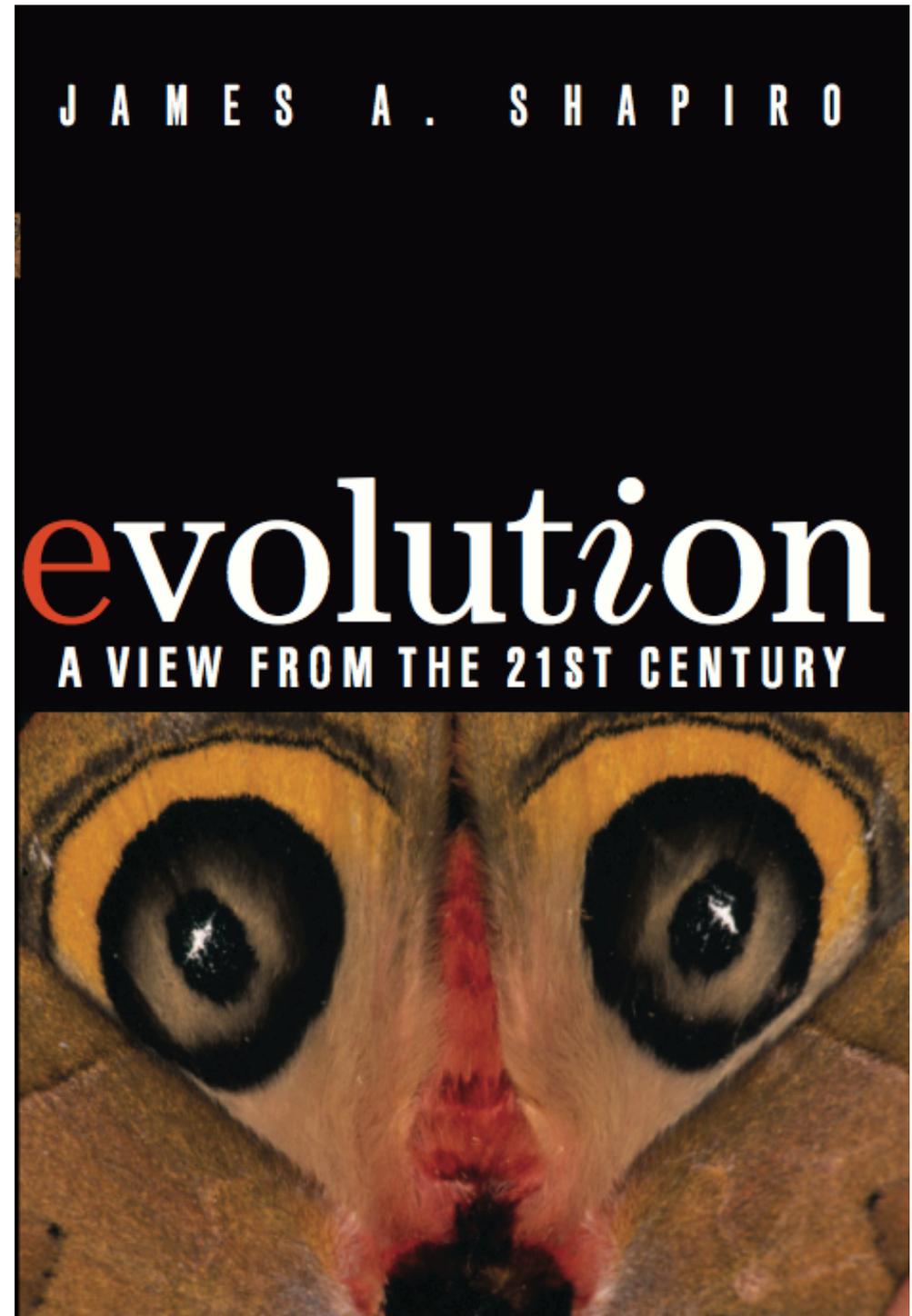


The RW Genome,
Epigenetics, Evolution
and Pregnancy

James A. Shapiro
University of Chicago

Robert G. Edwards lecture
20th World Congress on
Controversies in
Obstetrics, Gynecology &
Infertility (COGI)

Paris, France - December
4-7, 2014



Hoping to Follow Robert Edward's Example

- Working in a scientific field with social, political and religious connotations
 - science education policy
 - militant religious fundamentalism vs. militant atheism
- Challenging long-held, comfortable certainties in the academic world: *i.e.*, natural selection and random changes are sufficient to explain evolutionary novelties in “read-only” genomes
- Letting rigorous science and empirical demonstrations settle the ideological debates

What does “RW Genome” Mean?

- Cells actively write information *onto* or *into* their DNA genomes as necessary for survival and reproduction.
- Genome writing can be transient (*e.g.*, transcription factor binding complexes).
- Genome writing can be heritable over multiple cell divisions (epigenetic chromatin modifications).
- Genome writing can alter the sequence and structure of the DNA itself (natural genetic engineering).

Why Are Theoretical Questions About the Genome Relevant to COGI?

- Gametogenesis, fertilization and embryonic development generate constantly changing conditions;
- Pregnancy evolved thanks to natural genetic engineering operators creating essential coding sequences and regulatory networks;
- The successful establishment and completion of pregnancy involves writing and rewriting genetic loci by epigenetic reformatting operations;
- Understanding the operation of epigenetic genome writing in pregnancy is key to developing successful new diagnostics and therapies for multiple reproductive disorders.

