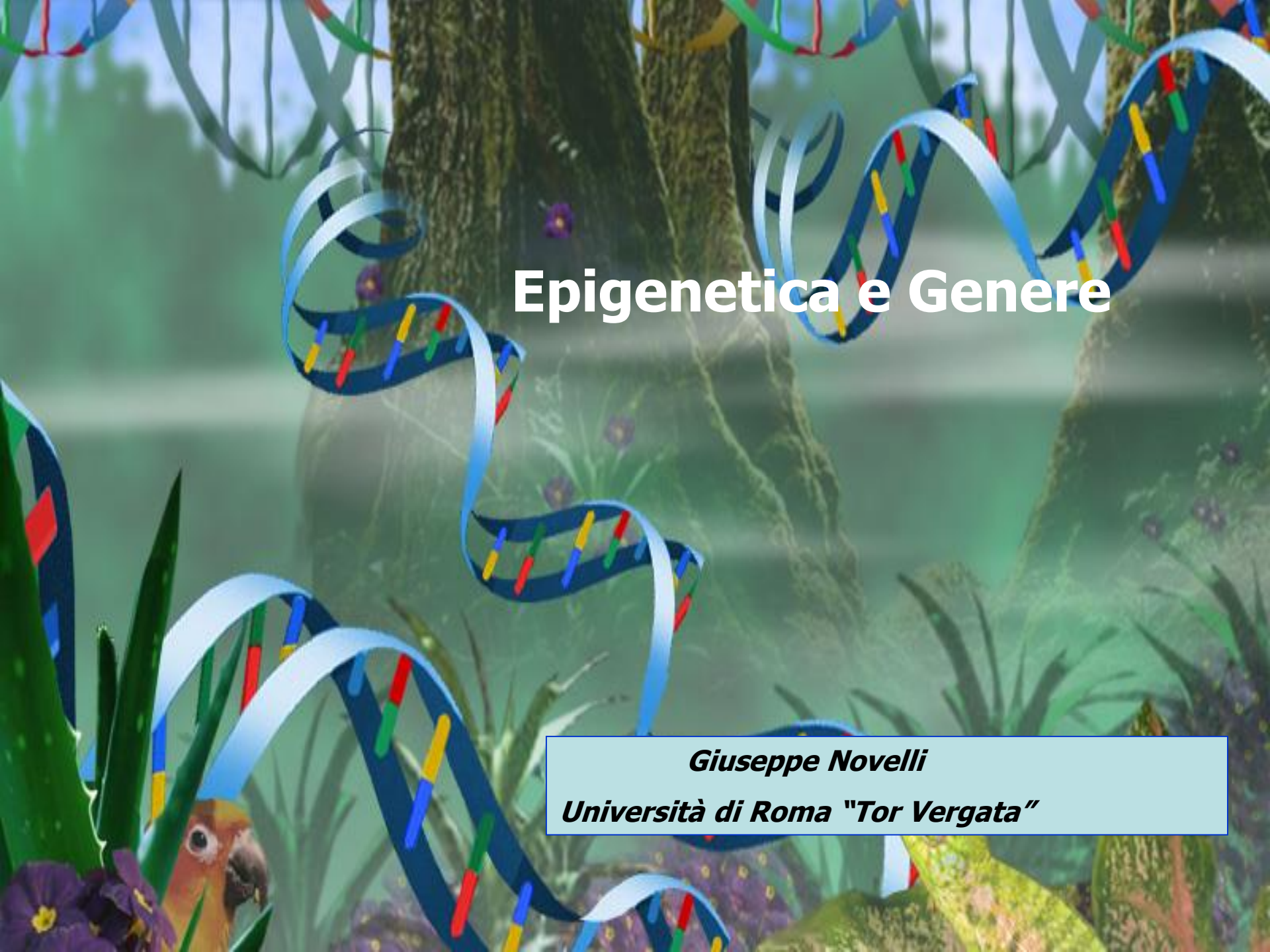


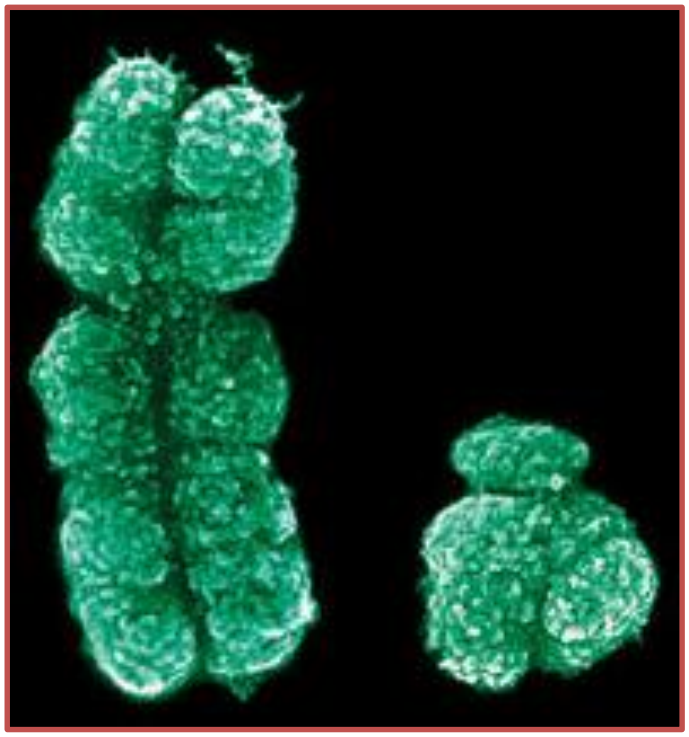
Epigenetica e Genere

Giuseppe Novelli

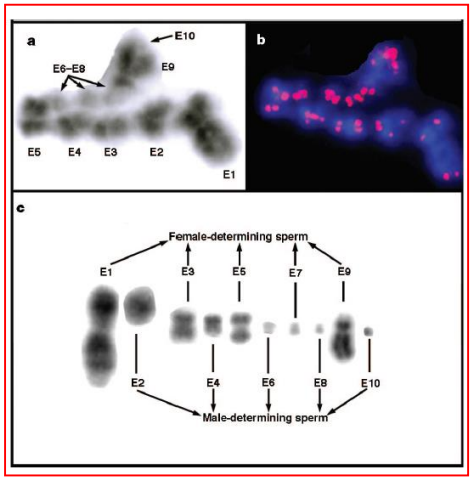
Università di Roma "Tor Vergata"

Le differenze morfologiche e comportamentali tra l' uomo e la donna rappresentano l' esempio più evidente di diversità fenotipica tra gli individui…

…ma in realtà quasi nessuna di queste differenze permette di distinguere biologicamente un uomo da una donna



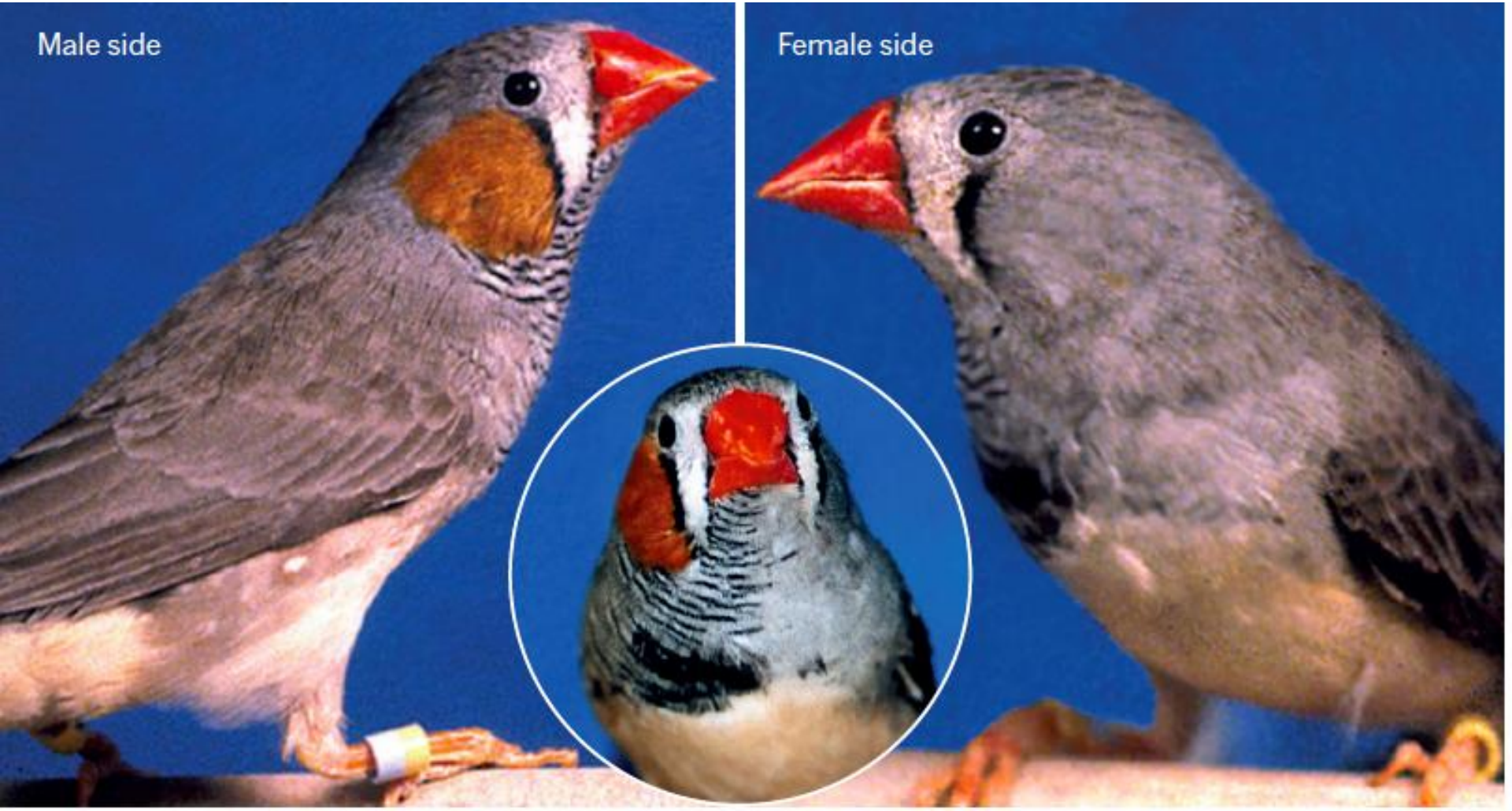
“There is a huge consequence to having two X chromosomes versus an X and a Y.”



