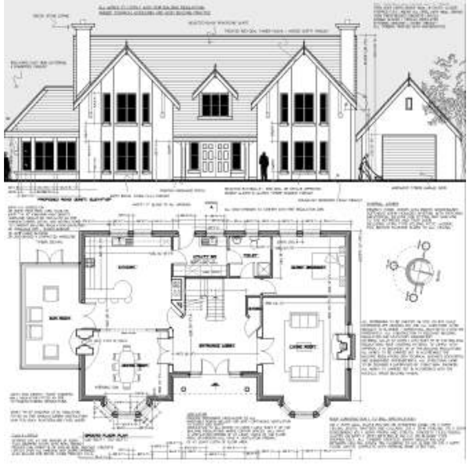
Written on the genome:
a life history of epigenetics

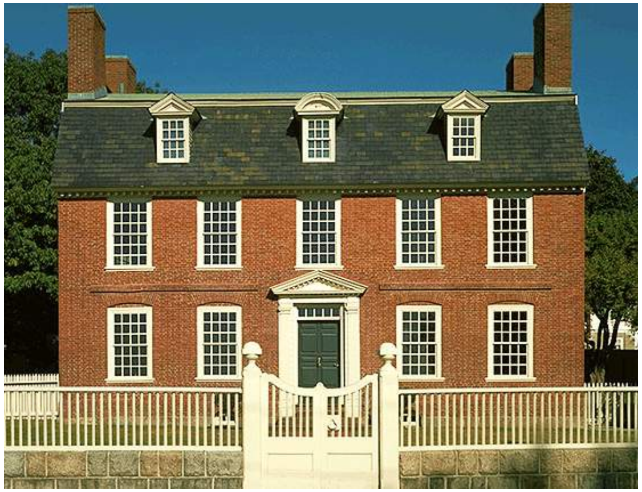
Deborah Mackay

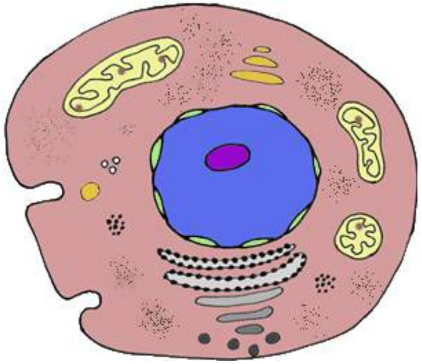
What is epigenetics?

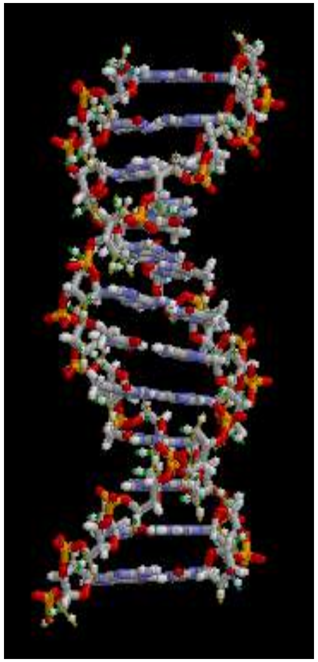
To address this question, we first ask, what are genes?

The ‘plans’ to make a human are coded in DNA in every cell



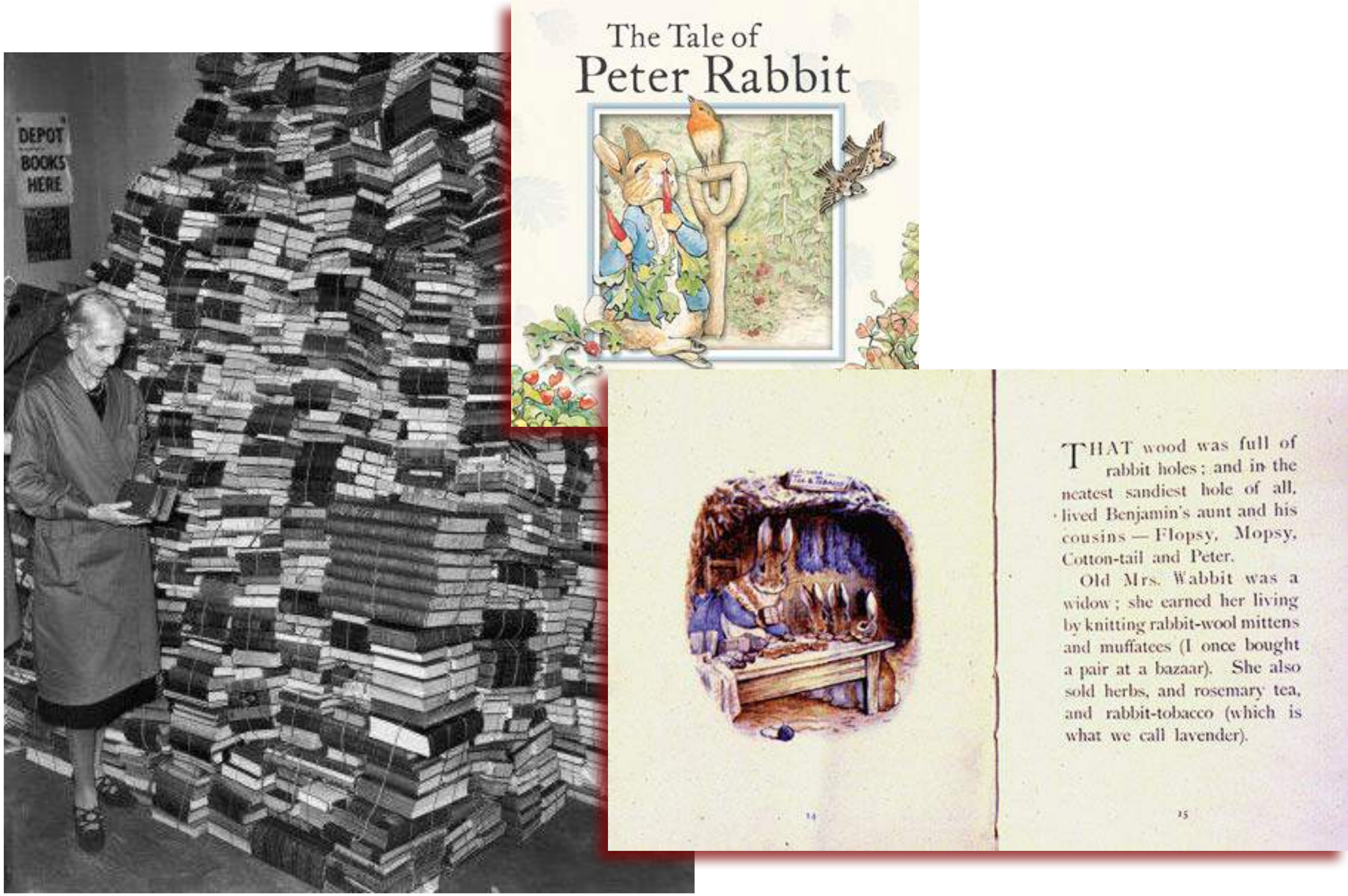






Every single cell contains all the instructions to make every single bit of a person (3,000,000,000 letters of code)