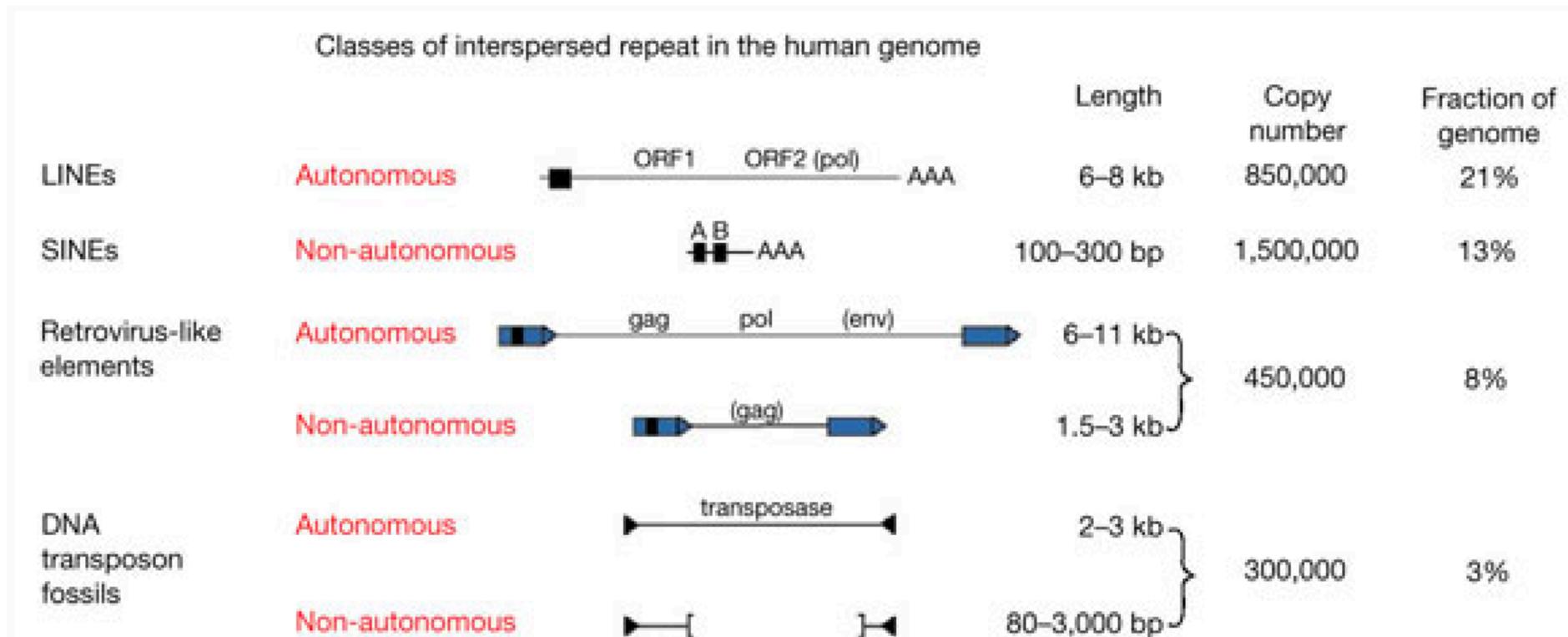
Two Take-Home Messages

1. Pregnancy provides the best example we have of evolutionary innovation by cell agents of genome rewriting (endogenous retroviruses and transposons).
2. Epigenetic control of the newly evolved placental reproduction system is deeply involved in the outcome of every pregnancy.

What have 60 years of DNA and molecular biology taught us about evolution?

- All organisms are related and can exchange hereditary information (“horizontal transfer”).
- Cells can merge to make new life forms (“syntrophogenesis”).
- Cells have multiple biochemical systems to proofread, repair, and restructure their RW genomes (“natural genetic engineering” = NGE).
- NGE is subject to regulation (activation, silencing and targeting) and responds to life history events.
- The DNA record tells us that responsive cell action has been a major factor in genome evolution.

Evolutionary time: Genome writing by natural genetic engineering – dispersed mobile elements

