Epigenetic Regulation of Health and Disease

Nutritional and environmental effects on epigenetic regulation

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Where do we stand?'
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Epigenetics?

«The study of ***somatically and/or meiotically heritable changes in gene function*** *that cannot be explained by changes in DNA sequence »*

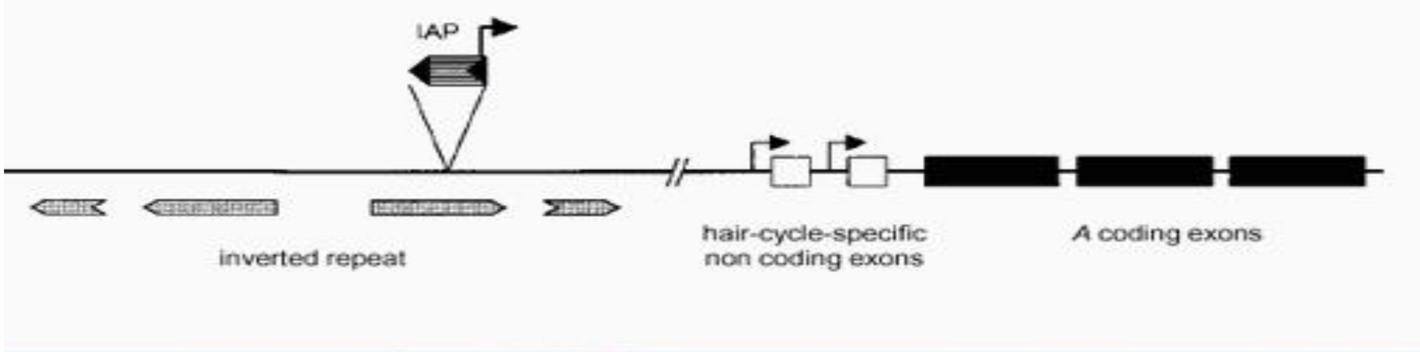
Russo, Martienssen, Riggs, *Epigenetic Mechanisms of Gene Regulation*,
Cold Spring Harbor Press (1996)

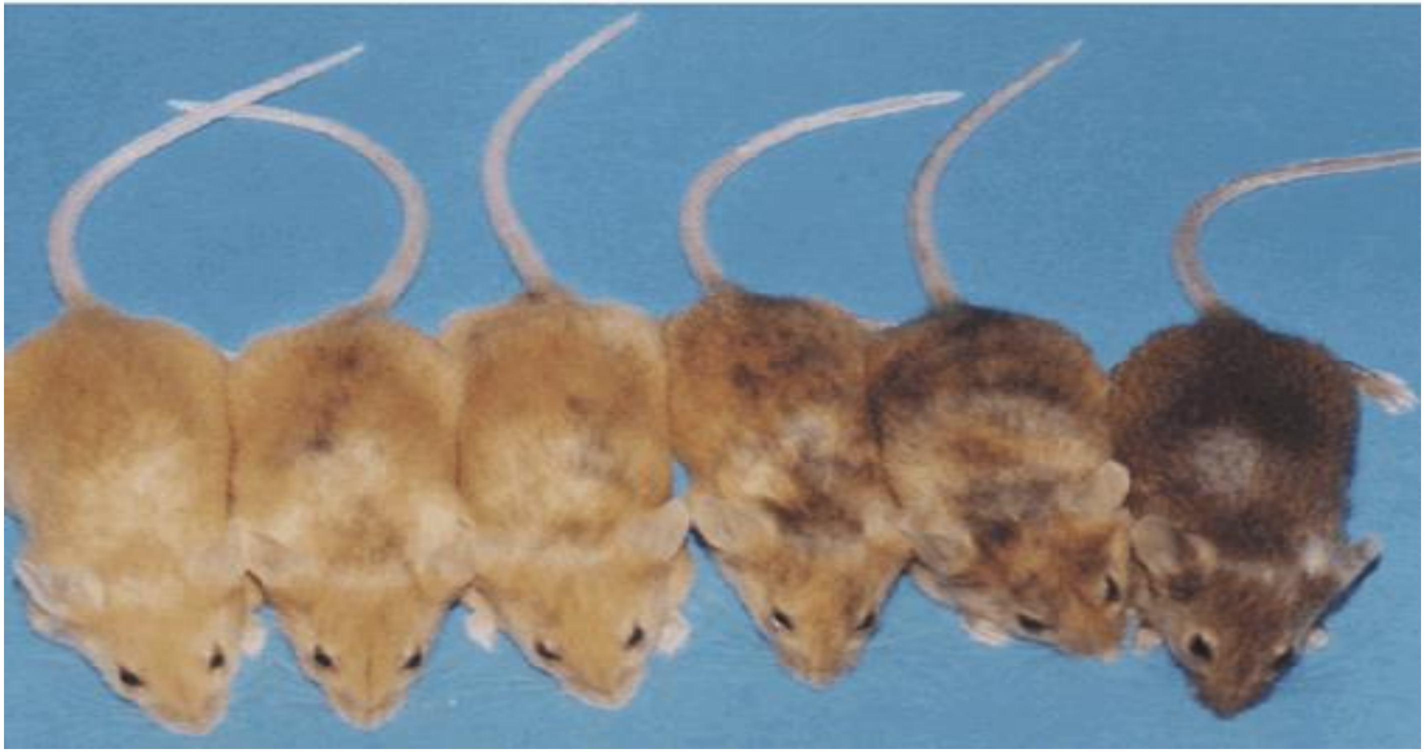
A heritable DNA methylation change at a gene involved in fruit ripening

Manning *et al*, *Nature Genet.* (2006)

Agouti (A^{vy}) coat colour gene in mice:

