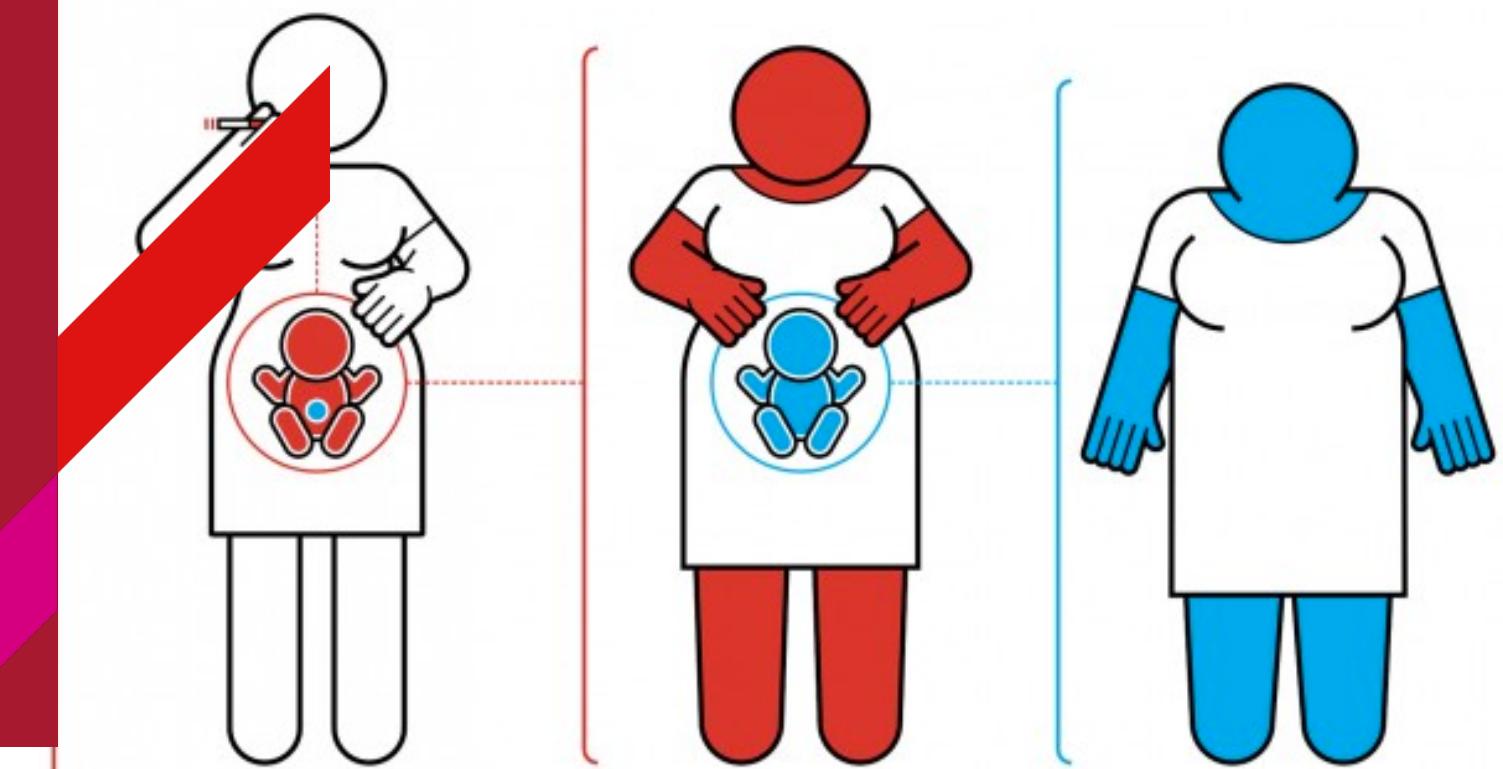


BIOL3120: Human genetics and evolutionary medicine

LECTURE 14: EPIGENETICS AND IMPRINTING





1. Epigenetics

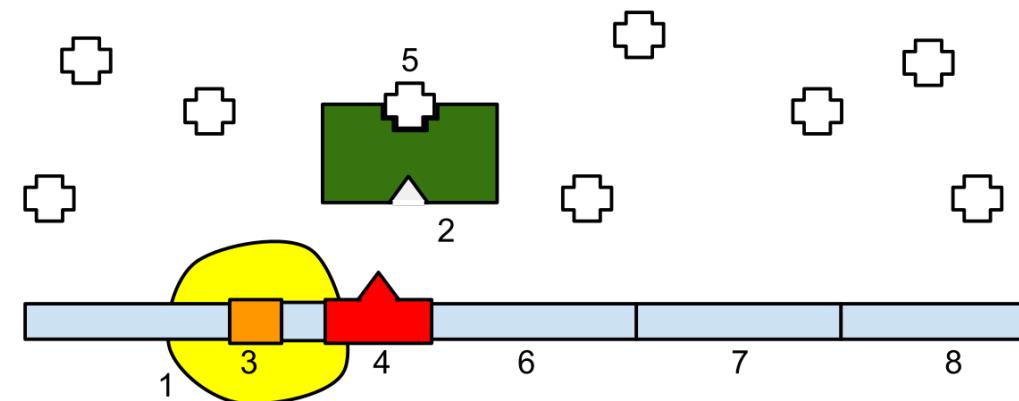
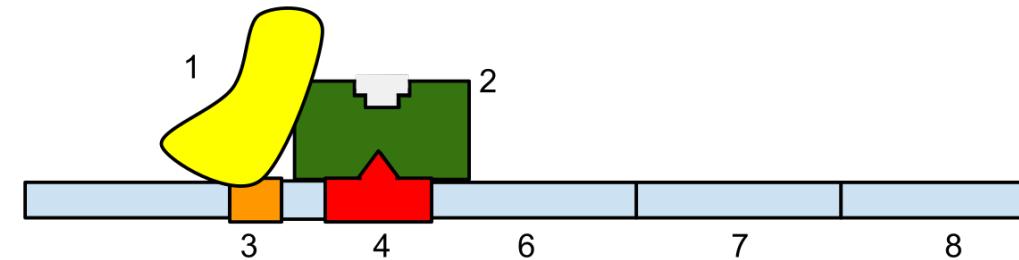
Objective: Describe the importance of epigenetic processes in human health and disease

2. Imprinting

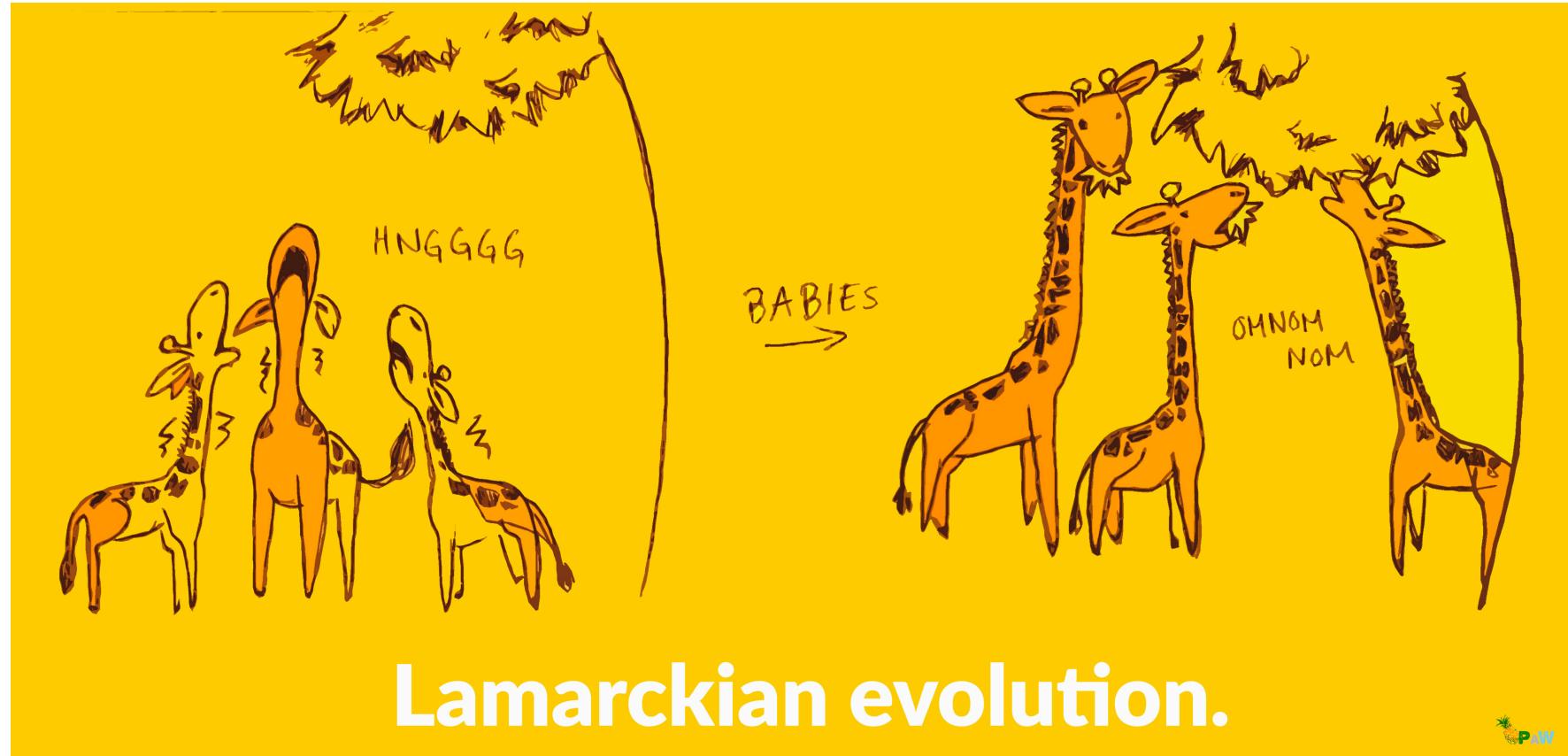
Objective: Explain the concept and mechanism of genomic imprinting, and its significance in specific human diseases

What epigenetics is not..