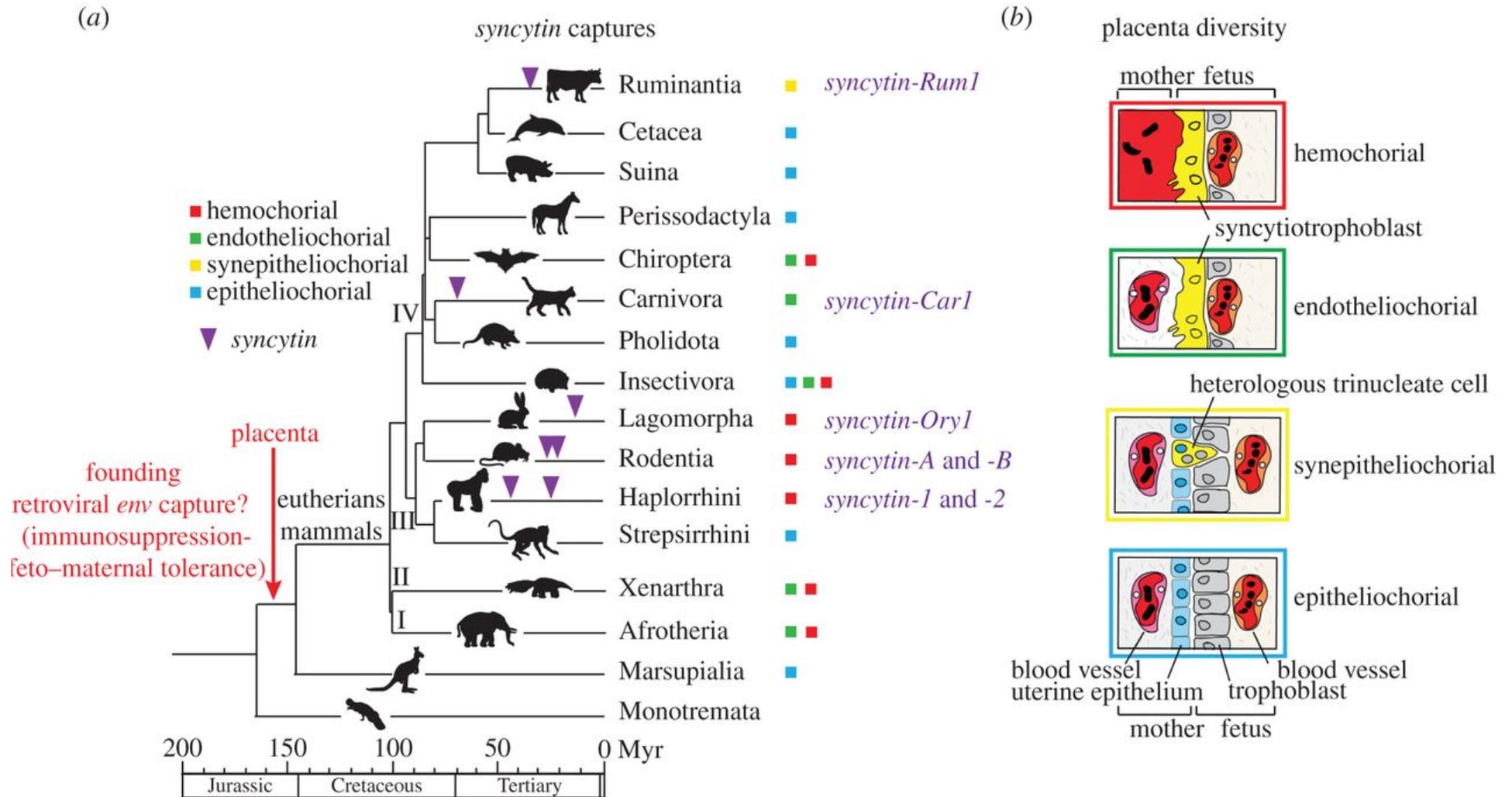


International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature* 409, 860 - 921 (2001)

Genomic Impact of Mobile Elements

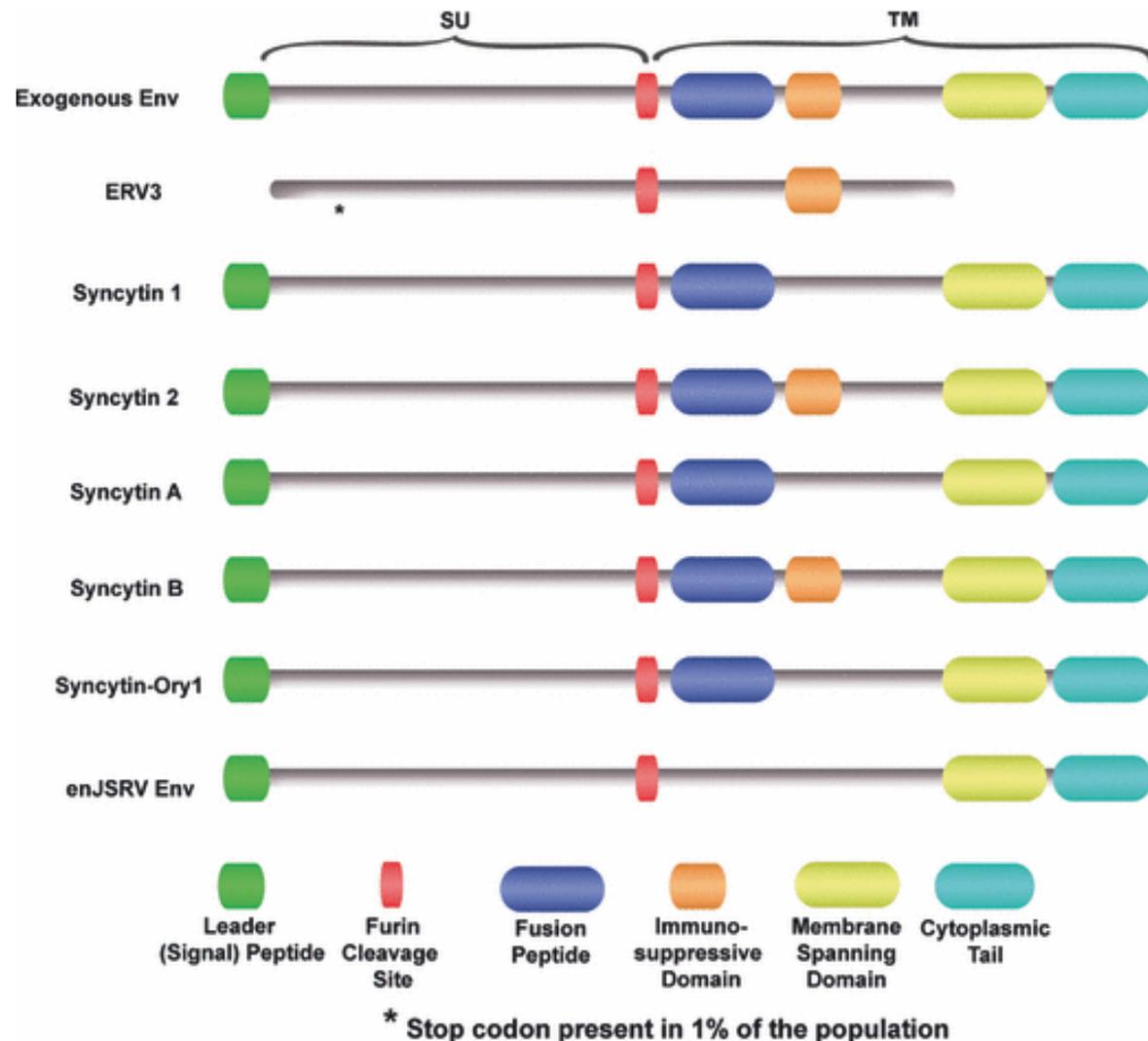
- Interrupt or alter coding regions (alternative splicing, novel exons = “exonization”);
- Promote protein evolution by “domain shuffling;”
- Introduce new transcriptional controls (promoters, terminators, alter rate of transcription);
- Provide sequences and targets for control by “non-coding” RNA molecules;
- Provide sites for epigenetic modification and imprinting;
- Distribute similar control cassettes to rewire multi-locus networks throughout the genome.