MAJOR phenotypic effects of differential DNA methylation

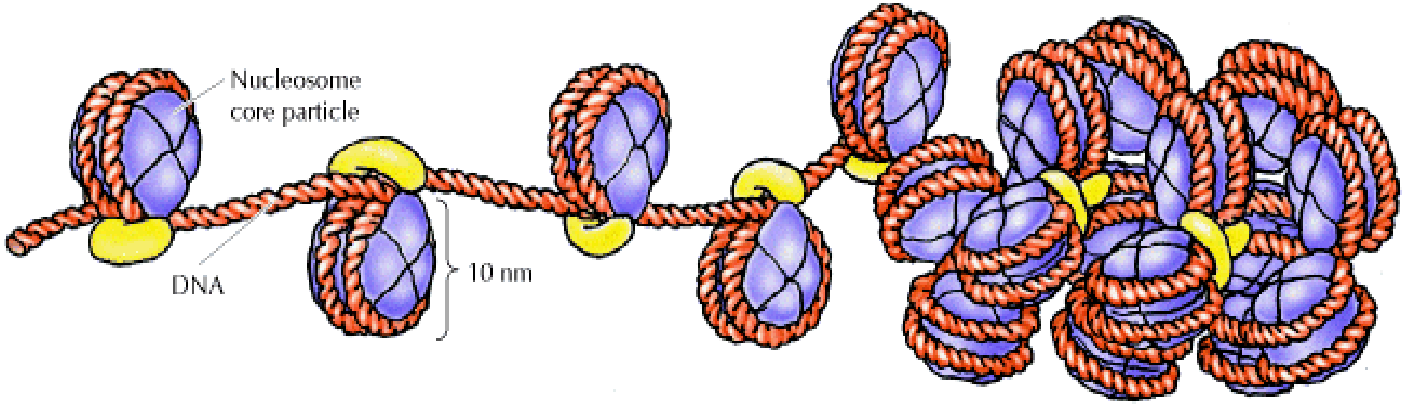




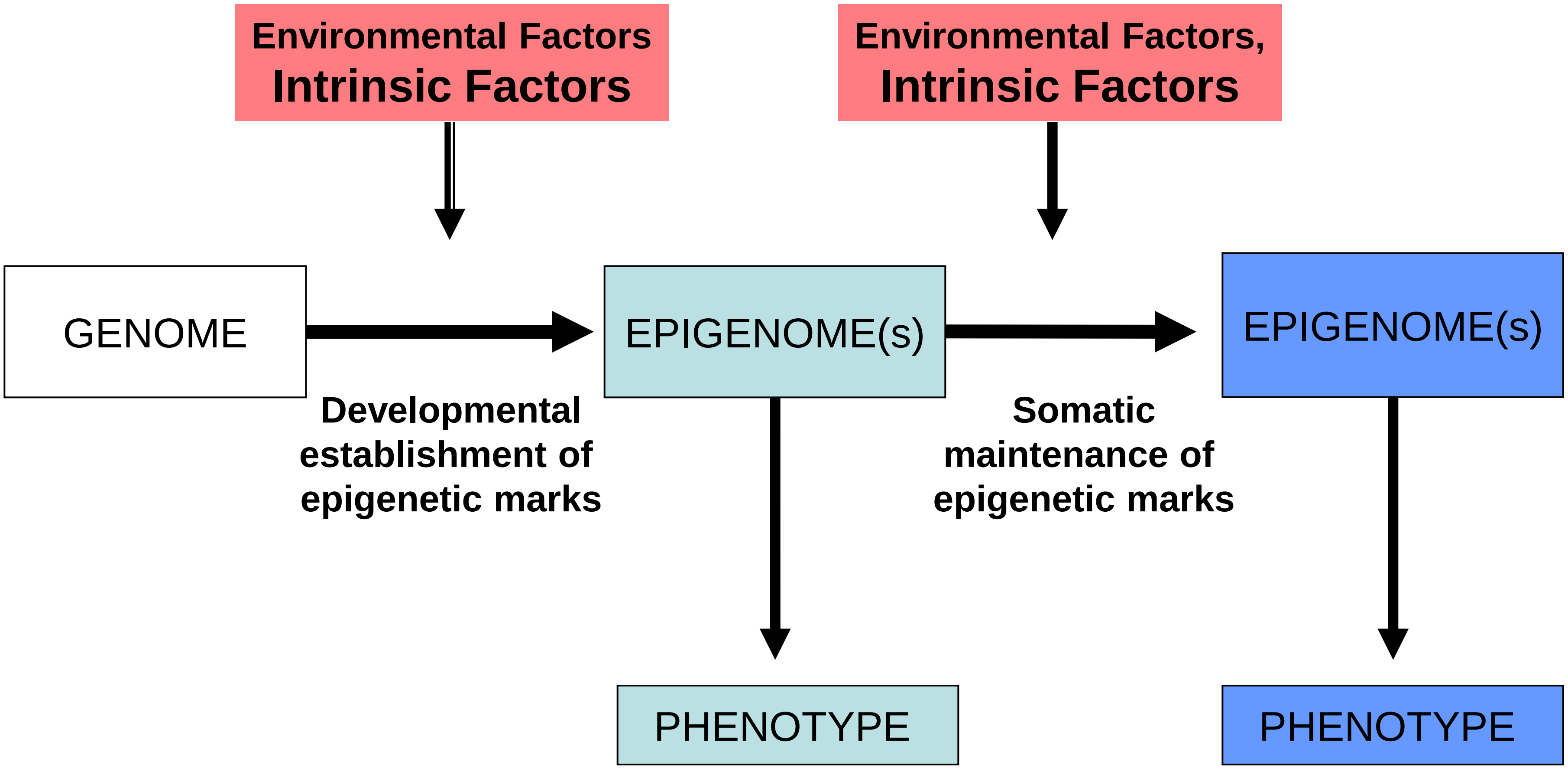
Drs. Emma Whitelaw, Randy Jirtle, others

Epigenetic modifications ?

* DNA methylation



* Stable histone modifications



Environmental Factors
Intrinsic Factors

Environmental Factors,
Intrinsic Factors

GENOME

EPIGENOME(s)

EPIGENOME(s)

Developmental establishment of epigenetic marks

Somatic maintenance of epigenetic marks

PHENOTYPE

PHENOTYPE

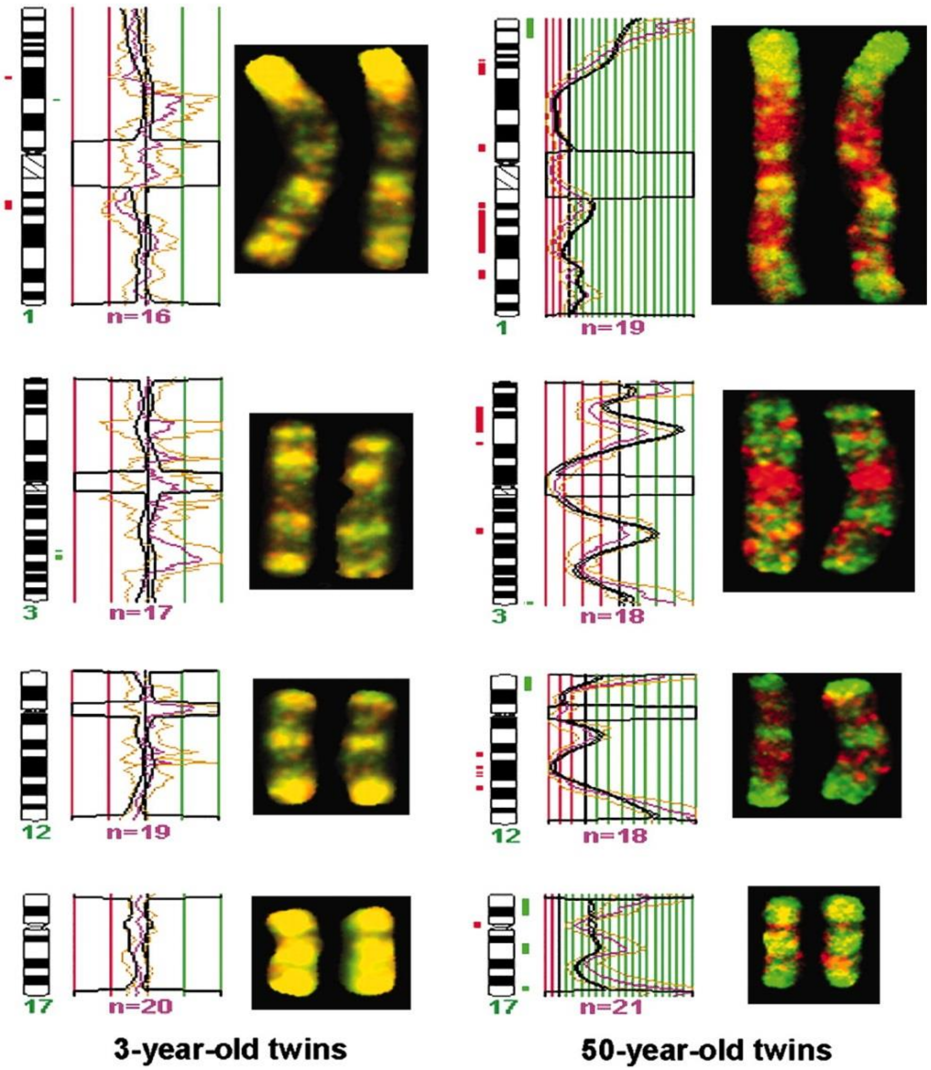
Feil R, *Mutation Research* 2006

The epigenome(s) undergoes changes during development and postnatal life

ENVIRONMENT

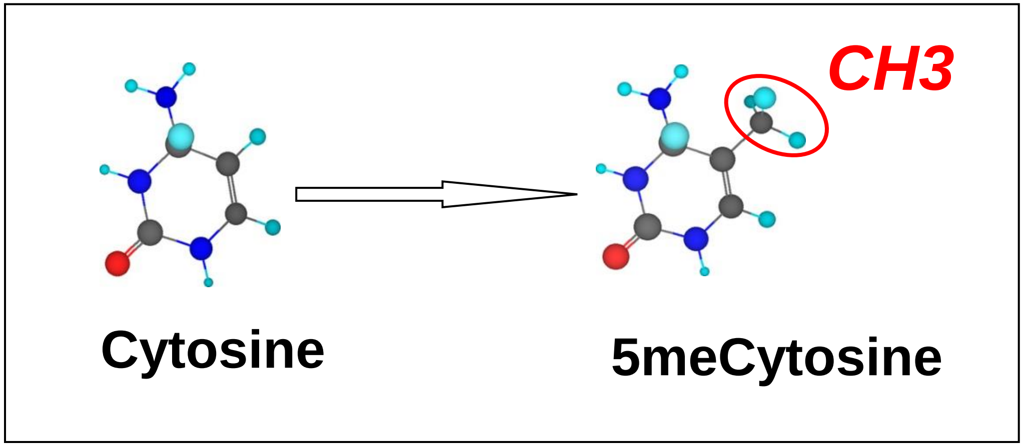
STOCHASTIC
EVENTS

Many chromosomal regions show differential DNA methylation between 'old' mono-zygotic twins



Fraga MF et al. *PNAS USA* (2005)