- Genes expressed under certain conditions, 
consider a very basic example, the lac operon: 

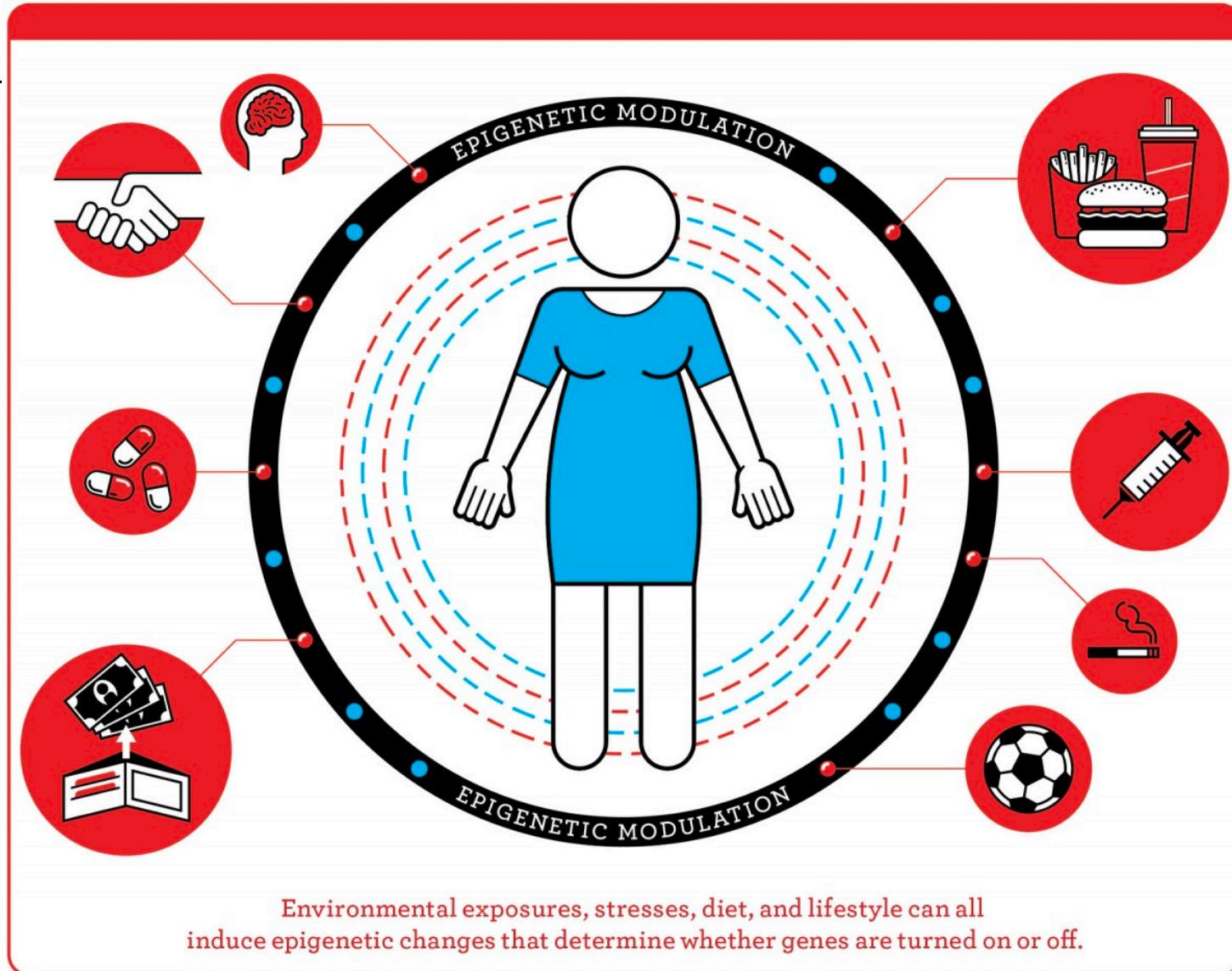


What epigenetics is not..

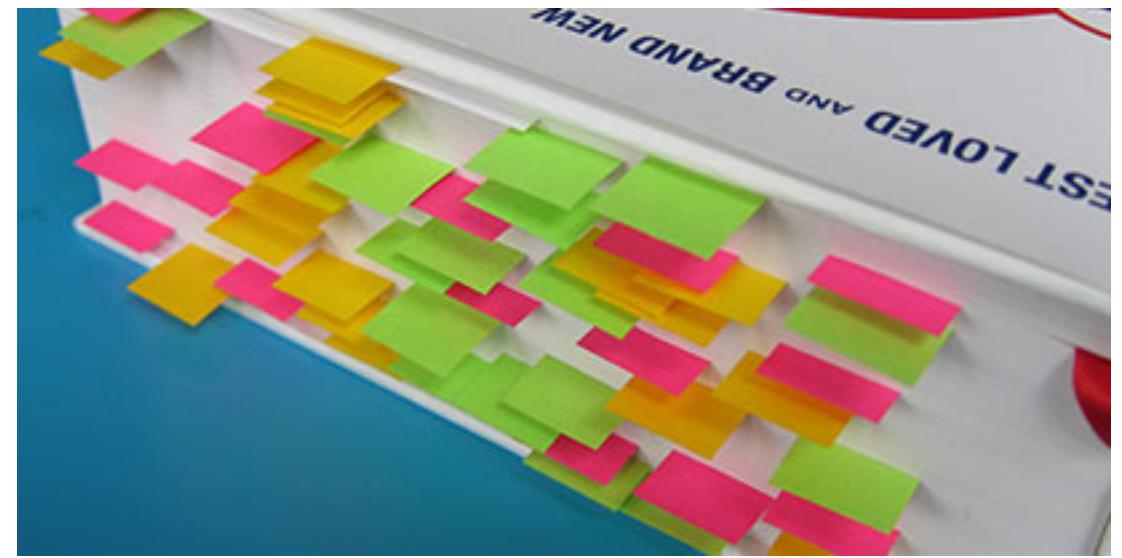
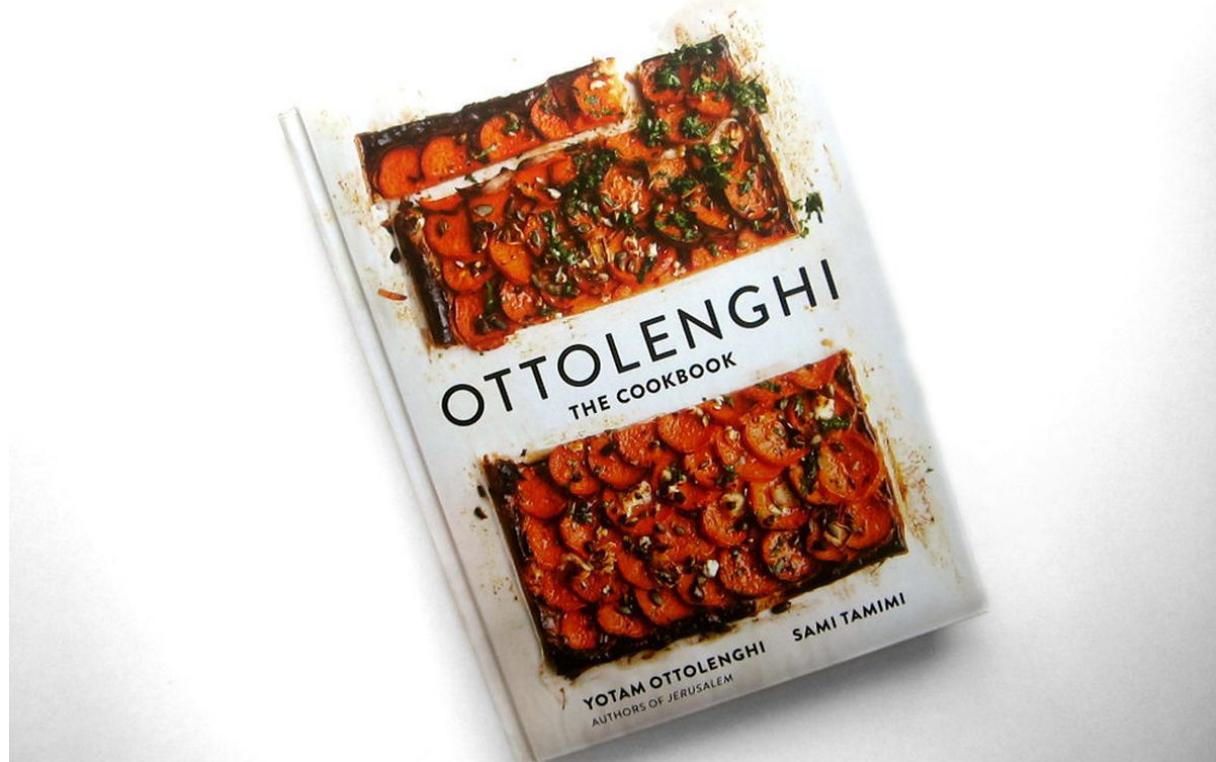


Epigenetics

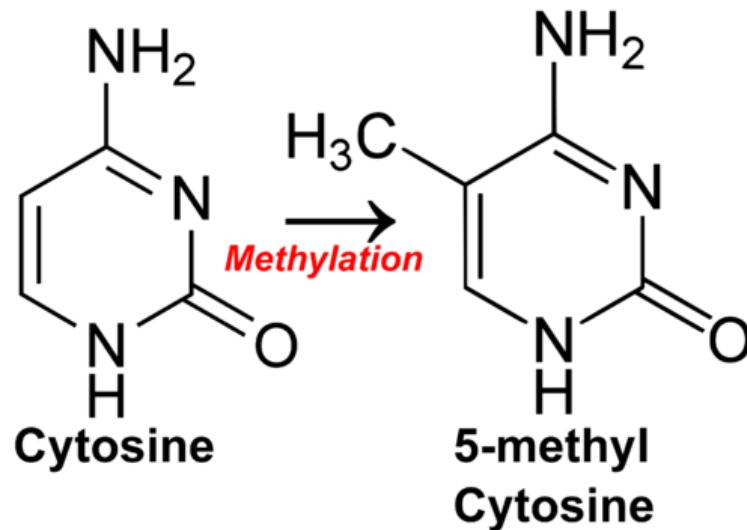
- Epi = over or upon
- Changes in gene expression that do not involve changes in DNA sequence
 - **But can be inherited**
- Changes due to our environment/experiences, that are "inherited" through cell division
- Mechanisms
 - Methylation on DNA at 'CpG islands'
 - Histone modifications / chromatin changes
 - microRNAs (associated with CpG islands)
 - more



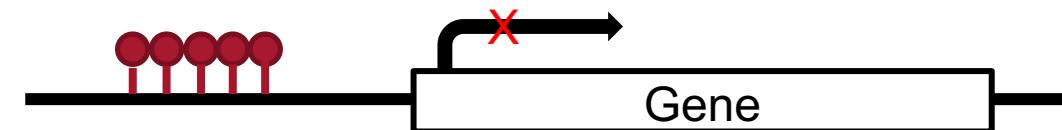
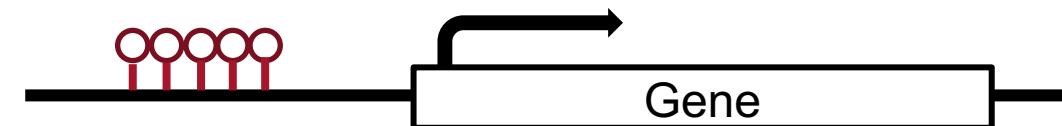
Epigenetics analogy