Multiple syncytin gene captures and diversity of placental structures in eutherian mammals.

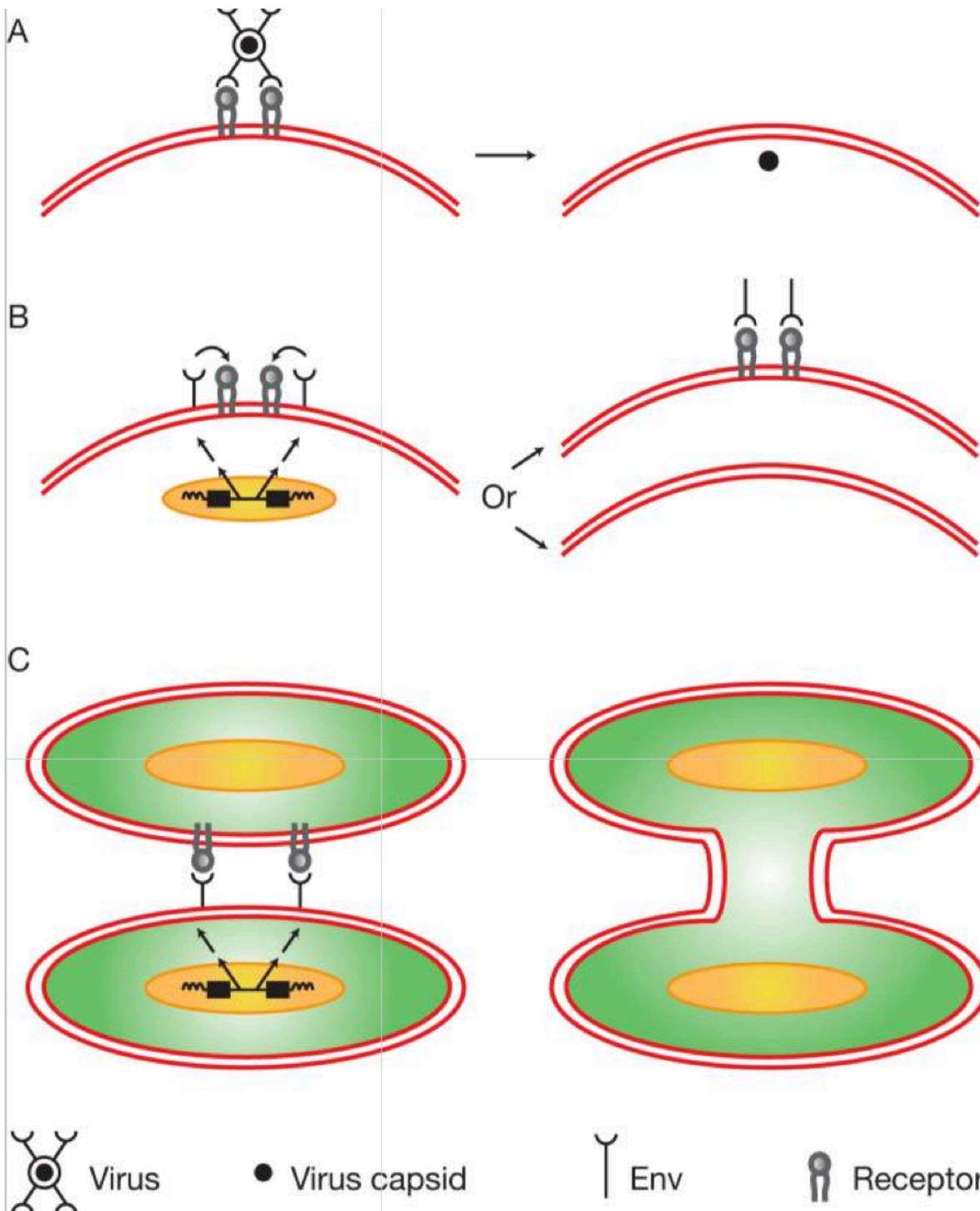


Lavialle C et al. Paleovirology of 'syncytins', retroviral *env* genes exapted for a role in placentation. *Phil. Trans. R. Soc. B* 2013;368:20120507

