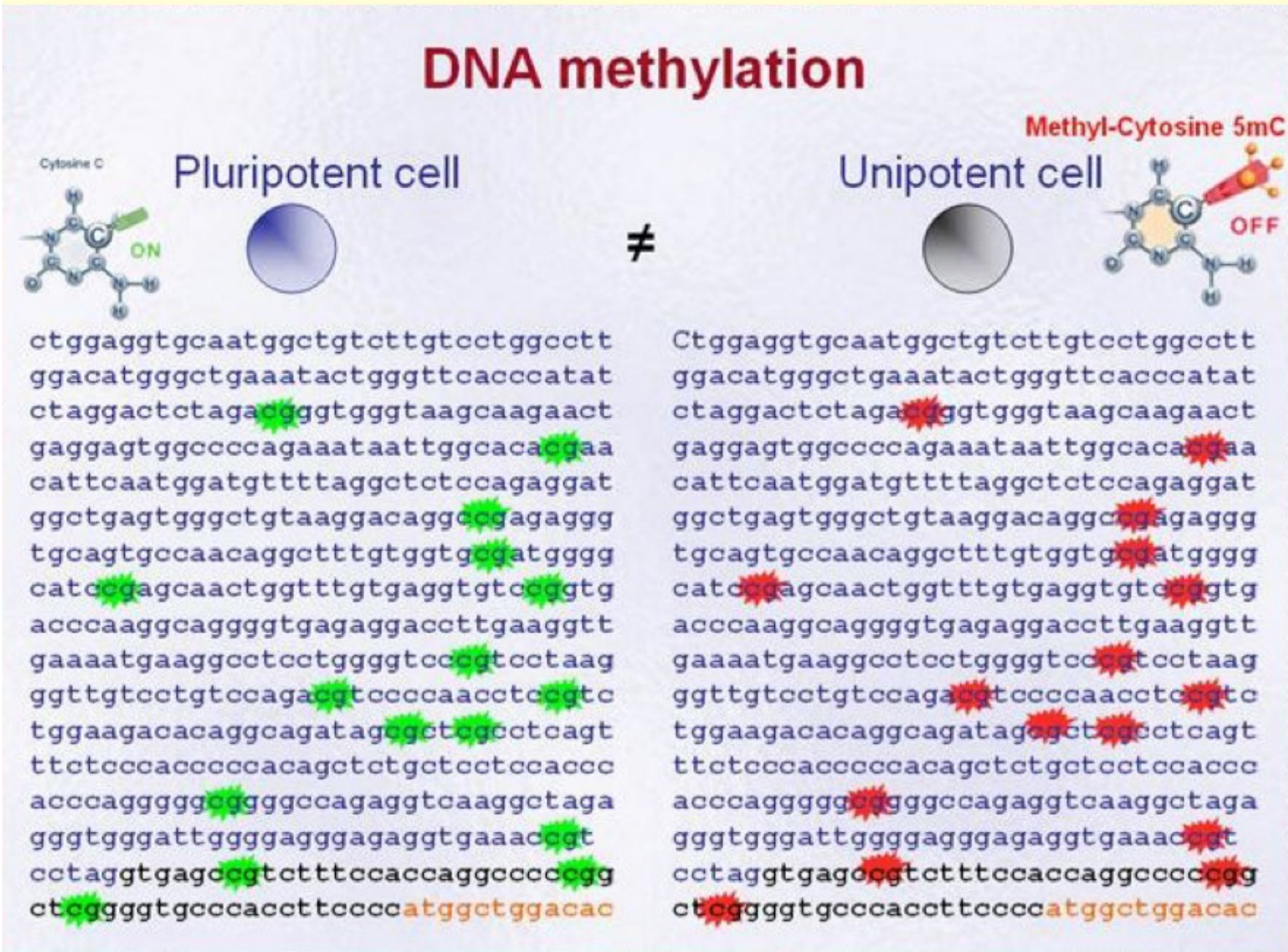
How is the diversity of cell types created and maintained in multi-cellular organisms?

ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGAT
GTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACC
AGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTAACA
TAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGATGTT
TTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACCAGT
AGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTTTATTAT
AGGACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCAT
GATGTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATG
ACCAGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTA
ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGAT

Methylated DNA from Zygote to Adult



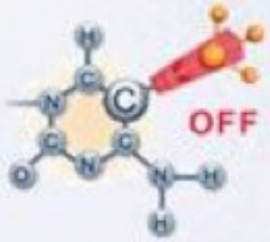
DNA Methylation Differentiates Totipotent Embryonic Stem Cells from Unipotent Adult Stem Cells



Critical CpG Sequences in CpG Islands Near Promoters

Genomic distribution of DNA methylation

Methyl-Cytosine

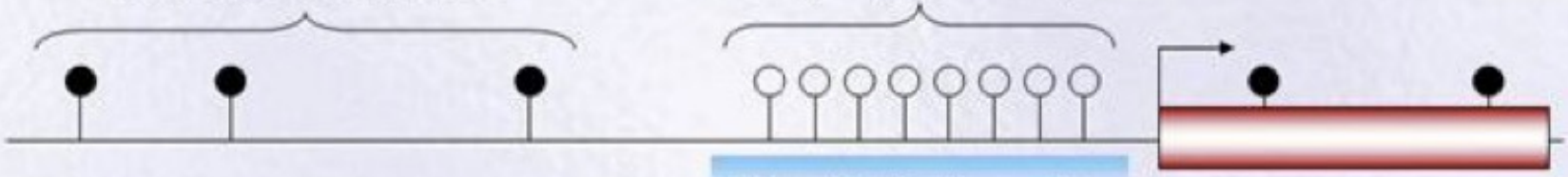


4% of all cytosines are methylated

70-80% of all CpGs are methylated

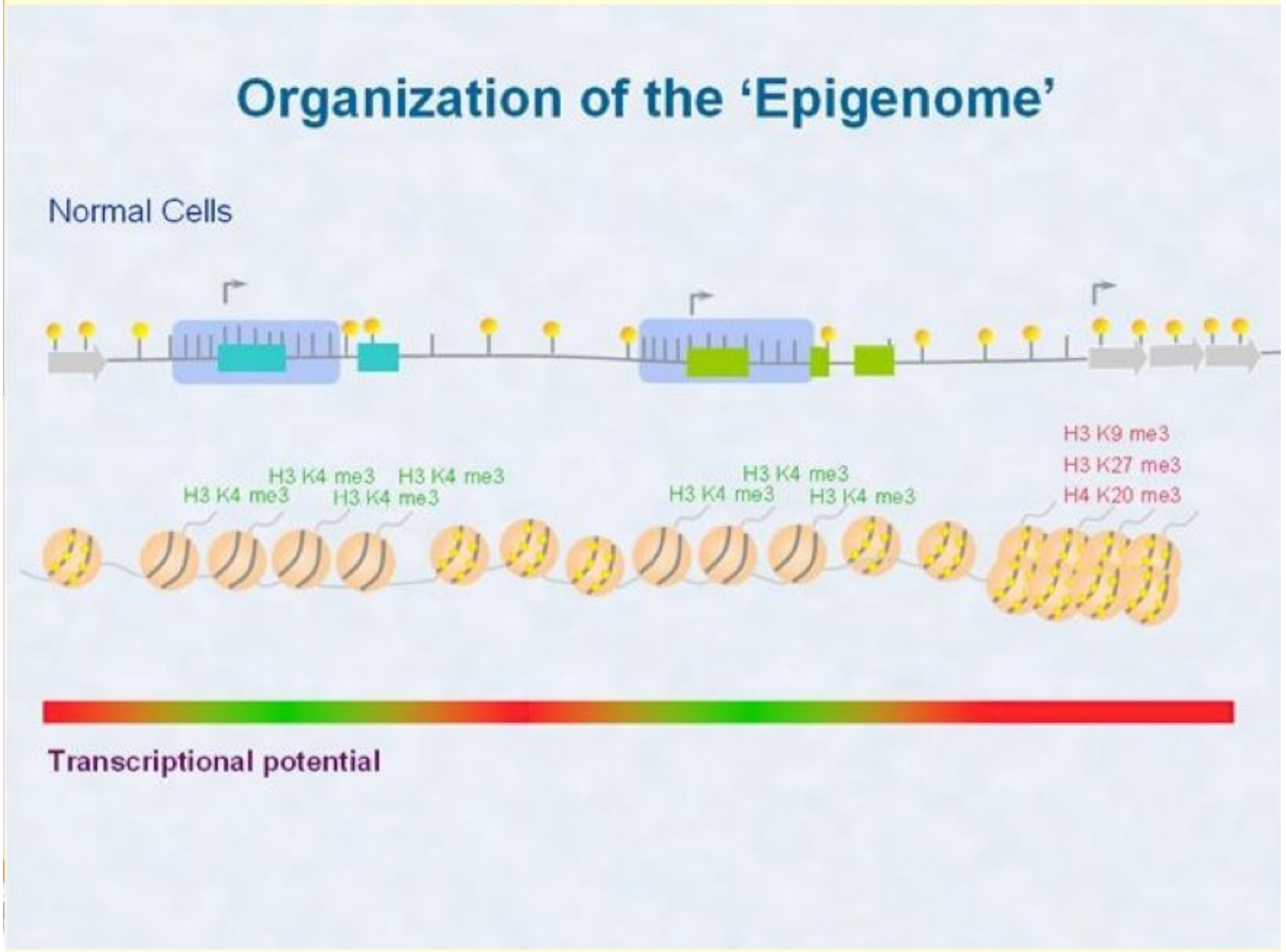
98% of the genome
1 CpG/100bp
majority methylated