- Nell' ornitorinco i maschi possiedono 5 cromosomi Y e cinque cromosomi X
- Le femmine 10 cromosomi X

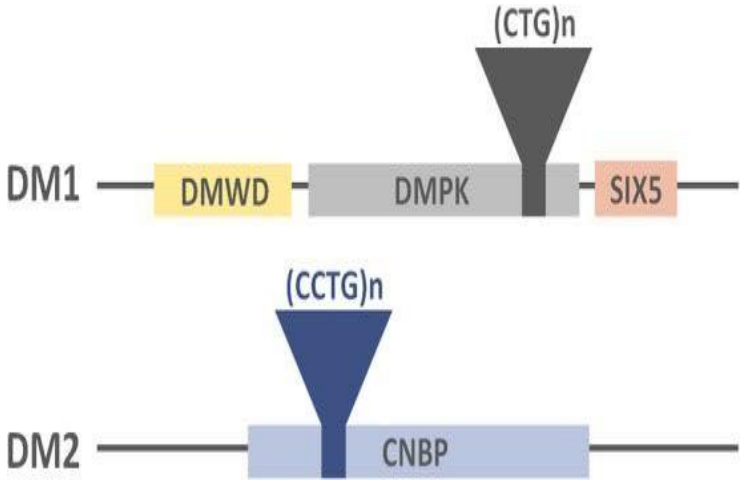
⇒ possono ricombinare tra loro e segregare a gruppi con la formazione di zigoti

L' assenza del gene ***Sry*** in questo sistema introduce alcuni dubbi sulla reale derivazione ancestrale del determinante sessuale dal cromosoma X e fornisce elementi per ipotizzare un' origine dal sistema ZW dei cromosomi sessuali dell' ornitorinco



The right side of Art Arnold's unusual zebra finch was genetically male but the left was genetically female.

Genetics of Myotonic dystrophies



→**DM1**: CTG expansion (>50 repetitions) in the 3' UTR of the *DMPK gene* (19q13.3)

→ **DM2**: CCTG expansion (>50-70 repetitions) in the first intron of the *CNBP gene* (3q21.3)

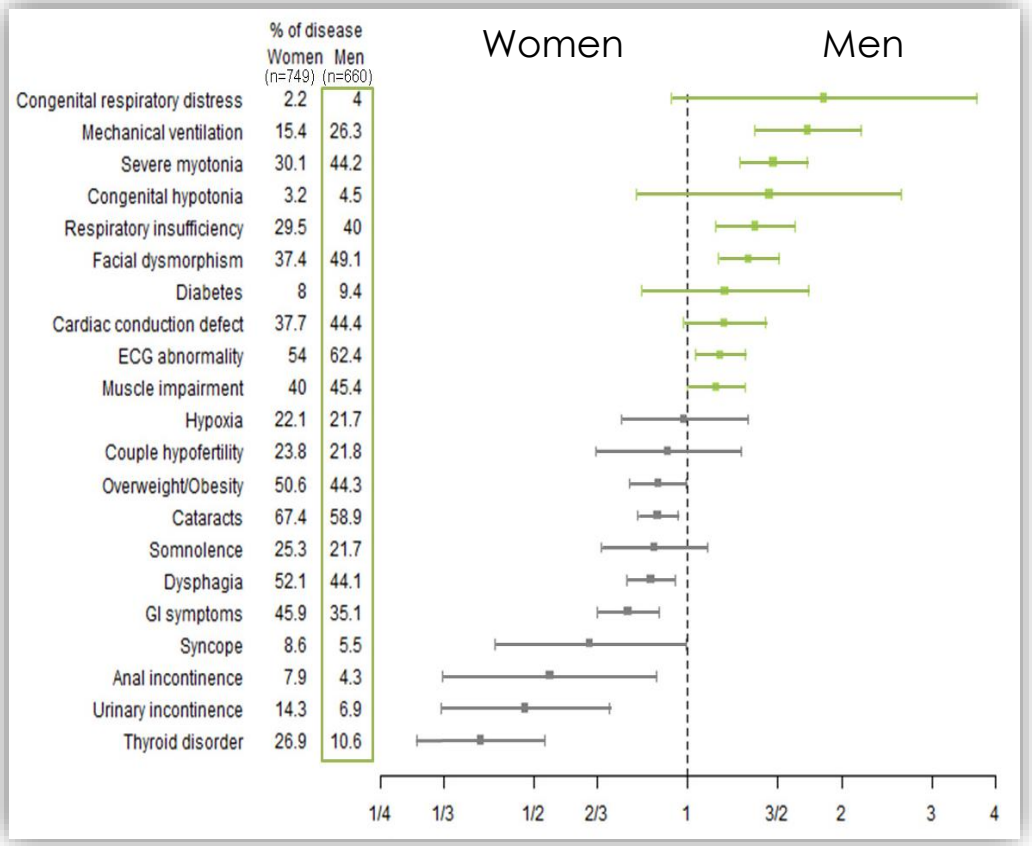
«Mutable» mutations:

- somatic and germline mosaicim
- genetic anticipation (DM1 only)
- maternal trasmission (DM1 only)

Gender influence in Myotonic Dystrophy type 1

Gender impact on severity of symptoms

- Men more frequently had developmental abnormalities, severe myotonia, severe cardiac and respiratory involvement and muscle weakness, as assessed by MRC testing (p = 0.001)



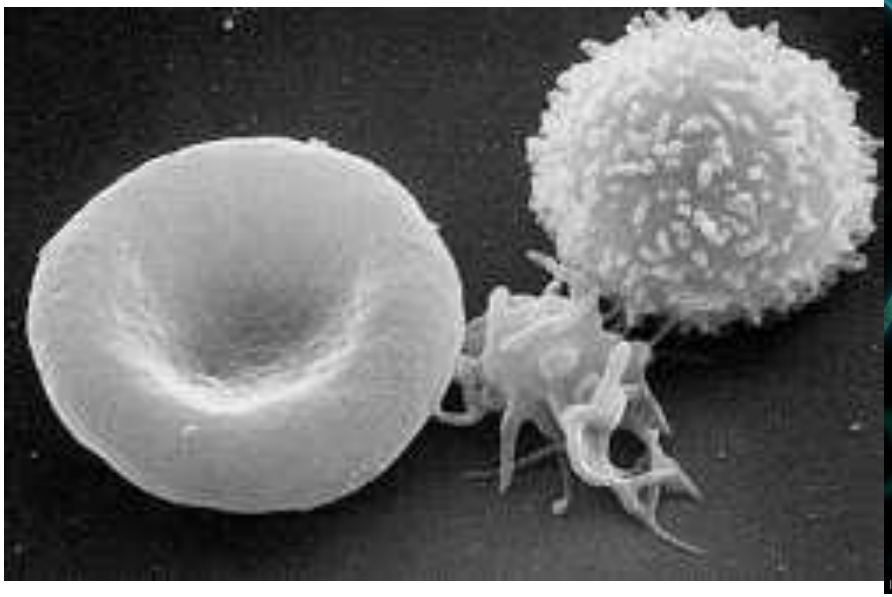
- Women had more frequently **cataracts**, **dysphagia**, **digestive tract dysfunction**, **incontinence**, **thyroid disorder and obesity**

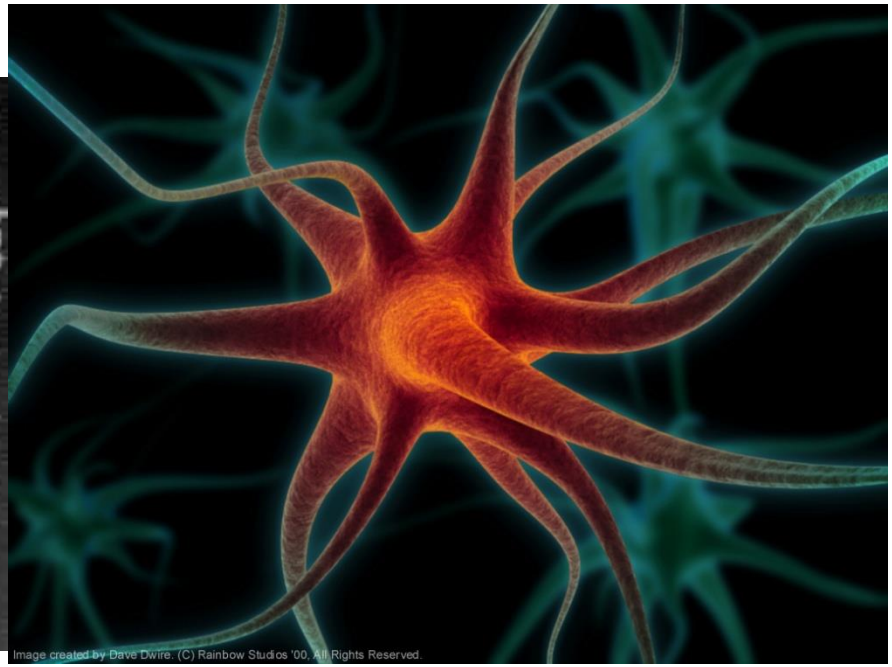
Dogan C. et al., 2016

X marks the spot

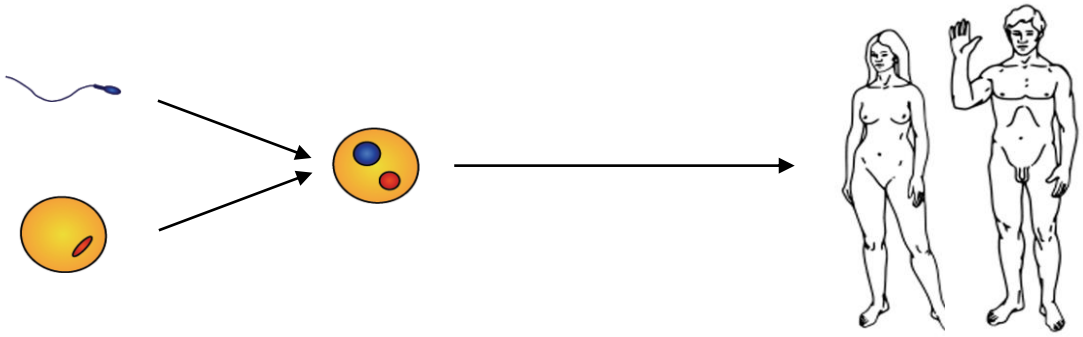
- About 80% of people with autoimmune disorders are female.
- Women tend to have a stronger immune response to infection, and often produce more antibodies in response to vaccination than men.
- Men are more cancer prone, are twice as likely to die of malignant disease, and respond differently to cancer therapy.
- But more women than men die from cardiovascular disease, and become obese.

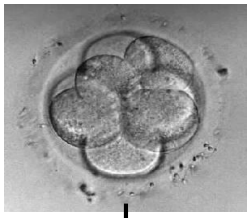
Every cell in the human body has the same DNA, but they definitely don't all do the same thing.