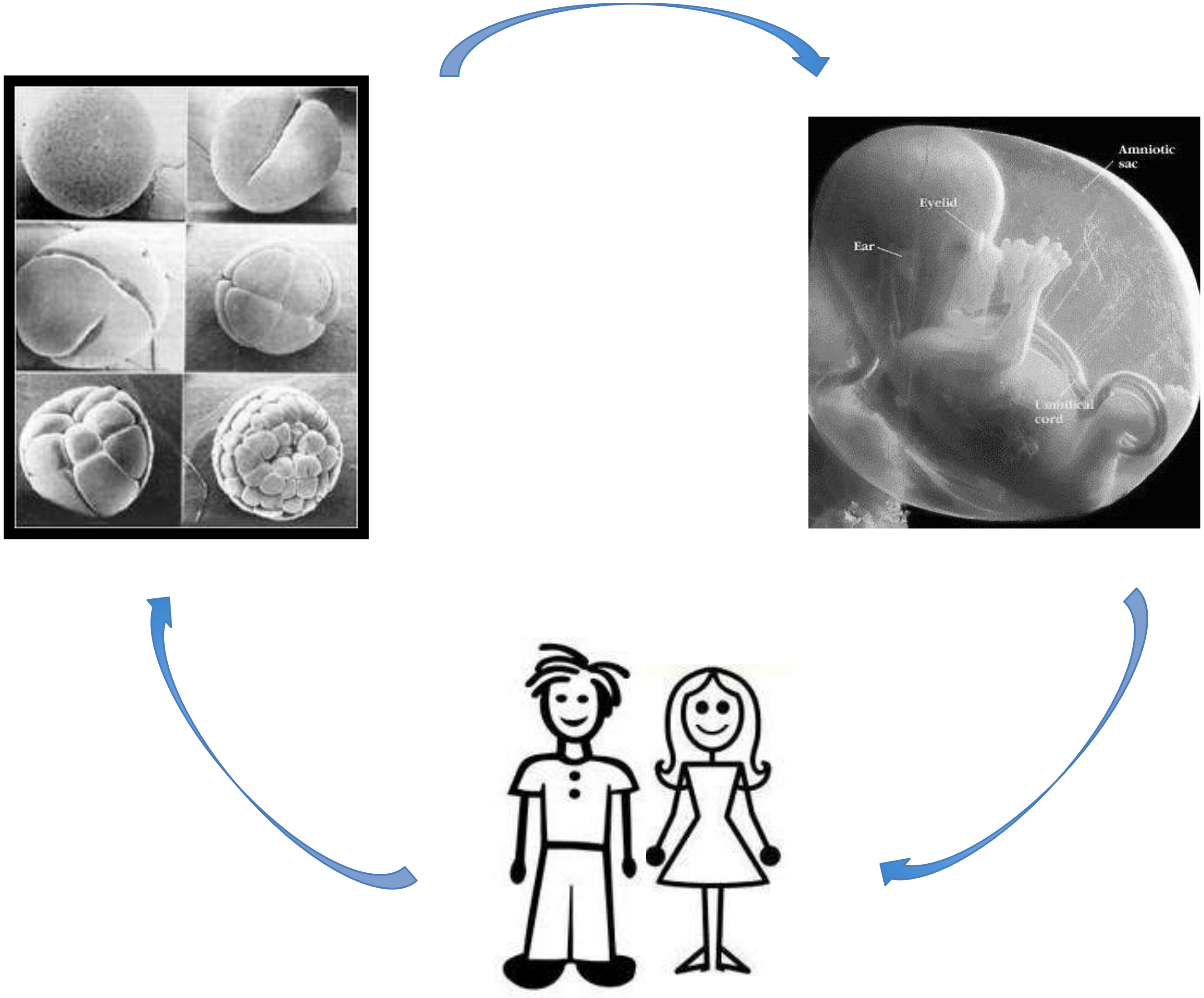
DNA is organised into genes.
About 25,000 genes are needed to make a person
These genes comprise only ~1.5% of the genome



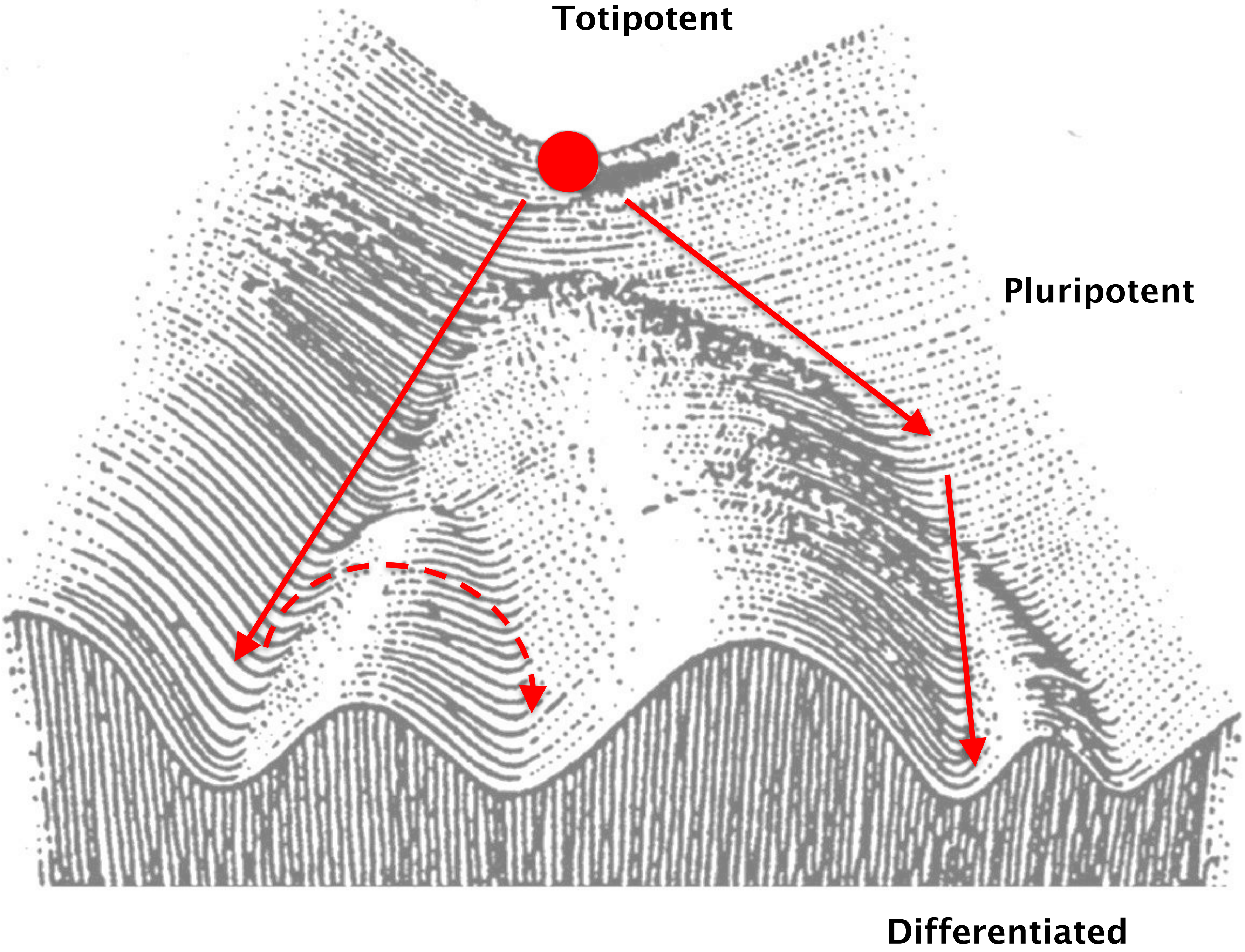
THAT wood was full of rabbit holes; and in the neatest sandiest hole of all, lived Benjamin's aunt and his cousins — Flopsy, Mopsy, Cotton-tail and Peter.

Old Mrs. Wabbit was a widow; she earned her living by knitting rabbit-wool mittens and muffatees (I once bought a pair at a bazaar). She also sold herbs, and rosemary tea, and rabbit-tobacco (which is what we call lavender).

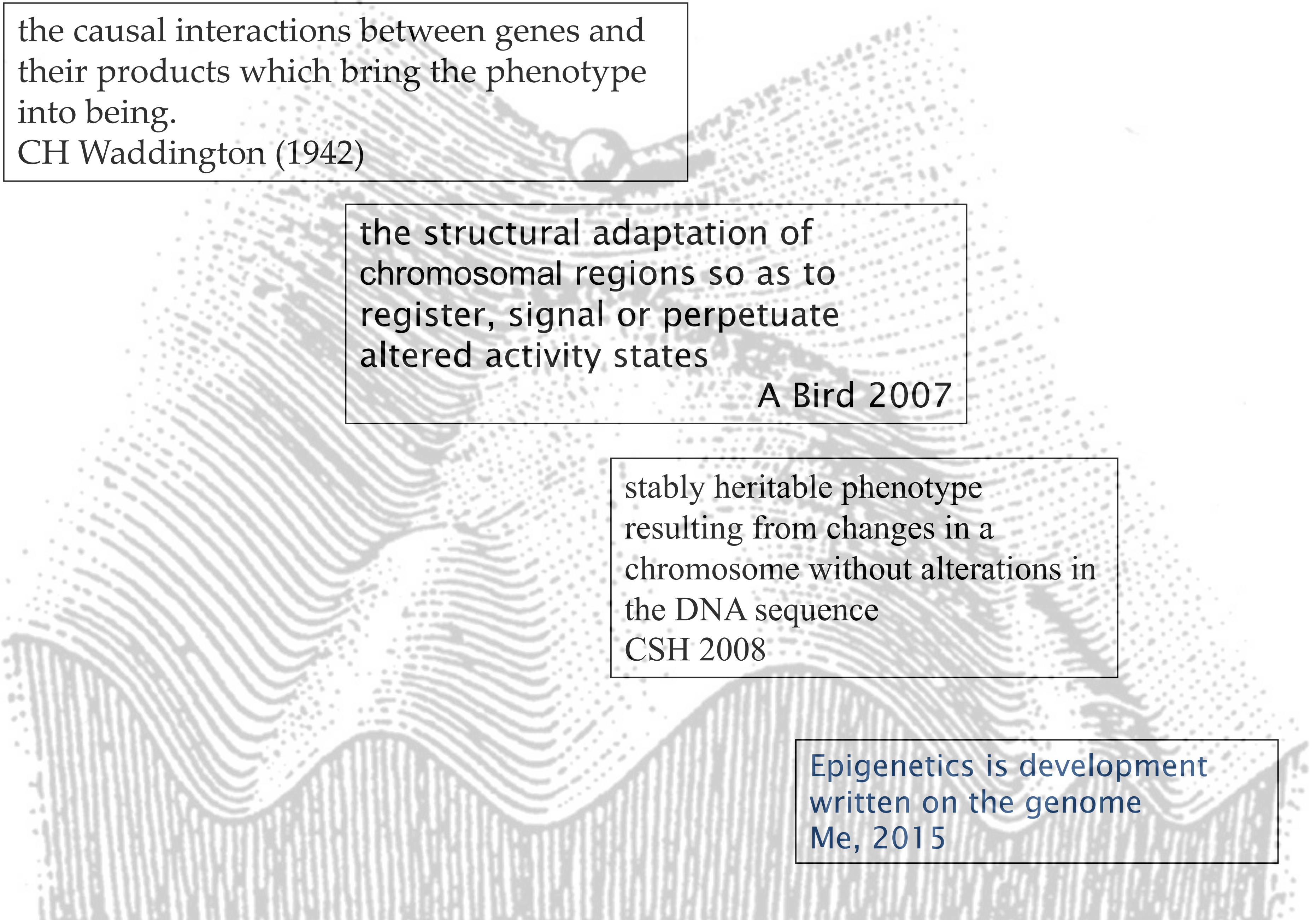
Cells use different sets of genes at different times and places