<2% of the genome
1 CpG/10bp short stretches (~1000bp)
majority unmethylated

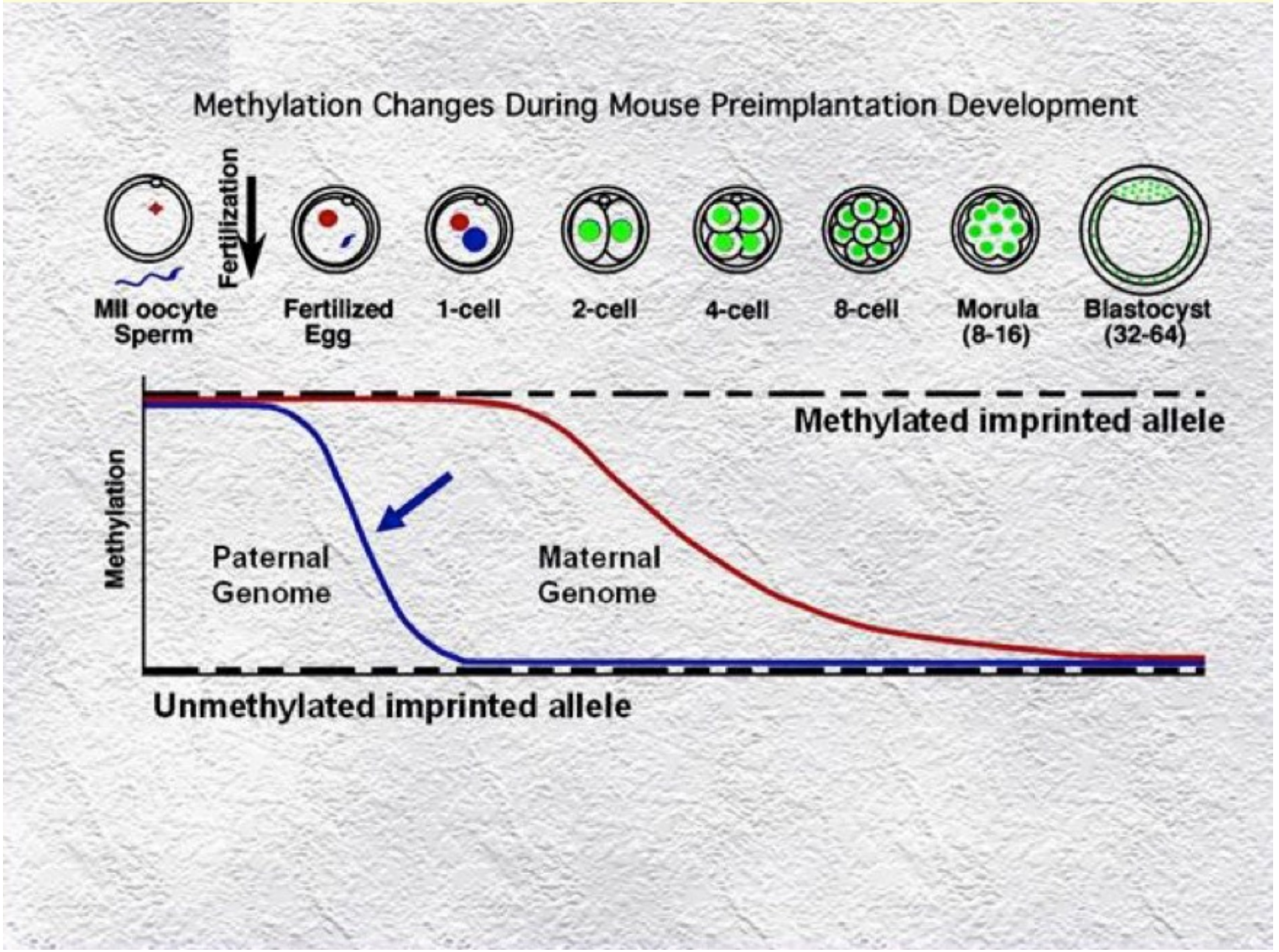


CpG islands

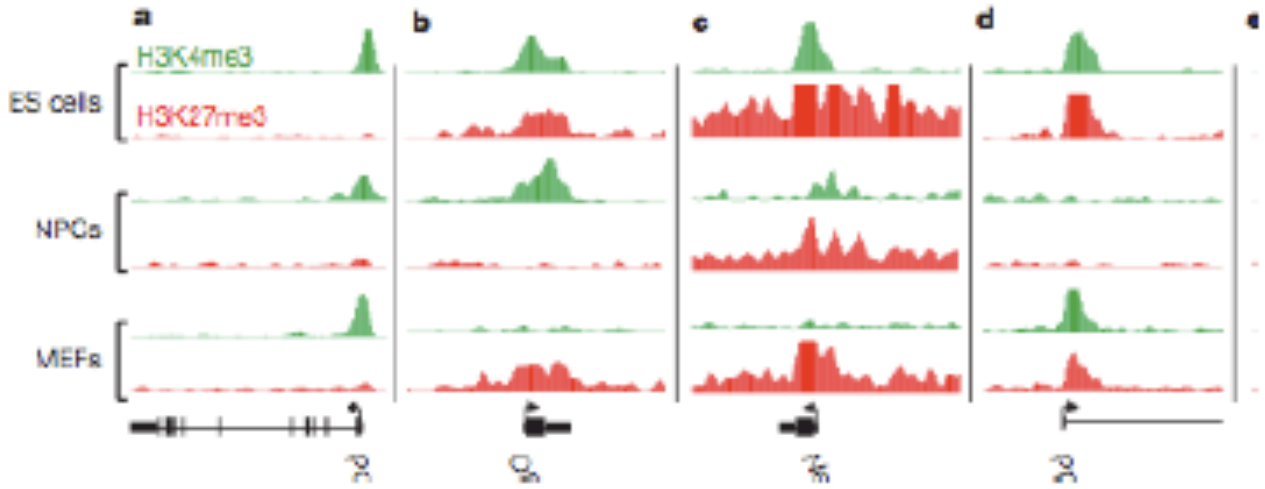
Organization of the Epigenome



Methylation Changes During Development

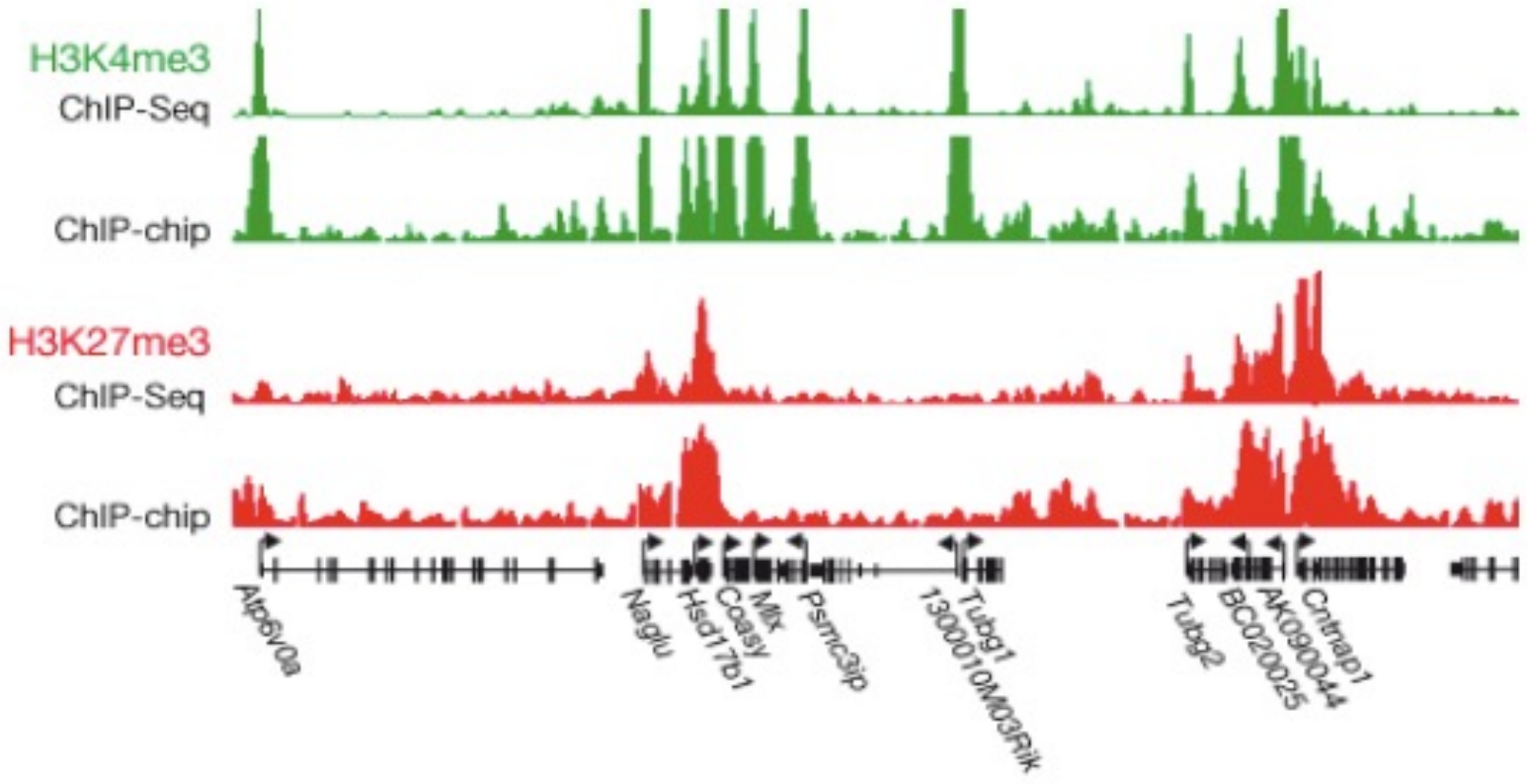


Histone modifications change during development



Mikkelsen et al. Nature 2007

Modification of histones can influence gene transcription



Mikkelsen et al. Nature 2007

Chromatin dynamics during cellular reprogramming

Effie Apostolou[1,2,3,4] & Konrad Hochedlinger[1,2,3,4]

Induced pluripotency is a powerful tool to derive patient-specific stem cells. In addition, it provides a unique assay to study the interplay between transcription factors and chromatin structure. Here, we review the latest insights into chromatin dynamics that are inherent to induced pluripotency. Moreover, we compare and contrast these events with other physiological and pathological processes that involve changes in chromatin and cell state, including germ cell maturation and tumorigenesis. We propose that an integrated view of these seemingly diverse processes could provide mechanistic insights into cell fate transitions in general and might lead to new approaches in regenerative medicine and cancer treatment.

What Drives Our Genes? Researchers Map The First Complete Human Epigenome

Stem cells offer enormous potential for repairing damaged tissue but historically they have been hard to obtain. Recent discoveries have shown that normal skin cells can be induced to form stem cells. This provides a readily available source of stem cells, but it's not known if these "induced" stem cells are really equivalent to embryonic stem cells, or if the range of adult cell types made from them are normal and could be used for therapeutic purposes. An important step to answer these questions is the development of "fingerprints" of all cell types. Chemical modifications to DNA occur in different patterns in each type of cell. These modifications serve as one type of molecular fingerprint that defines what makes a liver cell a liver cell vs. a heart cell vs. a neuron vs. a "pluripotent" stem cell that has the potential to become any one of these cell types and more. To understand how an embryonic stem cell differentiates to become any type of cell in the body, we need to decipher its molecular fingerprint. We also need to know if induced stem cells have the same molecular fingerprint as embryonic stem cells.

Researchers in the Common Fund's Epigenomics Program have taken the first step toward this goal. They have determined a high resolution fingerprint of one type of chemical group on the DNA of human embryonic stem cells and have compared it to what is found in fibroblasts, a type of cell found in many tissue types, including skin. They found that the fingerprints varied drastically between the two cell types. In addition, an analysis of limited regions of DNA from induced stem cells yielded a partial fingerprint that showed the same characteristics as in human embryonic stem cells. This discovery yields fundamental knowledge about stem cells and indicates that induced stem cells are molecularly similar to embryonic stem cells. It provides a method to identify cells as stem cells, and it is important for future work in which these cells will be used to regenerate adult tissues.

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Lister R, Pelizzola M, Dowen RH, Hawkins RD, Hon G, Tonti-Filippini J, Nery JR, Lee L, Ye Z, Ngo QM, Edsall L, Antosiewicz-Bourget J, Stewart R, Ruotti V, Millar AH, Thomson JA, Ren B, Ecker JR. Human DNA methylomes at base resolution show widespread epigenomic differences. Nature. 2009 Nov 19;462(7271):315-22. Epub 2009 Oct 14.PMID: 19829295. Link: http://www.nature.com/nature/journal/v462/n7271/full/nature08514.html

Age-dependent –loss of epigenetic control of differentation

MEDICINE & HEALTH

Hereditary Acquisitions

Acquired diseases that get passed on highlight epigenetic forces in human health BY JR MINKEL

How are researchers exploring the epigenome?

In a field of study known as epigenomics, researchers are trying to chart the locations and understand the functions of all the chemical tags that mark the genome.

Until recently, scientists thought that human diseases were caused mainly by changes in DNA sequence, infectious agents such as bacteria and viruses, or environmental agents. Now, however, researchers have demonstrated that changes in the epigenome also can cause, or result from, disease. Epigenomics, thus, has become a vital part of efforts to better understand the human body and to improve human health. Epigenomic maps may someday enable doctors to determine an individual's health status and tailor a patient's response to therapies.

As part of the ENCODE (ENCyclopedia Of DNA Elements) project-which aims to catalog the working parts of the genome-the National Human Genome Research Institute is funding researchers to make epigenomic maps of various cell types. Other NIH-supported investigators have developed a number of epigenomic maps from several human organs and tissues. These NIH projects are part of an international effort to understand how epigenomics could lead to better prevention, diagnosis and treatment of disease.

Double Meaning: Researchers Discover Hidden Codes in Genes

Researchers in the Common Fund's Epigenomics program have discovered a hidden layer of meaning contained within genes. Dr. John Stamatoyannopoulos at the University of Washington, along with his colleagues, have discovered some regions of DNA serve a double purpose. These regions contain instructions for how to make a protein, as well as information about when and how much of the protein should be made. Scientists previously thought that a particular stretch of DNA could be part of the genetic code, specifying the sequence of amino acid "building blocks" used to make a protein, or part of the regulatory code, containing elements that control expression of the protein. Dr. Stamatoyannopoulos and colleagues have identified "duons," stretches of DNA within the genetic coding regions that also contain a regulatory sequence called a transcription factor binding site. The researchers created a map showing where transcription factors were bound within genetic coding regions. Looking across 81 diverse human cell types, they found that approximately 15 percent of DNA within genetic coding regions has this dual purpose. This study suggests that mutations within these duons could alter the protein sequence itself, the regulation of the protein, or possibly both simultaneously. These results have important implications for how researchers interpret genetic mutations to provide information about human health and disease.

NIH Common Fund researchers link genetic variants and gene regulation in many common diseases

Dr. Stamatoyannopolous and colleagues found that some of the genetic variants linked to adult-onset diseases lie in regions of DNA that regulate genes during the early stages of development, providing a potential mechanism to explain the observation that some environmental exposures in utero or during early childhood are known to increase risk of diseases that produce symptoms years or even decades later. The researchers were also able to link genetic variants in non-coding regions with the genes they regulate, which has been a major challenge in genetic studies because the genes are often located a great distance away. In addition, researchers were able to pinpoint which cell types are affected by different diseases. These results provide new insight into disease mechanisms, and suggest novel targets for therapeutics development and disease prevention strategies.