Endogenous Retroviruses in Trophoblast and Placental Development: Syncytin Evolution from ERV Envelope Protein



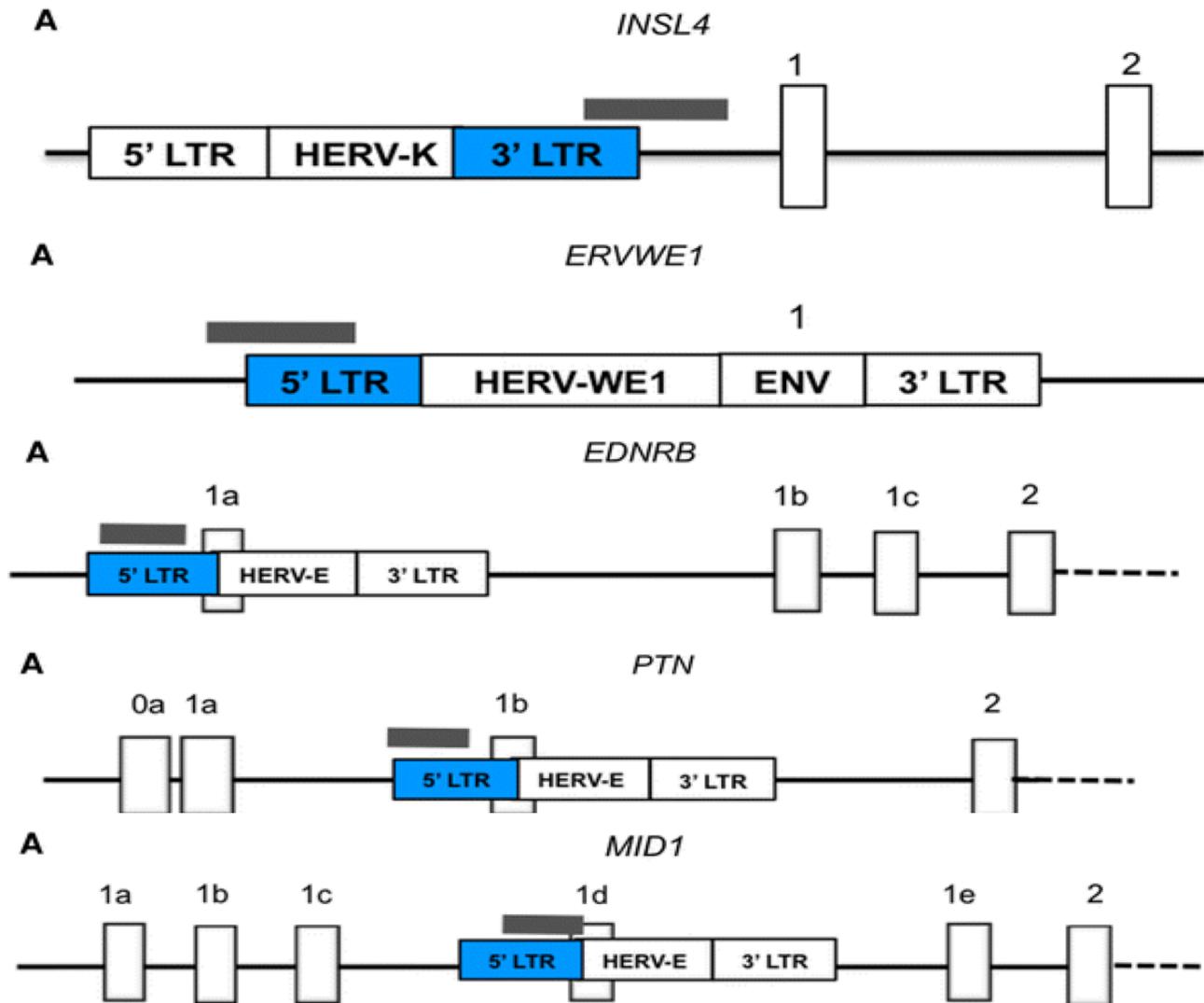
Sarah G. Black et al. **Endogenous Retroviruses in Trophoblast Differentiation and Placental Development.** *American Journal of Reproductive Immunology*. [Vol 64 \(4\)](#), pages 255-264, 2010 DOI: 10.1111/j.1600-0897.2010.00860. <http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0897.2010.00860.x/full#f2>



Proviral
protein
provides
placental
function

Stoye, J. P. (2009). "Proviral protein provides placental function." *Proc Natl Acad Sci U S A* 106(29): 11827-11828.
<http://www.ncbi.nlm.nih.gov/pubmed/19617545>.

ERVs as Promoters for Human Placental-Specific Transcripts and Sites for Epigenetic Regulation