But as we know, every cell has the same genetic material. Therefore, cells 'choose' which DNA to use, not using genetics, but epigenetics – marks ON the DNA, effectively volume switches on individual genes. These epigenetic marks can be changed, or maintained, from each cell to its children


Totipotent
Pluripotent
Differentiated

What is epigenetics?



the causal interactions between genes and their products which bring the phenotype into being.
CH Waddington (1942)

the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states
A Bird 2007

stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence
CSH 2008

Epigenetics is development written on the genome
Me, 2015

Yes, but… What is epigenetics? What does it consist of?

To come at this question, again, we
need to start by thinking about DNA.
Let me show you an example…

If I profane with my unworthiest hand this holy shrine the gentle fine is this my lips two blushing pilgrims, ready stand to smooth that rough touch with a tender kiss good pilgrim you do wrong your hand too much which mannerly devotion shows in this for saints have hands that pilgrims' hands do touch, and palm to palm is holy palmers' kiss have not saints lips and holy palmers too ay pilgrim lips that they must use in prayer o then dear saint let lips do what hands do they pray grant thou lest faith turn to despair saints do not move though grant for prayers' sake then move not while my prayer's effect I take thus from my lips by yours my sin is purged then have my lips the sin that they have took sin from thy lips o trespass sweetly urged give me my sin again

If I profane with my unworthiest hand
This holy shrine, the gentle fine is this:
My lips, two blushing pilgrims, ready stand
To smooth that rough touch with a tender kiss.
Good pilgrim, you do wrong your hand too much,
Which mannerly devotion shows in this;
For saints have hands that pilgrims' hands do touch,
And palm to palm is holy palmers' kiss.
Have not saints lips, and holy palmers too?
Ay, pilgrim, lips that they must use in prayer.
O, then, dear saint, let lips do what hands do;
They pray, grant thou, lest faith turn to despair.
Saints do not move, though grant for prayers' sake.
Then move not, while my prayer's effect I take.
Thus from my lips, by yours, my sin is purged.
Then have my lips the sin that they have took.
Sin from thy lips? O trespass sweetly urged!
Give me my sin again.

ROMEO If I profane with my unworthiest hand
This holy shrine, the gentle fine is this:
My lips, two blushing pilgrims, ready stand
To smooth that rough touch with a tender kiss.
JULIET Good pilgrim, you do wrong your hand too much,
Which mannerly devotion shows in this;
For saints have hands that pilgrims' hands do touch,
And palm to palm is holy palmers' kiss.
ROMEO Have not saints lips, and holy palmers too?
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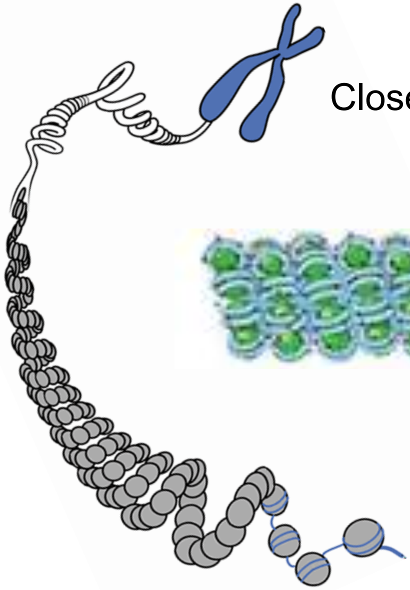
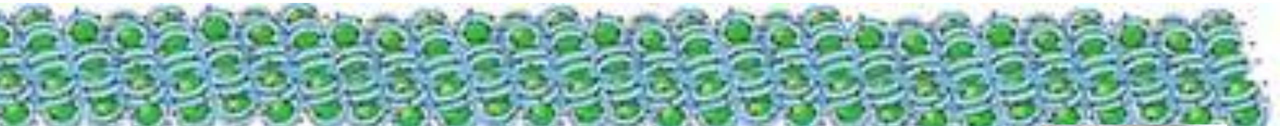
- Two actors
- Costume, makeup and props
- Direction – time and place!!
- Sound and lighting
- Set and staging
- FOH, audience, bar…
- *It’s not just what is expressed, but when, how and by whom – this is epigenetics!!*

Epigenetic (*around the genes!*) marks change the structure of DNA and thereby its function