Roles of DNA methylation in mammals



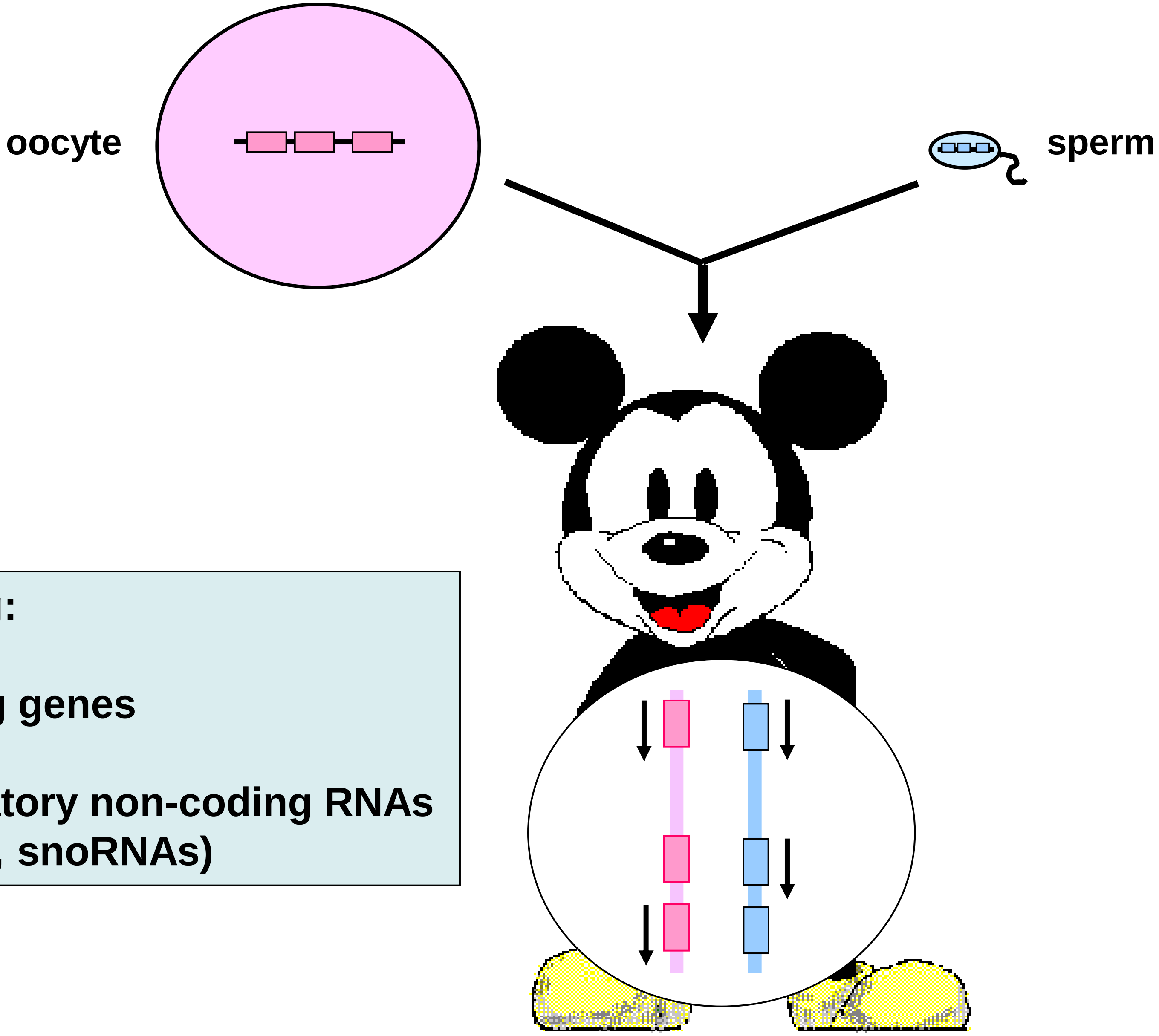
* Chromosome stability

* Repression of DNA elements of foreign origin

* Tissue-specific repression of genes

* ‘X-chromosome inactivation’ in females

*** Genomic Imprinting**



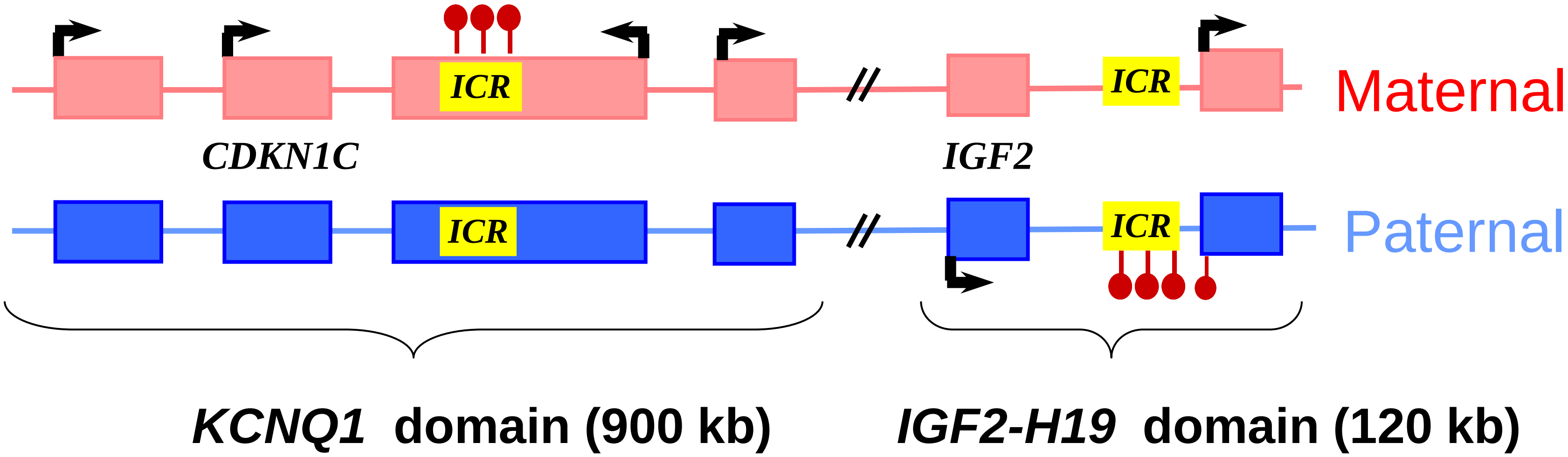
Genomic Imprinting:

~120 protein-coding genes

-hundreds of regulatory non-coding RNAs
(lncRNAs, miRNAs, snoRNAs)

genomic imprinting

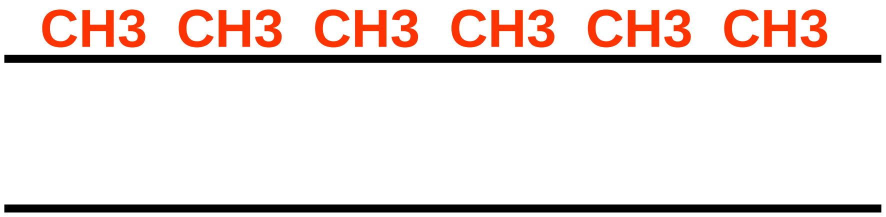
Two growth-related imprinted domains
involved in cellular proliferation and fœtal growth