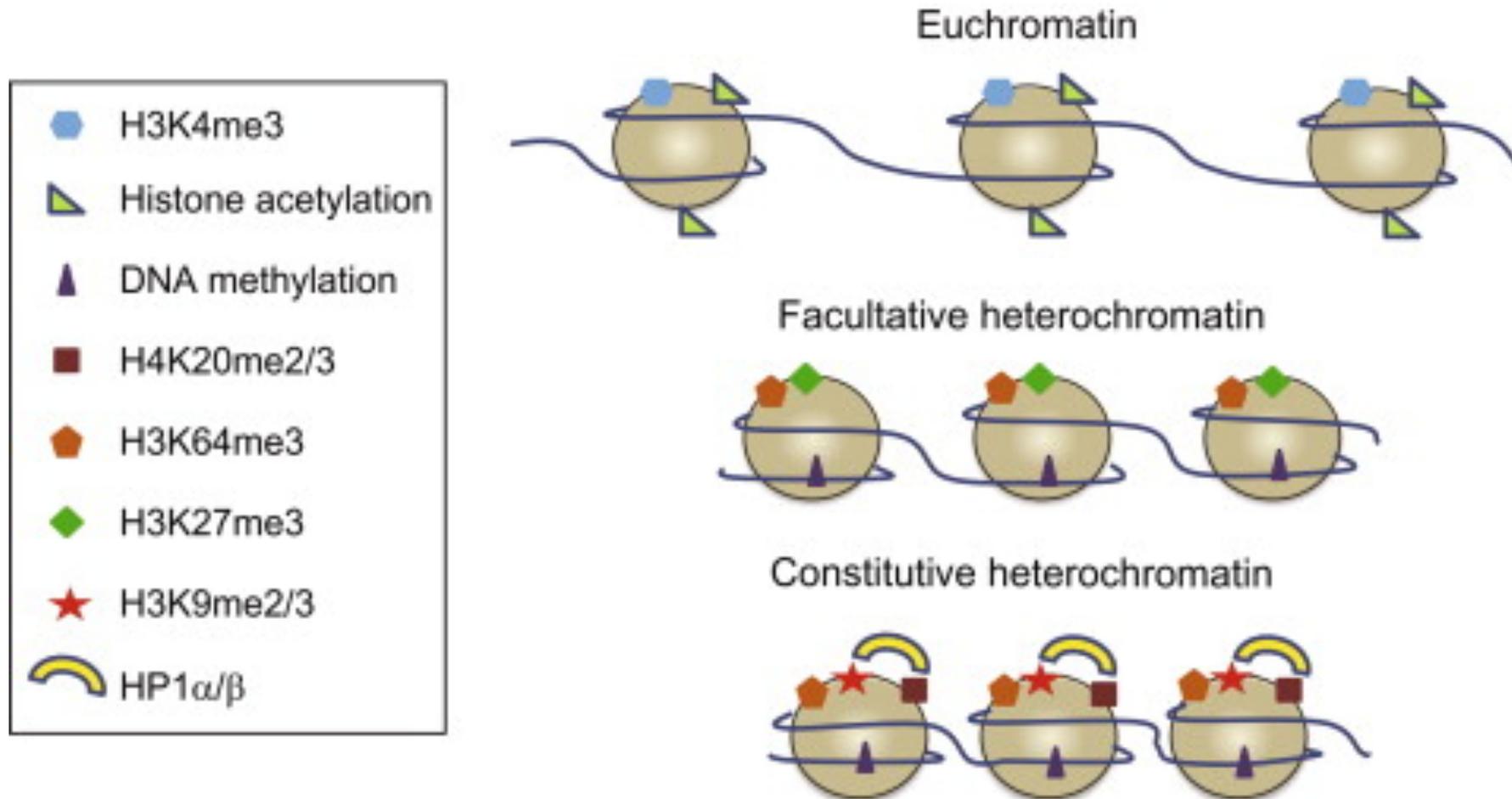
Lynch VJ, Leclerc RD, May G & Wagner GP. (2011). Transposon-mediated rewiring of gene regulatory networks contributed to the evolution of pregnancy in mammals. *Nat Genet* 43, 1154-1159.

“...the transposable element, MER20, contributed to the origin of a novel gene regulatory network dedicated to pregnancy in placental mammals, particularly by recruiting [progesterone induction and] the cAMP signaling pathway into endometrial stromal cells.”

Macaulay EC, Weeks RJ, Andrews S, Morison IM. Hypomethylation of functional retrotransposon-derived genes in the human placenta. Mamm Genome. 2011 Dec;22(11-12):722-35.