Closed DNA – inaccessible – illegible



A WORKING TRACTOR

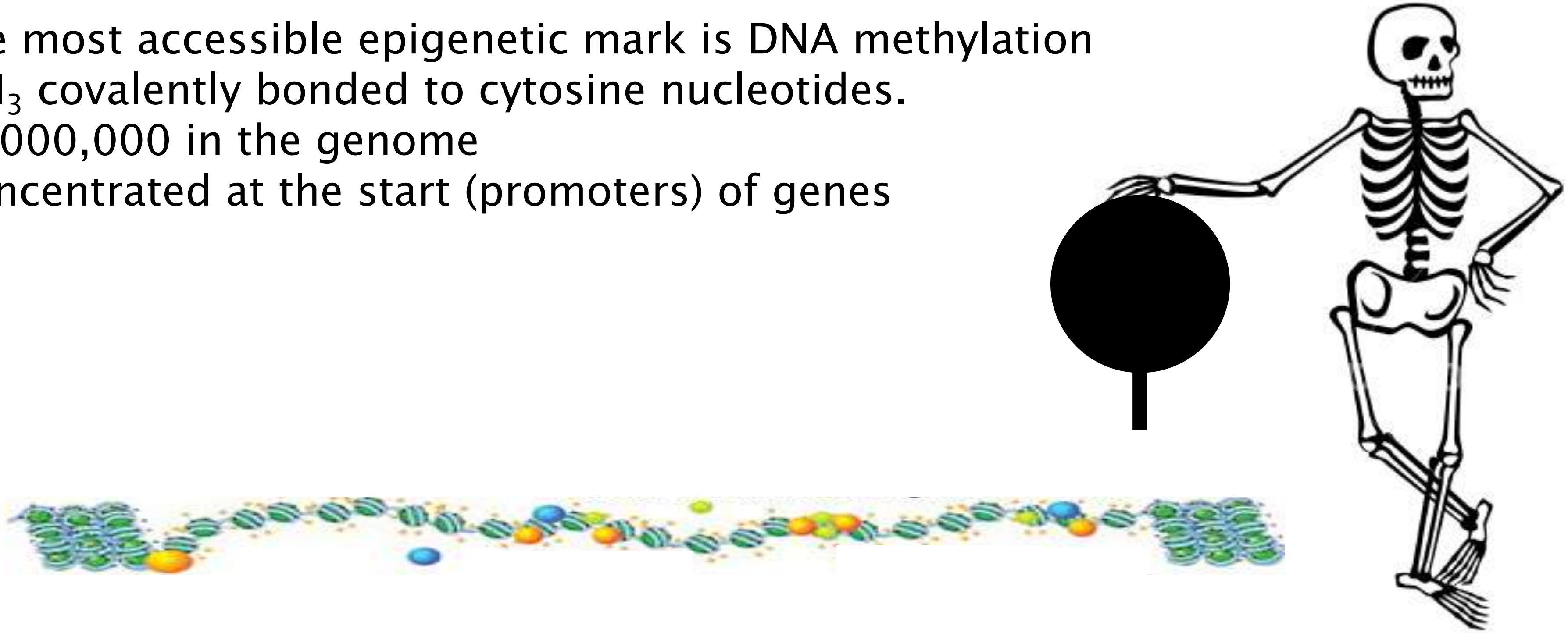
Open DNA – accessible – legible

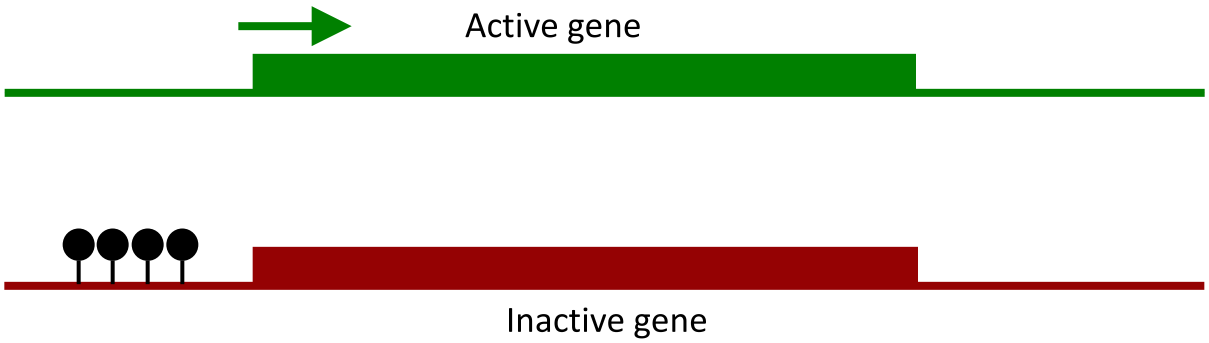
The most accessible epigenetic mark is DNA methylation

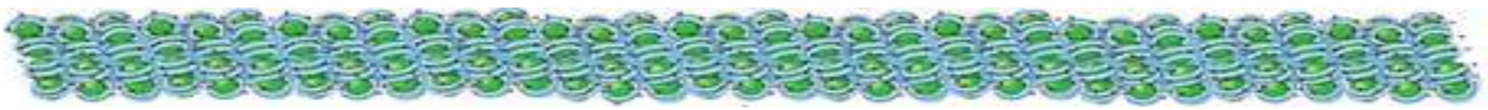
-CH_3 covalently bonded to cytosine nucleotides.

~5,000,000 in the genome

-concentrated at the start (promoters) of genes







-just as the genome can be read, so can the methylome

-but you have ONE genome, but trillions of methylomes

Why do we care about epigenetics?

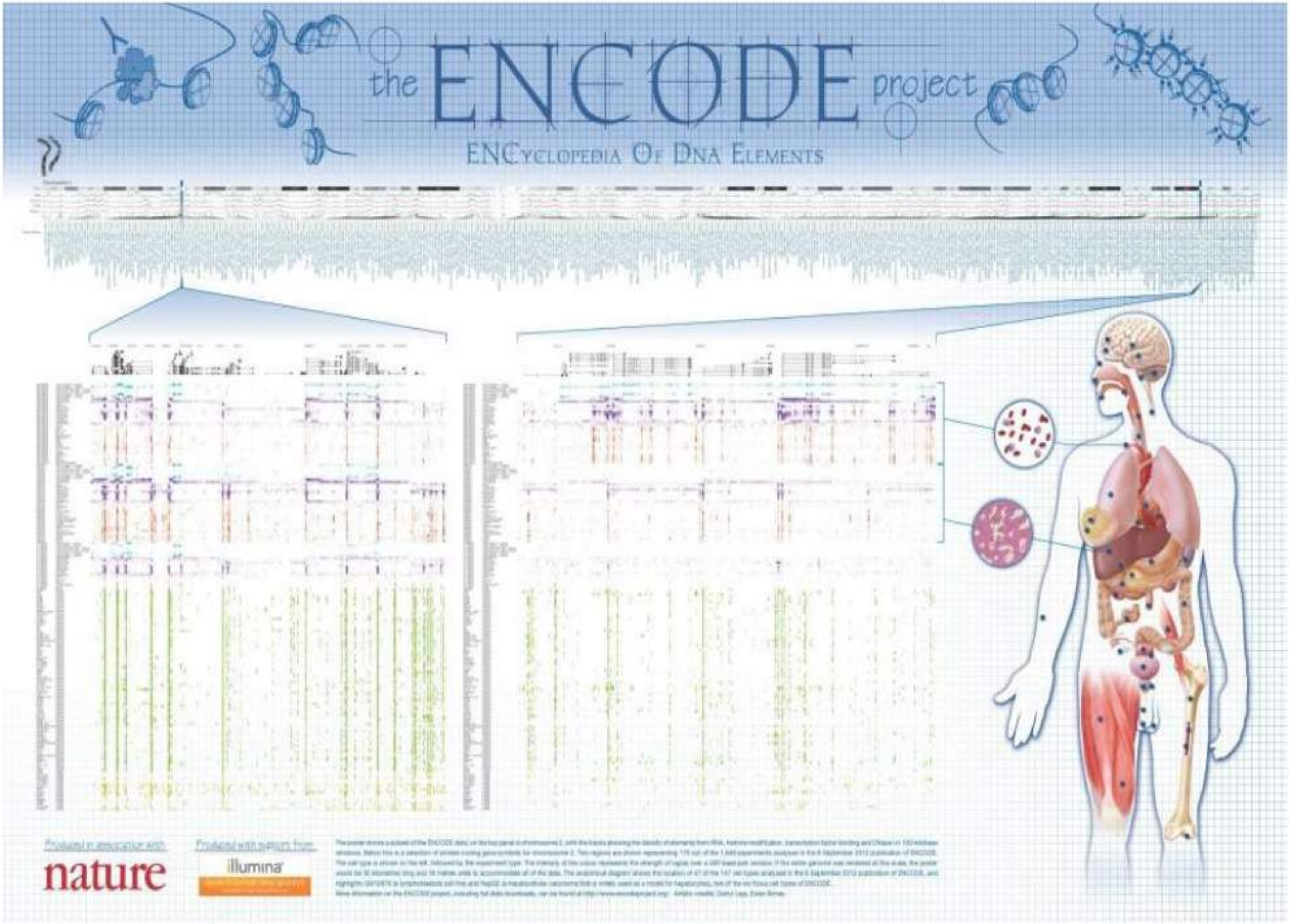
-your genome contains ALL the instructions, not only for making the ~20,000 proteins (etc) that make you, but also when, where and how much – as well as the plasticity to modify these directions in the face of external challenges

-this means, one genome, but trillions of epigenomes

-the epigenetic marks on DNA, from cells, through tissues and organs, to individuals persons, are their life-histories, written on the genome.

Some examples…

(1) Epigenetic marks define tissues and organs (1 genome, 5e10 interpretations!)



(2) Epigenetic marks mark time

353 ‘clock’ CpGs predict age – except...

cancers (+30yr)