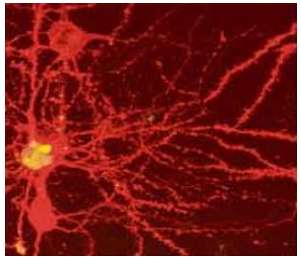


Expression of the genome is regulated by epigenetic mechanisms

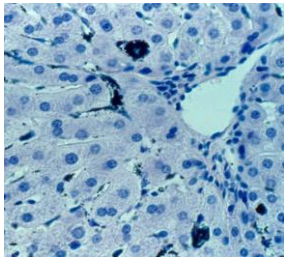




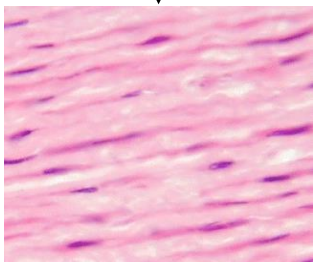
Pluripotent
Stem cells



Neuron

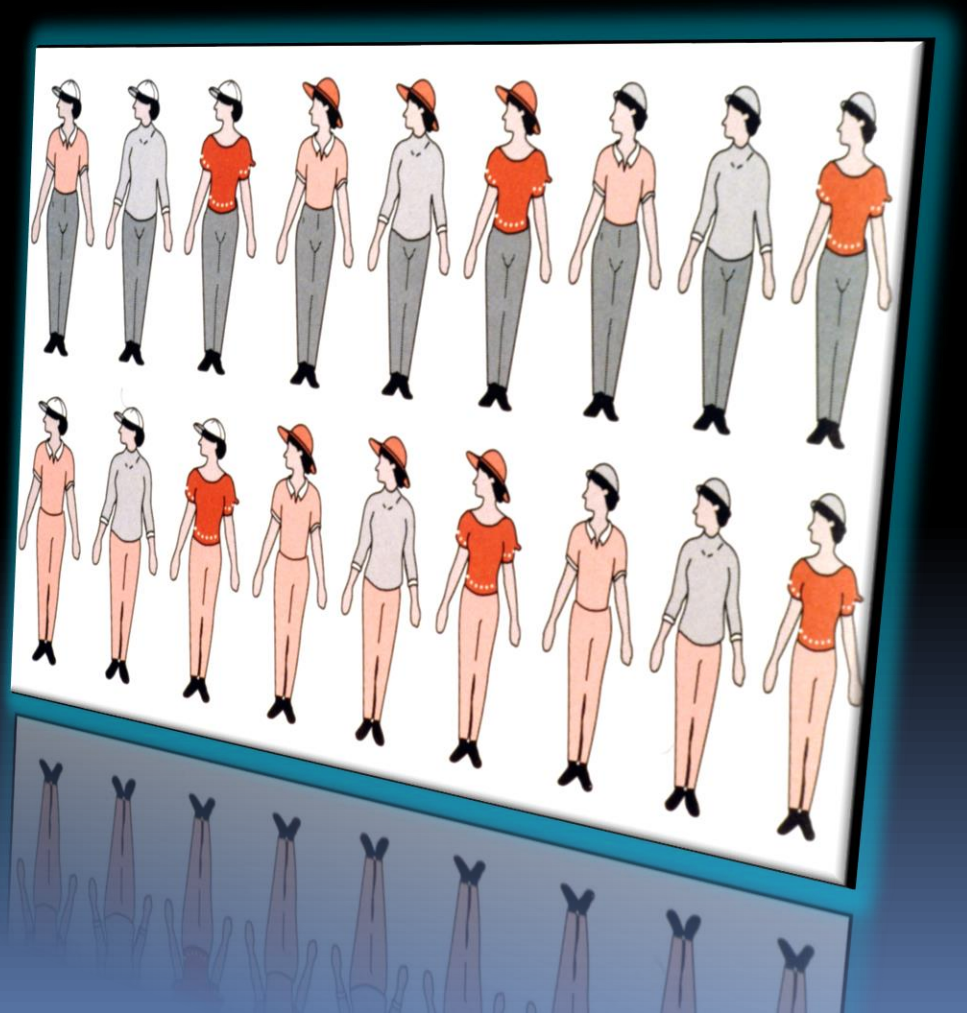


Liver

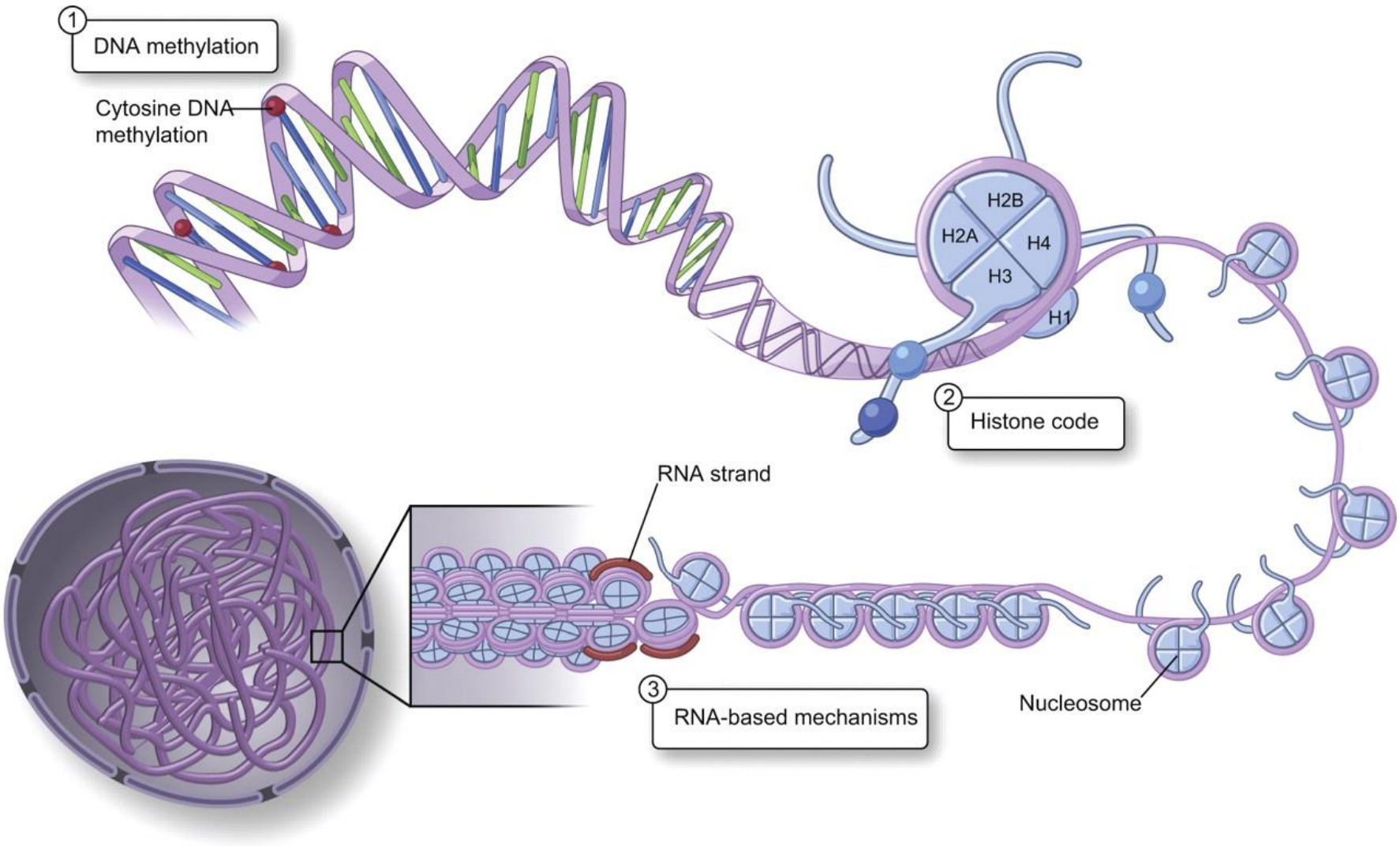


Muscle

L’epigenetica: Che cos’hanno addosso i geni



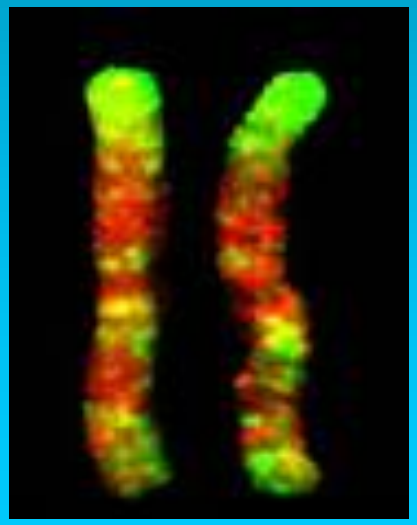
Meccanismi epigenetici



Monozygous twins share a common genotype and are genetically identical

There is significant phenotypic discordance:

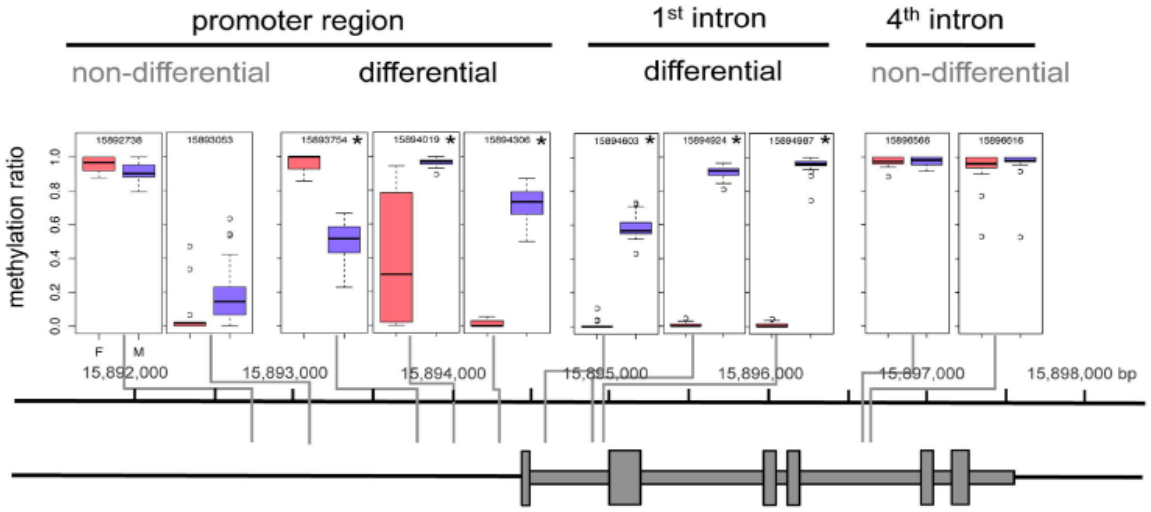
- **Mental disorders**
- **Cancer**



Populus balsamifera

Sexual epigenetics: gender-specific methylation of a gene in the sex determining region of Populus balsamifera

Scientific Reports | 7:45388 | DOI: 10.1038/srep45388



Processi cellulari dovuti a meccanismi epigenetici con implicazioni nelle differenze di genere