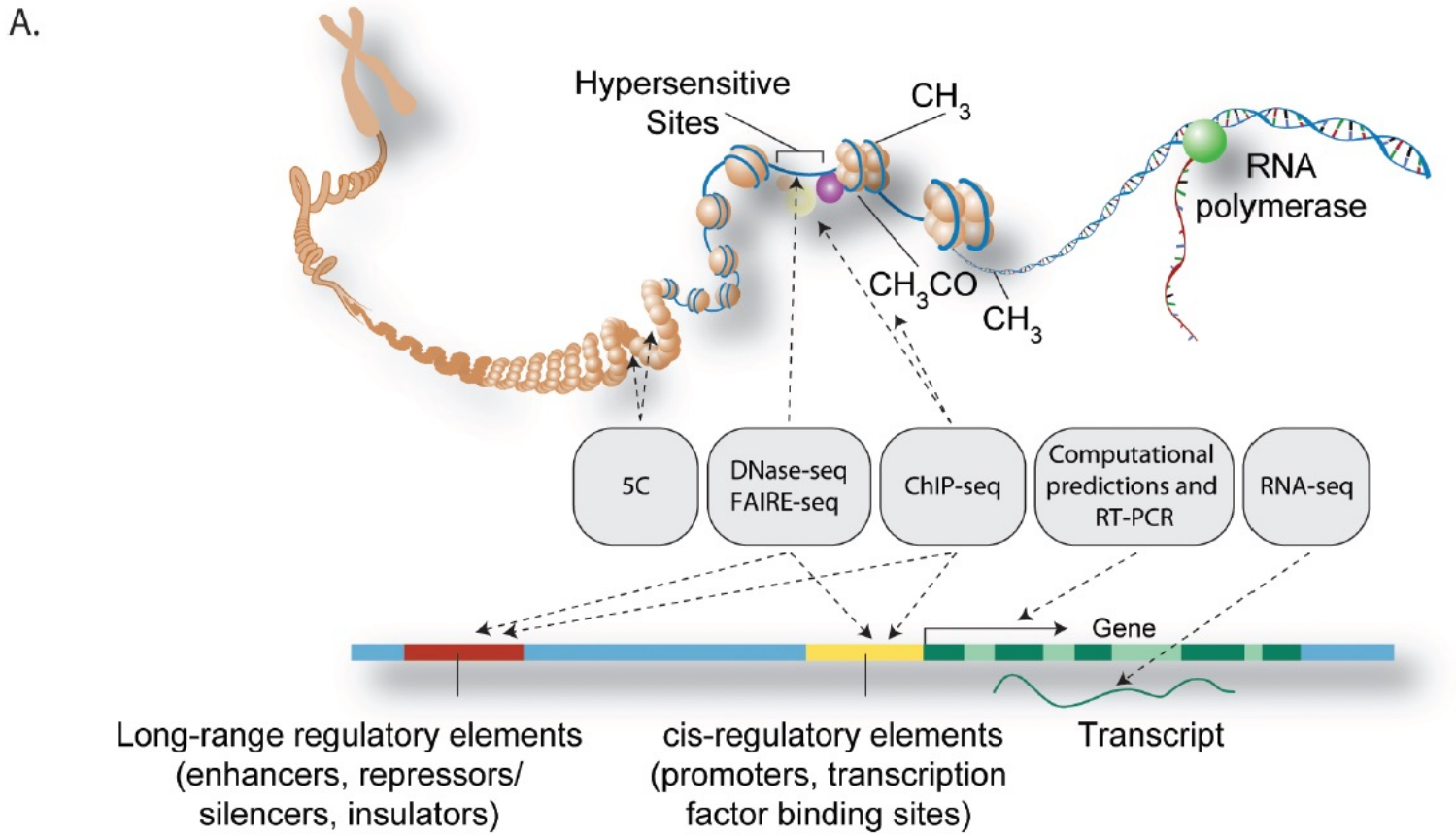
X-Linked Disorders: When One Healthy Gene Isn't Enough

NIH Roadmap Epigenomics program investigator Dr. Jeannie Lee led a research team to explore a new method of X reactivation that combines two approaches – inhibiting DNA methylation and simultaneously interfering with the RNA responsible for X inactivation (Xist). The team tested this approach in mouse cells to treat Rett Syndrome, which results from the mutation of a gene on the X chromosome that codes for the protein “MECP2.” MECP2 is important for development of nerve cells. Using this approach, the researchers saw 30,000 times greater production of MECP2 due to reactivation of the inactive X chromosome containing the healthy gene. The next step will be to test this treatment approach in a Rett Disorder animal model. The results of this study indicate that this new mixed approach is a promising treatment strategy for some X-linked disorders.

ENCODE

- Encyclopedia of DNA Elements
  - "The ENCODE Consortium is integrating multiple technologies and approaches in a collective effort to discover and define the functional elements encoded in the human genome, including **genes, transcripts, and transcriptional regulatory regions, together with their attendant chromatin states and DNA methylation patterns**. "
  - Ref: A User's Guide to the Encyclopedia of DNA Elements (ENCODE) (PLoS Biology, 2011)
- Initial phase launched in 2003—1% of the human genome
  - Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project (Nature, June 13, 2007)

Figure 1. The Organization of the ENCODE Consortium.



The ENCODE Project Consortium (2011) A User's Guide to the Encyclopedia of DNA Elements (ENCODE). PLoS Biol 9(4): e1001046. doi:10.1371/journal.pbio.1001046
http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.1001046

Key findings in cancer

1. Hypermethylation of CpG islands

   CpG islands in the promoters of tumor suppressor genes are methylated

   ↓

   Tumor suppressor genes are inactivated

   ↓

   Tumors are able to grow

2. General Hypomethylation

Epigenetic gene silencing in cancer – a mechanism for early oncogenic pathway addiction?

- Epigenetic gene silencing, which is associated with aberrant methylation of promoter DNA and transcriptional repression, is an important mechanism for the loss of gene function in cancer.
- Silencing can occur during the early stages of human tumour progression — in pre-invasive lesions — and involves disruption or over-activation of key developmental pathways and cell-signalling properties.
- These early gene-silencing events might be crucial for inducing the aberrant, early, clonal expansion of cells through the above alterations in key cell pathways.
- Early gene-silencing events might 'addict' cells to certain oncogenic pathways. This 'epigenetic addiction' could predispose cells to the accumulation of genetic mutations in these same pathways, which drives tumour progression.

Table 1 | **Mutated and hypermethylated genes in colon cancer cells***

Pathway or function	Hypermethylated genes	Mutations	Biological effects
Wnt signalling	*SFRP1*, *SFRP2*, *SFRP4* and *SFRP5*	Activating mutation in *CTNNB1*	Pathway activation; stem-cell and progenitor-cell expansion; cell survival
Mismatch repair	Wild-type *MLH1* allele	Second *MLH1* allele	Defects in DNA mismatch-repair
Cell-cycle regulation	Wild-type *CDKN2A* allele	Second *CDKN2A* allele	Blocks cyclin D–RB1 pathway, which results in cell proliferation
Epithelial-cell differentiation	*GATA4*, *GATA5*, *TFF1*, *TFF2*, *TFF3* and *INHA*	*TGFBR2*	Loss of normal differentiation
p53-mediated DNA damage response	*HIC1*		Loss of apoptosis response to DNA damage
Cell invasion	*TIMP3*		Loss of inhibition of matrix metalloproteinase enzymes, which promotes cell invasion

*Partial list of genetic mutations and heritable gene-silencing events that were identified in a single culture line (HCT116) of human colon cancer cells. *CDKN2A*, the gene that encodes p16; *CTNNB1*, the gene that encodes β-catenin; *GATA*, genes that encode GATA-binding transcription factors; *HIC1*, hypermethylated in cancer 1; *INHA*, inhibin-α; MLH1, a DNA mismatch-repair protein; RB1, retinoblastoma 1; *SFRP*, secreted frizzled protein; *TFF*, trefoil factor; *TGFBR2*, gene that encodes the transforming-growth-factor-β receptor 2; TIMP3, tissue inhibitor of metalloproteinase 3.

Human Epigenome Atlas

BCM
Baylor College of Medicine

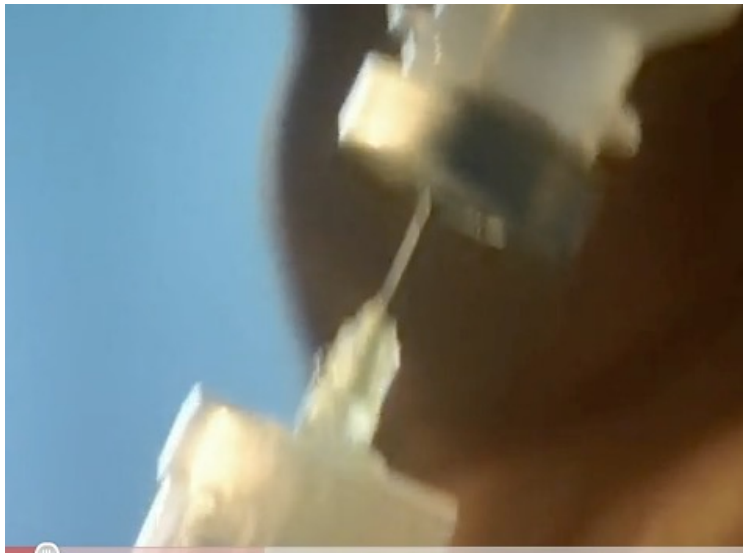
How do changes in the epigenome contribute to cancer?

Adding or removing methyl groups can switch genes involved in cell growth off or on.

For example, in a type of brain tumor called glioblastoma, doctors have had some success in treating patients with a drug, called temozolomide, that kills cancer cells by adding methyl groups to DNA.

Πολλά teratogens ασκούν τα συγκεκριμένα αποτελέσματα στο έμβρυο από τους epigenetic μηχανισμούς.

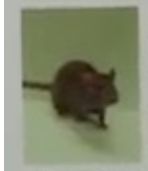
Pesticides : καρκινογονος ουσια και επιγενετικα αποτελεσματα



Pesticides Cause Lasting Damage to Rats' Sperm

Finding could have implications for humans, study suggests

By Amanda Gardner
HealthDay Reporter

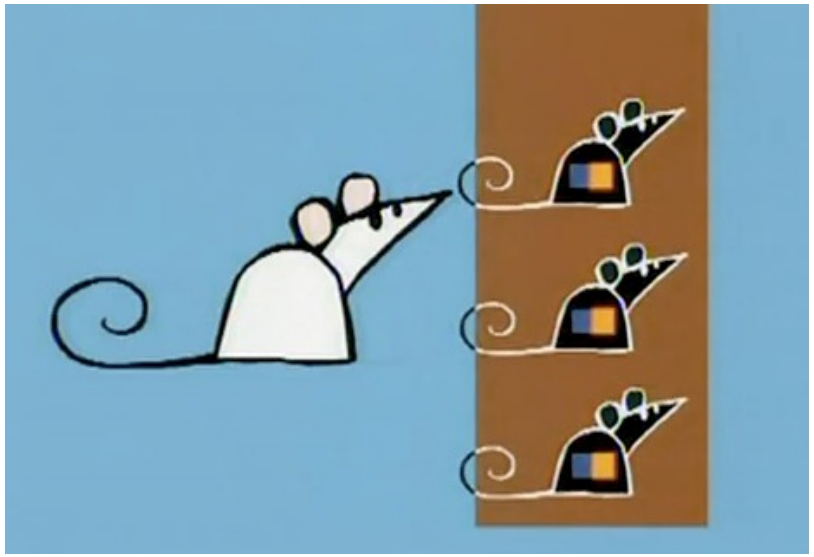


THURSDAY, June 2 (HealthDay News) -- Pregnant rats exposed to environmental toxins gave birth to four generations of males with decreased sperm function, a new study reports. It's not clear what these findings mean for humans, but the researchers aren't discounting the potential significance.

"It's not a large leap to show that similar things could be happening in humans, but we need to show it," said Michael K. Skinner, senior author of the study and a professor of molecular biosciences and director of the Center for Reproductive Biology at Washington State University, in Pullman, Wash. Perhaps more important, the findings also show that one exposure to an environmental toxin can generate permanent effects evident in several subsequent generations of rats -- and possibly other species, including humans, Skinner said. "If a pregnant woman is exposed to that environmental toxin during mid-gestatio it could actually cause a disease state in adult offspring which is heritable," he explained. "It looks like male sperm is being affected and permanently reprogrammed." The study appears in the June 3 issue of the journal Science.

Dr. Frederick Licciardi, associate director of reproductive endocrinology at New York University Medical Center, said there was no reason for humans to be unduly alarmed, but the various implications of the new findings were significant.

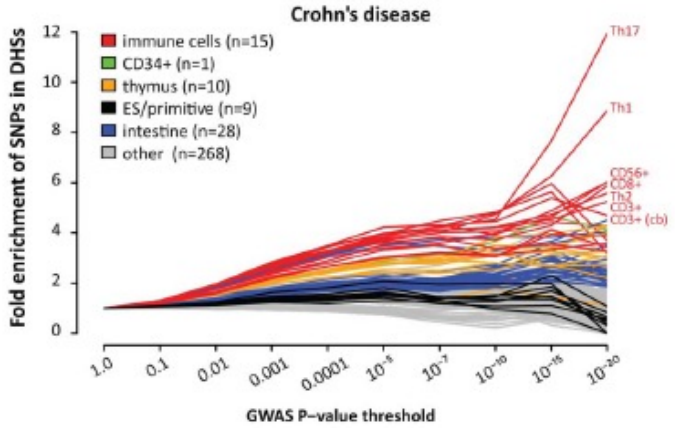
"Just the fact that there might be ways to epigenetically change the fetus from generation to generation by something that happens with the female rat or human is also interesting," he said.