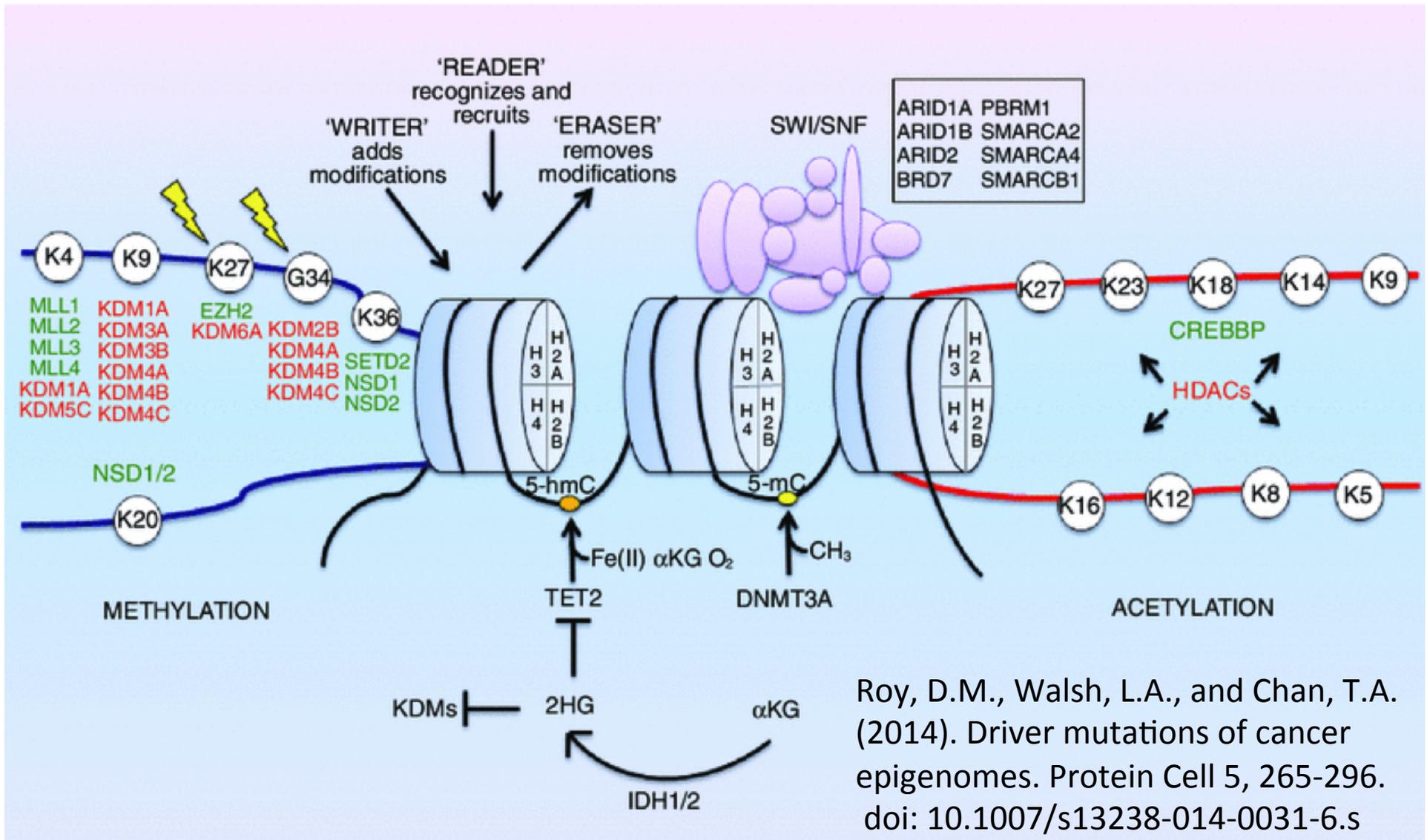
Epigenetic Control of Genome Action and Compaction

Figure 1.1 Histone posttranslational modifications and chromatin states.



Anas Fadloun , André Eid , Maria-Elena Torres-Padilla. **Chapter One - Mechanisms and Dynamics of Heterochromatin Formation During Mammalian Development : Closed Paths and Open Questions.** Current Topics in Developmental Biology, Volume 104, 2013, 1 – 45. <http://dx.doi.org/10.1016/B978-0-12-416027-9.00001-2>

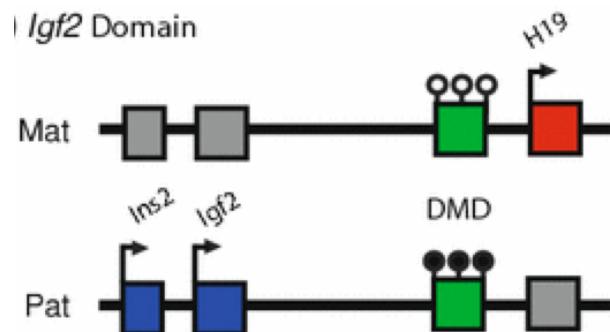
Rewritable Epigenetic Chromatin Modifications Mark Functionally Distinct Regions of the Genome ==> Multiple Factors Influence Maintenance of Correct Epigenetic Status



Roy, D.M., Walsh, L.A., and Chan, T.A. (2014). Driver mutations of cancer epigenomes. *Protein Cell* 5, 265-296. doi: 10.1007/s13238-014-0031-6.s

Epigenetic “Imprinting”

- Parental-specific expression of an extended genome locus (i.e. same DNA sequences behave differently if inherited through male or female gamete)
- ==> Erasure and imprinting in germline or during gametogenesis
- Differential DNA methylation and histone modification of paternal, maternal alleles
- Tissue-specific expression of imprinted locus at specific stage in development (e.g., placenta or endosperm)
- Dependent on DNA methylation of specific sequences, often derived from mobile elements



Weaver, J. R., M. Susiarjo, et al. (2009). "Imprinting and epigenetic changes in the early embryo."

Mamm Genome 20(9-10): 532-543.

[http://www.ncbi.nlm.nih.gov/pubmed/19760320.](http://www.ncbi.nlm.nih.gov/pubmed/19760320)