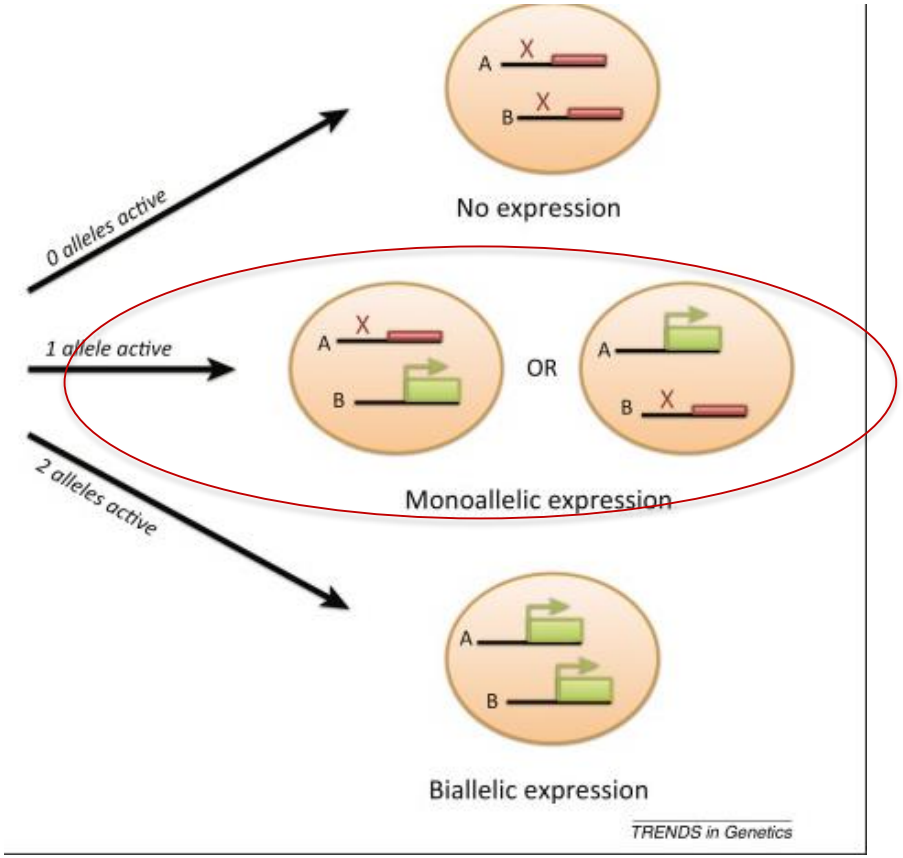
- Imprinting genomico (effetto parentale)
- Inattivazione di un cromosoma X nelle femmine
- Effetti miRNAs/non coding RNAs

Imprinting genomico

L'effetto parentale in genetica viene evidenziato nella seconda metà del secolo scorso

(Surani et al. 1984)

Consiste nell' espressione differenziale degli alleli ereditati per via paterna o materna



L'imprinting è un fenomeno epigenetico e reversibile

Jirtle and Weidman, 2007

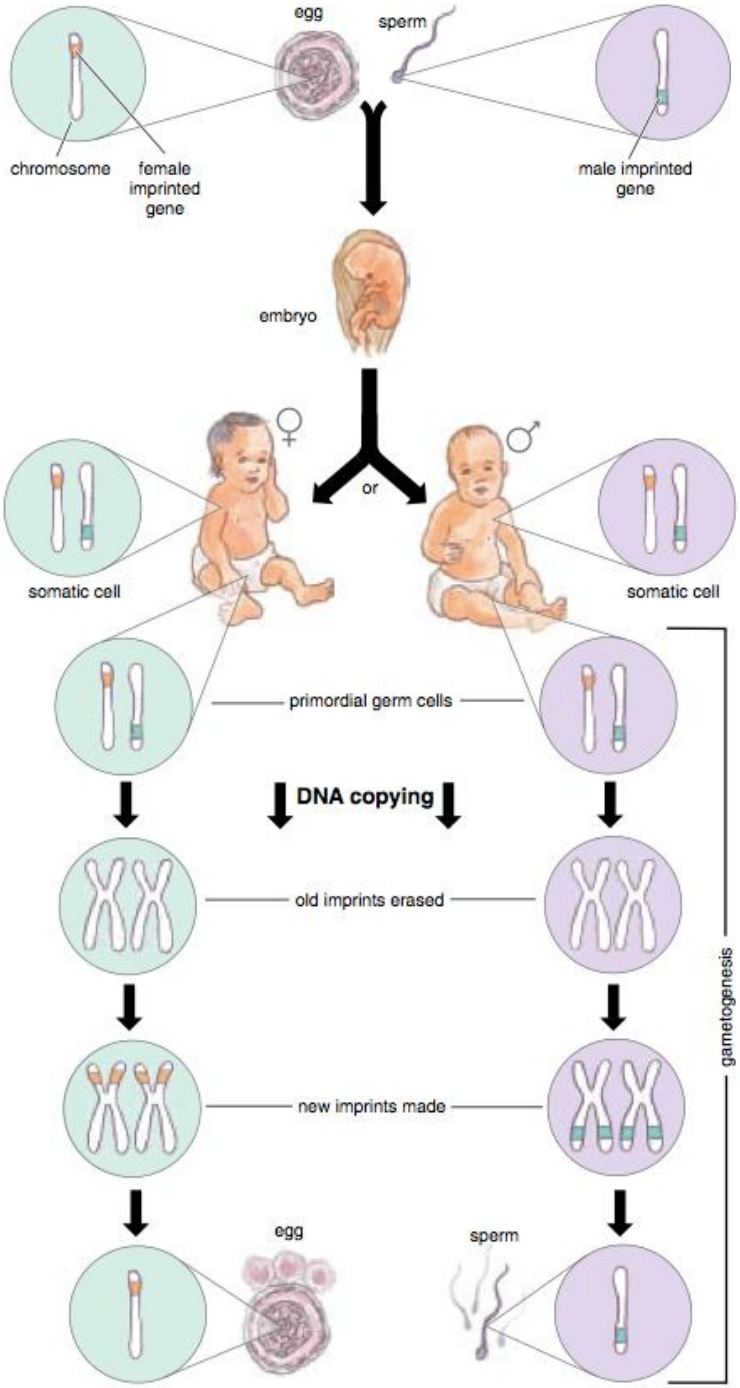
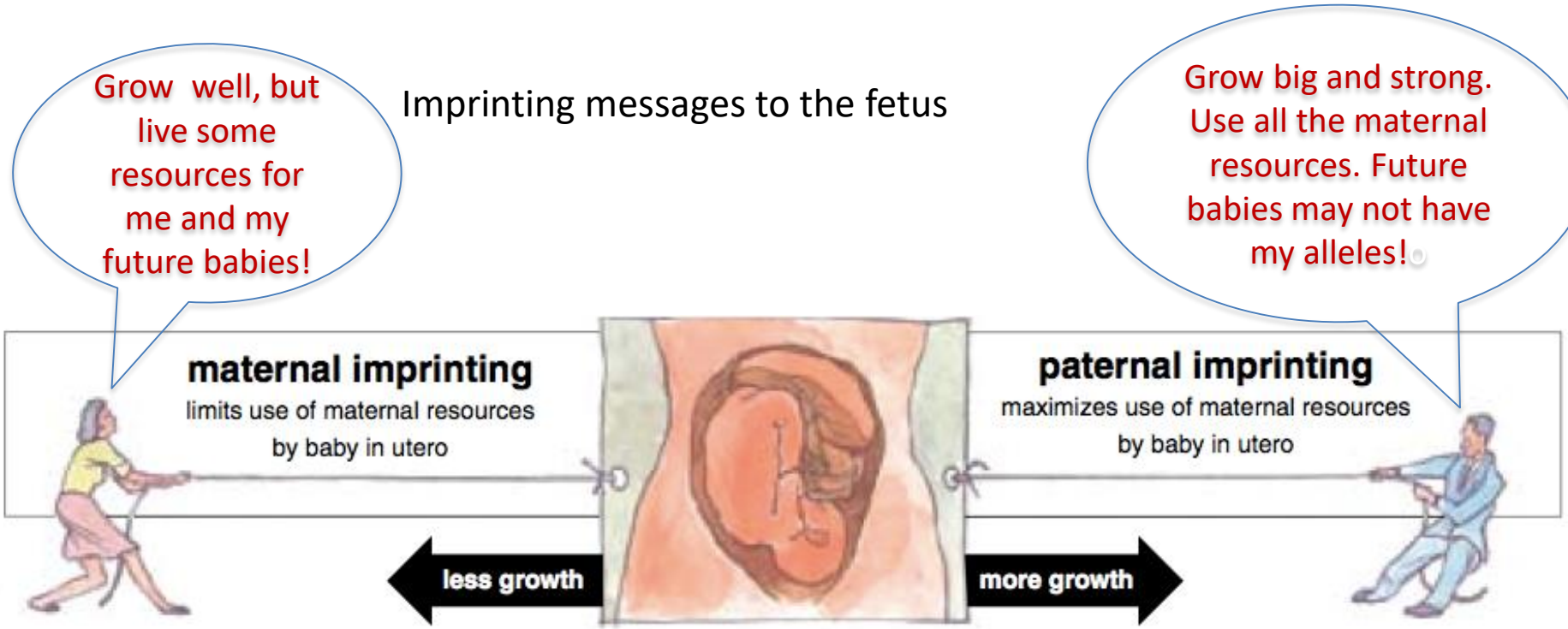


Figure 3. Imprints must be reset in each new generation to ensure appropriate gene activity.