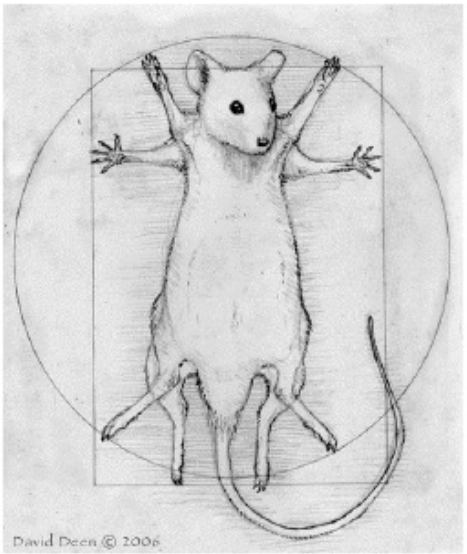


Εμφανιση του καρκινικου φαινοτυπου στους απογονους(3 γενιες)

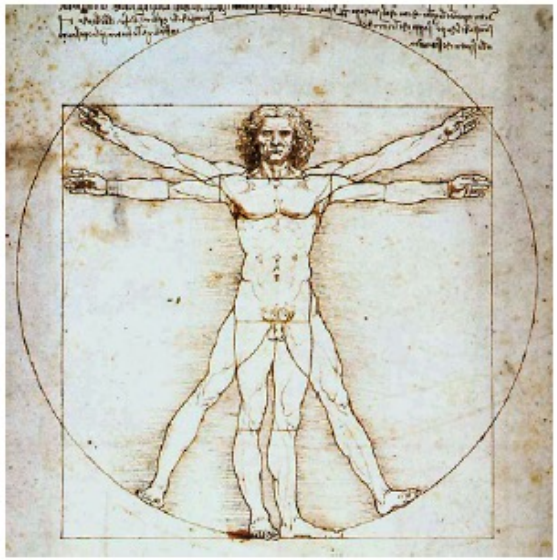
Human Brain Epigenomics

More neuronal epigenomes to interpret GWAS





Validation of animal epigenetic studies in post-mortem human brain



DeJager et al. 2014 Nat Neuro epub
Lunnon et al. 2014 Nat Neuro epub

Epigenetic Factors Can Explain Lower Than 100% Transmission of Schizophrenia in Identical Twins

- Identical twin studies show a schizophrenia concordance rate of 48-60%.
- If schizophrenia were a genetic disorder the concordance rate should be 100% .

Inheritance plays a part, but doesn't determine everything, or identical twins would be at 100%.

Image credit: http://www.pages.drexel.edu

Epigenetics of Schizophrenia

The first systematic **Genom- Wide DNA methylation study** was published in September 2011 in Human Molecular Genetics.

- This study showed that identical twins discordant for schizophrenia had a different metylation pattern.
- The twins with schizophrenia presented with a hypometylated promoter in a specific locus on chromosome 17 as compared with the unaffected twin.
- This explains why identical twins are not 100% concordant for schizophrenia.
- (Human Molecular Genetics, Sept.9,2011. Epigenetic Clue To Schizophrenia & Bipolar Disorder).

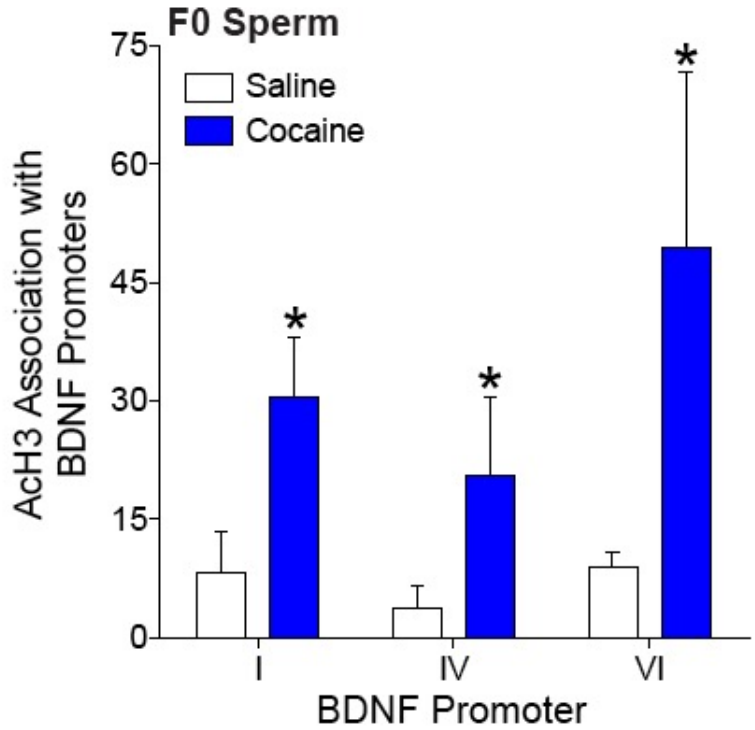
Stress

Stress –shock----→anxiety disorder (children)

Hongerwinter 1944

- German's blocked food to the Dutch in the winter of 1944.
- Calorie consumption dropped from 2,000 to 500 per day for 4.5 million.
- Children born or raised in this time were small, short in stature and had many diseases including, edema, anemia, diabetes and depression.
- The Dutch Famine Birth Cohort study showed that women living during this time had children 20-30 years later with the same problems despite being conceived and born during a normal dietary state.

What is the mechanism of cocaine-associated information transmission from father to son?



Increased BDNF promoter acetylation in sperm of cocaine-exposed fathers.

Cocaine can reprogram the sperm epigenome.

Vassoler et al. 2013 Nat. Neuro. 16: 42-47

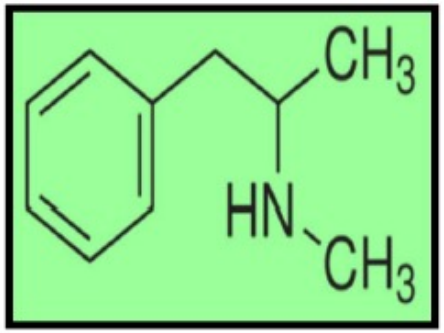
Drugs of Abuse and Epigenetic Changes

Cocaine

Nestler lab, Science, 2010
Nestler lab, PNAS 2011
Cowan lab, Neuron, 2012

Nicotine

Kandel lab, Sci Transl Med, 2011
Guidotti lab, PNAS 2008



Methamphetamine

Itzak lab, Mol Psychiatry, 2014
Cadet lab, PlosOne 2014
Grant lab, PlosOne 2014

Cannabinoids

Hurd lab, Biol Psych. 2012
Hurd lab, Neuropsychopharm 2014
Nagarkatti lab, JBC 2014

Opioids

Kreek lab,Neuropsychopharm.2008
Loh and Wei lab, PNAS 2012

Alcohol

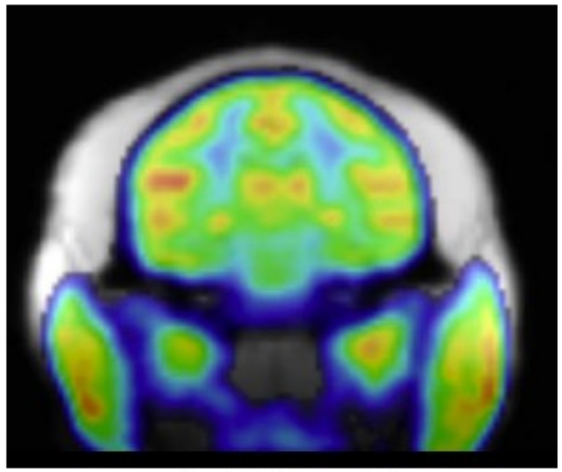
Goldman lab, PNAS 2011
Atkinson lab, PlosGenetics
2013Lanfumey lab, Mol Psych 2014

Intergenerational Effects of Drugs of Abuse

	EXPOSURE	PHENOTYPE (generation)
	**Morphine (*i.p.*) adolescent female rat**	**Increased morphine analgesia, male F1 progeny** *Byrnes et. Al. Brain Behav. Res 2011, 218: 200-205*
	**THC (*i.p.*) adolescents rat**	**Compulsive heroin seeking and altered striatal plasticity, male F1 progeny** *Szutorisz et al. Neuropsychopharm. 2014, 39: 1215-1323*
	**Cocaine self admin. adult male rat**	**Delayed acquisition of cocaine self-administration, male F1 progeny** *Vassoler et al. 2013 Nat. Neuro. 16: 42-47*

Epigenetic Imaging and Biomarkers

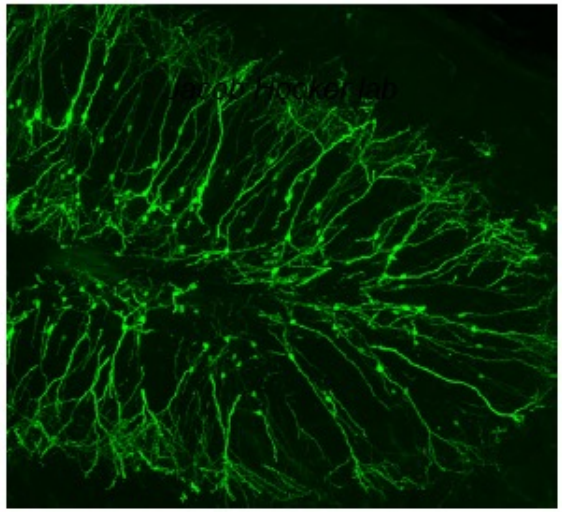
Improved *in vivo* imaging of epigenetic enzymes or changes



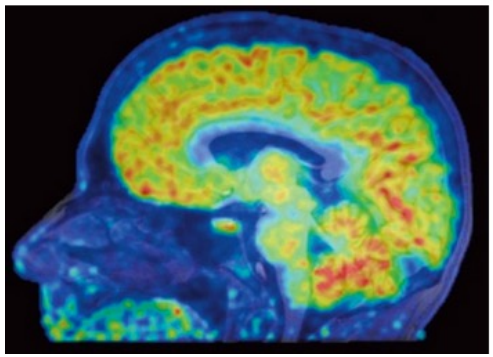
Jacob Hooker lab

Explore epigenetic biomarkers (e.g. chronic drug exposure)?