Methylation



○ Unmethylated
● Methylated



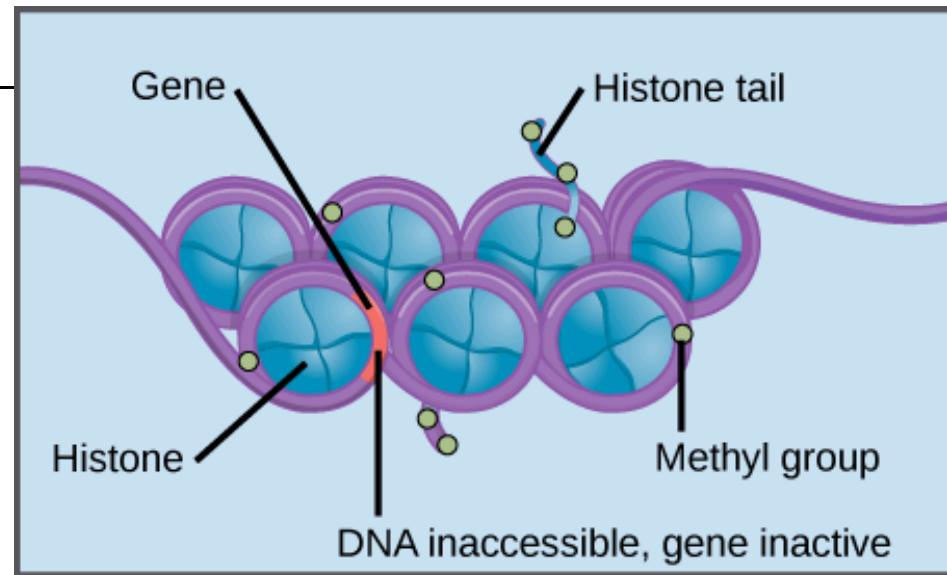
CpG sites & Islands



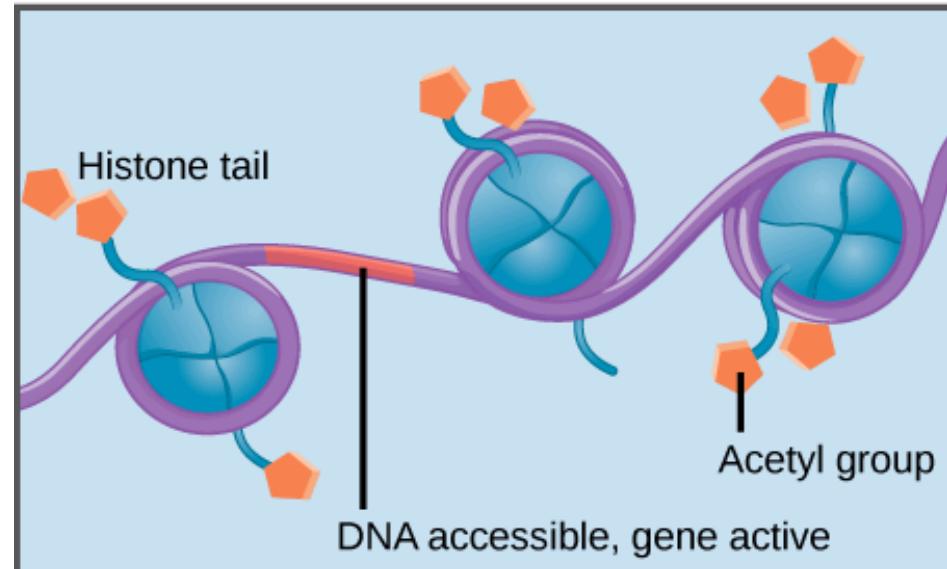
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Histone modification



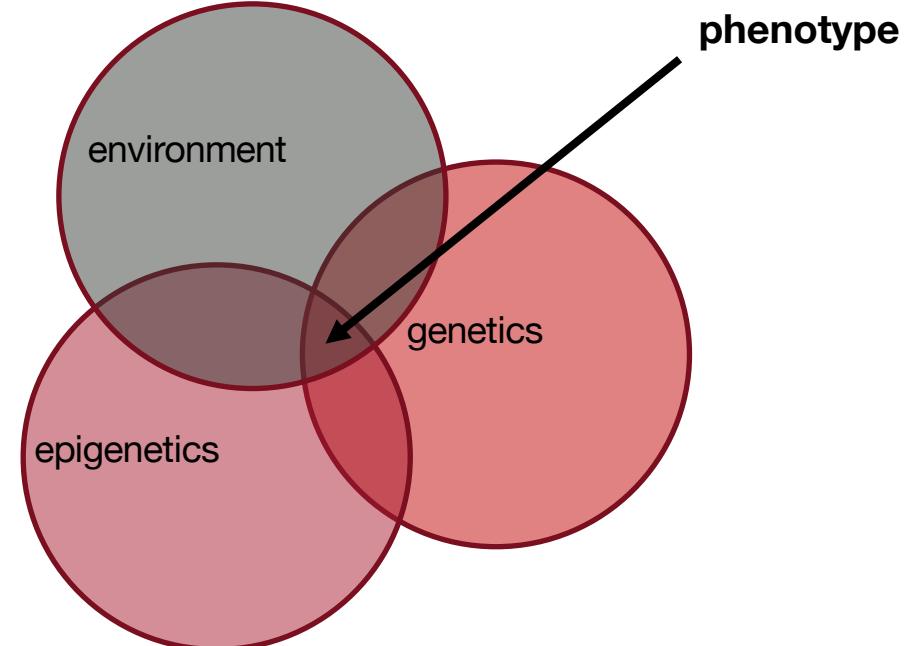
Methylation of DNA and histones causes nucleosomes to pack tightly together. Transcription factors cannot bind the DNA, and genes are not expressed.



Histone acetylation results in loose packing of nucleosomes. Transcription factors can bind the DNA and genes are expressed.

Epigenetics

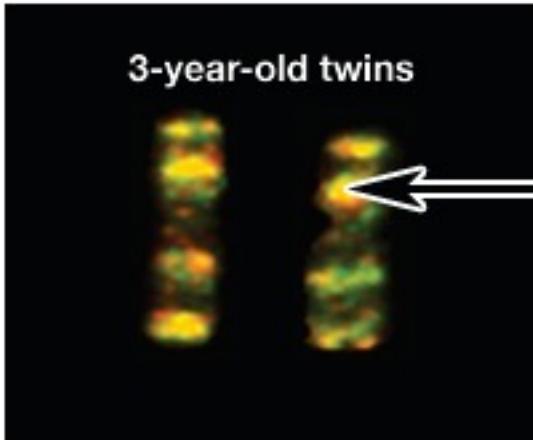
The term ‘epigenetics’ now used to explain phenotypic variation among individuals



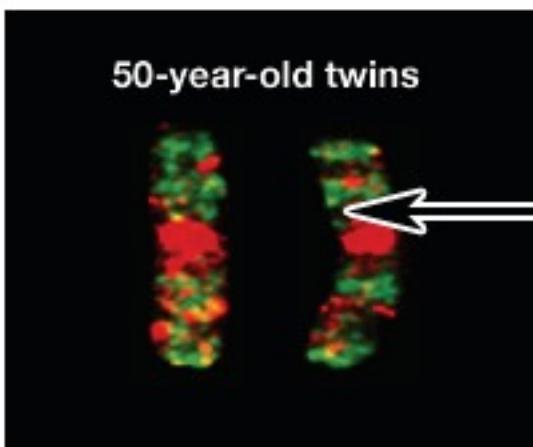
Environmentally induced epigenetics modifications

Chromosome 3 Pairs

3-year old twins vs. 50-year-old twins



Yellow shows where the twins have epigenetic tags in the same place.



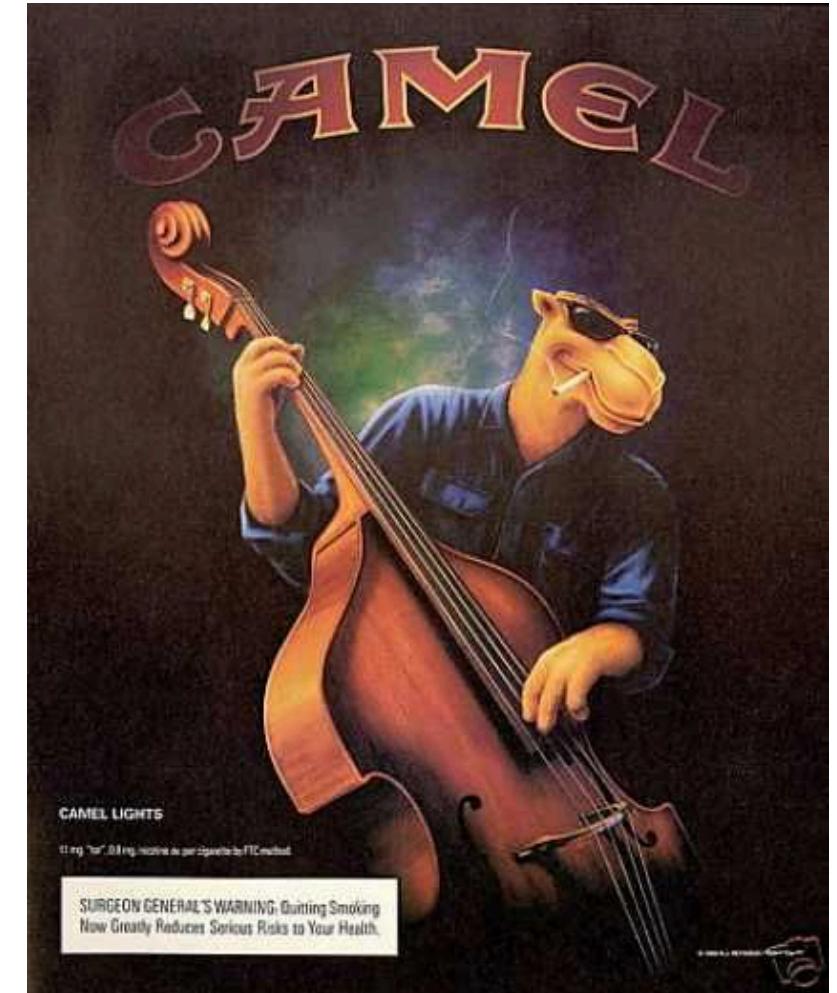
Red and green show where the twins have epigenetic tags in different places.