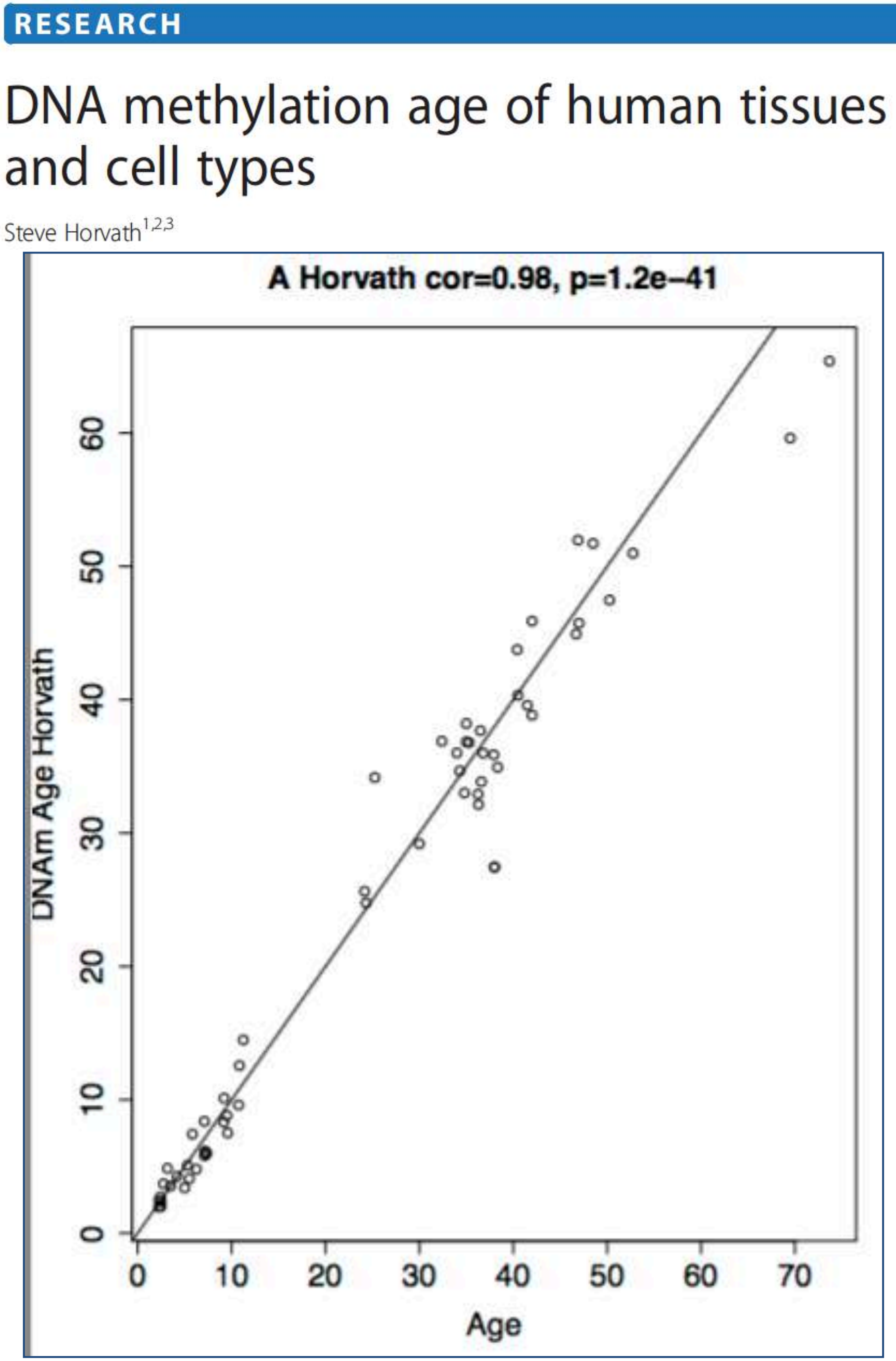
T21 (+6yr in blood and brain)

obesity (liver)

Alzheimer’s disease (prefrontal cortex)

Menopause (blood)

Being male!

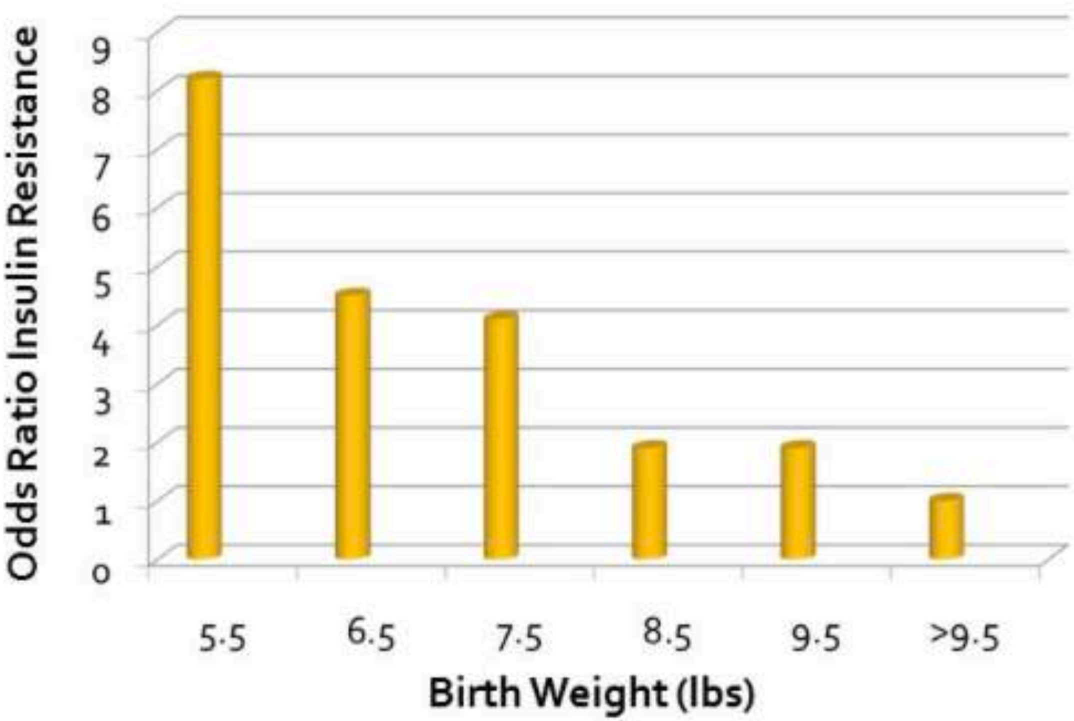


RESEARCH

DNA methylation age of human tissues and cell types

Steve Horvath[1,2,3]

(3) Epigenetic marks record the life-history



Hales CN et al. BMJ 1991; 303:1019-22

Fetal and infant growth and impaired glucose tolerance at age 64

"Reduced growth in early life is strongly linked with impaired glucose tolerance and non-insulin dependent diabetes … Reduced intrauterine growth is linked with high blood pressure, which may explain the association between hypertension and impaired glucose tolerance…