ICR = *'Imprinting Control Region'*

●●● = *DNA methylation*

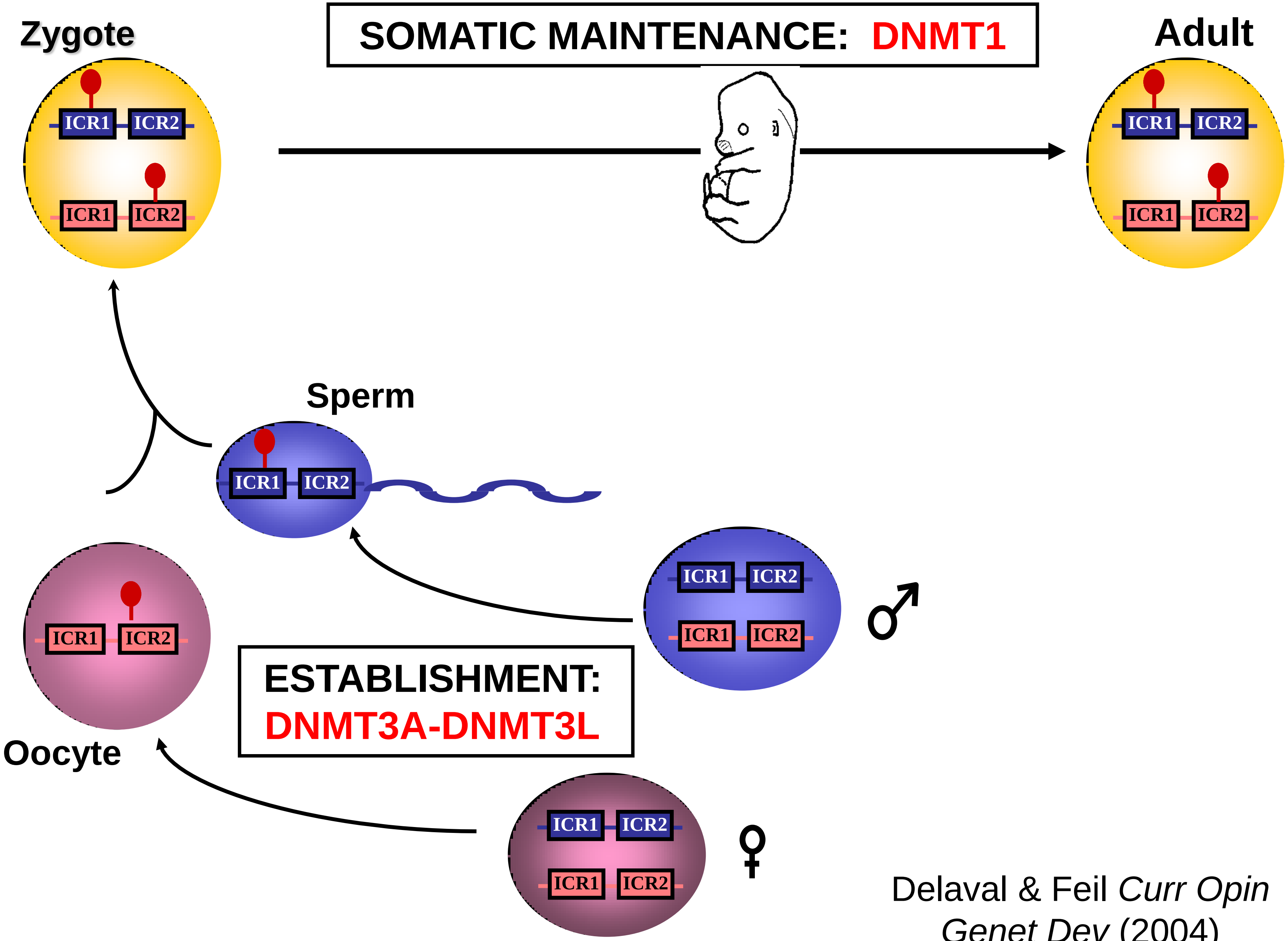
Imprinting Control Regions (ICRs)



Parental allele WITH
DNA methylation

Parental allele WITHOUT
DNA methylation

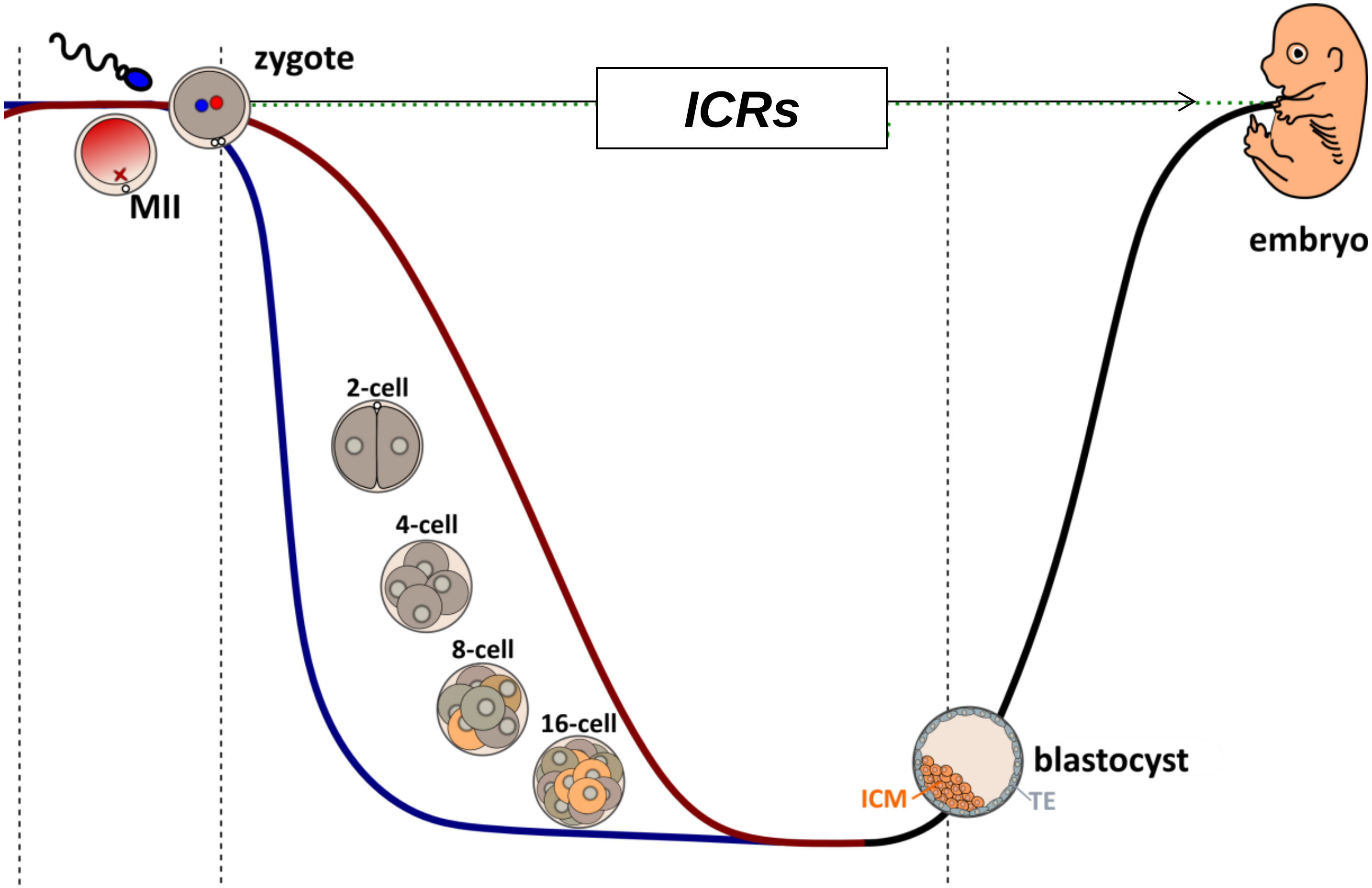
SOMATIC MAINTENANCE: DNMT1



ESTABLISHMENT:
DNMT3A-DNMT3L

Delaval & Feil *Curr Opin Genet Dev* (2004)
Kota & Feil, *Dev. Cell* (2010)