- **Olfactory neurons**
- **Cerebral spinal fluid**
- **Other cell types?**

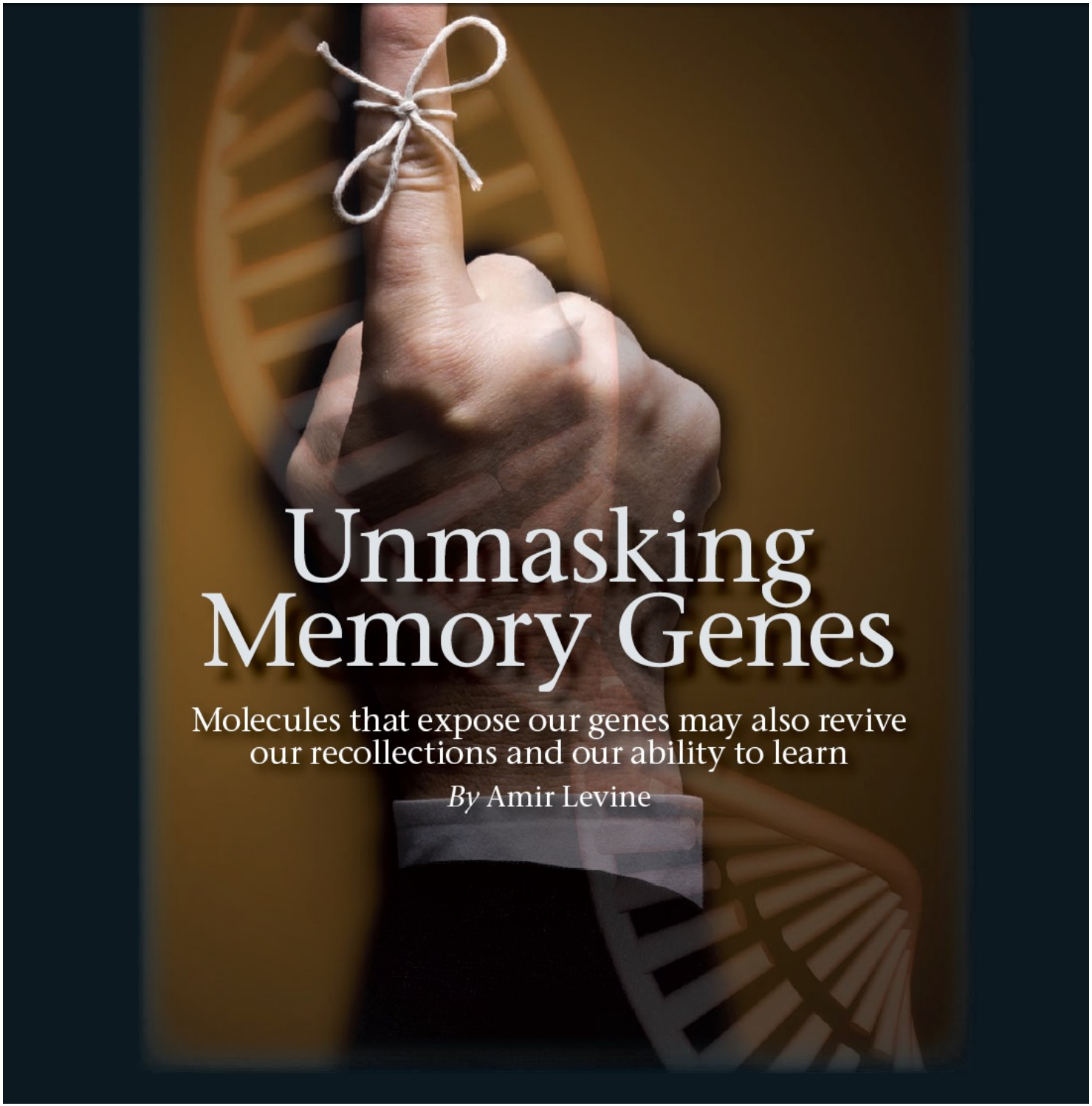


Epigenetic Imaging Shows Gene Activation in Living Brains for the First Time



Epigenomics grantee Dr. Jacob Hooker and collaborators have used a new neuroimaging tool to show, for the first time, where genes are being turned off or on in living human brains. Histone deacetylases (HDACs) are enzymes that regulate gene expression through epigenetic modifications and are therefore useful therapeutic targets. Using a specific HDAC imaging probe called Martinostat and positron emission tomography (PET) scanning, Dr. Hooker's group has visualized HDAC expression in the living brain of eight healthy volunteers. In addition to observing distinct regions of HDAC expression within human brains regions, they also saw strikingly conserved regions of HDAC expression levels between these individuals. These conserved patterns within and between healthy individuals are significant because this lays the groundwork for understanding epigenetic information in the human central nervous system (CNS) and related diseases. "I'm hoping these colorful maps let us compare healthy brains with the brains of people with schizophrenia, Alzheimer's, and other diseases," said Hooker. The authors conclude that this work provides a "critical foundation for how to quantify epigenetic activity in the living brain and in turn accomplish HDAC inhibition in the CNS as a therapy for human brain disorders".

Common Fund-supported Researchers Map Epigenome of More Than 100 Tissue and Cell Types



Unmasking Memory Genes

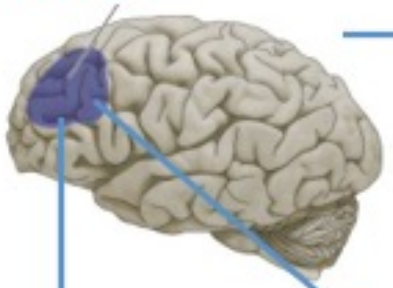
Molecules that expose our genes may also revive our recollections and our ability to learn

By Amir Levine

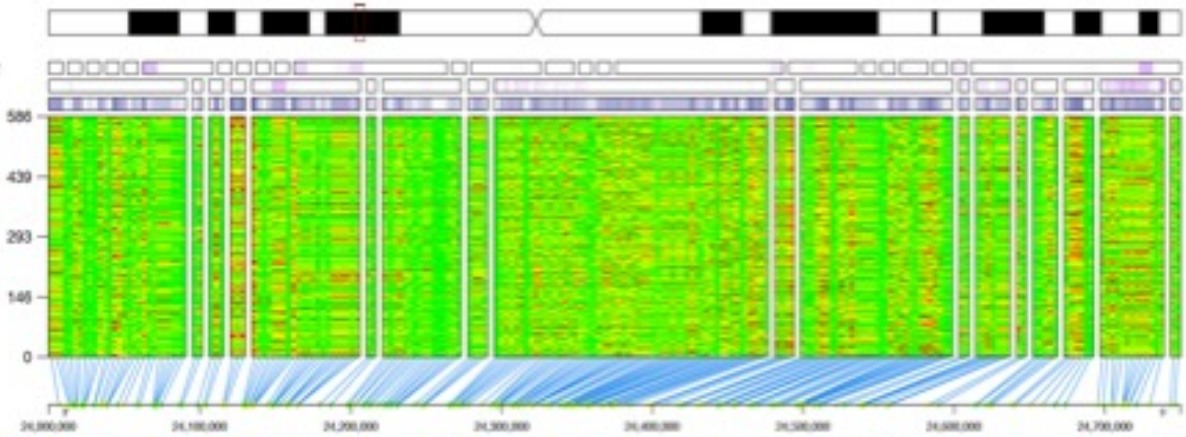
Brain methylation changes in Alzheimer's patients

MAP Memory and Aging Project
+ ROS Religious Order Study

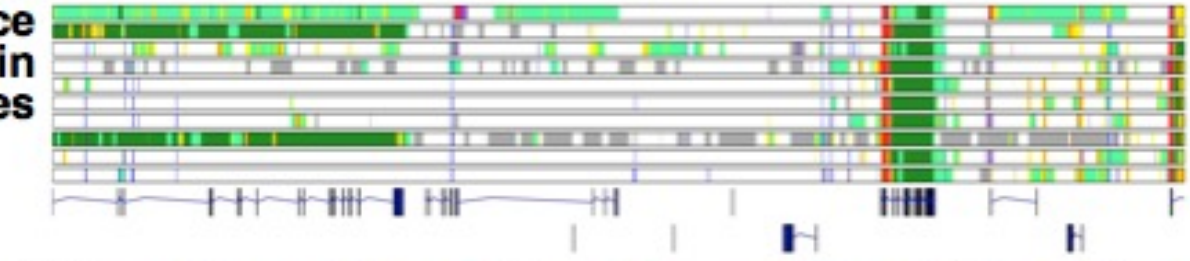
Dorsolateral PFC

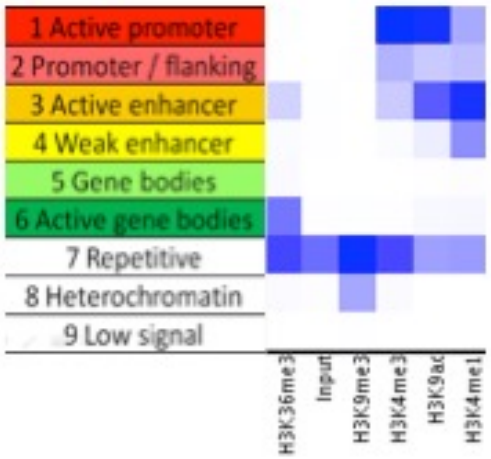


Genotype (1M SNPs x700 ind.)

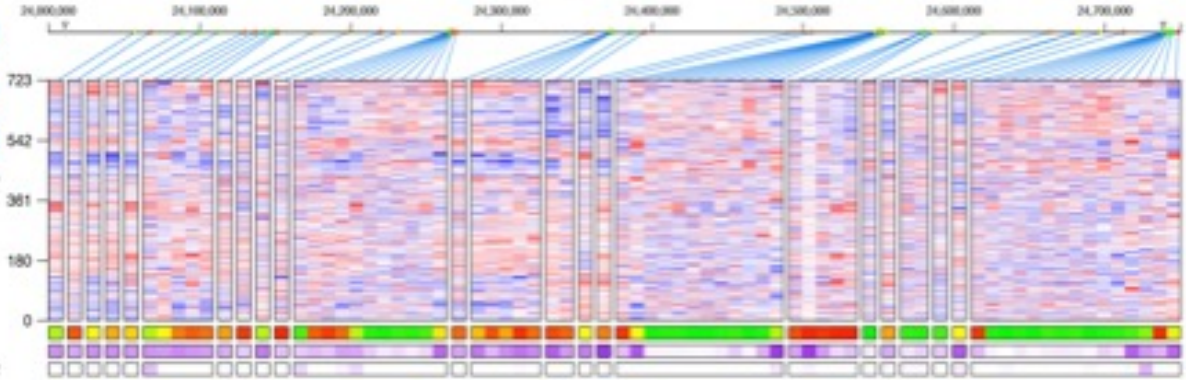


Reference Chromatin states





Methylation (450k probes x 700 ind)



- Variation in methylation patterns largely genotype driven
- Global signature of repression in 1000s regulatory regions: hypermethylation, enhancer states, brain regulator targets

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Epigenomics

Epigenomics

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- Initiatives
- Press Releases
- Highlights
- In the News

For Researchers

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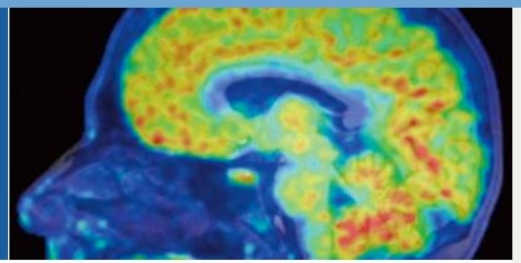
- Funding Opportunities
- Resources
- Publication Search
- Meetings and Workshops
- NIH Working Group

Epigenetic Imaging Shows Gene Activation in Living Brains for the First Time

Read more...



ROADMAP epigenomics PROJECT

Program Snapshot

The Common Fund's **Epigenomics Program** has generated a set of reference epigenomes and new research tools, technologies, datasets, and infrastructure to accelerate our understanding of how genome-wide chemical modifications to DNA regulate gene activity without altering the DNA sequence itself and what role these modifications play in health and disease.

The Roadmap Epigenomics program issued its first round of awards in 2008. The program issued 77 awards and produced 111 reference maps of epigenomic modifications in a variety of healthy human cells and tissues, as well as other resources and tools that are extensively used by the biomedical research community. The Roadmap datasets are available through the Roadmap Epigenomics Mapping Consortium website and the Baylor Epigenome Atlas. The Roadmap Epigenomics program became a founding member of the International Human Epigenome Consortium (IHEC) in 2010. Roadmap Epigenomics awardees have published over 800 peer-reviewed articles. An integrative analysis paper, together with more than 20 companion papers, was published in a 2015 special edition of *Nature*. Program funding ended in 2017.

NIH Roadmap Epigenomics

Information about the data, protocols, reagents, and analytical tools generated by the Epigenomics Program, including over 100 comprehensive reference epigenomic datasets from hundreds of human cell types and tissues, can be found on the Roadmap Epigenomics Website.

Epigenomes Around the World

The Epigenomics Program is part of the International Human Epigenome Consortium that aims to coordinate worldwide epigenome mapping and characterization efforts. Read more about the IHEC...

IHEC International Human Epigenome Consortium

Creative Mind

Anshul Kundaje was recently featured on the NIH Director's Blog. He led the integrative analysis of the Roadmap Epigenomics data as part of a team funded by the NIH Common Fund

Uncovering Important Epigenetic Changes in Neuronal Cell Development

Duke Researchers funded by the Common Fund are utilizing epigenomics to enrich our understanding of development of the human brain. With increased understanding of how and when epigenetic marks are influencing gene expression, researchers may be able to predict and understand more about the fate of particular neurons and understand fundamental principles of gene regulation in the brain. Highly comprehensive epigenomic data generated from the West lab at Duke University is uncovering more information about the extremely dynamic system coordinating the intricate temporal pattern of neuronal development.

The study uses a technique called DNase I Hypersensitivity (DHS) to map chromatin accessibility - sites in the genome that are structurally accessible to the cellular machinery that turn on and off genes- in different stages of neuron development. Using the developing mouse cerebellar cortex that is primarily comprised of a single type of neuron, a cerebellar granule neuron (CGN), they were able to study a highly specific cell population. They mapped chromatin accessibility in these cells at three key times in postnatal development and found highly dynamic changes at over 20,000 regulatory sites during these different stages. Upon further analysis many of these enhancer sites contained binding sites for several transcription factor families; including zinc finger proteins of the cerebellum (ZIC). Following up with functional studies, the researchers confirmed a previously unknown role for these ZICs in coordinating gene expression in the growth and maturation of neurons. Furthermore they found that marks remained even after a gene was turned off—labeling the genes for an easy "start up" later. This raises the possibility that the accessibility of enhancer sites can be in a "primed" state which has implications for learning and memory. Ultimately, understanding more about these the epigenetic changes in neuronal cell development across the genome may help researchers understand and potentially design therapies targeting diseases of the brain.

Reference:

Regulation of Chromatin Accessibility and Zic Binding at Enhancers in the Developing Cerebellum. Frank, C. L., F. Liu, R. Wijayatunge, L. Song, M. T. Biegler, M. G. Yang, C. M. Vockley, A. Safi, C. A. Gersbach, G. E. Crawford, and A. E. West. *Nature Neuroscience*. 18(5): 647-656.

www.nature.com/collections/vbqgtr/
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Epigenome Roadmap

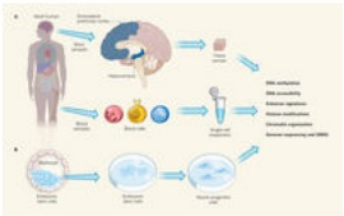
Welcome to the Epigenome Roadmap! Here, we have collected research papers describing the main findings of the NIH Roadmap Epigenomics Program, the aim of which was to systematically characterize epigenomic landscapes in primary human tissues and cells. The papers are complemented by eight threads each of which highlights a topic that runs through more than one paper. Threads are designed to help you explore the wealth of information collectively published across several Nature Research journals. Each thread consists of relevant paragraphs, figures and tables from across the papers, united around a specific theme.