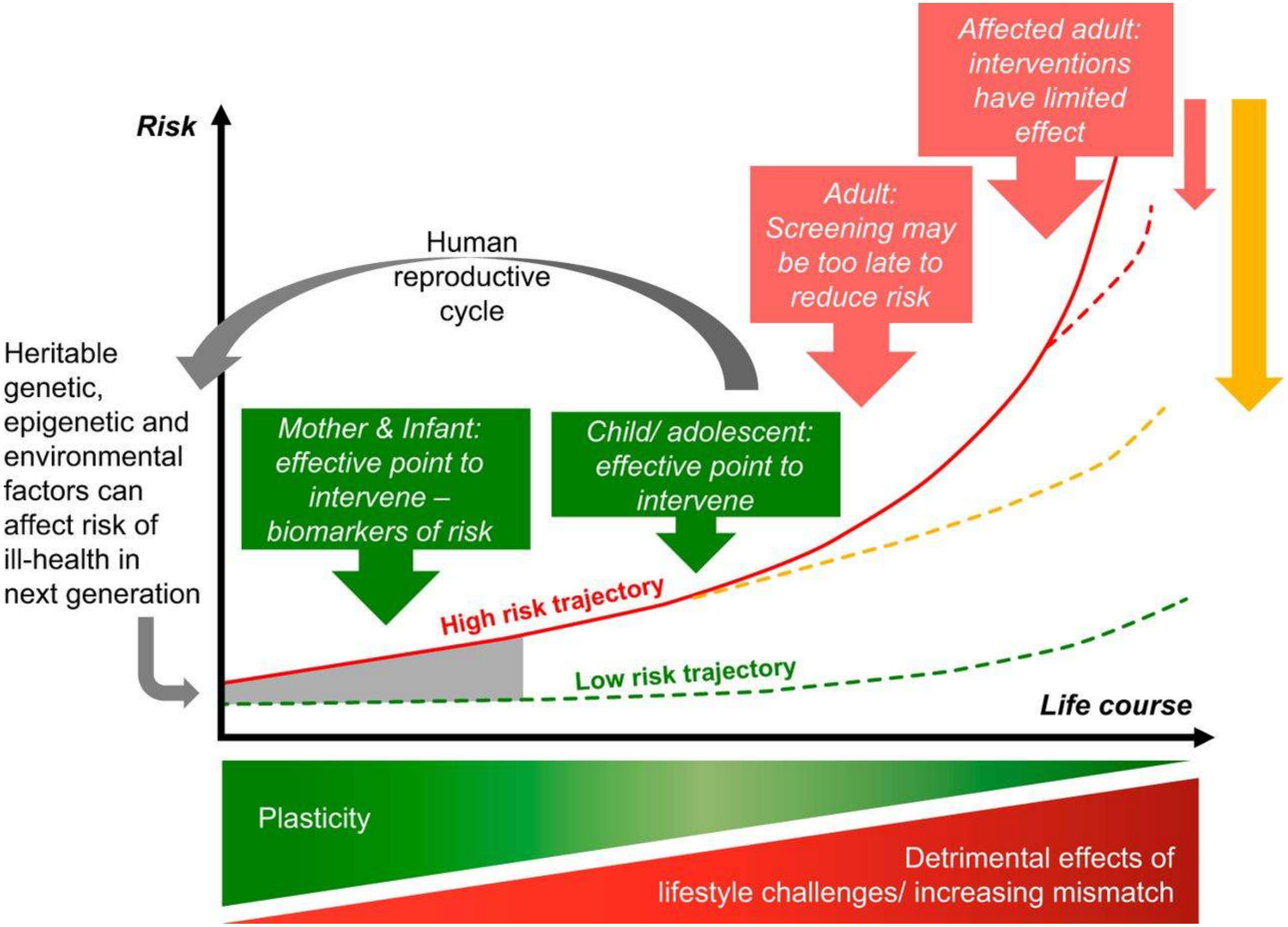
Hales et al, 1991

The Dutch Hunger Winter: November 1944 - May1945

Early gestation:
Heart disease
Hyperlipidaemia
Obesity
Reduced IGF2 methylation

Late gestation:
Lower birth weight
Normal IGF2 methylation

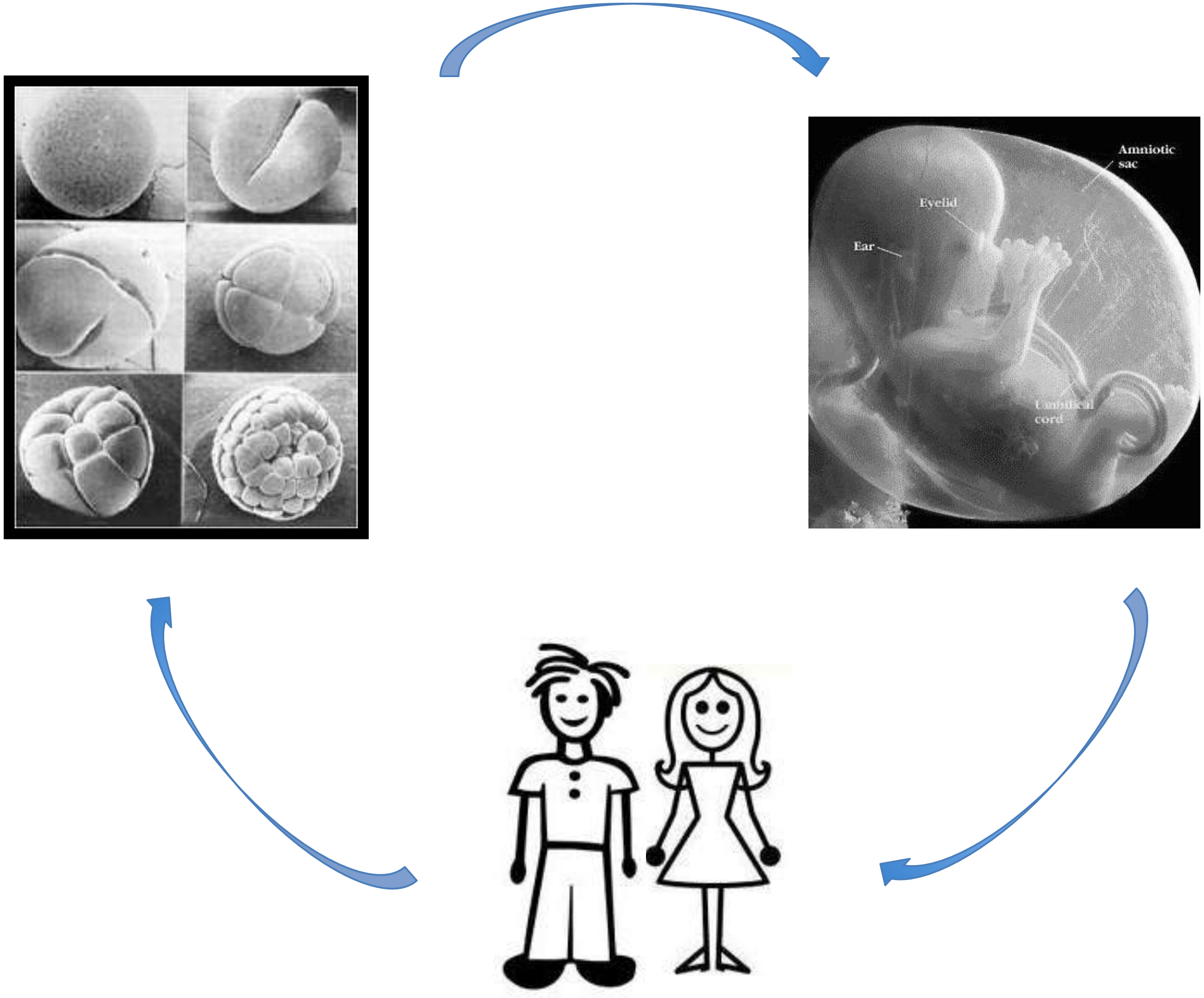
The DOHaD hypothesis - early life influences exert long-term effects on health (and potentially transgenerational inheritance).



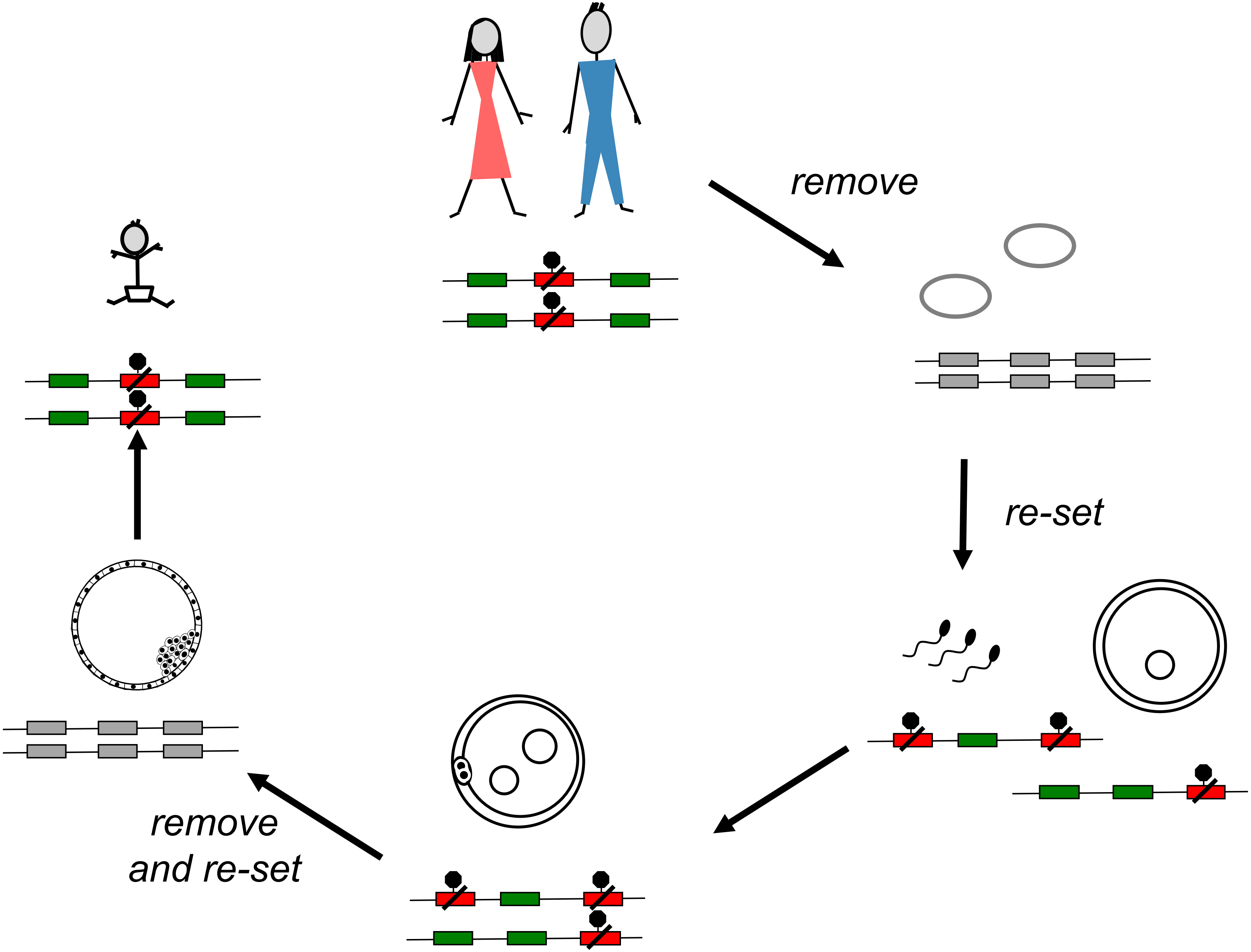
Hanson Physiol Rev 94:1027

In my view, both epigenetic and genetic dialogue carry a risk of negativity, eg: "I've got the gene for X" – "X is 'in his DNA'" – "The sins of the fathers (and the mothers) visited on their children unto the third and fourth generation"

But how does this happen? Isn’t the epigenetic slate cleaned every generation?