Epigenetic signatures of cigarette smoking

Joehanes et al., 2016 compared DNA methylation of:

- 2,433 current smokers
- 6,518 former smokers
- 6,956 never smokers
- Comparing current to never smokers: 2,623 significantly different methylation sites linked to 1,405 genes.
- These genes more likely to be linked to pulmonary function, cancer, inflammatory disease, heart disease 
- Comparing former vs. never smokers, 185 of these remained significantly different = “persistent altered methylation” 



Epigenetics in space?

ISS environment for one year:

- Telomeres significantly lengthened, returned to normal 2 days after landing
- Many genes differently expressed, 93% returned to normal postflight, subset of several hundred “space genes” still disrupted after return to Earth.
- Methylation changes to areas near telomere regulating gene and collagen gene



Transgenerational epigenetics? Violence during pregnancy

- Analysed methylation of children 10-19 years whose mothers experienced intimate partner before, during, or after pregnancy
- Methylation of glucocorticoid receptor (GR) gene – linked to response to stress, higher likelihood of anxiety

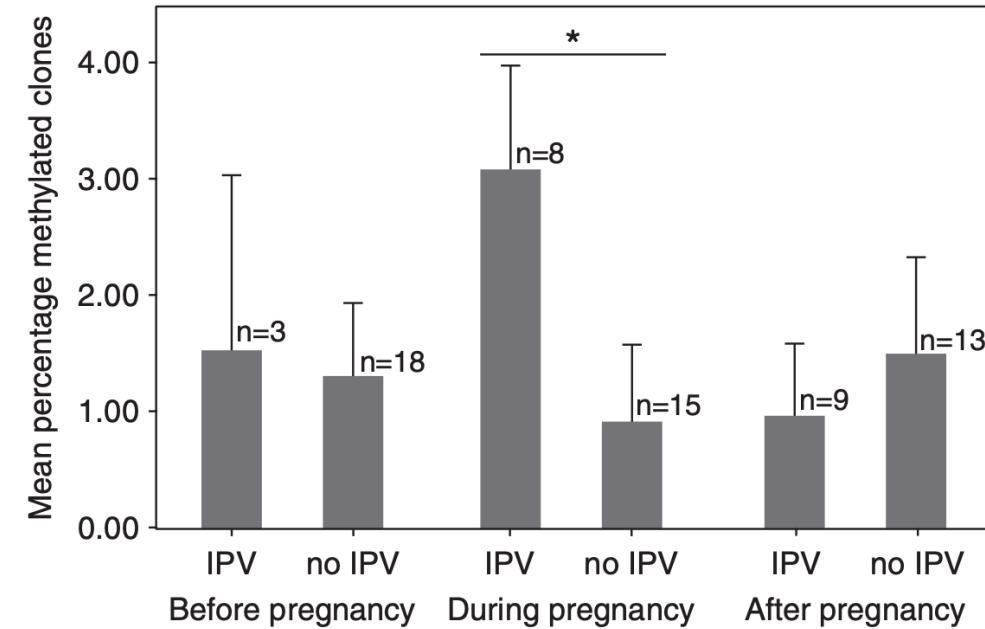


Figure 2 Gestational effects of IPV on methylation of the *GR* promoter in the children. Mean \pm s.e.m. of percentage of methylated clones for the children of women exposed to IPV. IPV only associates with increased methylation, if maternal exposure occurred during pregnancy. The percentage of methylated clones was calculated as the number of clones containing at least one methylated CpG site divided by the total number of clones. * $P < 0.05$; IPV, intimate partner violence.

Transgenerational: The Dutch Hongerwinter



1944 - 1945

Food supplies in Nazi-occupied Holland became increasingly limited

A harsh winter froze canals, cutting off supply

Rations ~500 calories per day

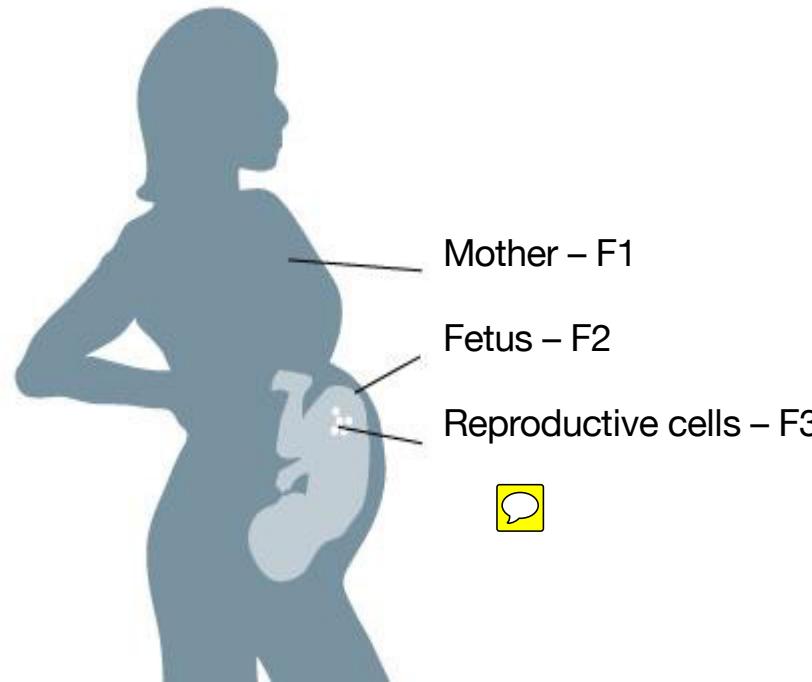
The Dutch Famine Birth Cohort Study

Found that the **children and the grandchildren** of pregnant women exposed to famine were more susceptible to obesity, diabetes, cardiovascular disease and other health problems.

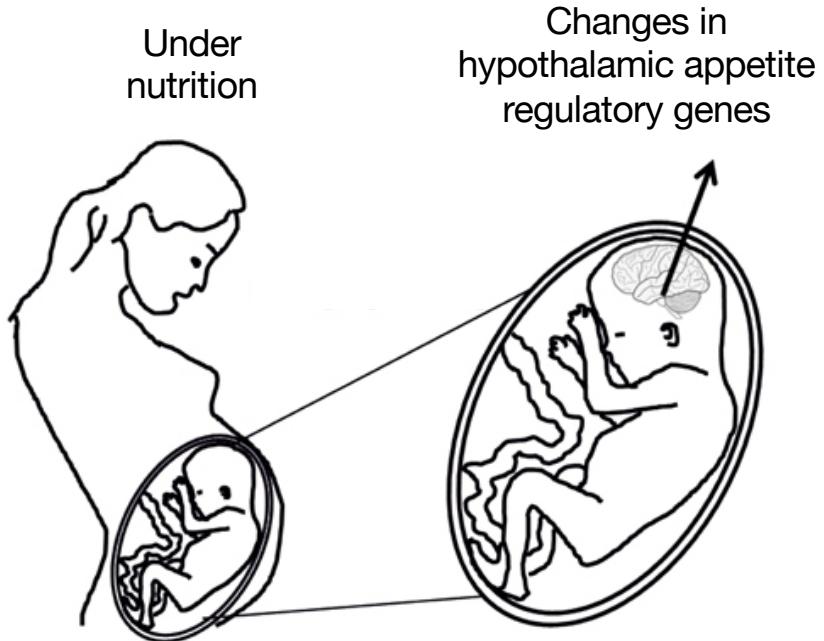
The children who were affected in the second trimester of their mother's pregnancy had an increased incidence of schizophrenia in these children.

In utero influences

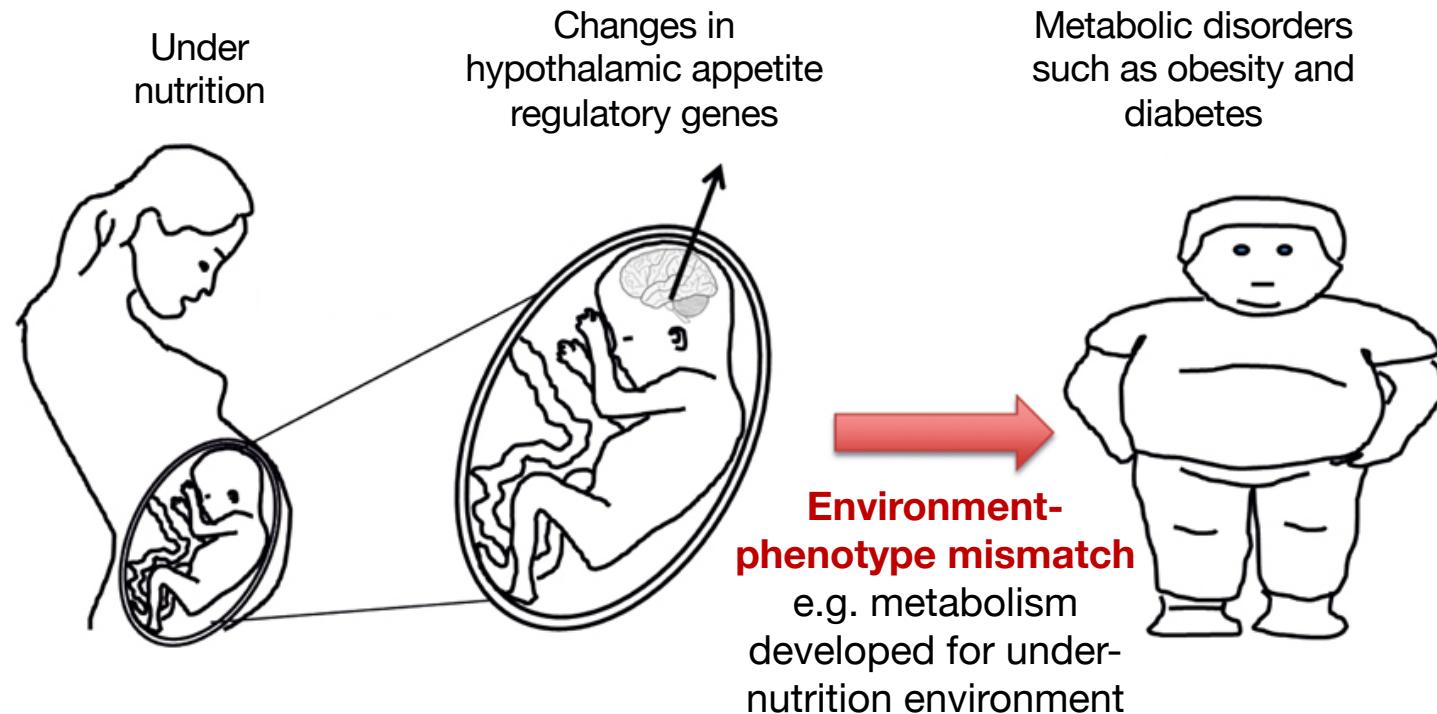
e.g. maternal nutrition, smoking, depression,
etc.