We invite you to explore the research content, the News & Views, the video and other associated material.

News and Multimedia

Nature News | Editorial

Beyond the genome



Nature | News and Views

Epigenomics: Roadmap for regulation

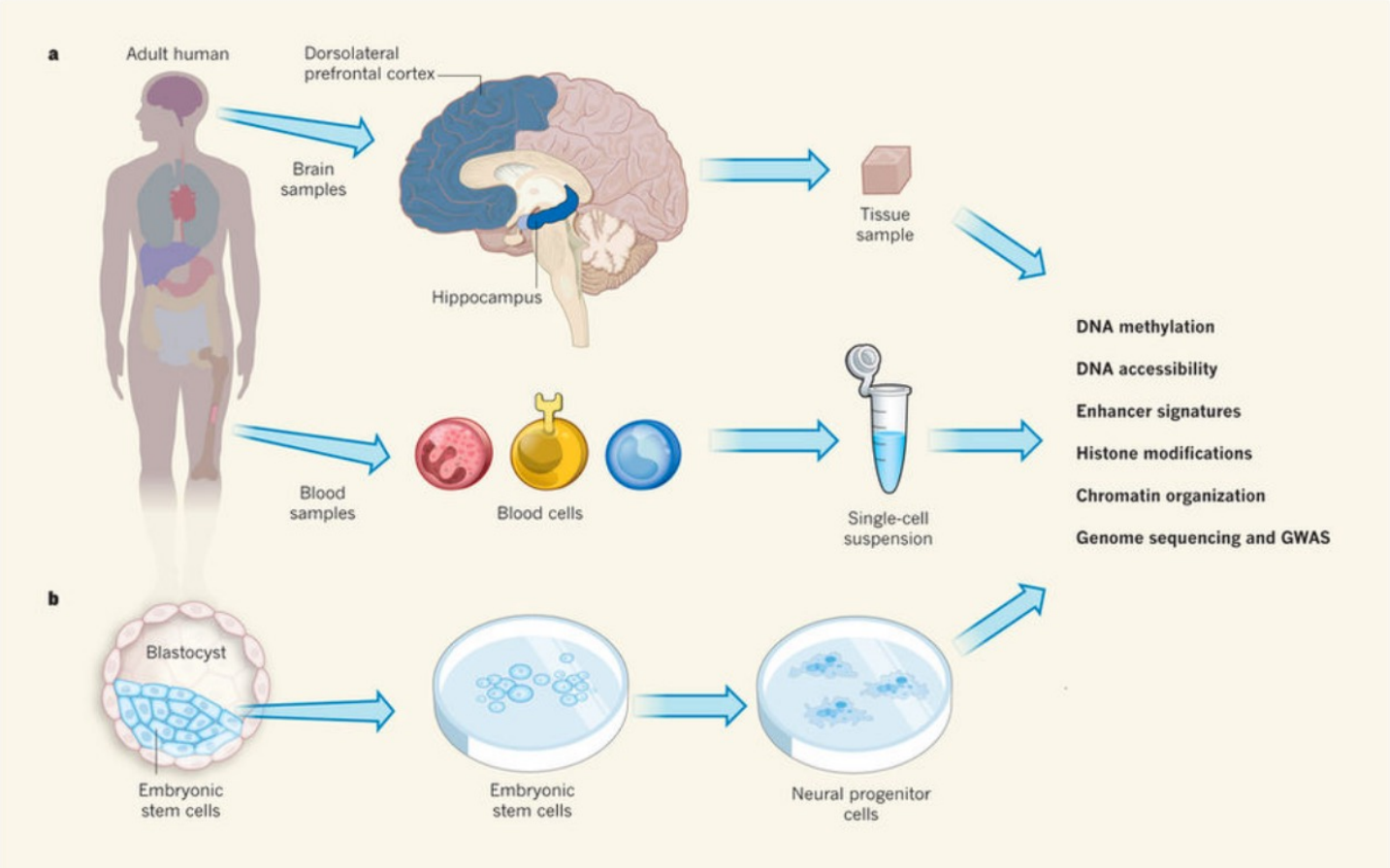
Casey E. Romanoski, Christopher K. Glass, Hendrik G. Stunnenberg, Laurence Wilson, Genevieve Almouzni

Nature News | News

Epigenome: The symphony in your cells

Kerri Smith

From: Roadmap for regulation



The Roadmap Epigenomics Project has produced reference epigenomes that provide information on key functional elements controlling gene expression in 127 human tissues and cell types and encompassing embryonic and adult tissues, from healthy individuals and those with disease.

ROADMAP epigenomics PROJECT

Search: GO

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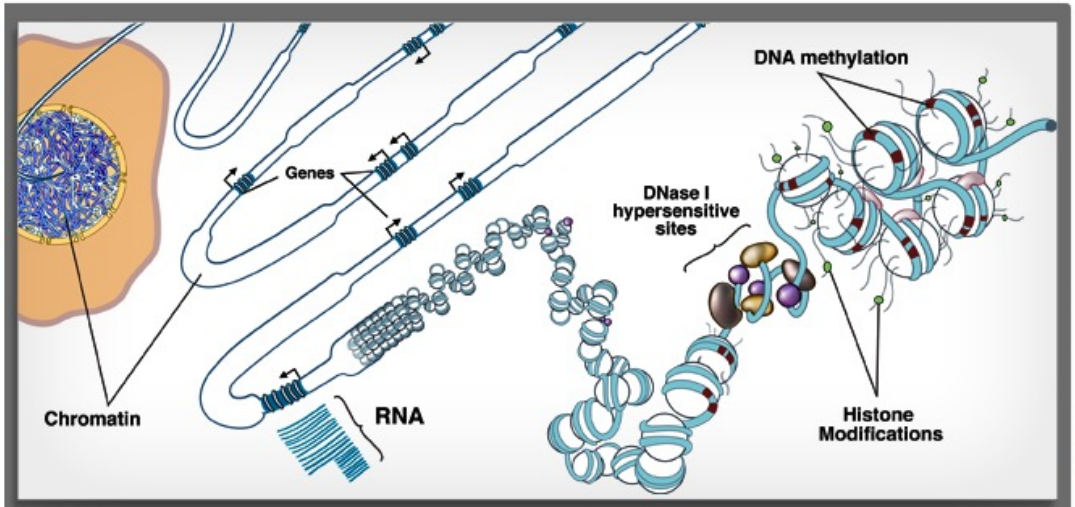
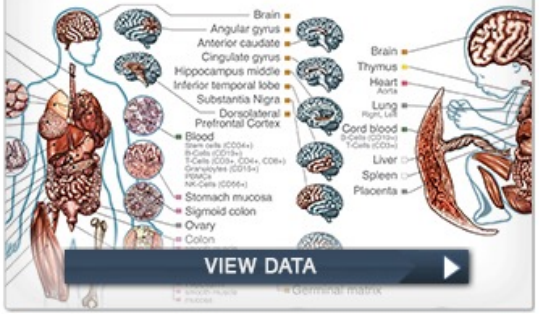
OVERVIEW | PROJECT DATA | MAPPING CENTERS | PROTOCOLS & STANDARDS | PUBLICATIONS



NIH Roadmap Epigenomics Mapping Consortium

The NIH Roadmap Epigenomics Mapping Consortium was launched with the goal of producing a **PUBLIC** resource of human epigenomic data to catalyze basic biology and disease-oriented research. The Consortium leverages experimental pipelines built around next-generation sequencing technologies to map DNA methylation, histone modifications, chromatin accessibility and small RNA transcripts in stem cells and primary ex vivo tissues selected to represent the normal counterparts of tissues and organ systems frequently involved in human disease. The Consortium expects to deliver a collection of normal epigenomes that will provide a framework or reference for comparison and integration within a broad array of future studies. The Consortium also aims to close the gap between data generation and its public dissemination by rapid release of raw sequence data, profiles of epigenomics features and higher-level integrated maps to the scientific community. The Consortium is also committed to the development, standardization and dissemination of protocols, reagents and analytical tools to enable the research community to utilize, integrate and expand upon this body of data.

INTEGRATIVE ANALYSIS of 111 REFERENCE HUMAN EPIGENOMES



VIEW/DOWNLOAD QUICK LINKS

Genome Browsers

- http://genomebrowser.wustl.edu/
- http://epigenomegateway.wustl.edu/

Data Repositories

- NCBI Epigenomics Gateway
- Epigenome Atlas

NEWS

18 FEB NIH-supported researchers map epigenome of more than 100 tissue and cell types

4 SEP IHEC data portal online

Archives

Human Epigenome Atlas

The Current Release (Release 9) of the Human Epigenome Atlas

The Current Release (Release 9) of Uniformly Processed Data

The Human Epigenome Atlas is produced by the NIH Epigenomics Roadmap Consortium.

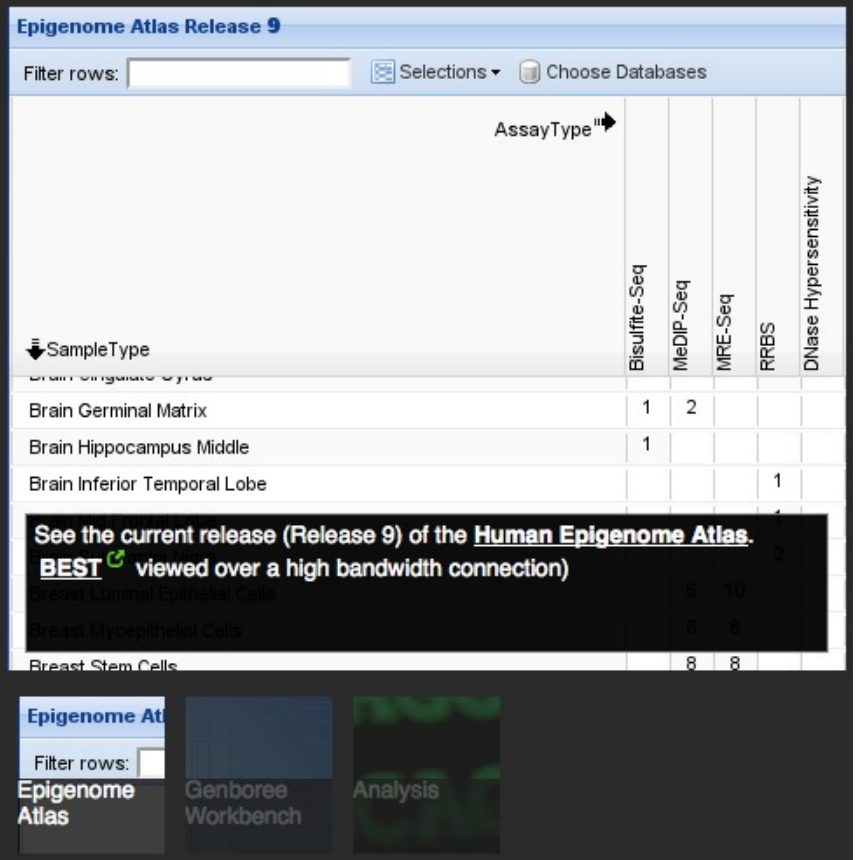
The Human Epigenome Atlas includes human reference epigenomes and the results of their integrative and comparative analyses. Human Epigenome Atlas provides detailed insights into locus-specific epigenomic states like histone marks and DNA methylation across tissues and cell types, developmental stages, physiological conditions, genotypes, and disease states.