The parental conflict hypothesis

Imprinting messages to the fetus



IGF2 off
IGF2R on

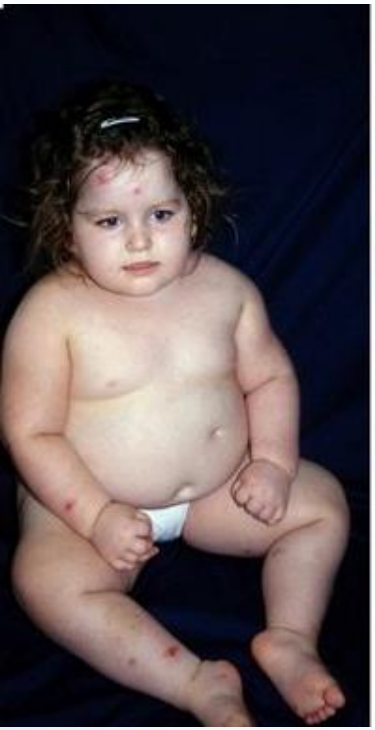
IGF2R reduces effects of *IGF2*

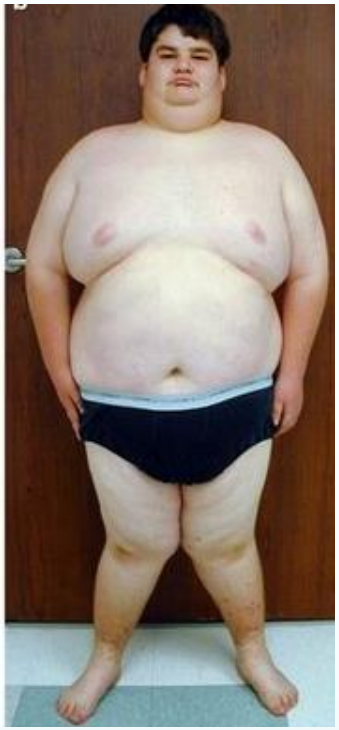
IGF2 on
IGF2R off

IGF2 stimulates growth of the fetus

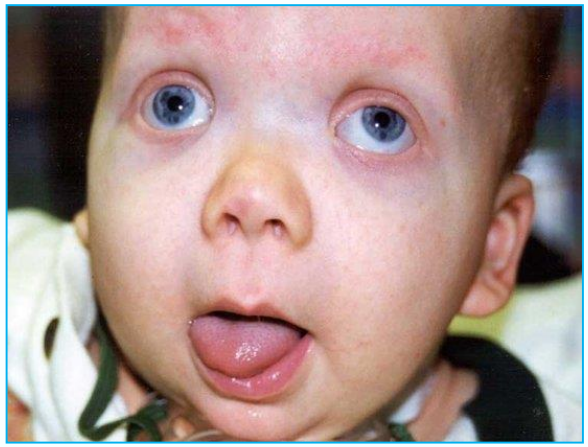
From Jirtle and Weidman, 2007

Disordini dell'imprinting genomico

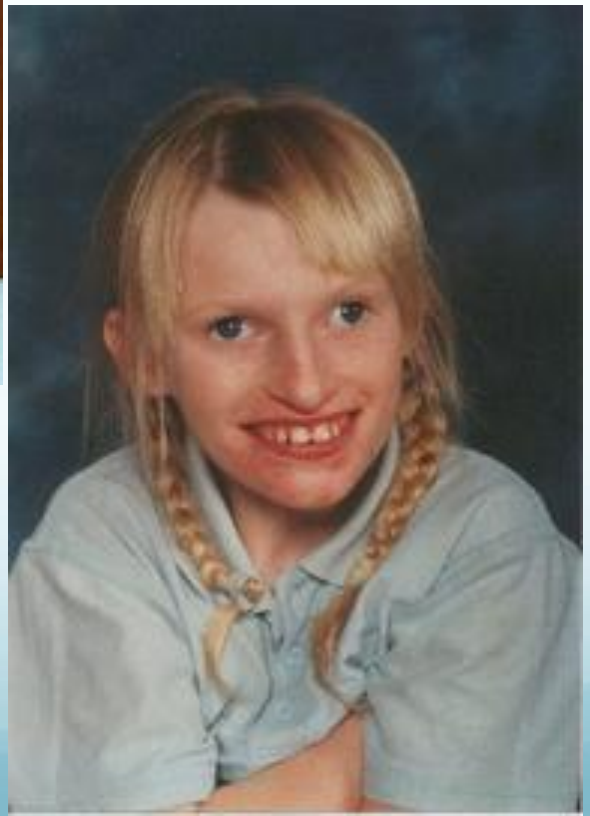




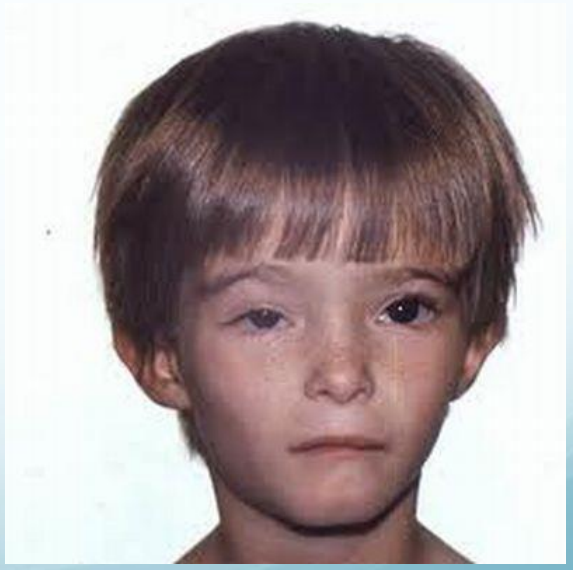
S. di Prader-Willi



S. di Beckwith-Wiedemann



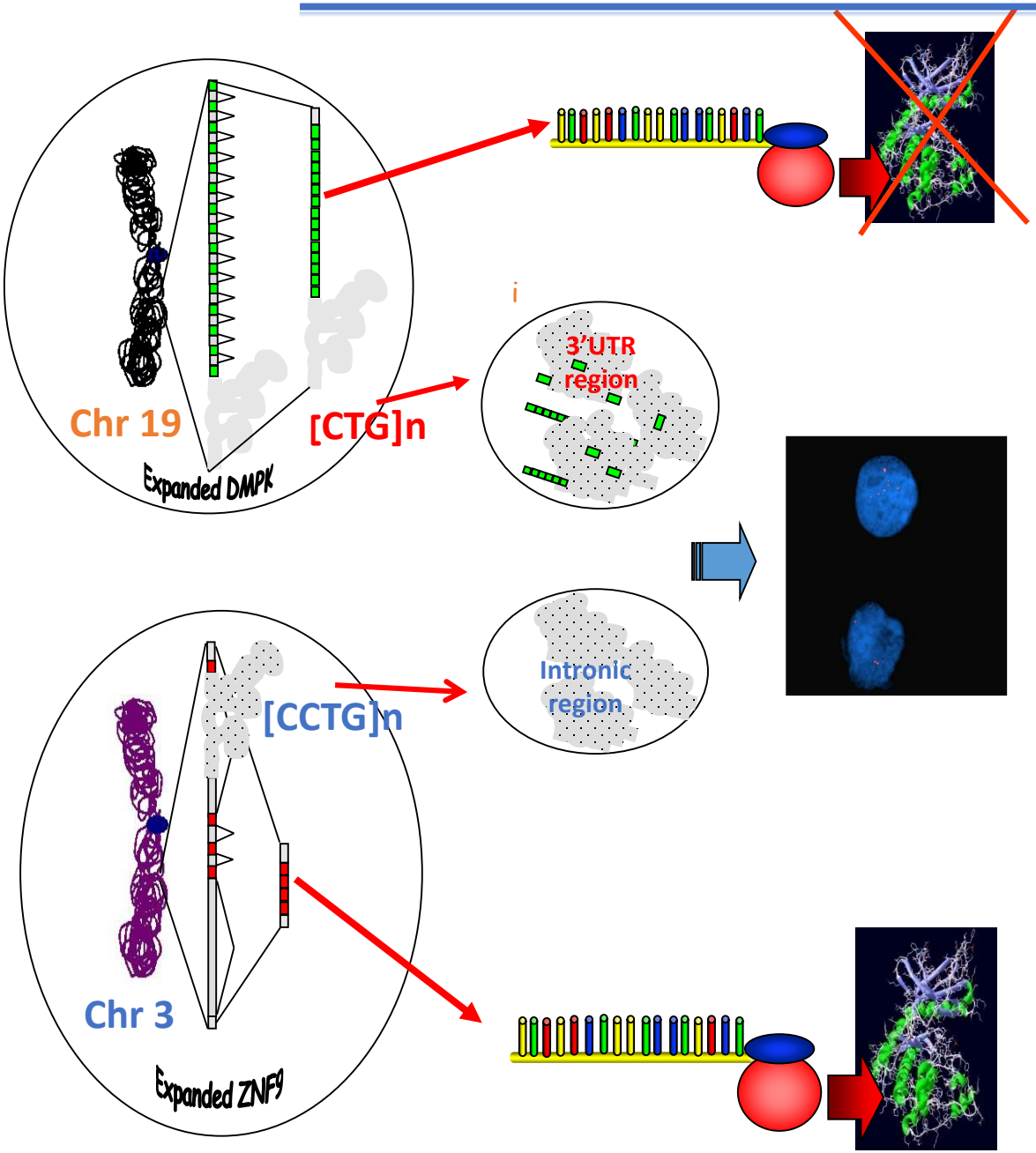
S. di Angelman



S. di Silver-Russell

EPIGENETICA: Il vestito che indossano i geni

In *cis* effects of the C/CTG expansions



DMPK

- Haploinsufficiency of the DMPK protein
- Silencing effects on neighbouring genes (e.g. *Six5*) and *DMPK* itself
- KO DMPK-/- mice develop cardiac anomalies which resemble the DM1 cardiac phenotype

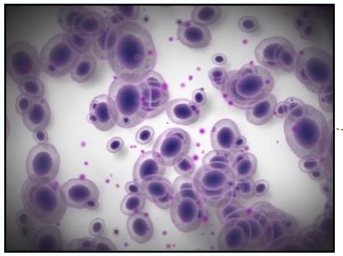
CNBP

- Controversial data about the effects of CCTG expansions on ZNF9 expression levels
- KO CNBP -/- mice develop a phenotype similar, but not identical, to DM2 patients

Epigenomics: Connecting disease, pathway biology and environment

Cancer

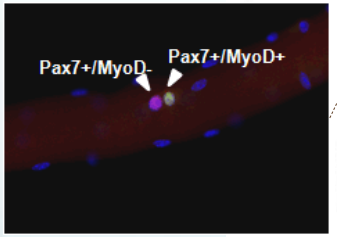
Control of gene expression by epigenetic modification plays a role in tumor formation, and could explain how environmental factors trigger cancer

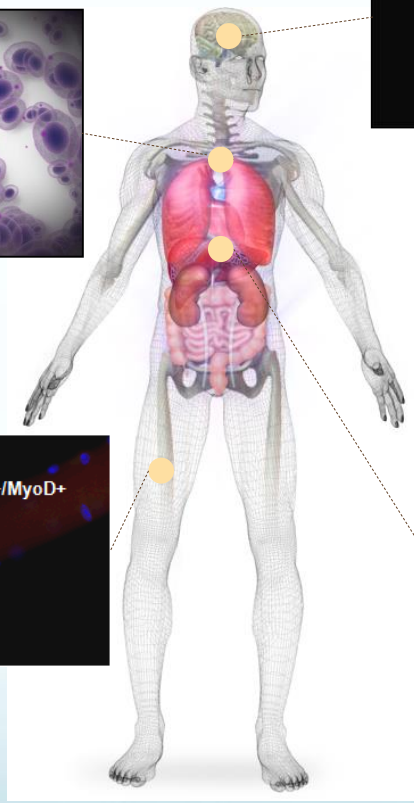


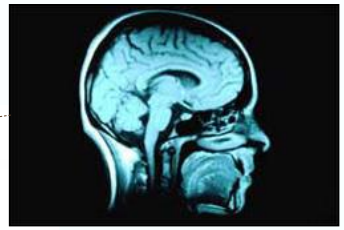
Regenerative Medicine

Multipotent stem cells hold great promise for regenerative therapy

Aging may affect stem cells

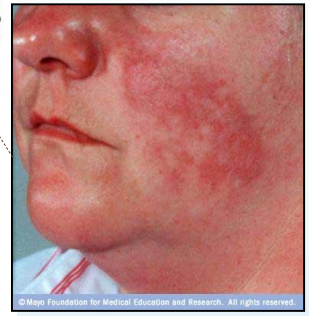






Brain Disorders

Epigenetic changes have been implicated in brain health, from cognitive decline in normal aging to autism



Chronic Diseases

Complex chronic conditions such as systemic lupus erythematosus are thought to have an environmental component

Studies aim to identify how this can cause epigenetic changes that might affect disease progression

Epigenetic phenomena

Example – Chromosomal dosage and compensation

- Women are XX, men are XY
- How are levels of all essential X-encoded gene products similar between men and women if women have twice the number of alleles?

Mary Lyon – 1961

- in cells with multiple X chromosomes, all but one is inactivated during mammalian embryogenesis – the "*Lyon effect*"
- X-inactivation; which X? Usually random
- … but always paternal in marsupials
- and variable in calico cats representing regional expression of differing pigmentation genes on alternate X chromosomes

Geni che sfuggono all'inattivazione sul cromosoma X possono render conto di sensibilità differenziale nelle femmine a certe patologie

Trends in Genetics

CellPress

Review

Escape Artists of the X Chromosome

Bradley P. Balaton[1] and Carolyn J. Brown[1,*]

Over 15% of human X-linked genes continue to be expressed from the inactive X chromosome.