Transgenerational Phenotypic Effects

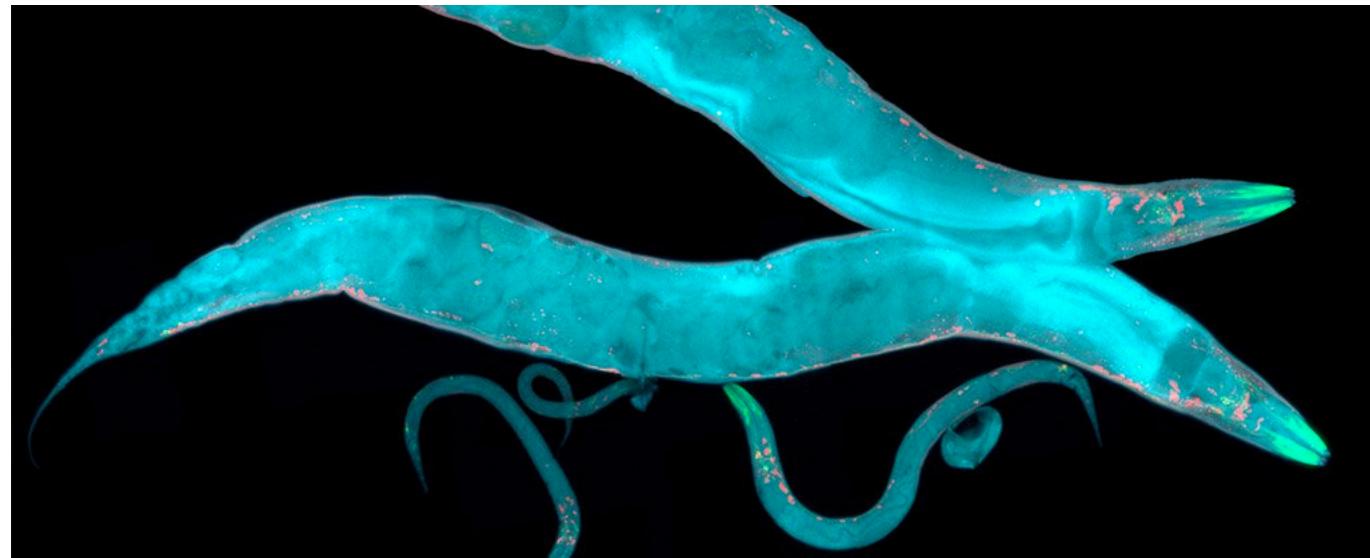


Transgenerational Phenotypic Effects

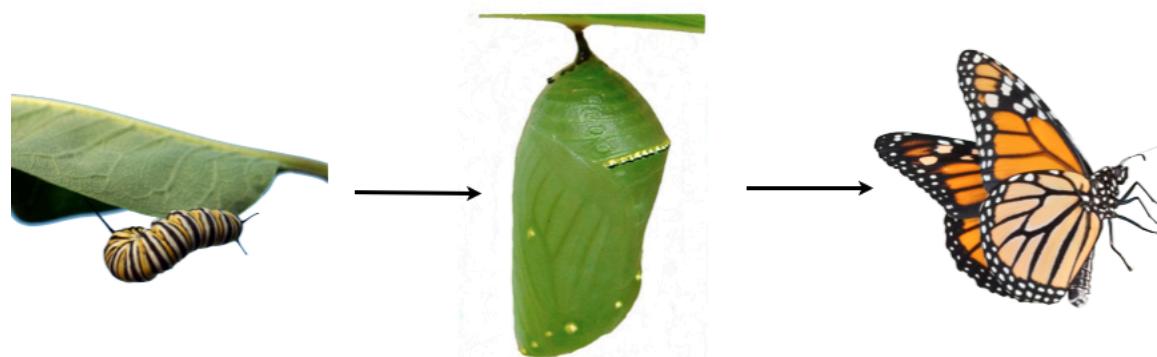


Transgenerational epigenetics? Worm studies

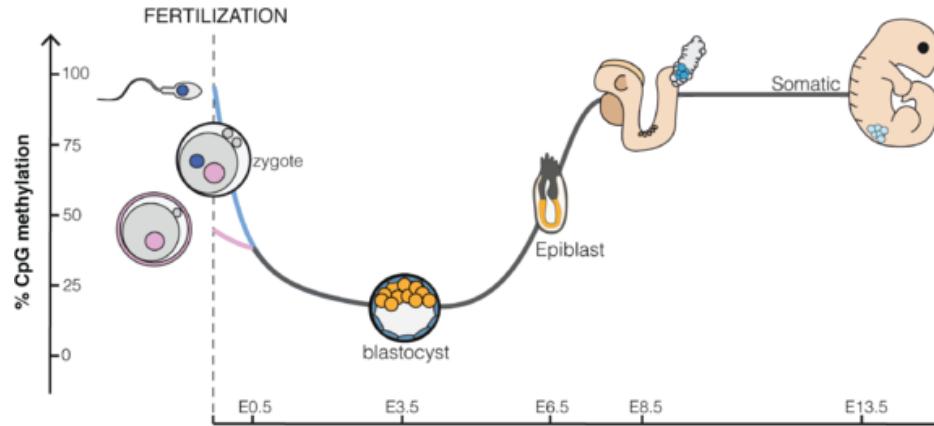
- *C. elegans* kept in 25°C show increase expression in heat tolerance gene HSP90 (HSP90 promoter: fluorescence expression)
- Exposure to 25°C for 1 generation, increased expression for 7 generations
- Exposed to 25°C for 5 generations, Increased expression for 14 generations
- Histone modifications apparent cause



Epigenetics and phenotypic plasticity



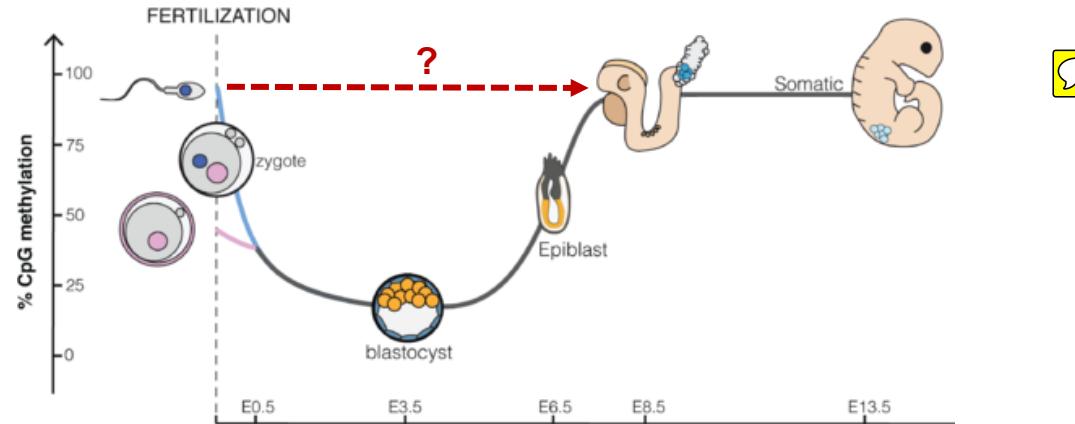
Epigenetic Reprogramming



For inheritance of DNA Methylation patterns, some cells must escape epigenetic reprogramming during development

Only epigenetic modifications in the germ line will be passed on → are epigenetic modifications maintained during meiosis?

Epigenetic Reprogramming



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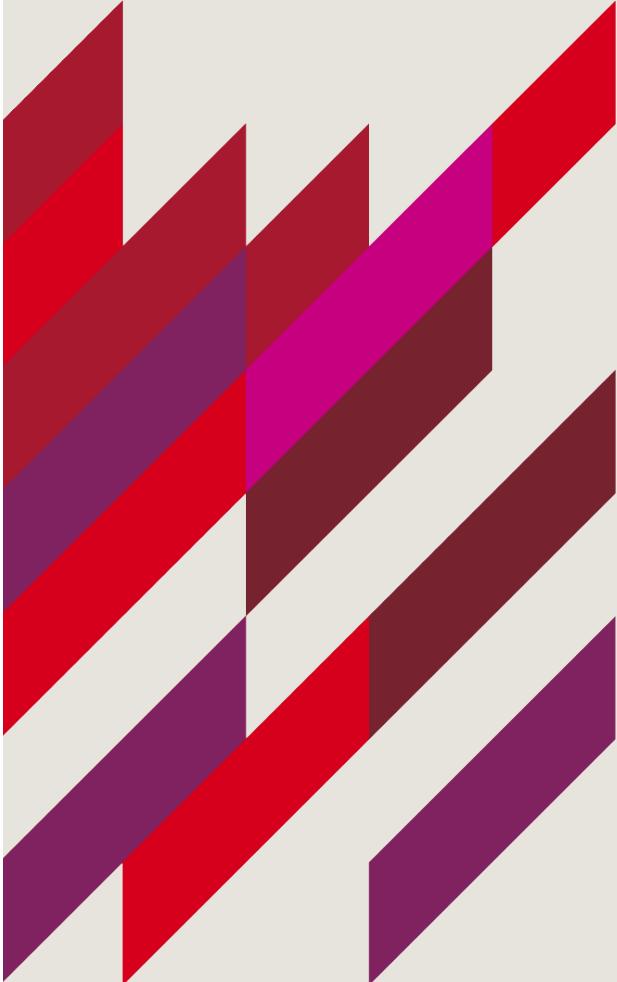
Human Epigenome Pilot Project

The Human Epigenome Consortium is a public/private collaboration that aims to identify and catalogue Methylation Variable Positions (MVPs) in the human genome. As a prelude to the full-scale Human Epigenome Project (HEP), we have recently completed a pilot study of the methylation patterns within the Major Histocompatibility Complex (MHC) - a region of chromosome 6 that is associated with more diseases than any other region in the human genome.

We have identified MVPs in the vicinity of the promoter and other relevant regions of approximately 150 loci within the MHC in tissues from a range of individuals. This will provide an unprecedented insight into the complex relationship between genetics and epigenetics that underlies both normal cellular homeostasis and disease states, in particular autoimmune diseases.