DNA methylation dynamics in the early embryo: only ICRs are stably maintained

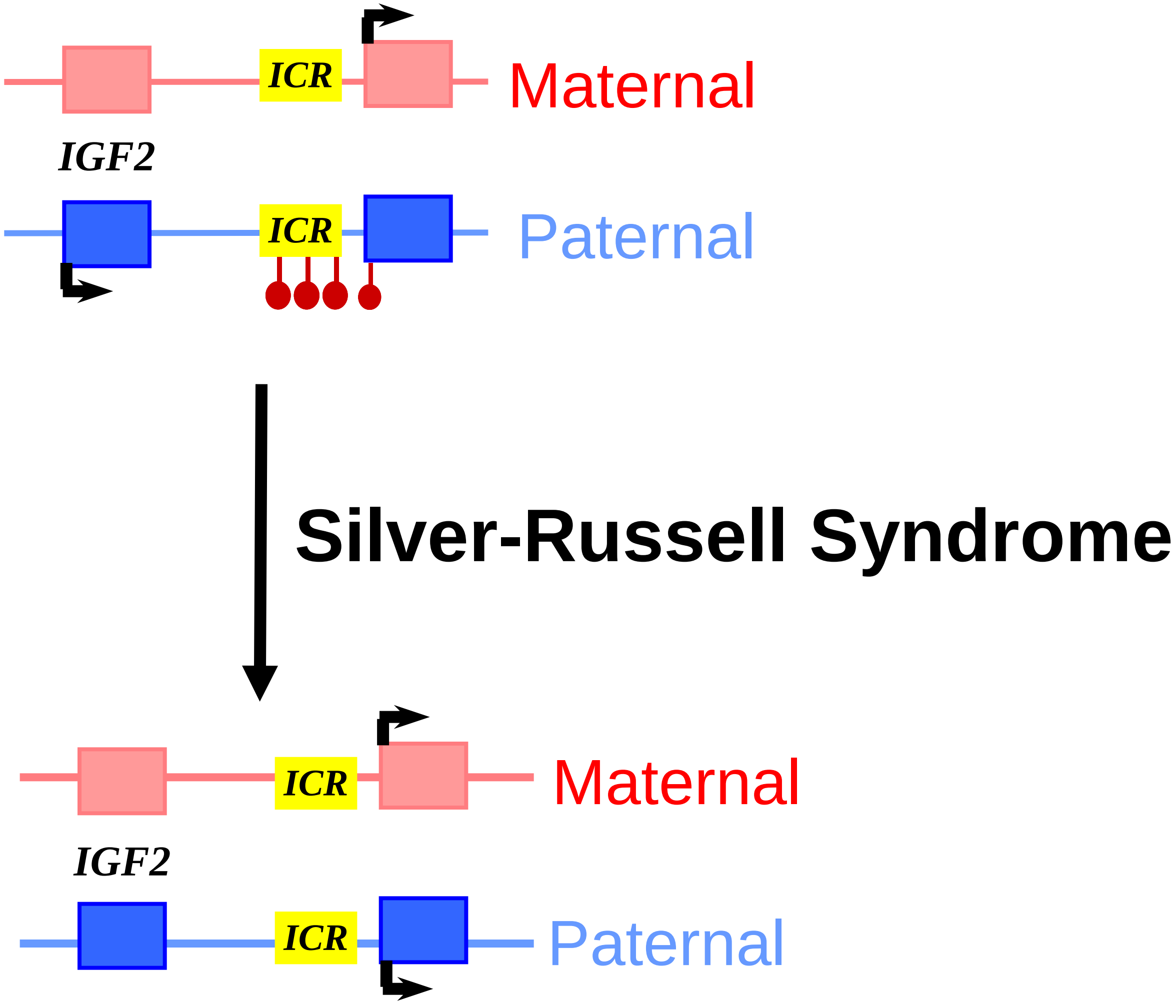


Kelsey and Feil, *Phil. Trans. R. Soc. B* (2013).
Smallwood and Kelsey, *Trends Genet* (2012).

‘epigenetic diseases’:

Silver-Russell Syndrome (SRS)

- Intra-uterine growth restriction (IUGR)
- Postnatal growth deficiency
- Learning disabilities
- Mostly sporadic

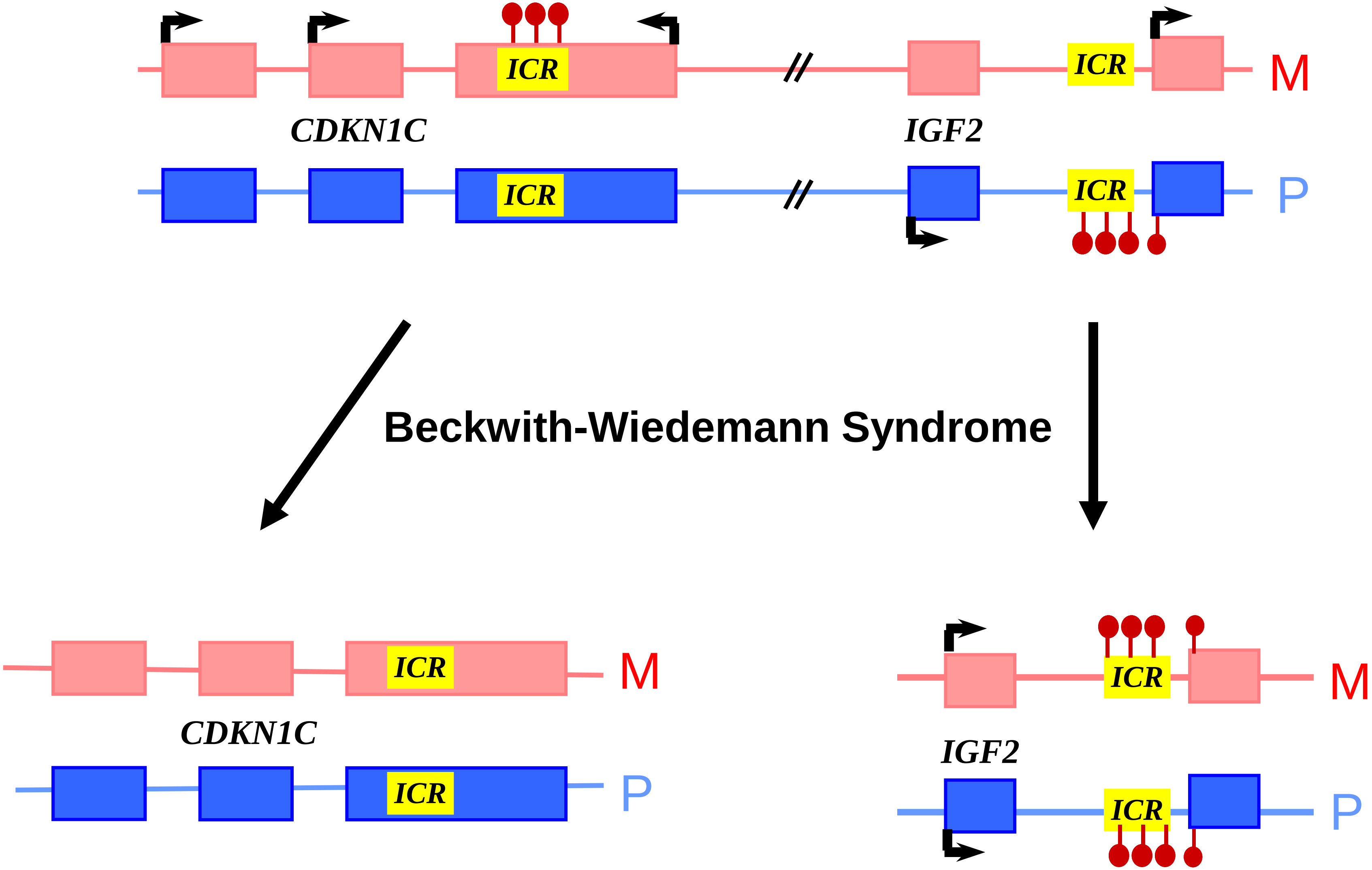


Silver-Russell Syndrome

‘epigenetic diseases’:

Beckwith-Wiedemann Syndrome (BWS)

- Foetal overgrowth
- Large internal organs, large tongue
- Predisposition to Wilms’ tumour of the kidney
- Mostly sporadic



Beckwith-Wiedemann Syndrome

Frequent perturbation of methylation imprints upon *in vitro* culture and manipulation

* **Derivation and culture of ES cells**	Dean *et al.* 1998; Humpherys *et al.* 2001
* **Pre-implantation embryo culture**	Khosla *et al.* 2001; Young *et al.* 2001
* **Super-ovulation**	Fortier et al. 2008; Market-Velker *et al.* 2010
• **Reprogramming into induced pluripotent stem cells (iPS cells)**	Stadtfeld *et al.* 2010, Kota *et al.* 2014.
* **Somatic cell nuclear transfer**	Humpherys *et al.* 2001 Young *et al*. 2003