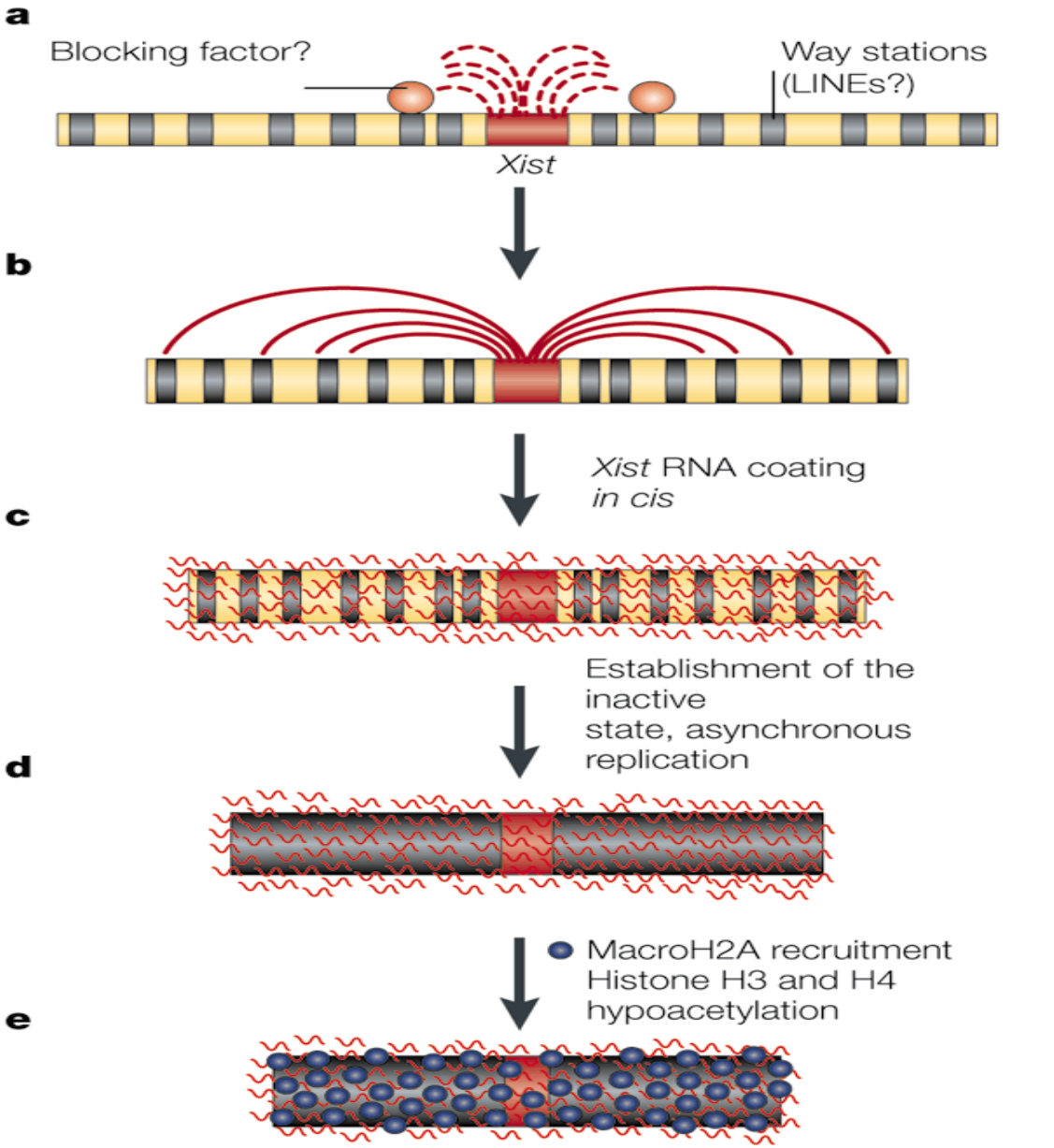
Balaton and Brown, Trends in Genetics, 2016

X marks the spot

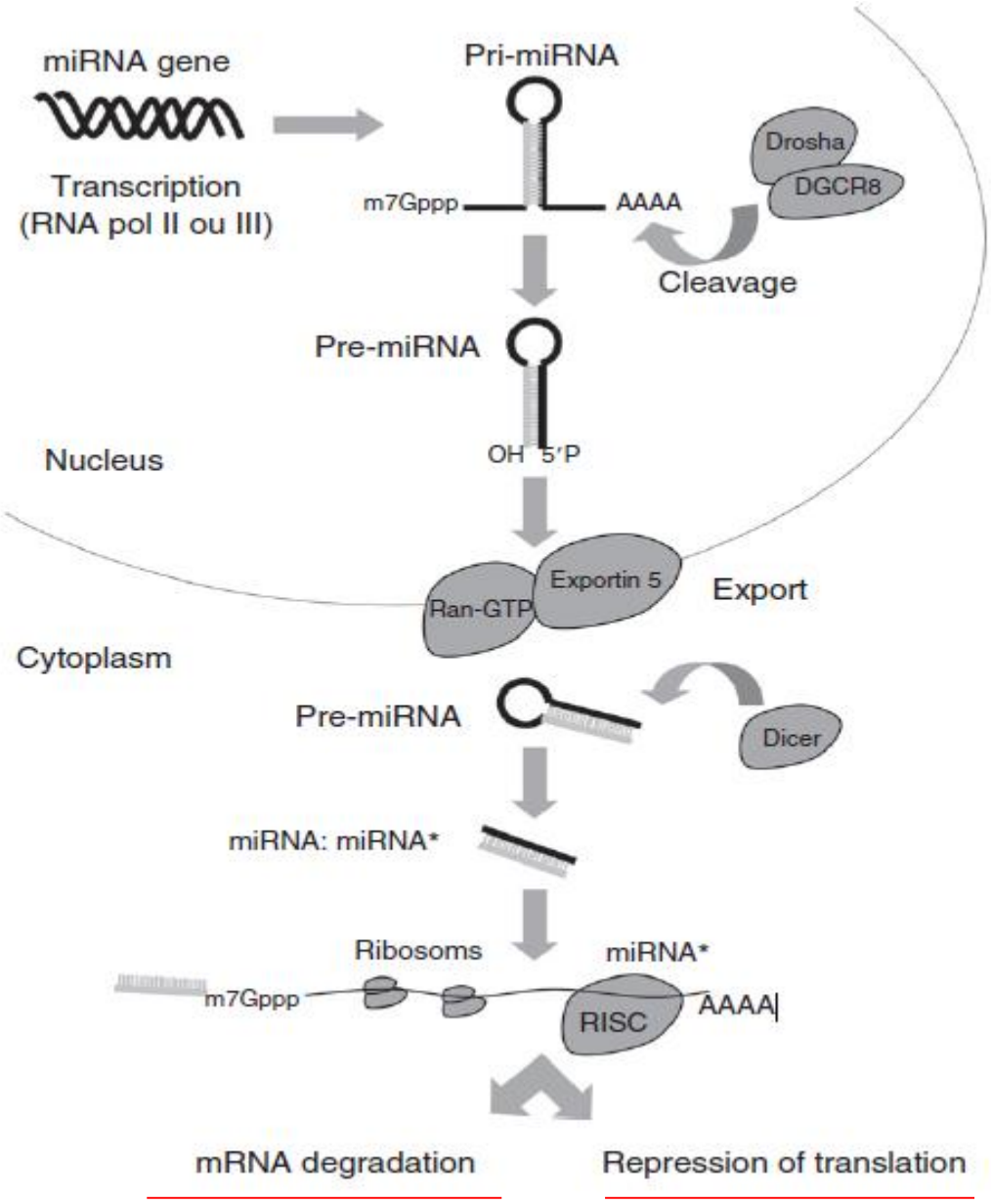
- These vary in the amount of their activity but never reach the level of their counterparts on the active X.
- *Example: ITM2A* contributed to a person's stature, pointing to a possible role in generating sex differences in height.

X marks the spot

- The inactive X frequently reactivates in cancers, especially breast cancer, and there are signs that some of its sleeping genes reawaken as women age.
- Mosaicism: the X destined for inactivation is picked at random early in embryonic development, making females a patchwork, or mosaic, of different active X chromosomes.


a
Blocking factor?
Way stations
(LINEs?)
Xist
b
Xist RNA coating
in cis
c
Establishment of the
inactive
state, asynchronous
replication
d
MacroH2A recruitment
Histone H3 and H4
hypoacetylation
e

Biogenesis of miRNAs



RISC
(RNA-induced silencing complex), which is a complex of proteins that localizes the miRNA to its complementary target mRNA

Insights & Perspectives

Hypotheses

X-chromosome-located microRNAs in immunity: Might they explain male/female differences?

The X chromosome-genomic context may affect X-located miRNAs and downstream signaling, thereby contributing to the enhanced immune response of females

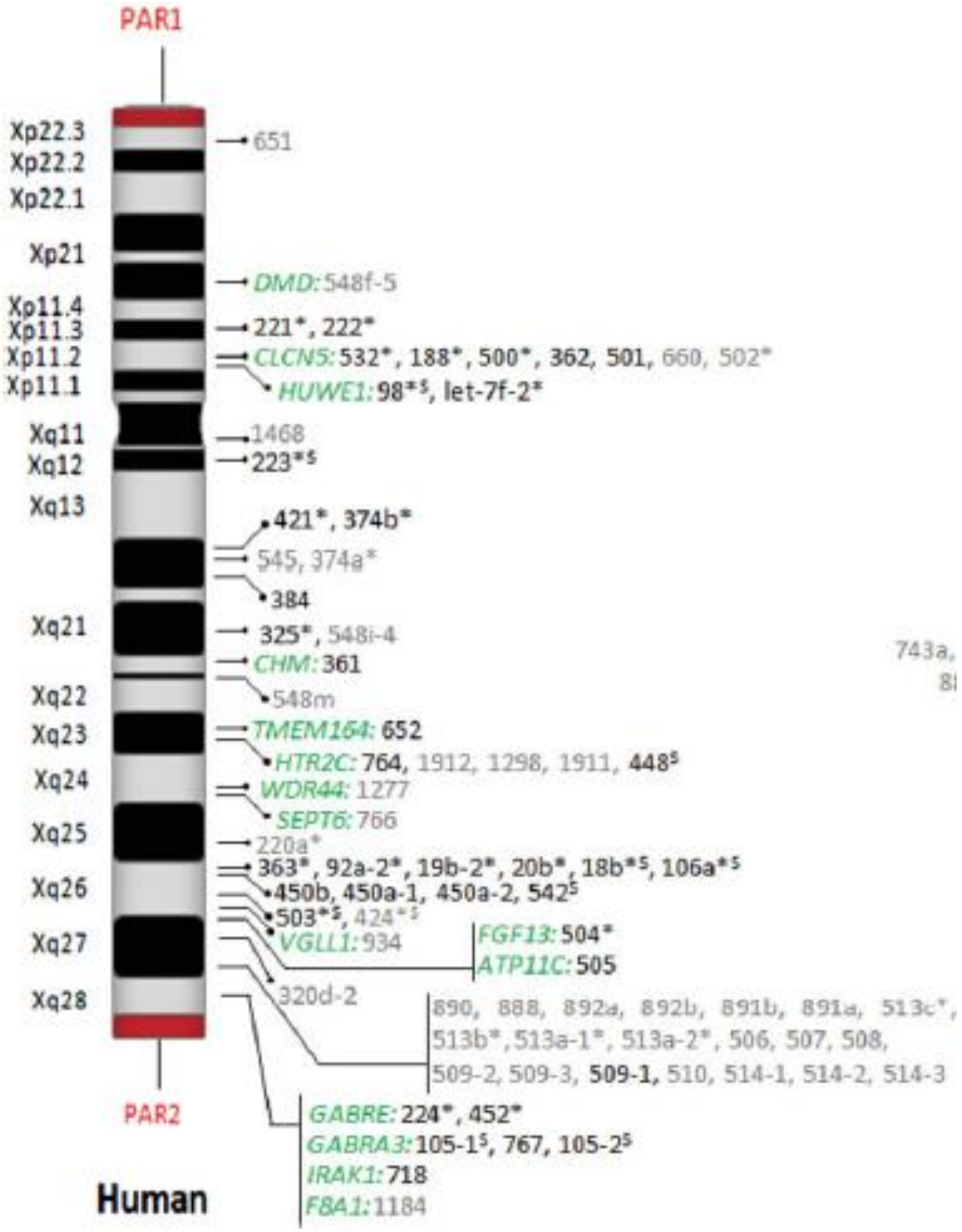
Iris Pinheiro[1)2)], Lien Dejager[1)2)] and Claude Libert[1)2)]*

The human X chromosome contains 10% of all microRNAs detected so far in the human genome.