For the pilot project, we developed an integrated genomics-based technology platform. The pipeline involves the automated bisulphite treatment of DNA from minute tissue biopsies, gene-specific bisulphite PCR and large-scale sequencing of PCR amplicons. Analysis and quantification of methylation patterns is achieved by mass spectrometric and microarray assays.

- Consortium
- Human Epigenome Pilot Project
 - Data Analysis
 - Epigenotyping
- Human Epigenome Project
- Data
- Data Release Policy
- Publications
- Home



1. Epigenetics

Objective: Describe the importance of epigenetic processes in human health and disease

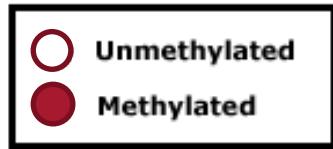
2. Imprinting



Objective: Explain the concept and mechanism of genomic imprinting, and its significance in specific human diseases

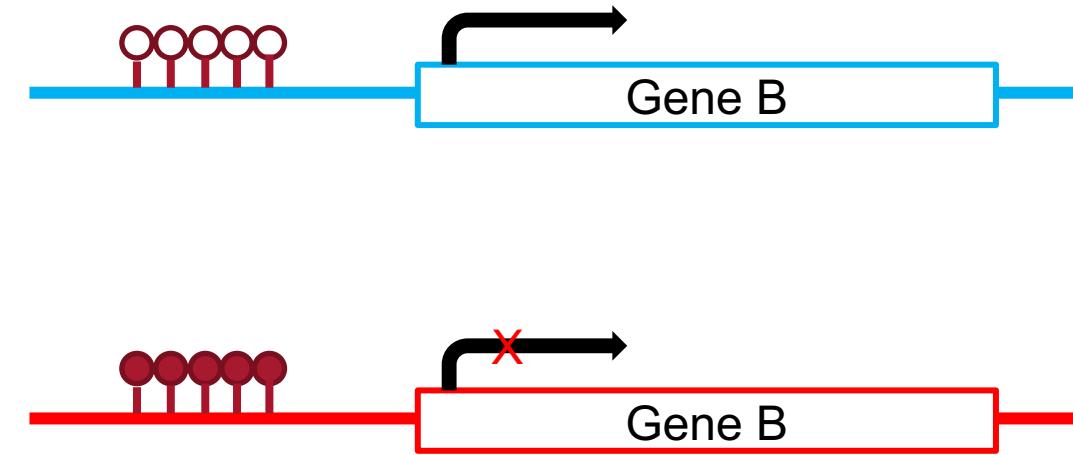
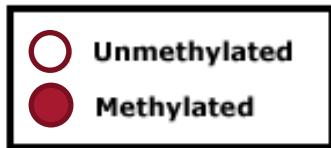
Genomic Imprinting

The unequal expression of the maternal and paternal alleles of a gene



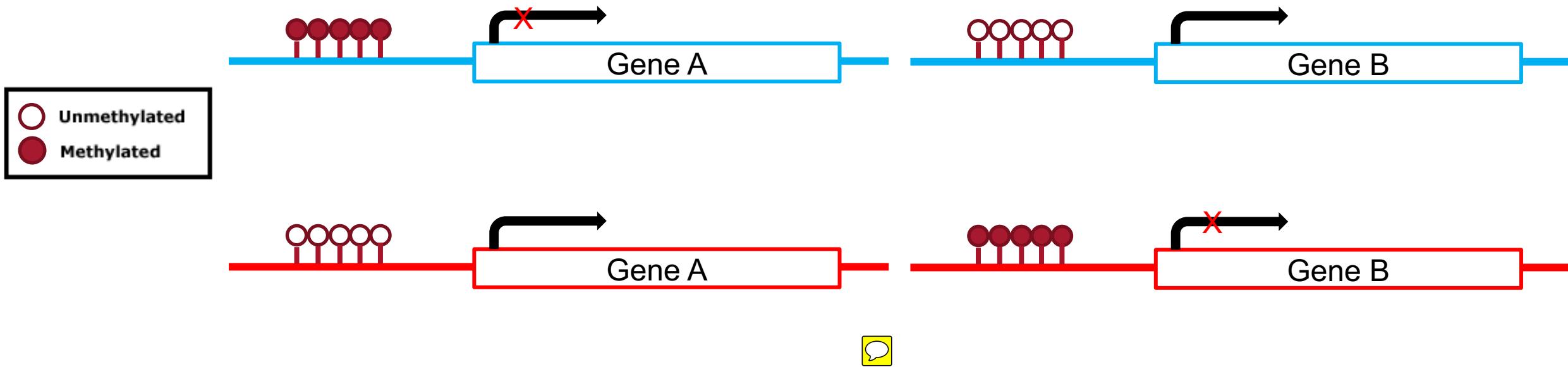
Genomic Imprinting

The unequal expression of the maternal and paternal alleles of a gene



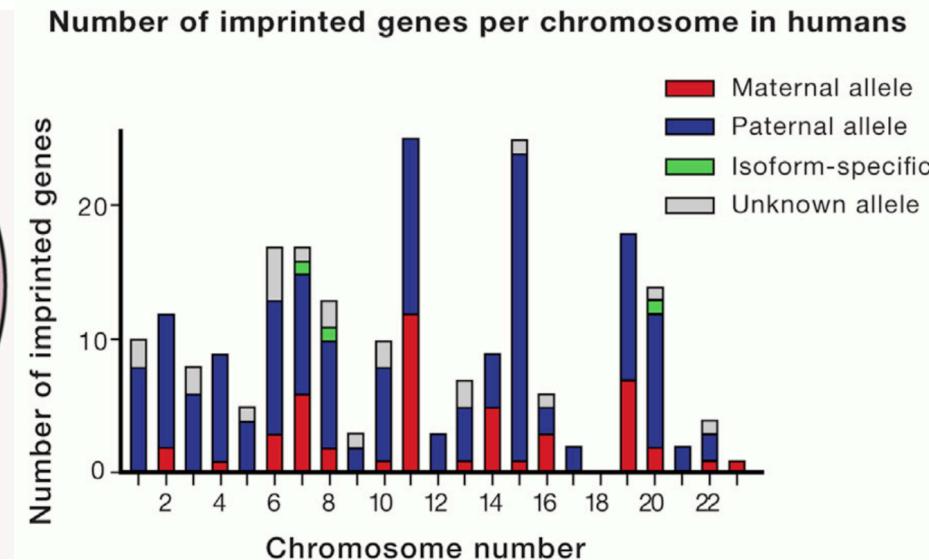
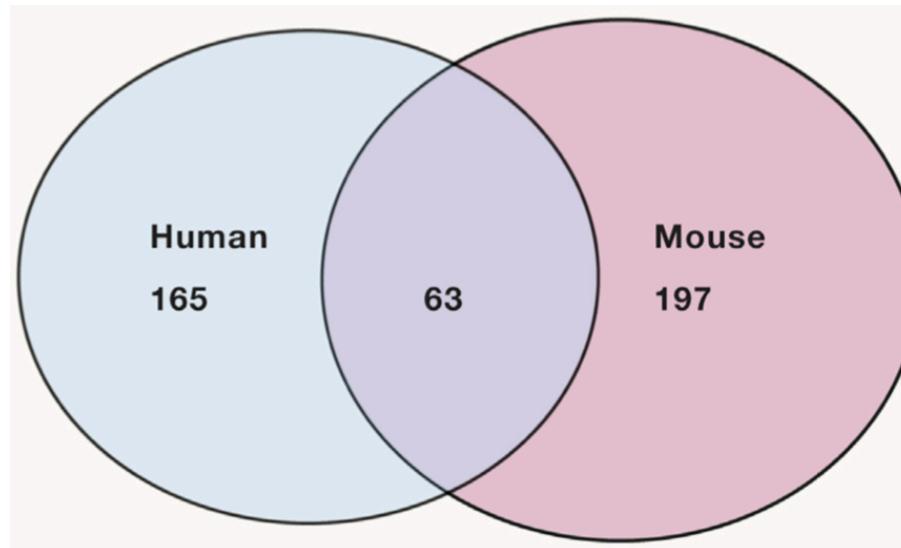
Genomic Imprinting