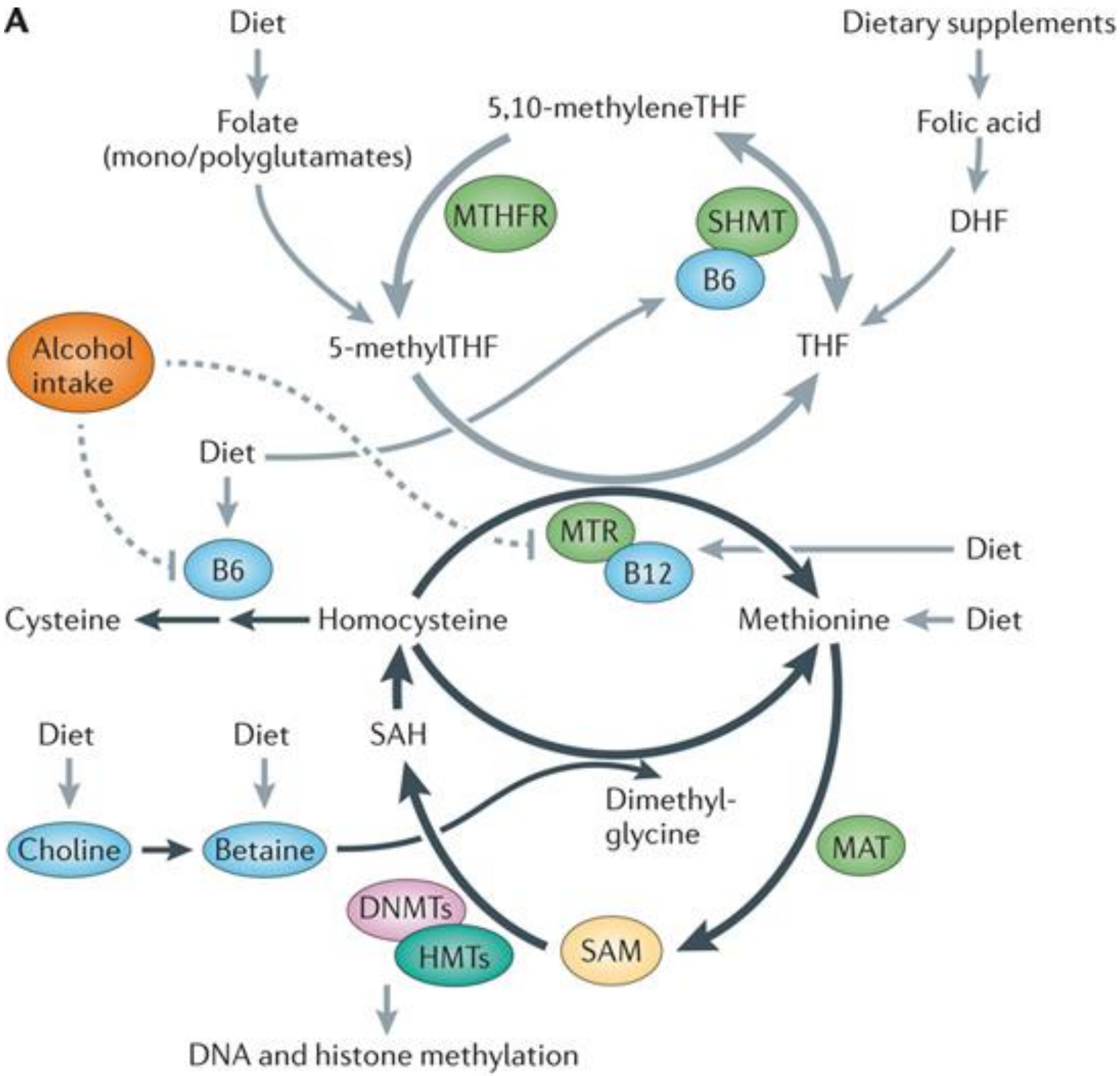
Increased occurrence of epigenetic ‘Imprinting Disorders’ in cohorts of ‘Assisted Reproduction’ babies

Beckwith-Wiedemann Syndrome (BWS)
Silver-Russell Syndrome (SRS)
Angelman Syndrome (AS)
Transient Neonatal Diabetes Mellitus (TNDM) (?)

Causal mechanism(s) unclear: ART or ‘predisposing infertility’?

Dias and Maher, *Epigenomics* 2013.
Sato *et al. Reproduction Med. Biol.* 2014.
Faugue *Fertil Sterility* 2013.
Lim *et al. Hum Reprod* 2009.
Sutcliffe *et al*. *Human Reprod.* 2006.
Cox *et al. Am. J Hum Genet* 2002.

Nutrition influences the mono-carbon cycle



Feil and Fraga, *Nature Rev. Genet. (*2013)

MINOR effects of nutrition on imprinted DNA methylation in human and animal studies

- **Dutch Hunger Winter, peri-conceptional exposure to famine:**
  -Decreased DNA methylation at imprinted genes in children.

- **Increased folate, or altered choline, during pregnancy** (human, rat):
  Increased DNA methylation at *IGF2*.

* **High-fat diet during gestation** (mouse):
Altered DNA methylation at the *IGF2R* locus in placenta.

- **Alcohol consumption during pregnancy** (mouse):
  Decreased DNA methylation at *H19* ICR and *IGF2* in offspring.

- **Alcohol consumption in adult males** (mouse, human):
  Aberrant DNA methylation at ICRs in sperm

Feil and Fraga, *Nature Rev. Genet. (*2013)

Endocrine disruptors:

* Long-term effects on reproduction

* **MINOR effects on DNA methylation imprints**

- Vinclozolin (50mg/kg, E10-18) and methoxychlor (10 mg/kg E10-18) administration to females <u>during pregnancy</u>:

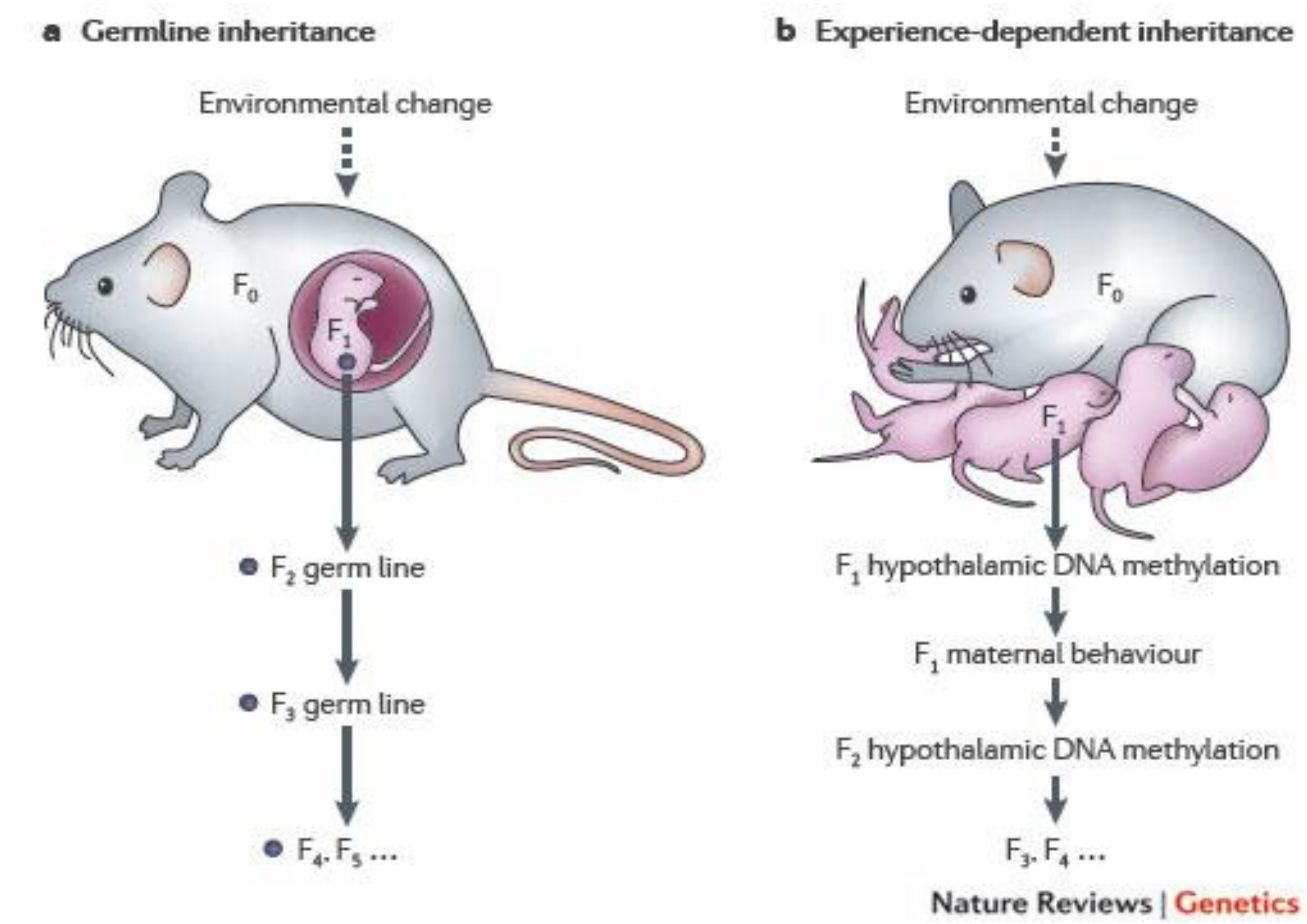
Altered methylation in sperm of F1, F2 & F3 males:

* Slight reductions in DNA methylation at ‘paternal ICRs’

* Gains in DNA methylation at ‘maternal ICRs’