Several X chromosome-located microRNAs have important functions in immunity and cancer.

The unique mode of inheritance of the X chromosome is ultimately the cause of the immune disadvantage of males and the enhanced survival of females following immunological challenges.

Maps of miRNA located on human X chromosome



Some miRNA are intragenic and gene names are depicted in green before the miRNAs they contain
(*) indicates miRNA that have a confirmed or putative role in immunity and (s) in oncogenesis

Pinheiro et al., 2011

Research Article Lizarraga et al., 2016

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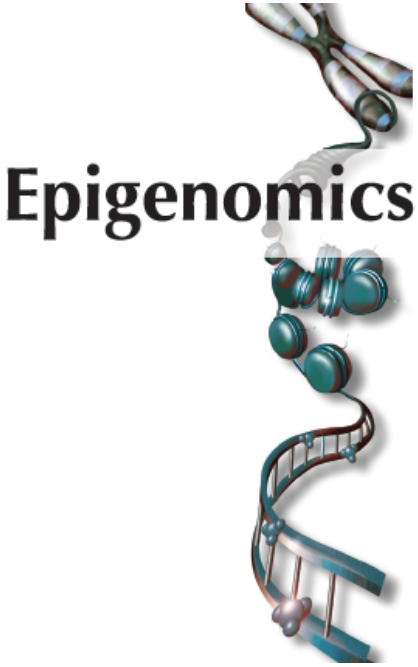
miRNAs differentially expressed by next-generation sequencing in cord blood buffy coat samples of boys and girls



Among more than 2200 miRNAs characterized by NGS in cord blood from 89 newborn children, 94 miRNAs differentially expressed by sex were identified

The sex-associated miRNA gene targets were mainly involved in nervous system development, nucleic acid metabolism and transcription control

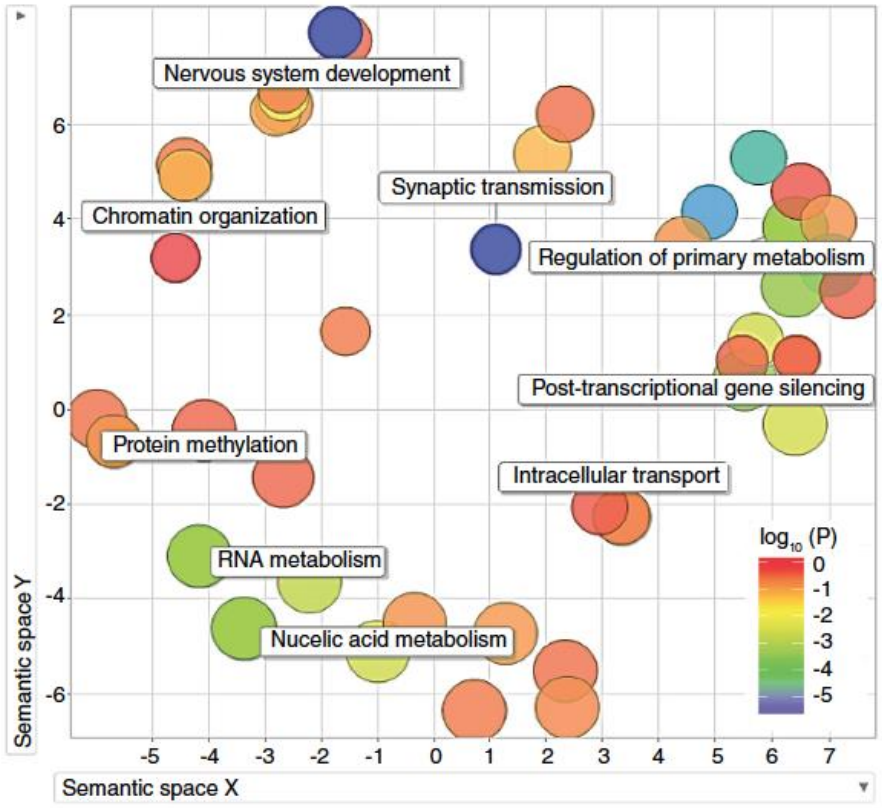


Figure 5. Visualization of enriched gene ontology terms. Gene ontology terms significantly enriched ($q \leq 0.05$) in miRNAs differentially expressed by sex.

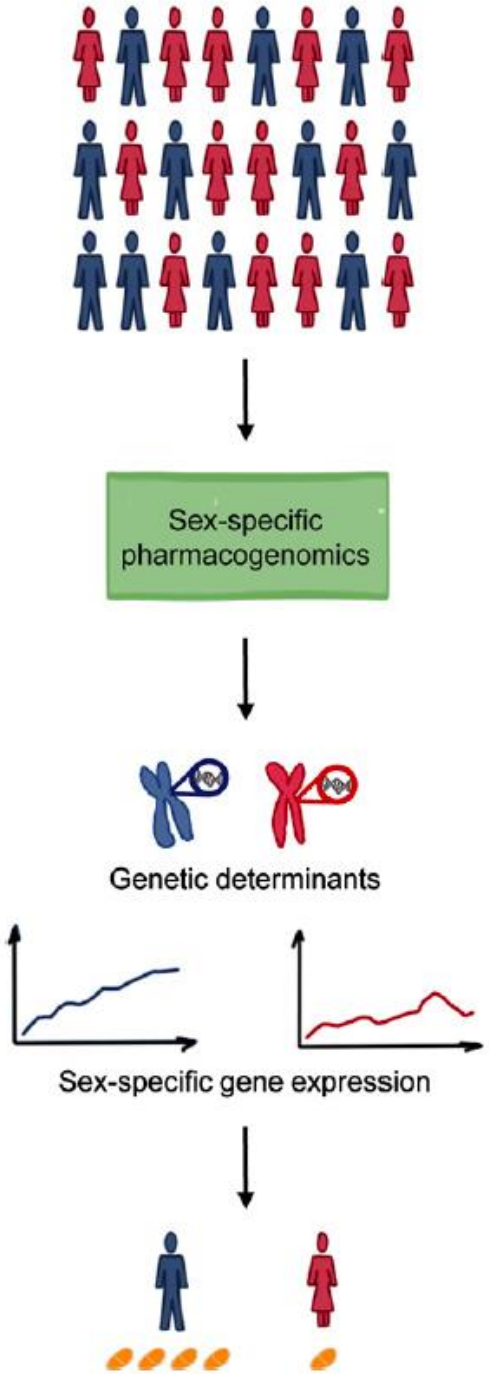
Lizarraga et al., 2016

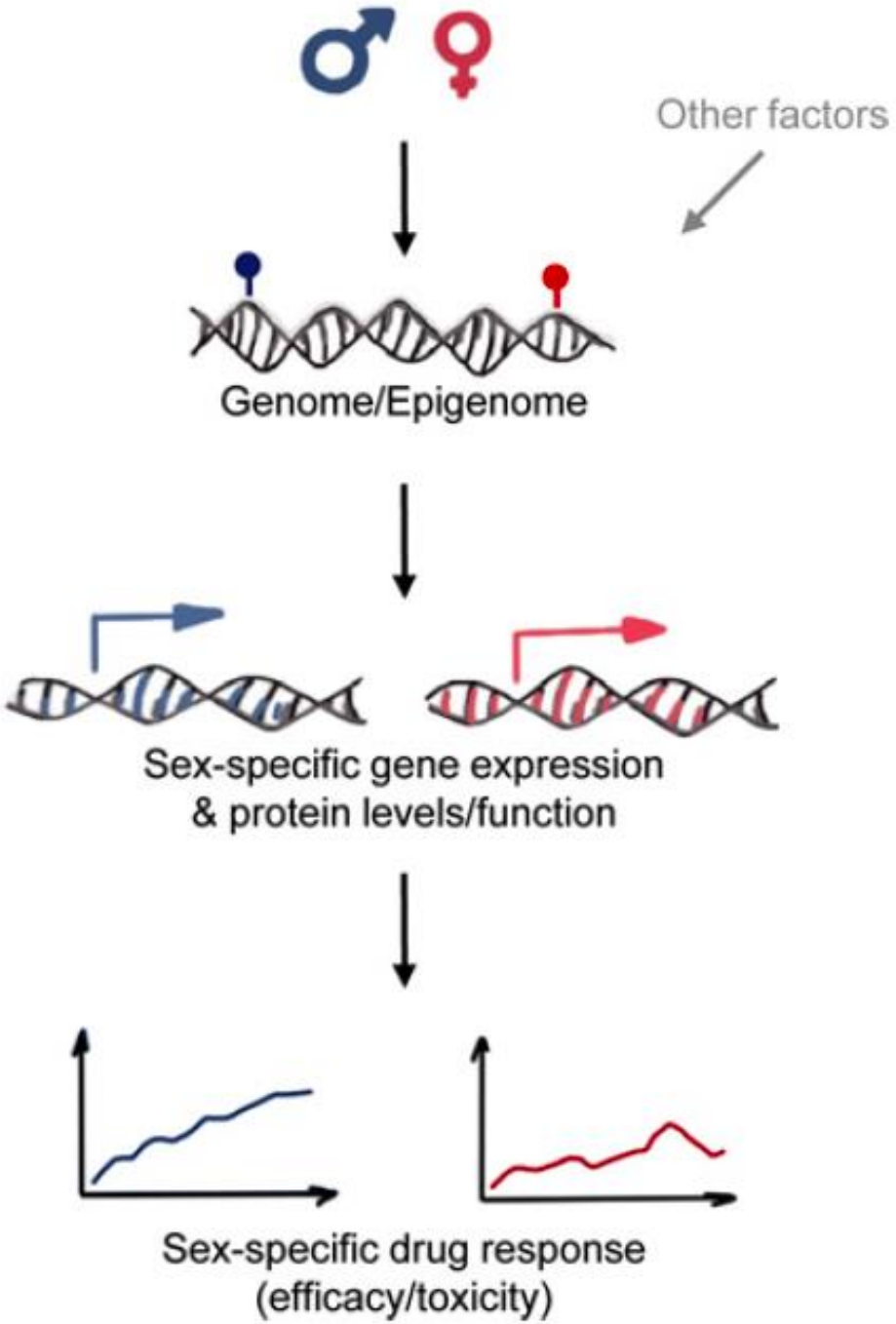
Sex-specific expression of metabolic enzymes