Epigenome Atlas Release 9

- Interactive Visualization and Download
- Data Download via http
- Data Download via ftp

Other resources from the Roadmap Epigenomics Project:

- Epigenome Browser at Washington University in Saint Louis
- Roadmap Epigenomics Data at NCBI/GEO



Bioinformatics Research Laboratory
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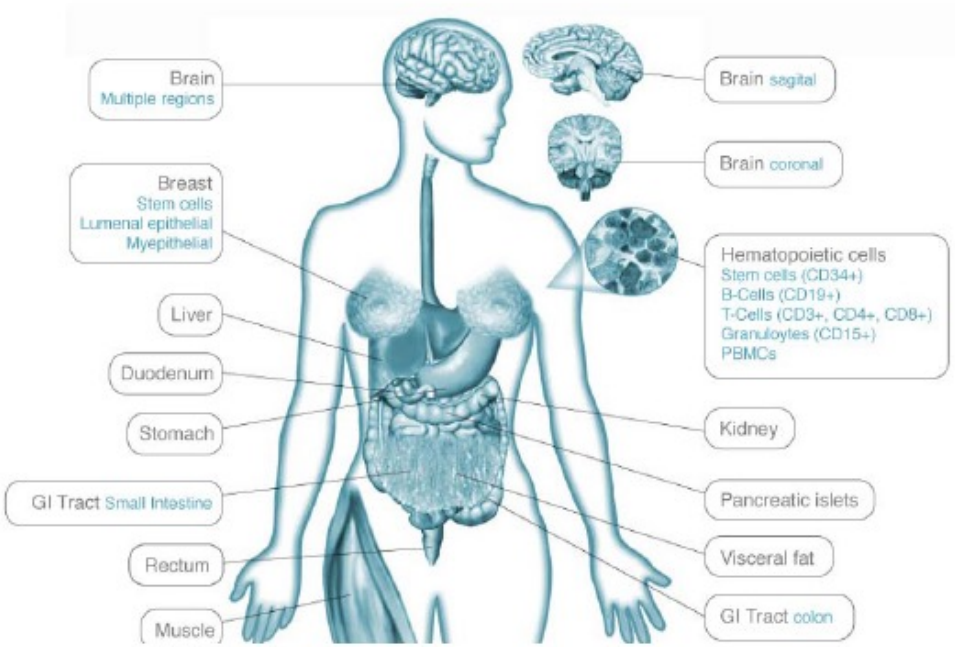
Human epigenome atlas

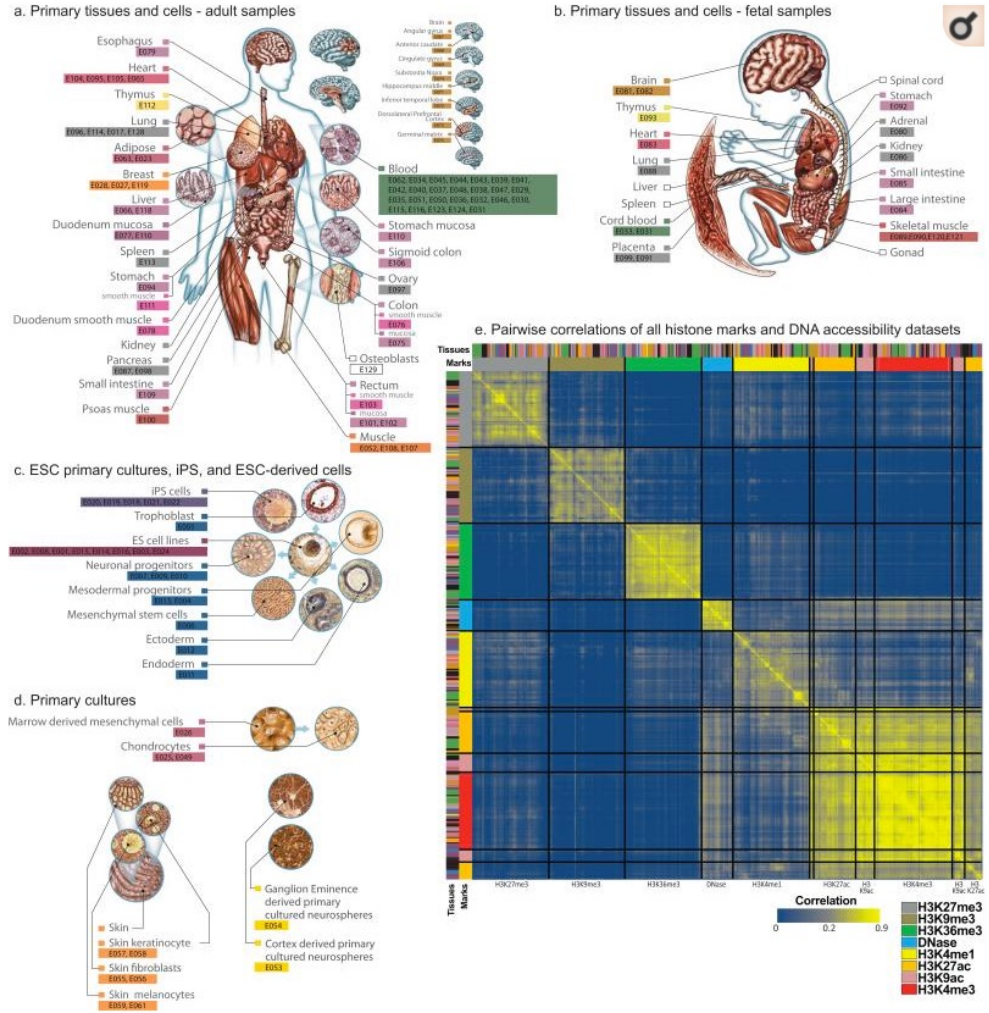
- Successive releases of the Atlas will provide progressively more detailed insights into locus-specific epigenomic states, including histone marks and DNA methylation marks across specific tissues and cell types, developmental stages, physiological conditions, genotypes, and disease states.

Epigenome Mapping Centers

GOAL: **Generate comprehensive epigenomic maps for "normal" human cells and tissues**

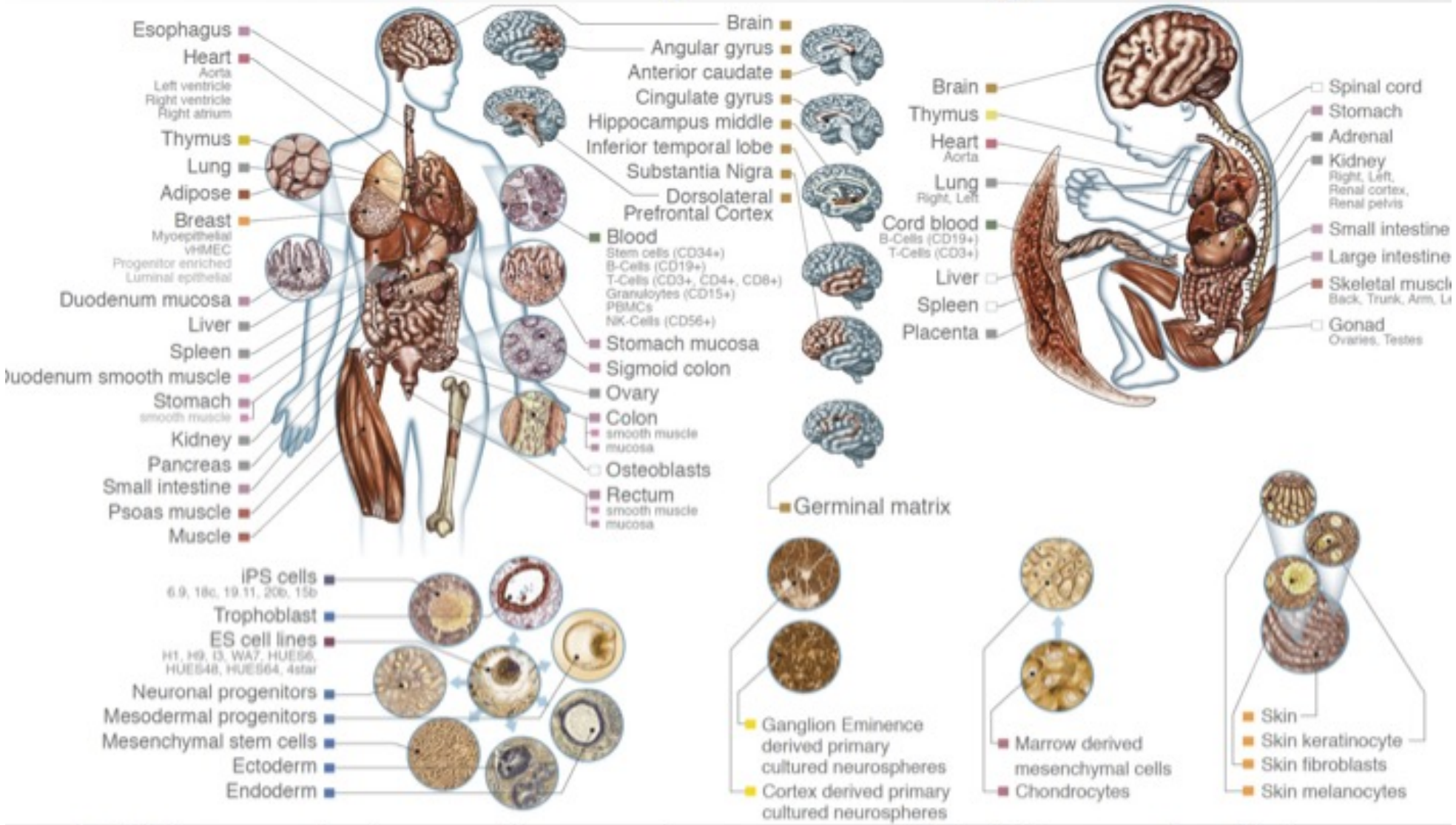


- **First human methylomes (*Nature* 2009)**
- **92 comprehensive epigenome datasets**
- **Data publically accessible:** http://www.roadmapepigenomics.org/



a-d. Tissues and Cell Types of Reference Epigenomes. Comprehensive listing of all 111 reference epigenomes generated by the consortium, along with epigenome identifiers (EIDs), including: (a) adult samples; (b) fetal samples; (c) ESC, iPSC, and ESC-derived cells; and (d) primary cultures. Colors indicate the groupings of tissues and cell types (as in Fig. 2b, and throughout the manuscript). For five samples (adult osteoblasts, and fetal liver, spleen, gonad, and spinal cord), no color is present, indicating that these are not part of the 111 reference epigenomes (ENCODE 2012 samples, or not all five marks in the core set were present), but datasets from these samples are high quality and were sometimes used in companion paper analyses, and are available to the public. **e. Assay correlations.** Heatmap of the pairwise experiment correlations for the core set of five histone modification marks (H3K4me1, H3K4me3, H3K36me3, H3K27me3, H3K9me3) across all 127 reference epigenomes, the two common acetylation marks (H3K27ac and H3K9ac), and DNA accessibility (DNase) across the reference epigenomes where they are available. Yellow indicates relatively higher correlation and blue lower correlation. Rows and columns were ordered computationally to maximize similarity of neighboring rows and columns

The most complete map of human gene regulation



- **2.3M regulatory elements across 127 tissue/cell types**
- **High-resolution map of individual regulatory motifs**
- **Circuitry: regulators→regions→motifs→target genes**

IHEC

International Human Epigenome Consortium

- International effort
- Generate comprehensive sets of reference epigenomes (1000)
- Common data standards
- Rapid data sharing
- Understand epigenomic basis of disease
- @$125M non-US effort on reference epigenomes, plus

The Roadmap Epigenomics Project opens new drug development avenues

The US National Institutes of Health's US$240-million epigenomics investment could improve the study of disease biology, the identification of new drug targets, the validation of animal models and more.

Asher Mullard

Fourteen years since publishing the first draft of the human genome, researchers have now laid out an unprecedented map of the epigenomic landmarks that cover the DNA of different cell and tissue types. Hundreds of collaborating scientists, brought together under the US National Institutes of Health (NIH)'s 10-year Roadmap Epigenomics Project, published 21 dense technical primary papers in *Nature* and its sister journals, potentially providing a key step towards understanding the diverse functions and differential gene expression profiles of different cell types that share the same genome (www.nature.com/epigenomeroadmap). The preparation of this roadmap was just a prelude to a long road trip ahead, but the implications for drug developers could be huge.

"This is extremely important science and a set of papers here that are going to be looked back on in several years as just ground-breaking work," says Mark Curran, Vice President of Systems Pharmacology and Biomarkers in the immunology therapeutic area at Janssen, who was not involved in the Roadmap. Although the data need to be validated at the bench, and some uncharted genomic regions remain to be filled in, he says the project could shed new light on disease, druggable targets, biomarkers and animal models.

Janssen and its parent company Johnson & Johnson are one of a few firms who are already digging in to the applicability of epigenomic data beyond oncology, the only therapeutic area in which epigenome-modulating drugs have so far been approved (see *Nature Rev. Drug Discov.* **14**, 225–226; 2015). In addition to its in-house efforts, Johnson & Johnson has co-bankrolled the formation of Rodin Therapeutics, a biotech that is developing histone deacetylase (HDAC) inhibitors for Alzheimer disease (AD), and Janssen is co-supporting academic research into the epigenomics of Crohn disease and ulcerative colitis. Other pharmaceutical companies are also gearing up their epigenomic engines.

They will have no shortage of data to work on, with a further deluge of epigenomic data on its way. The NIH's Roadmap sequenced reference epigenomes from over 111 different primary cells and tissue types, and the larger International Human Epigenome Consortium (IHEC), of which the Roadmap project is a member, is co-ordinating the analysis of a total of 1,000 primary cell and tissue epigenomes. The European Union's Blueprint project, another member of the IHEC, is set to publish another 100 reference epigenomes by next year.