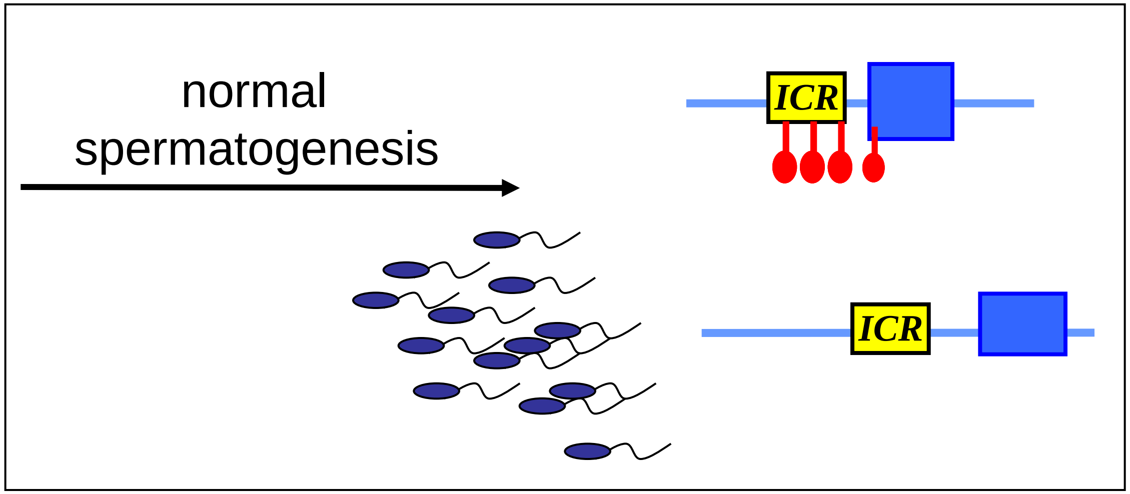
Stouder *et al*, *Reproduction (*2010) (2011)
Kang *et al, Epigenetics (*2011)
Somm *et al*., *Reprod Toxicol (*2013)

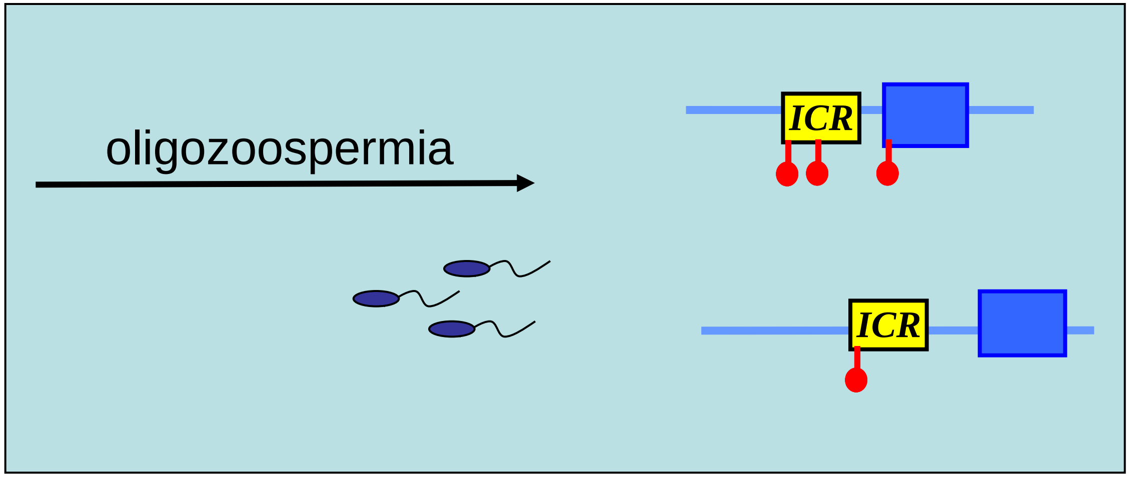
Inter-generational epigenetic effects of maternal diet and environmental cues



Danchin et al. Nature Rev. Genet. (2011)

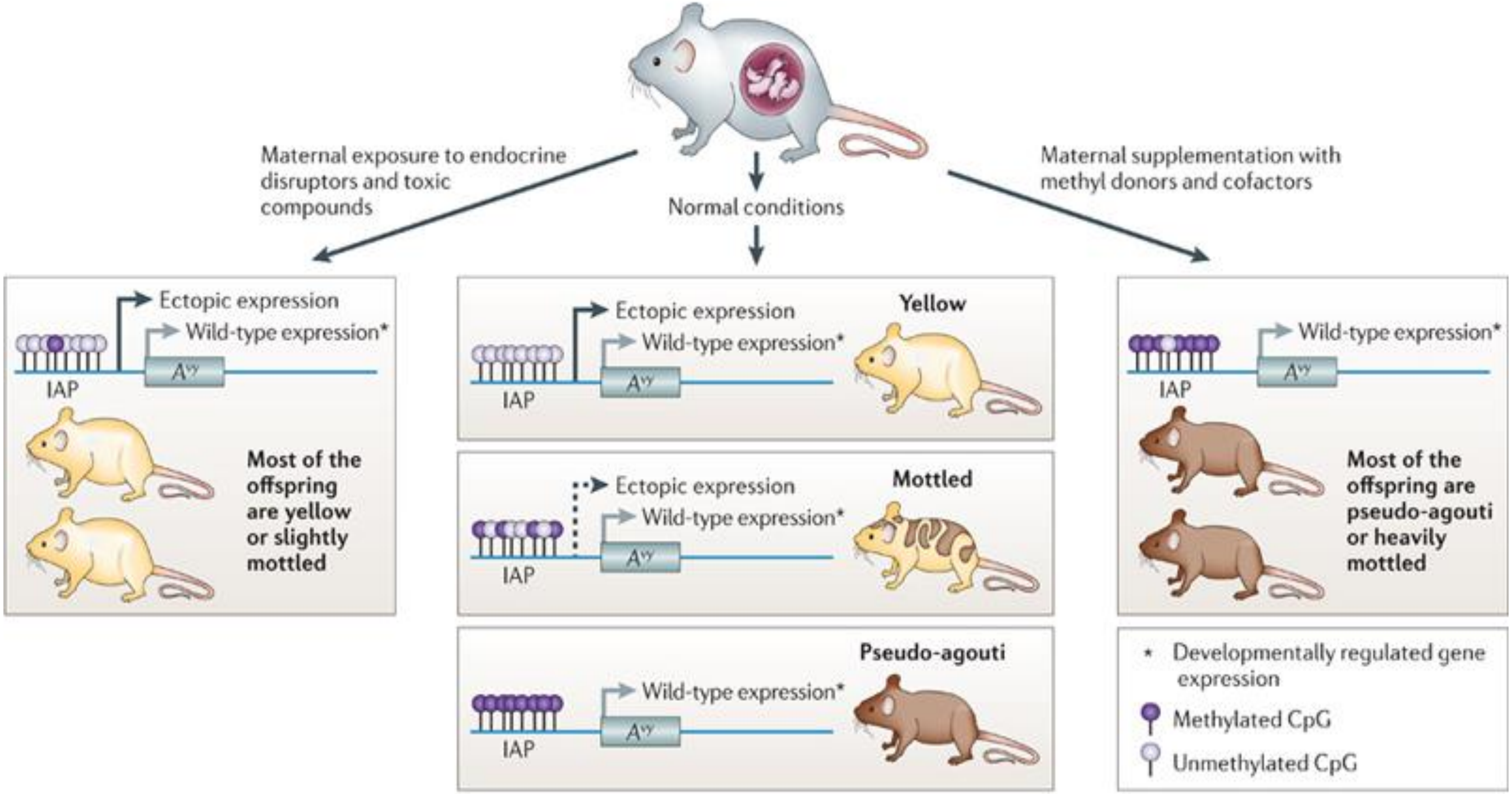
Altered DNA methylation imprints in sperm of oligozoospermic men





Marques *et al.* 2004, 2008
Kobayashi *et al.* 2007
Boissonnas *et al.* 2010
Reviewed in:
Filipponi and Feil,
Epigenetics 2009

Agouti (A^{vy}) locus in the mouse: MAJOR methylation effects of nutrition and endocrine disruptors