The unequal expression of the maternal and paternal alleles of a gene

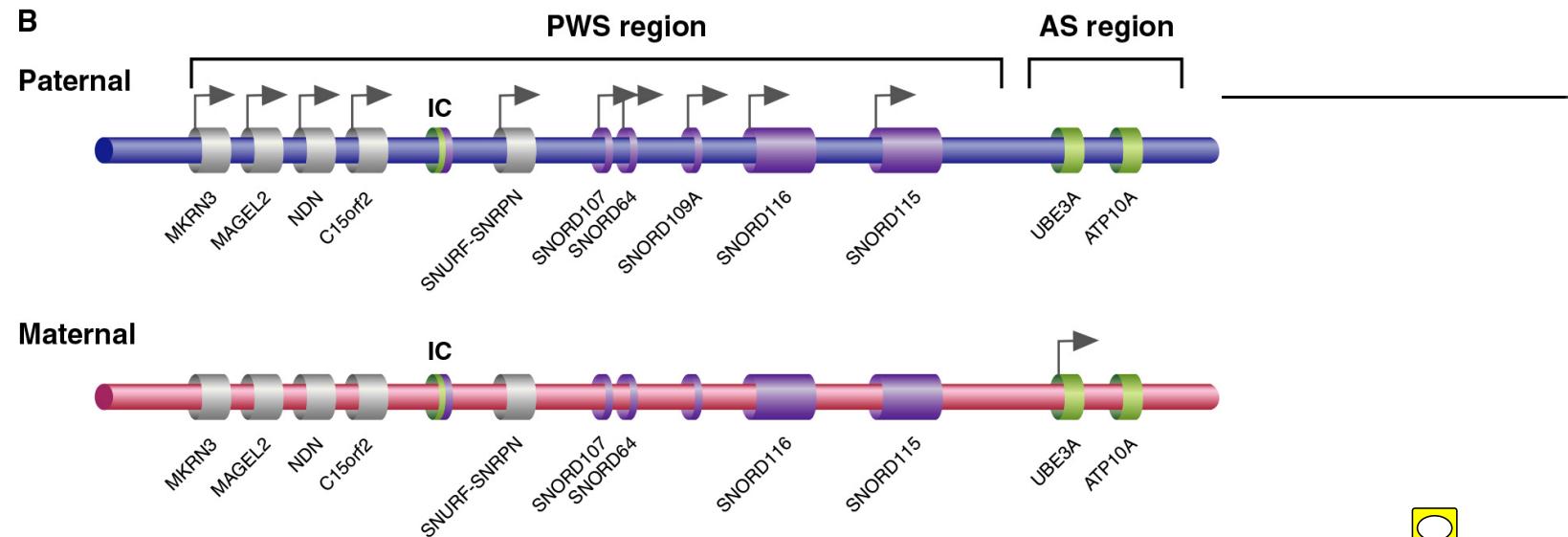


Genomic Imprinting - humans

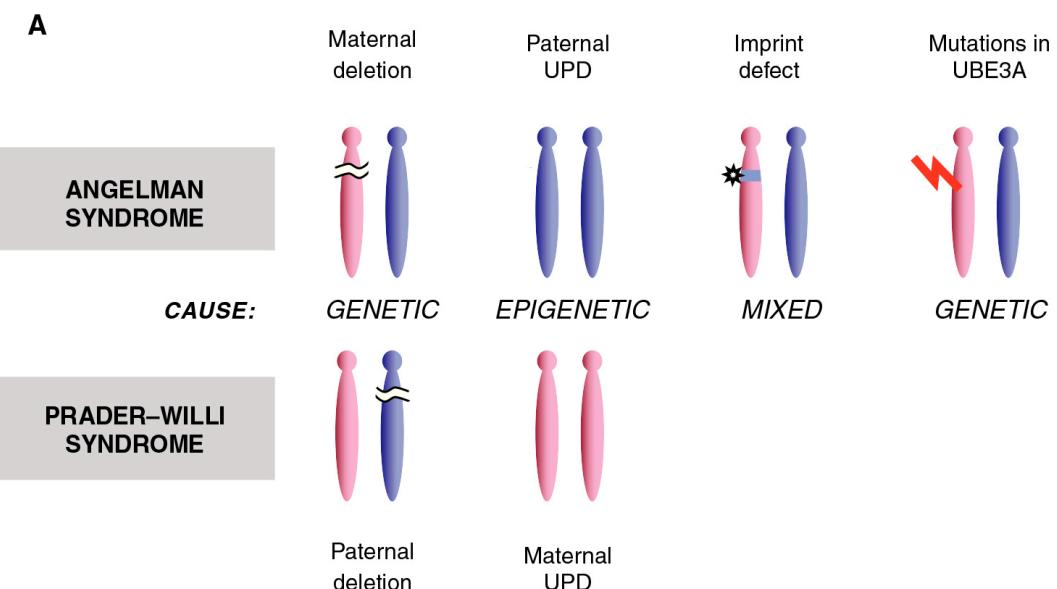
-
- Fetal growth
 - Placental biology
 - Homeostasis
 - Nervous system
 - Half of all imprinted genes are expressed in brain



Diseases associated with imprinting: 15q11-13 region

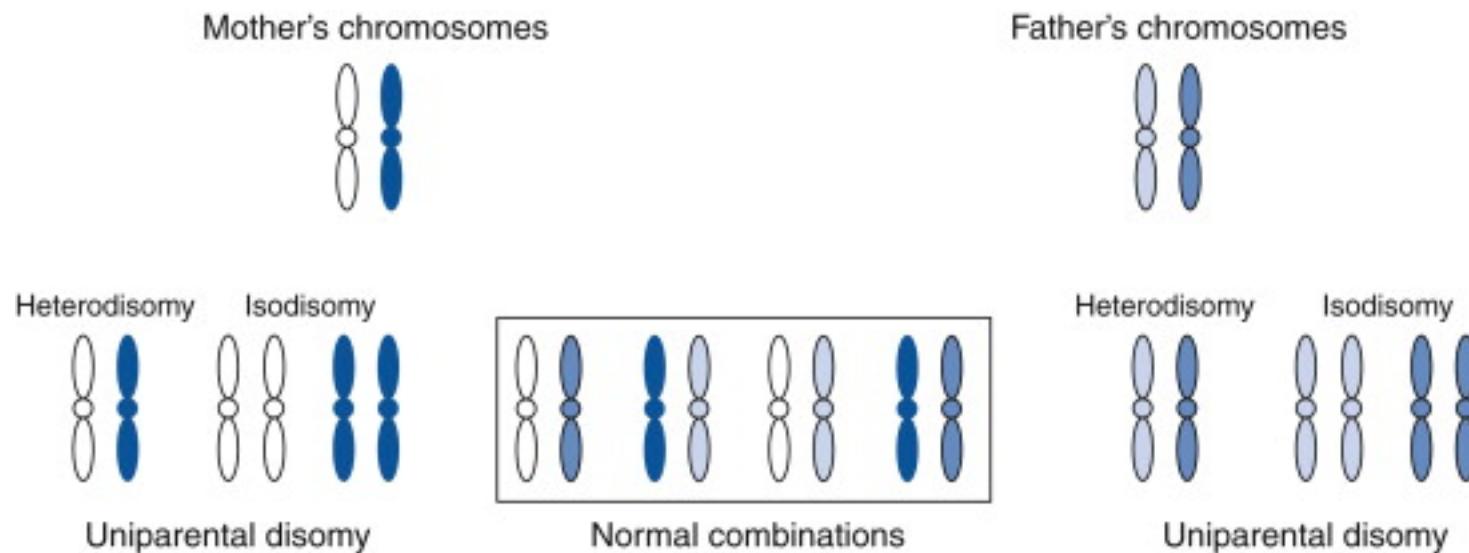


- Loss of paternal expression of 11 genes = **Prader-Willi syndrome**
- Loss of maternal expression of UBE3A = **Angelman syndrome**



Uniparental disomy (from previous lectures)

- When two copies of a chromosome are inherited from the same parent
- **Heterodisomy** = inherited both of one parent's chromosomes
 - Error in meiosis I
- **Isodisomy** = inherited two identical copies of a chromosome from one parent
 - Error in meiosis II

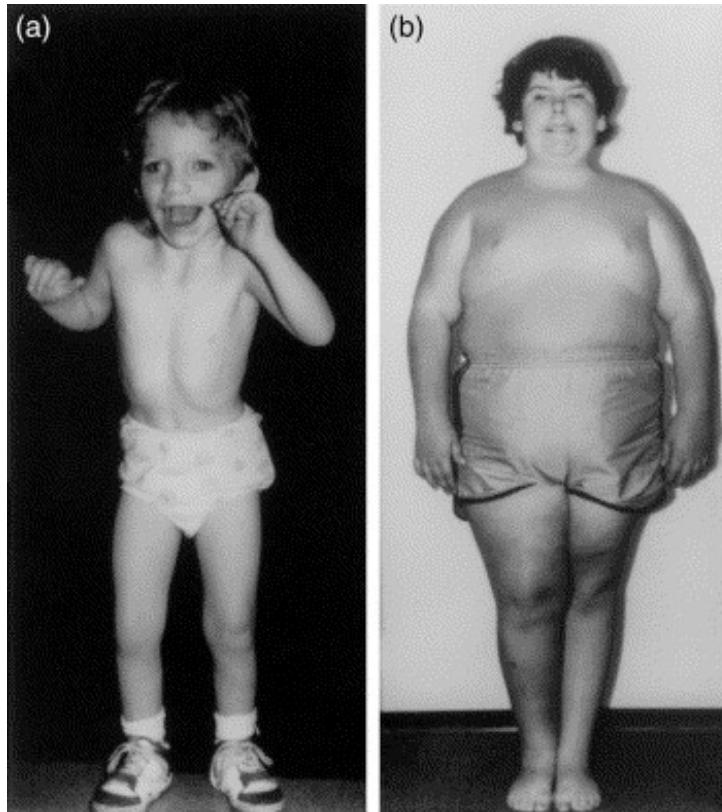


Angelman / Prader-Willi syndromes

Chromosome 15

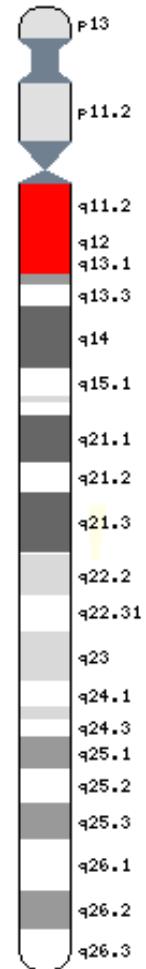
a) Angelman Syndrome (AS)

- jerky movements
- severe mental retardation
- growth retardation
- inappropriate laughter



b) Prader-Willi Syndrome (PWS)

- hypotonia (floppy baby)
- moderate mental retardation
- obesity beginning in childhood
(caused by insatiable appetite)



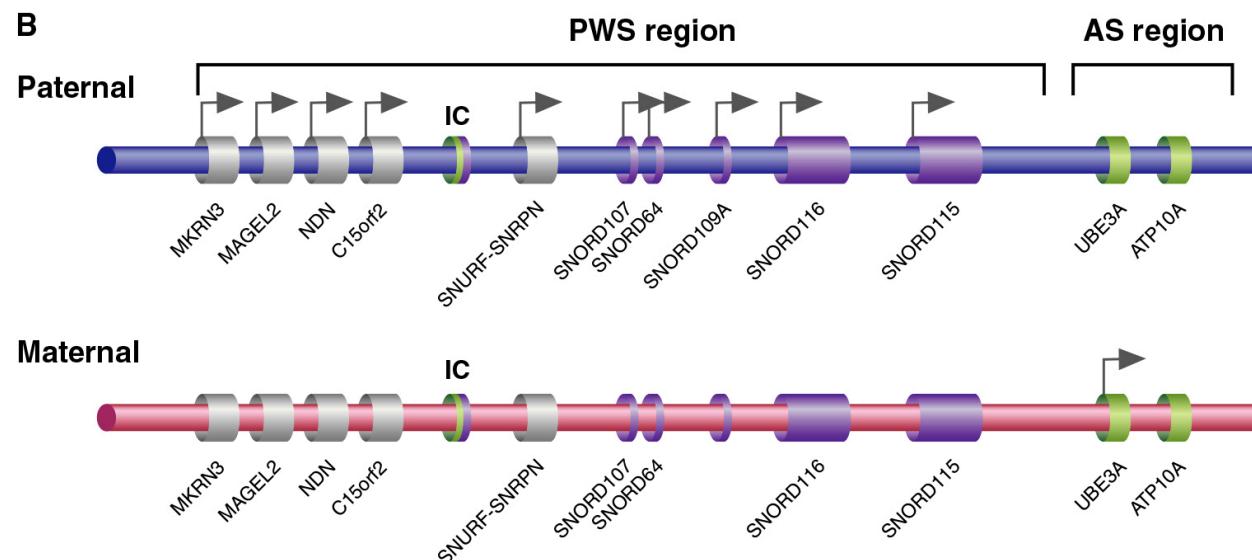
What do these genes do?