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Common Fund Researchers Detail Epigenomic Changes during Development

Most cells in the human body contain the same DNA, yet different types of cells have vastly different shapes, sizes, and functions. How do these differences arise? Chemical modifications to DNA and DNA-associated proteins, called epigenetic modifications, help instruct a cell to express only a sub-set of genes, giving rise to different characteristics for different cell types. Epigenetic regulation of gene expression changes during development, and can also change as a result of environmental exposures, pharmaceuticals, aging, and diet. Some epigenetic changes promote health and normal development, while others may contribute to a variety of diseases. Three recent publications in the journal *Cell* from the Epigenomics program's Reference Epigenome Mapping Centers reveal important insights about epigenomic changes that take place during development, as non-specialized stem cells differentiate into specific cell types, such as heart, brain, skin, and many more.

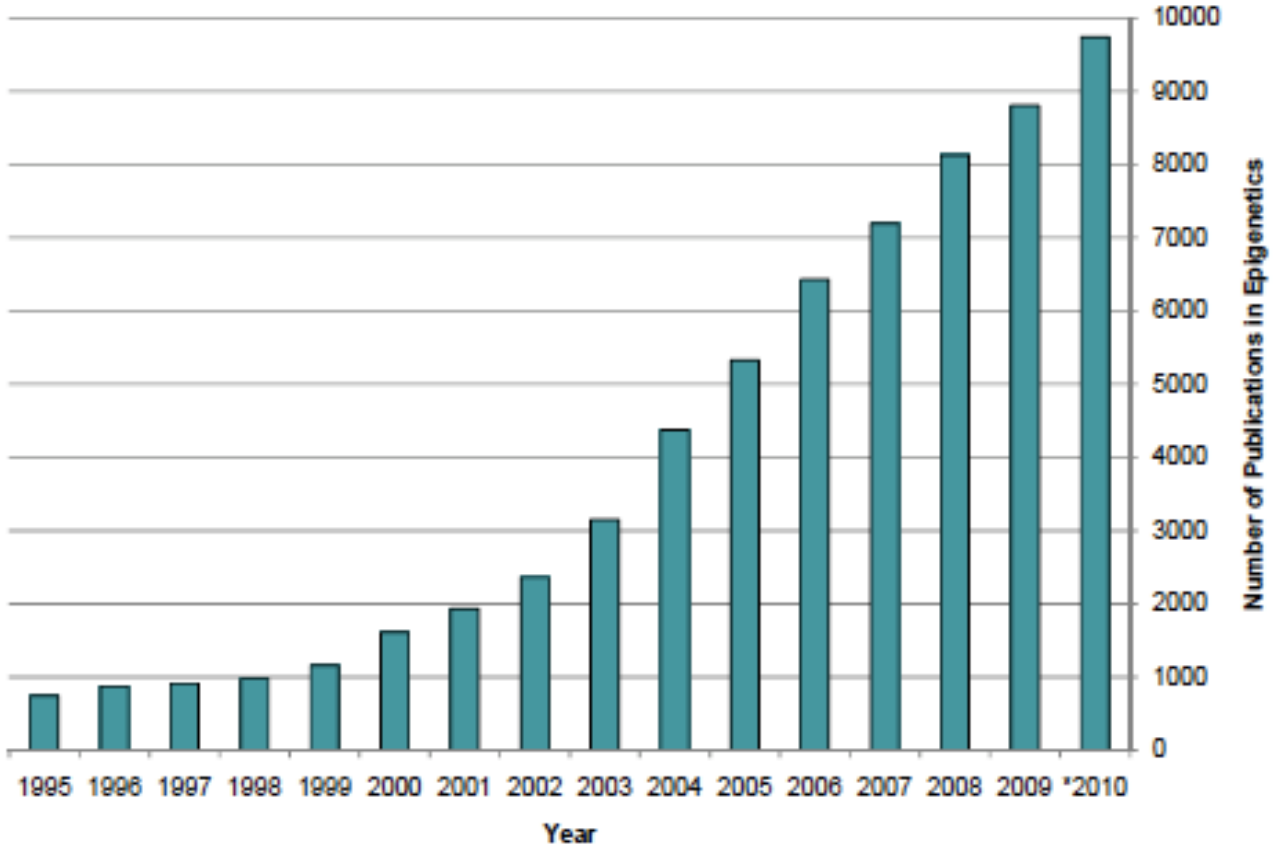
Dr. Bing Ren at the San Diego Epigenome Center examined epigenetic events that occur during early embryonic development, as stem cells begin to differentiate into specific cell lineages. Dr. Ren's work shows that distinct epigenetic mechanisms regulate early and late stages of stem cell differentiation. Interestingly, several gene families that are known to play important roles in development were notably lacking in one type of epigenetic mark, called DNA methylation, in early stages of development. Some of these same genes were found to have excess levels of DNA methylation in cancer, suggesting a possible role for epigenetic regulation of developmental genes in several types of cancer.

An additional study by Drs. Bradley Bernstein and Alexander Meissner, from the Reference Epigenome Mapping Center at the Broad Institute, examined epigenomic changes that occur as human embryonic stem cells differentiate into the three germ layers that develop in an embryo: ectoderm (which becomes epidermis, nervous system, eyes, and ears), mesoderm (which becomes muscle, bone, cartilage, the circulatory system, and the urogenital system), and endoderm (which becomes parts of the gastrointestinal tract, the liver, the pancreas, and the lungs). This study revealed several discrete events that occur during differentiation into each germ layer, providing new insight into how human germ layers are specified during development. Additionally, this information may prove useful to scientists who seek to differentiate induced pluripotent stem cells (iPSCs) for the purpose of repairing or replacing a wide range of tissues damaged by disease or injury.

In a separate study, Drs. Bernstein and Meissner, along with colleagues across the Epigenomics Mapping Consortium, systematically mapped global changes in chromatin, the physical structure of DNA and proteins inside a cell. The conformation of chromatin is regulated by epigenetic factors, leading to changes in gene expression (see "A Scientific Illustration of How Epigenetic Mechanisms Can Affect Health"). By generating over 300 chromatin state maps from diverse human tissues and stem cells, the researchers have discovered signature patterns of "active" chromatin, representing genes that are being expressed, versus "repressed" chromatin, representing genes that are not expressed. During development, chromatin changes from a largely accessible state to a more restrictive state. The chromatin state maps reveal that cells of different developmental stages, or exposed to different environmental conditions, can be distinguished by characteristic differences in chromatin state maps. Prior to this study, much of what scientists knew about chromatin states came from studying cell lines derived from various model organisms.

Collectively, these studies provide a wealth of information about epigenetic dynamics in human cells within different tissues, during various developmental stages, and under a variety of environmental conditions. The extensive data sets available in these publications will be a valuable resource for researchers in a wide range of biomedical fields.

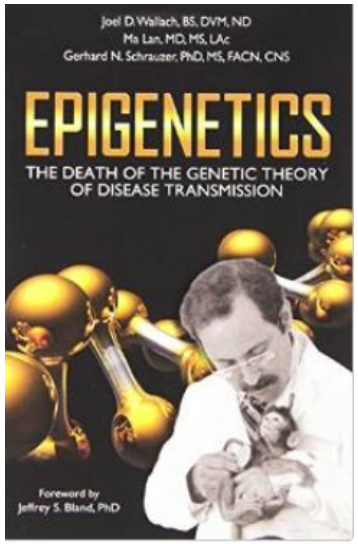
Papers on Epigenetics by Year

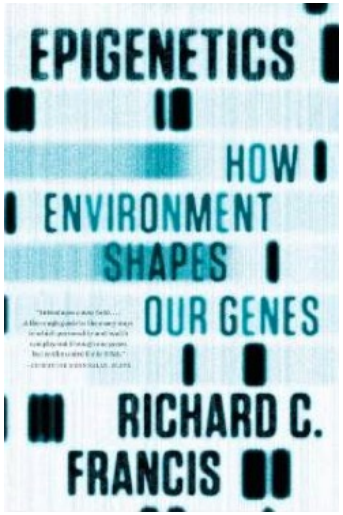


PubMed Query: epigenetics OR epigenetic OR "DNA Methylation"[MeSH]

Papers on “cancer” increased from 57,652 to 124,189 between 1995-2010


Father
Mother


Joel D. Wallach, BS, DVM, ND
Ma Lan, MD, MS, LAc
Gerhard N. Schrauzer, PhD, MS, FACN, CNS
EPIGENETICS
THE DEATH OF THE GENETIC THEORY OF DISEASE TRANSMISSION
Foreword by
Jeffrey S. Bland, PhD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HOW
ENVIRONMENT
SHAPES
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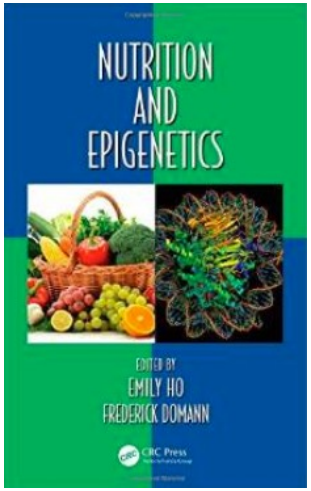
RICHARD C.
FRANCIS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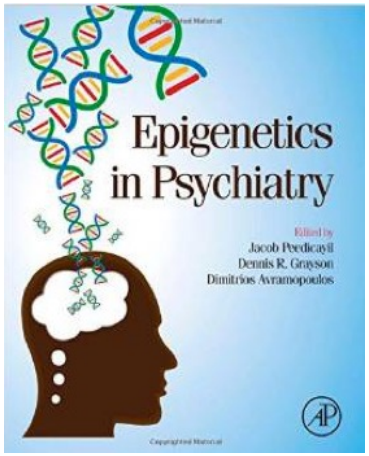
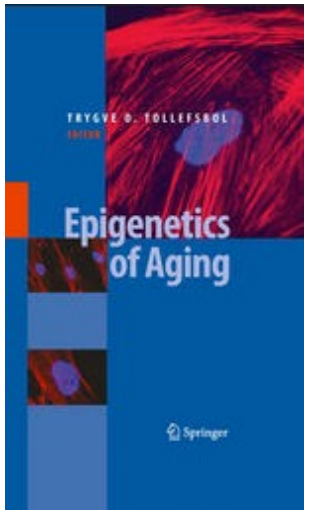
EDITED BY
EMILY HO
FREDERICK DOMANN
CRC Press


Epigenetics
in Psychiatry
Edited by
Jacob Peedicayil
Dennis R. Grayson
Dimitrios Avramopoulos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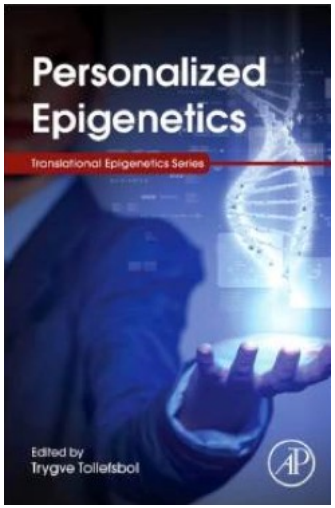
Epigenetics
of Aging
Springer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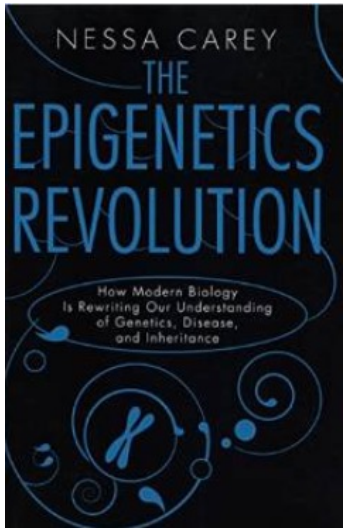
Trygve Tollefsbol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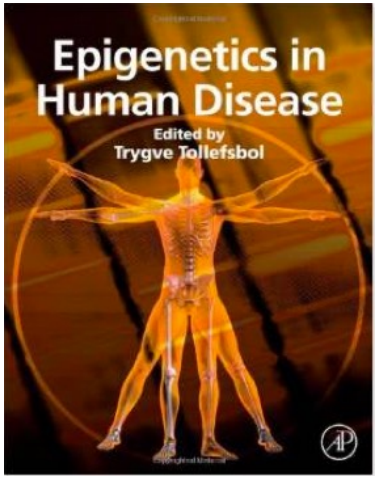
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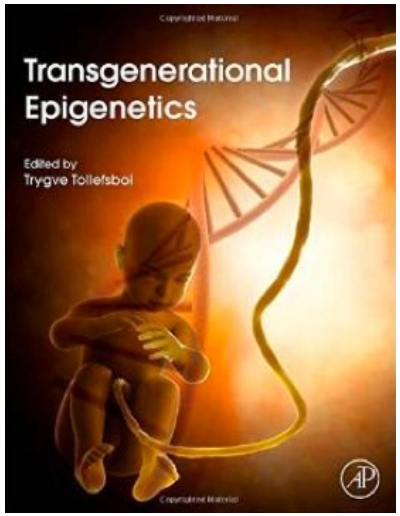
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- http://www.nature.com/epigenomeroadmap
- Additional research: http://www.nature.com/collections/vbqgtr/epigenome-roadmap-additional-research

http://www.computational-epigenetics.de

http://www.epigenome.org