Most of the offspring are yellow or slightly mottled

Most of the offspring are pseudo-agouti or heavily mottled

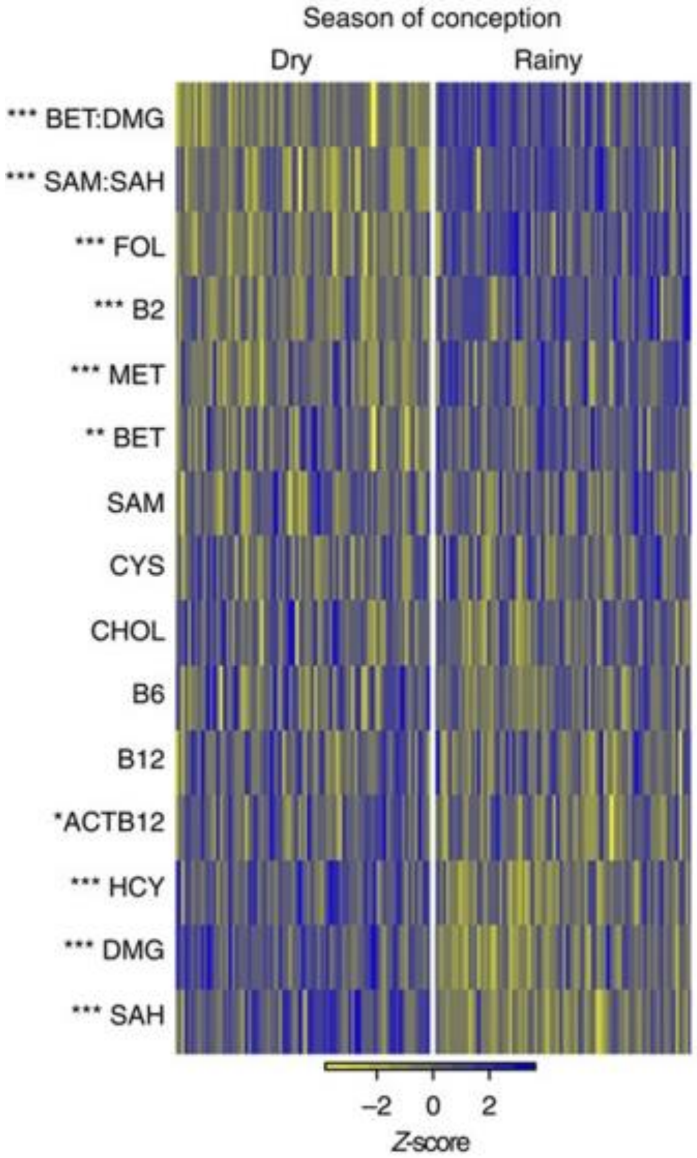
* Developmentally regulated gene expression

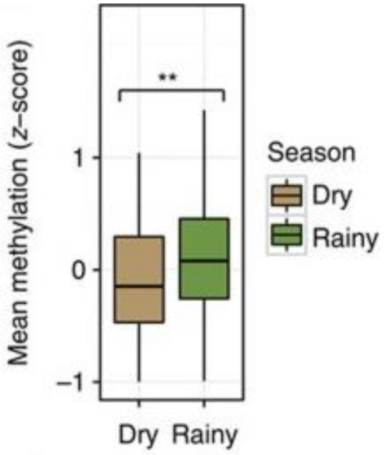
Methylated CpG

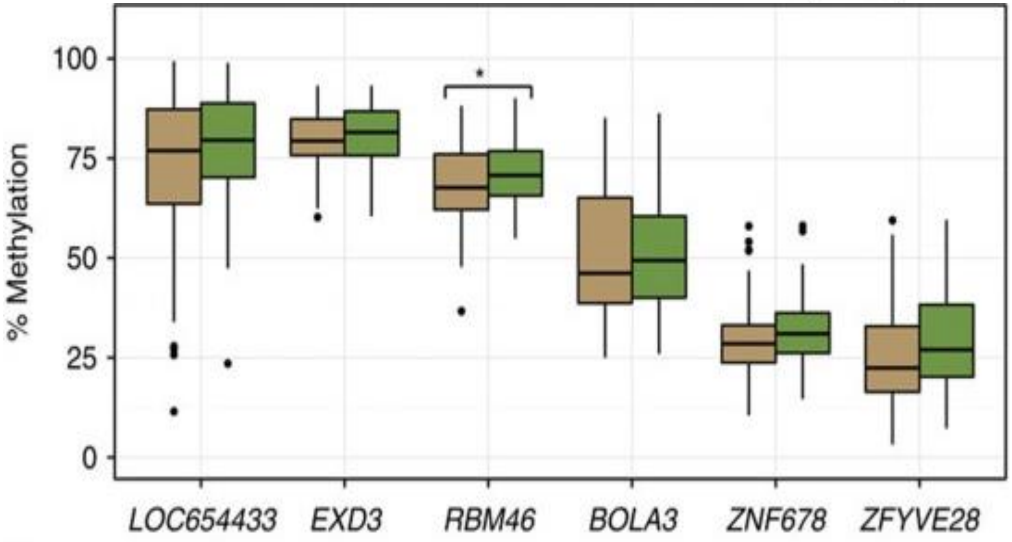
Unmethylated CpG

Feil and Fraga, *Nature Rev. Genet.* (2013)

Search for *'metastable alleles'* in humans: Seasonal gestational influence on child's DNA methylation

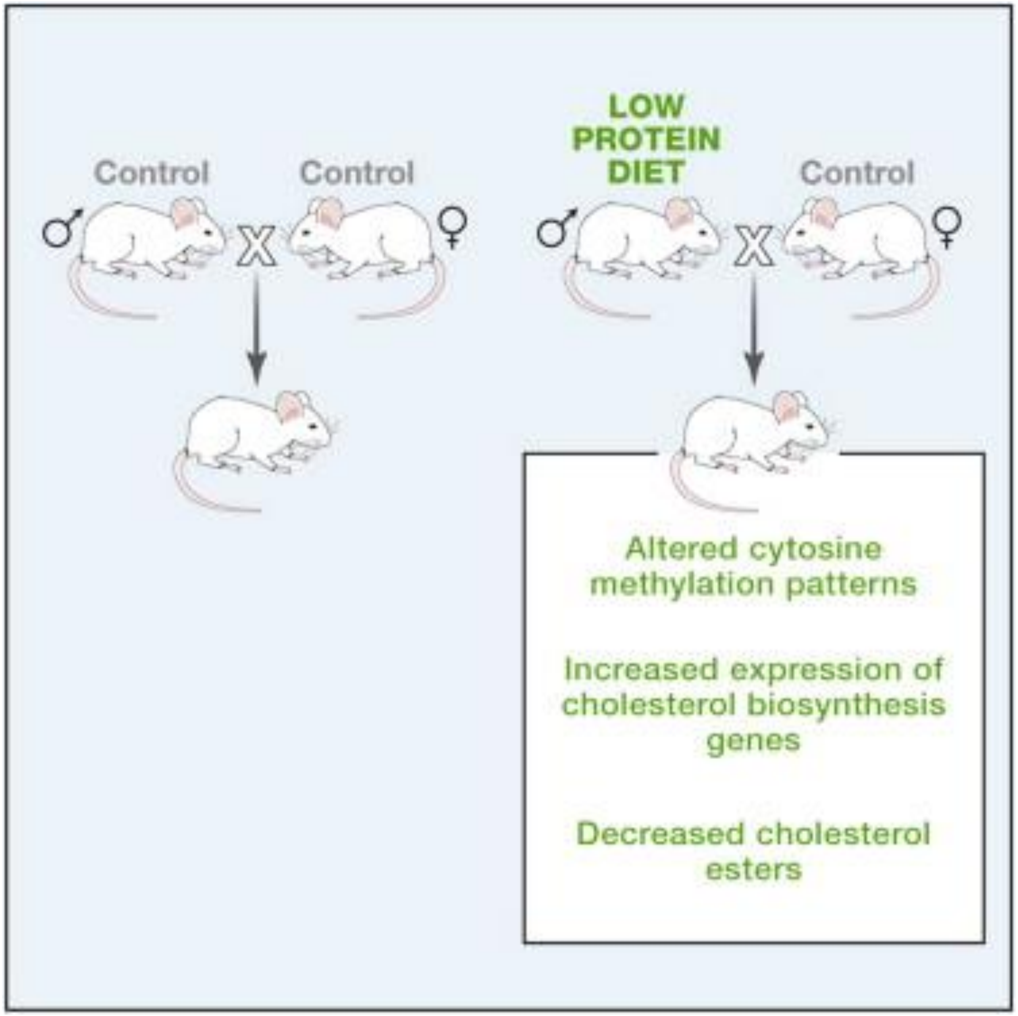






Waterland RA *et al. PLOS Genet. (*2010)
Dominguez-Salas *et al. Nature Comm. (*2014)

Different studies suggest that also paternal nutrition can influence phenotype and DNA methylation in offspring



**** Effects metabolism in offspring***

****MINOR changes in DNA methylation at specific metabolic genes in liver***

**** These methylation changes are not detected in sperm***

**** Sperm DNA methylation is largely normal***

Carone BR *et al. Cell* (2010)
Radford EJ *et al. Science (*2014)

Some discussion points……

- Are DNA methylation changes caused by the environmental cues? Or rather, do these changes reflect developmental or tissue alterations?
- Why are certain gene loci much more susceptible than others?
- Which mechanisms normally control these ‘metastable’ loci?
- Which genomic loci are most susceptible in humans?
- Are the epigenetic alterations at these genomic loci consistent and ‘big enough’ to be considered biomarkers?
- Besides DNA and histone methylation, which other epigenetic markers should be considered?