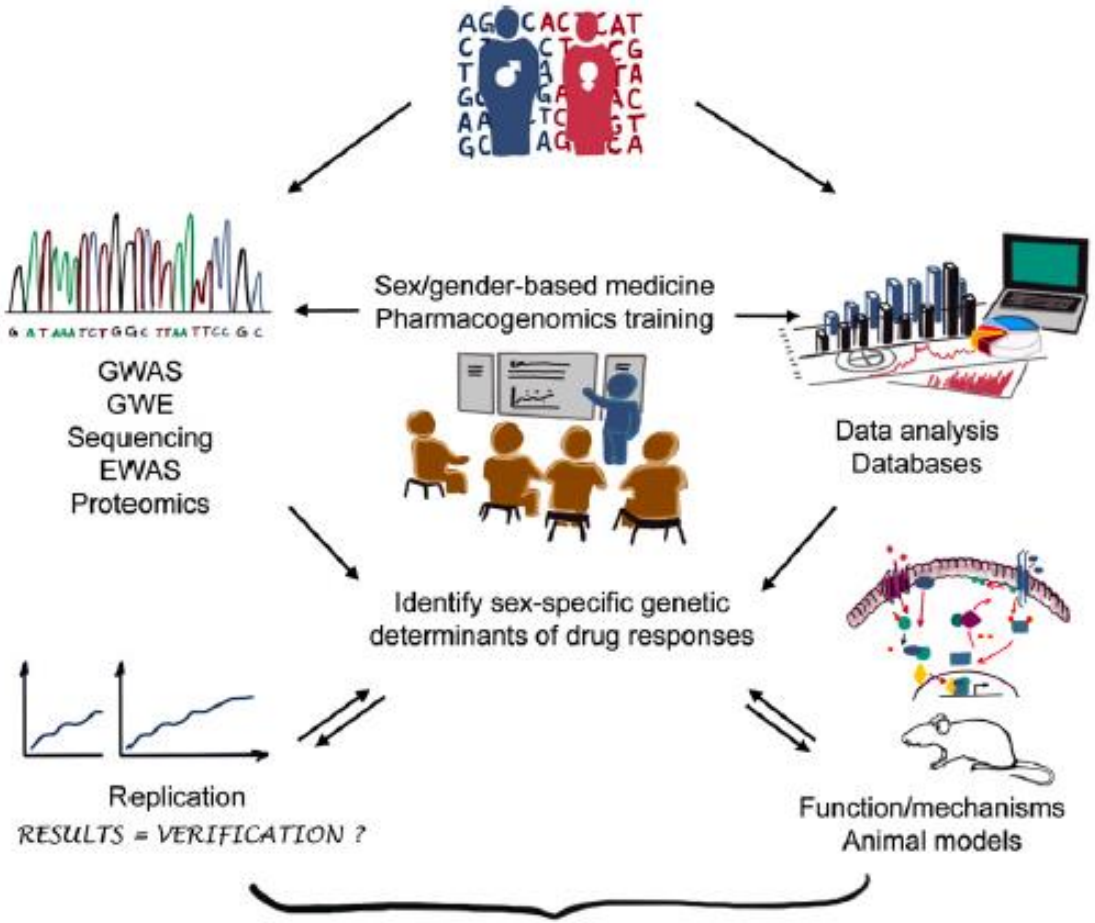
Males and females exhibit sex-specific expression of a wide range of genes, including metabolic enzymes, which impact both basic physiology and the response to environmental exposures

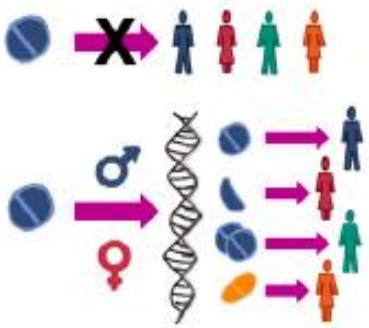
Sexually dimorphic gene expression is largely a function of endocrine differences between males and females, especially in the liver where approximately 1000 genes, including many CYPs, exhibit sexually biased expression.

Bowers and McCoullogh, Toxicol Sciences, 2017


Sex-specific pharmacogenomics
Genetic determinants
Sex-specific gene expression


Other factors
Genome/Epigenome
Sex-specific gene expression
& protein levels/function
Sex-specific drug response
(efficacy/toxicity)


Sex/gender-based medicine
Pharmacogenomics training
GWAS
GWE
Sequencing
EWAS
Proteomics
Data analysis
Databases
Identify sex-specific genetic
determinants of drug responses
Replication
RESULTS = VERIFICATION ?
Function/mechanisms
Animal models
Translation into sex-targeted pharmacotherapies → precision medicine



- Il DNA e' scritto a penna, non si può cambiare,
- L'epigenetica, invece, e' ciò che e' scritto a matita e può essere modificato
- Danielle Reed

Le modificazioni epigenetiche sono REVERSIBILI

Primo farmaco epigenetico

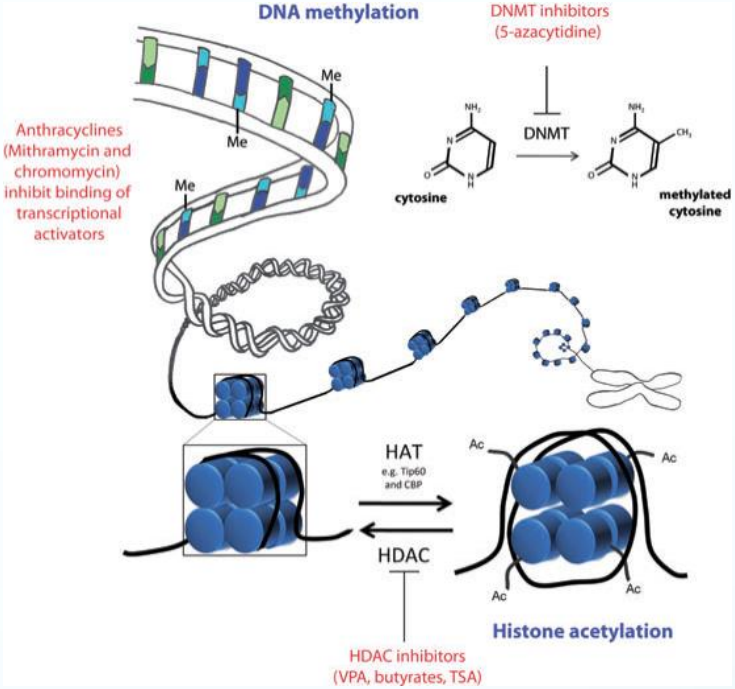
approvato dalla FDA nel 2004:

azacitidina (agente demetilante)

usato per trattare pazienti

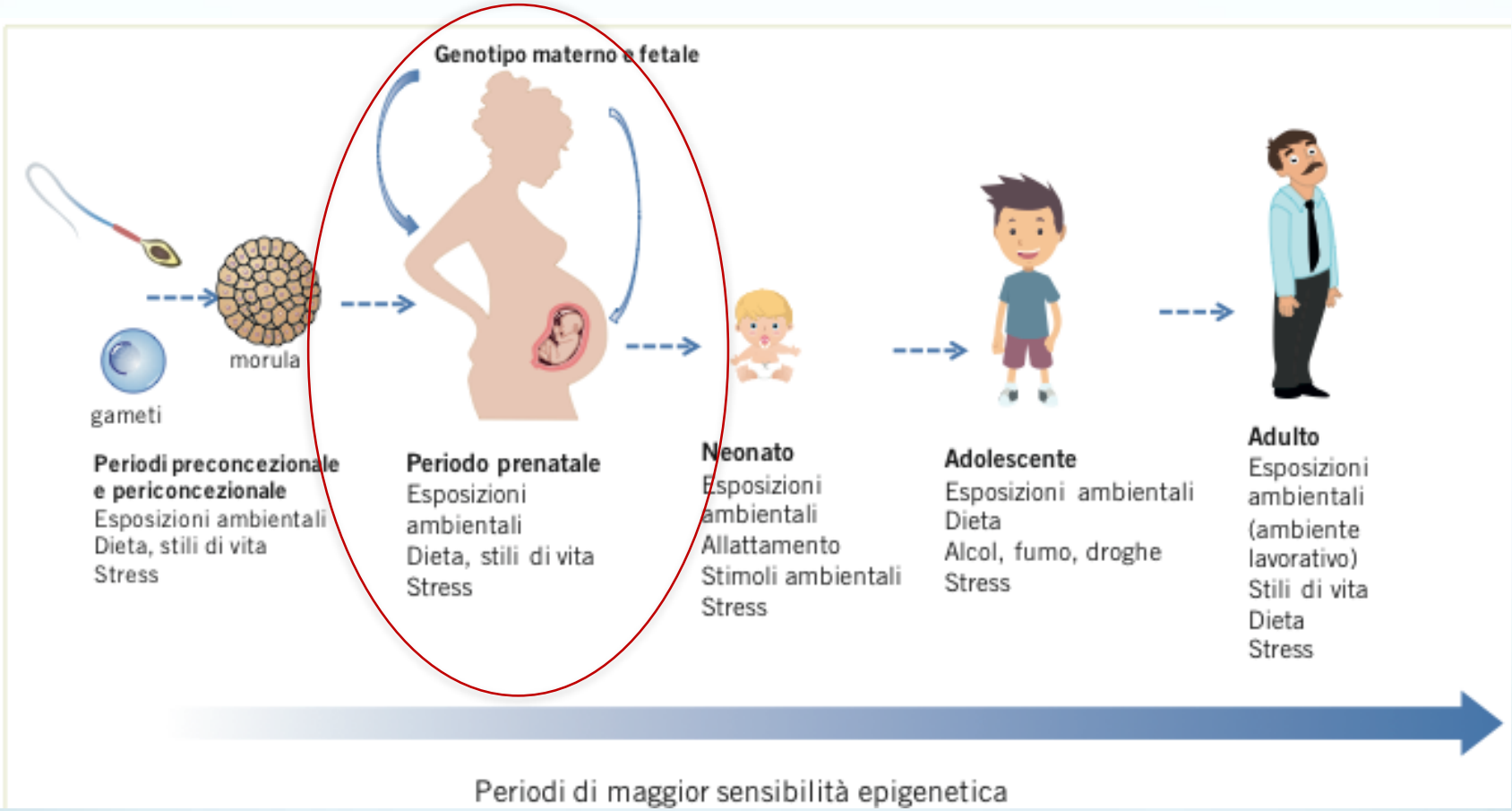
mielodisplastici (MDS).

- **inibitori delle deacetilasi degli istoni (HDACi)**
- **inibitori delle DNA metiltransferasi (DNMTi).**



Una teoria emergente: la DOHaD

Developmental Origins of Health and Diseases (Barker et al., 2002)



Ipotizza che le esposizioni ambientali precoci (prenatali e nei primi anni di vita) possano modificare il rischio di malattie ad insorgenza nell'età adulta

Nobody will ever win the Battle of the Sexes.
There's just too much fraternizing with the enemy.

(Henry Kissinger)