The epigenetic slate is cleaned twice, in fact: in gametogenesis, and after fertilisation

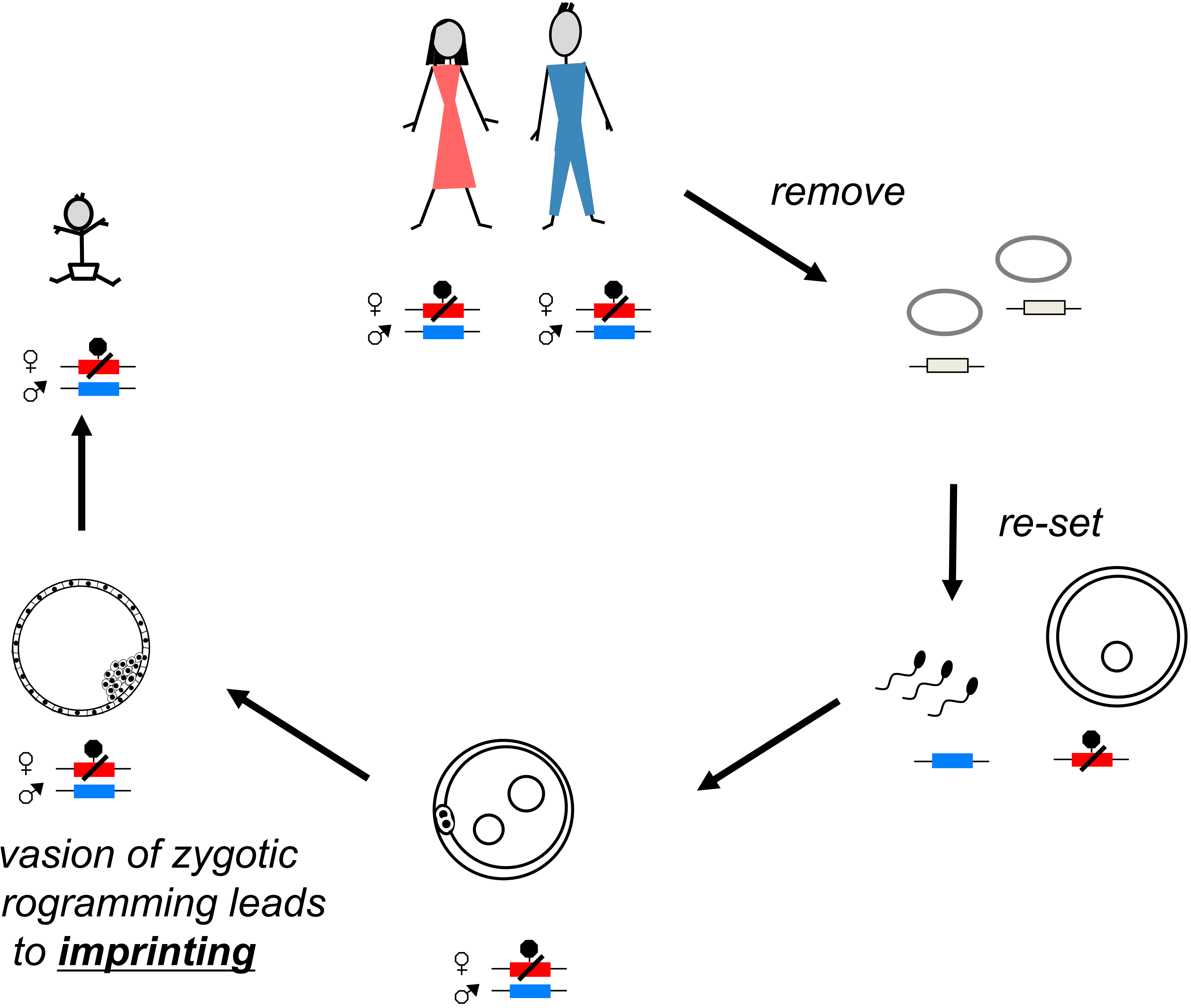


remove

re-set

remove
and re-set

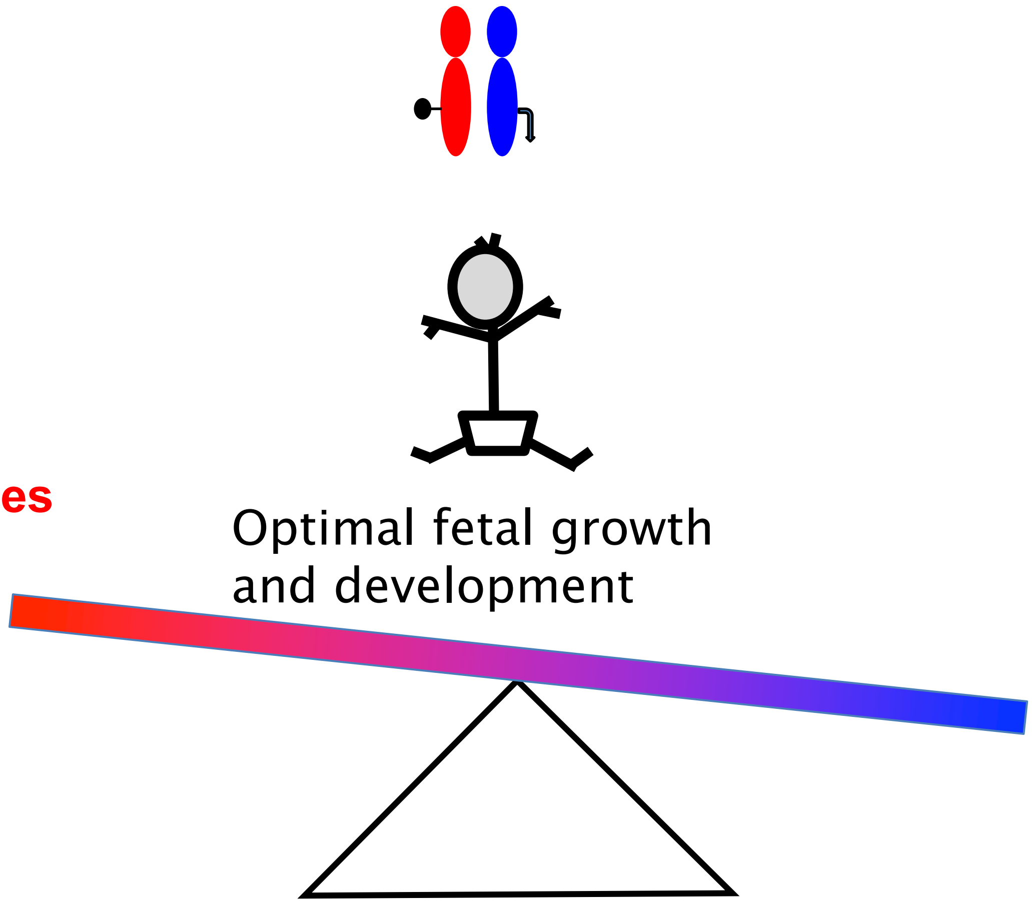
A small number of genes are known to evade the second, zygotic wave of reprogramming



remove

re-set

*Evasion of zygotic reprogramming leads to **imprinting***



Maternally-expressed genes tend to restrict growth

Optimal fetal growth
and development

Paternally expressed genes tend to enhance growth

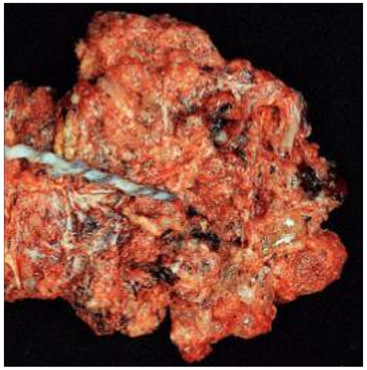
Imprinted genes are:
-few (100s)
-dispersed randomly across the genome
-(often) tightly regulated in growth and development
-hemizygously expressed (only one parental copy) and therefore
-vulnerable to altered expression – which leads to ***imprinting disorders***