Angelman genes:

- **UBE3A** important for regulation of protein synthesis at synapses (junctions between nerve cells)
 - only imprinted in brain – both copies expressed in most other body tissues

PWS genes:

- SNORD genes small nucleolar RNA – modify other RNAs
- SNORD116 most responsible for PWS symptoms?



Other imprinting regions/conditions

11p15.5

- maternal expression problems or paternal UPD = Beckwith-Wiedemann syndrome
- Paternal expression problems or maternal UPD = Silver-Russell syndrome

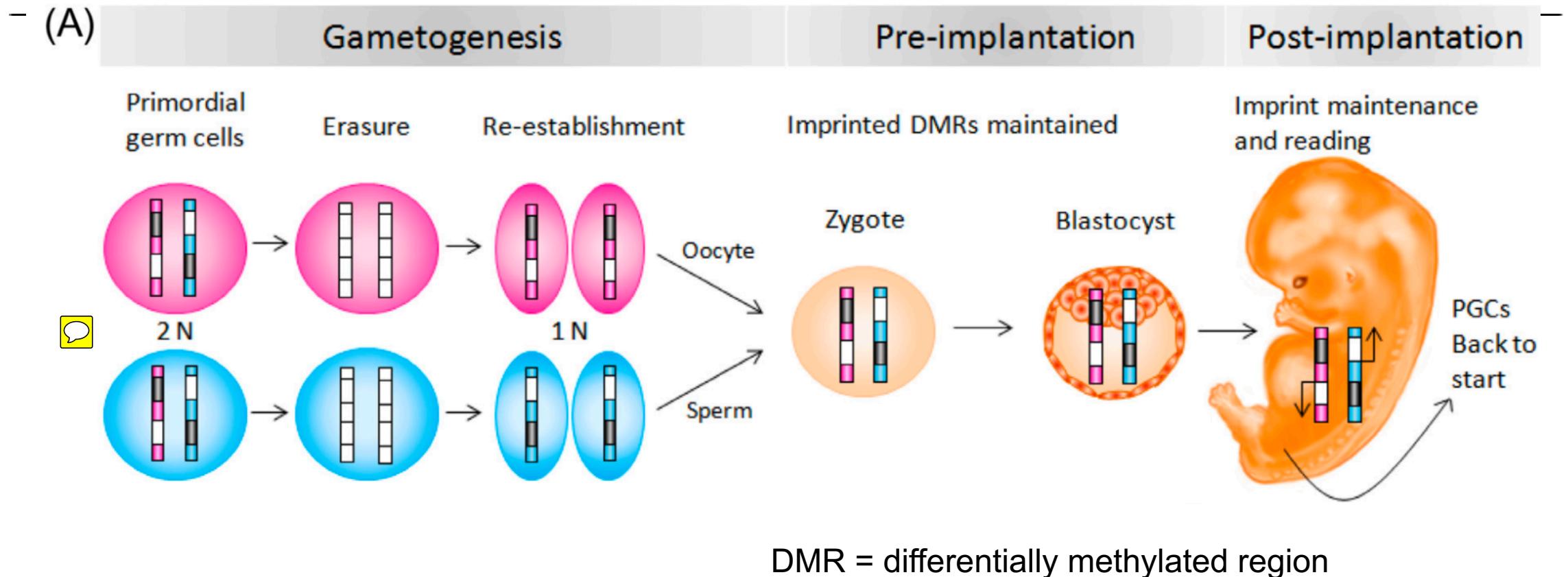
14q32

- MatUPD14 syndrome
- PatUPD14 syndrome

20q13.3

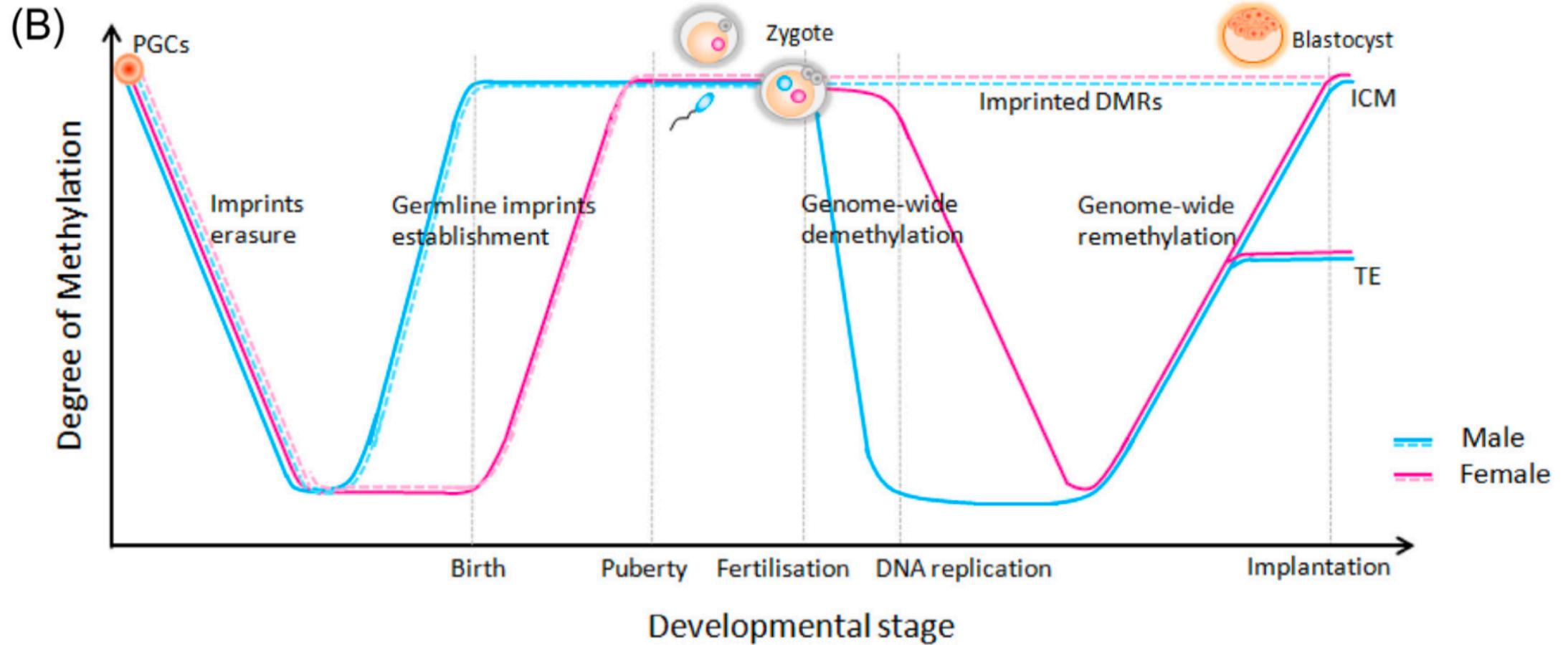
- Pseudo-hypoparathyroidism types 1a and 1b

How does imprinting work?



PGC = primordial germ cell

How does imprinting work?



DMR = differentially methylated region

ICM = inner cell mass, goes on to become fetus

TE = trophectoderm , goes on to become ²⁵ placenta

Why does imprinting exist?

Evolutionary explanation - “kinship theory”



The inequality between parental genomes due to imprinting is a result of the differing interests of each parent



David Haig
Harvard University

Father: greater fitness success of offspring at the expense of the mother; future babies might not have father's alleles → paternally expressed genes are growth-promoting

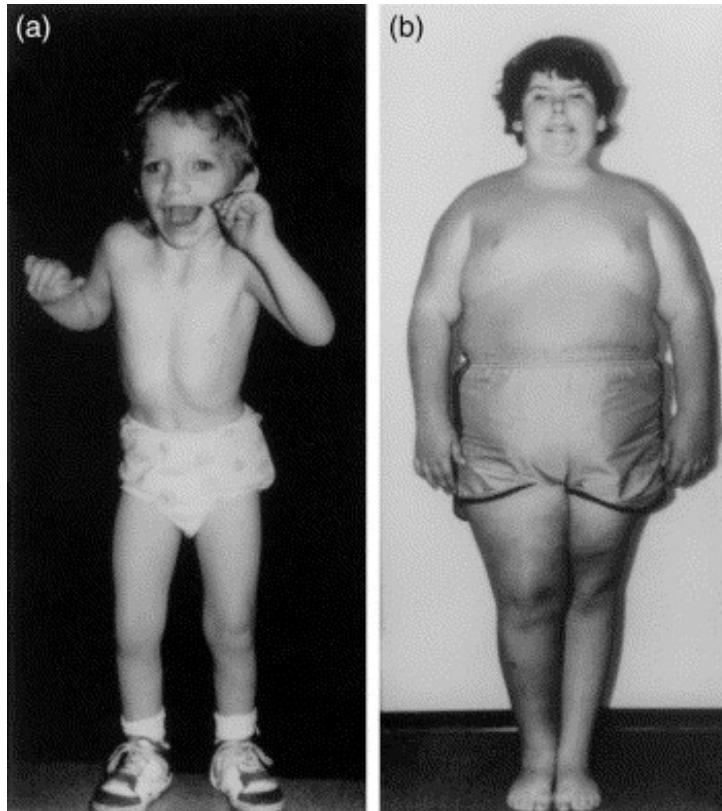
Mother: conserve resources for her own survival while providing sufficient nourishment to current and subsequent offspring → maternally expressed genes are growth-limiting

Angelman / Prader-Willi syndromes

Chromosome 15

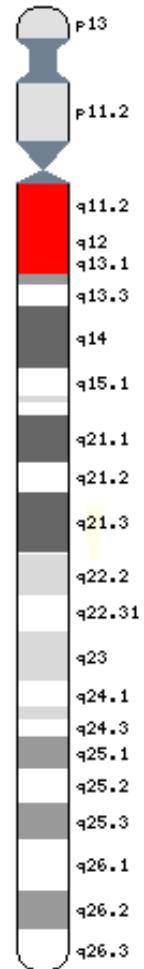
a) Angelman Syndrome (AS)

- jerky movements
- severe mental retardation
- growth retardation
- inappropriate laughter



b) Prader-Willi Syndrome (PWS)

- hypotonia (floppy baby)
- moderate mental retardation
- obesity beginning in childhood
(caused by insatiable appetite)





1. Epigenetics

- Subtle layer of gene regulation
- Can persist over time/generations

Objective: Describe the importance of epigenetic processes in human health and disease

2. Imprinting

- Differential expression of genes based on parent of origin
- methylation of CpG islands
- Angelman / Pader Willi syndromes as example conditions

Objective: Explain the concept and mechanism of genomic imprinting, and its significance in specific human diseases