Imprinting disorders are congenital disorders of growth / development / metabolism:

chr11

(&chr7)

chr14



chr15

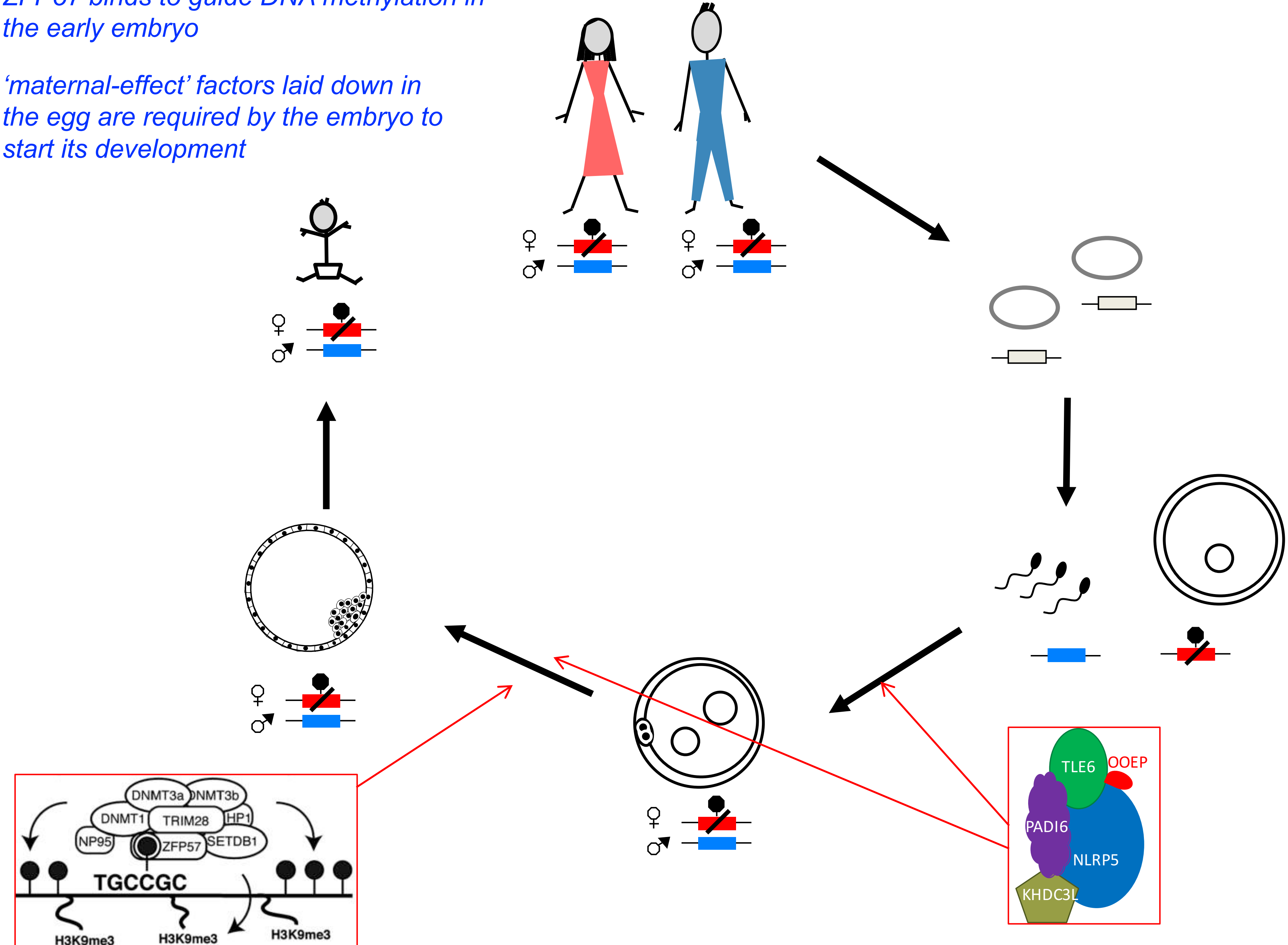
chr6

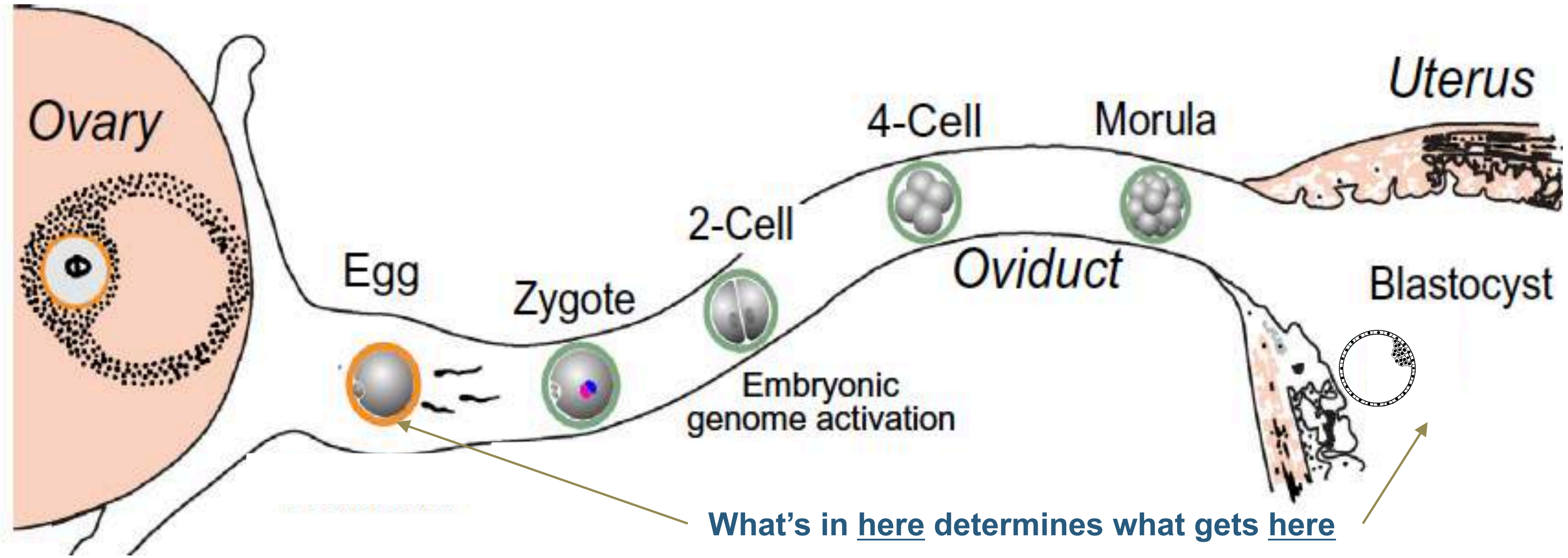
chr20

In some children with imprinting disorders, epigenetic errors are caused by genetic changes

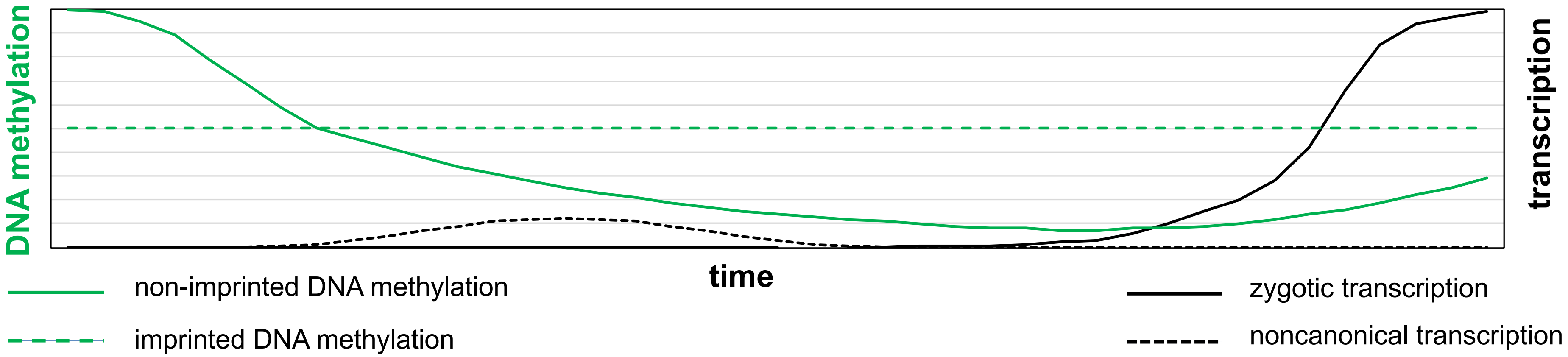
ZFP57 binds to guide DNA methylation in the early embryo

‘maternal-effect’ factors laid down in the egg are required by the embryo to start its development





What's in here determines what gets here



Li et al 2008, 2013

To summarise:
Epigenetic changes are associated with changes in gene expression patterns, and thus with changes in the phenotype of cells and organisms, across developmental time and space

Or:
Epigenetic changes biomark developmental events

Or:
Epigenetics is development written on the genome

Altered susceptibility to noncommunicable / multifactorial disease
Differentiative decision-making
Transgenerational inheritance
Genomic imprinting