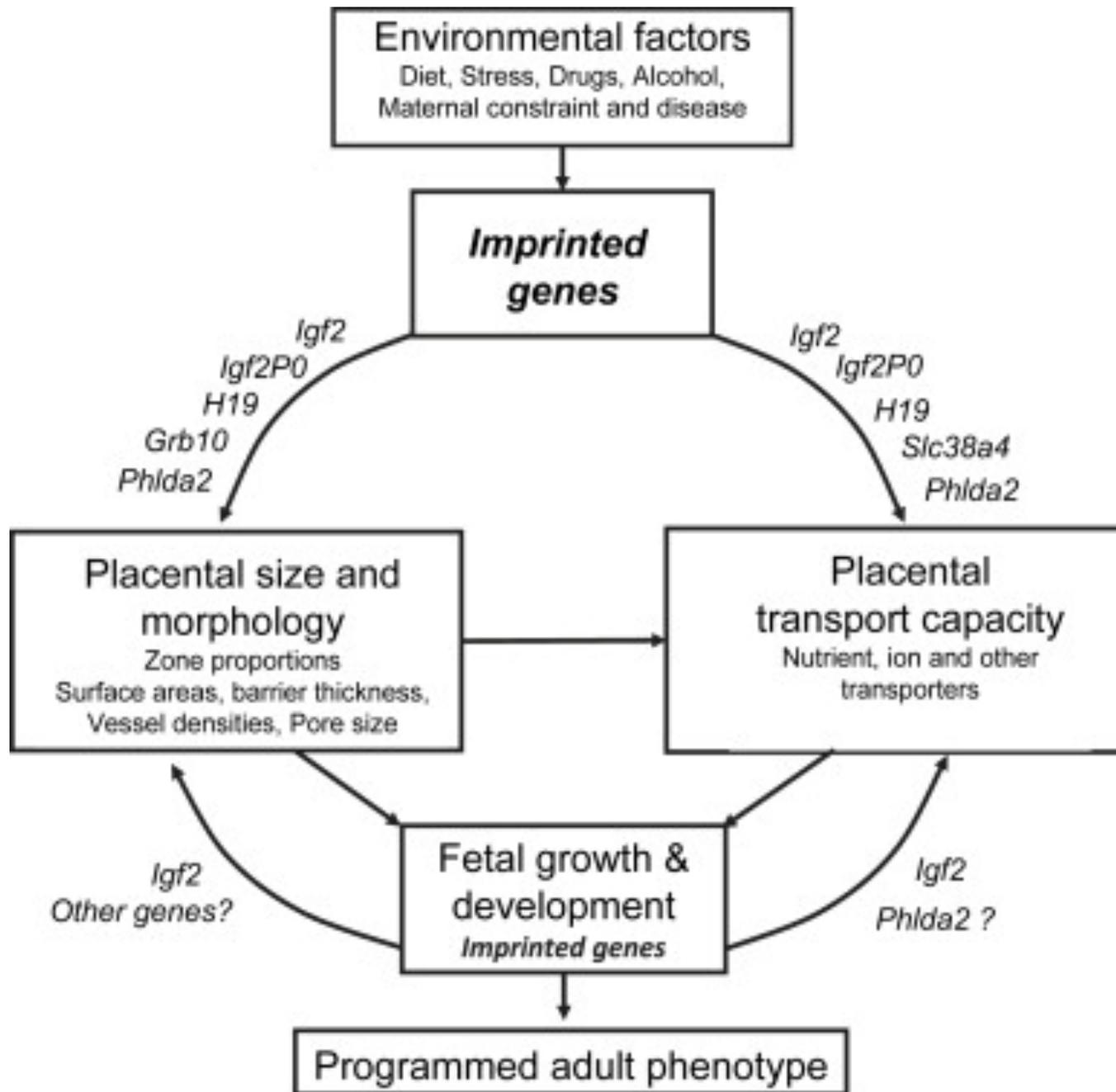


Fig. 3 Role of imprinted genes in determining placental phenotype. Schematic diagram showing the relationships between environmental factors, imprinted genes and fetal growth in regulating the nutrient transfer capacity of the mouse placenta.

A.L. Fowden , P.M. Coan , E. Angiolini , G.J. Burton , M. Constanica. **Imprinted genes and the epigenetic regulation of placental phenotype**. Progress in Biophysics and Molecular Biology, Volume 106, Issue 1, 2011, 281 – 288. <http://dx.doi.org/10.1016/j.pbiomolbio.2010.11.005>

Human Disorders Linked to Epigenetic Remodeling and Imprinting in Pregnancy

- Pre-eclampsia and HELLP Syndrome
- Prader Willi and Angelman Syndromes
- Beckwith-Wiedemann and Russell-Silver Syndromes (higher incidence following assisted reproduction technologies?)
- Low fetal birth weight
- Neurodegenerative disease (autism?)
- Predisposition to cardiovascular disease, obesity and type II diabetes

Trans- Generational Epigenetic Inheritance of Pregnancy Stress in International Newspapers August, 2014

Y. Yao et al., "Ancestral exposure to stress epigenetically programs preterm birth risk and adverse maternal and newborn outcomes," *BMC Medicine*, doi:10.1186/s12916-014-0121-6, 2014.

LA STAMPA SALUTE

Lo stress durante la gravidanza può essere tramandato attraverso le generazioni

Se la gravidanza presenta delle complicanze o problemi che non si spiegano altrimenti, potrebbe essere lo stress vissuto da una nostra ava (bisnonna, nonna) durante la gravidanza che, come suggerito da un nuovo studio, può essere trasmesso di generazione in generazione

The New Zealand Herald

Mothers pass on pregnancy stress - study

10:10 AM Friday Aug 8, 2014

http://www.nzherald.co.nz/lifestyle/news/article.cfm?c_id=6&objectid=11305859&utm_medium=BMCemail&utm_source=Emailvision



Zwangerschapsstress

benadeelt achterkleinkinderen

Geschreven op 7 augustus 2014 door [helena](#)



Wetenschappers hebben ontdekt dat stress tijdens de zwangerschap van ratten gevolgen kan hebben voor hun dochters, kleindochters en achterkleindochters.

http://www.kijkmagazine.nl/nieuws/stress-tijdens-zwangerschap-benadeelt-achterkleinkinderen/?utm_campaign=10_09_14_BMCUpdate&utm_content=7389020651&utm_medium=BMCemail&utm_source=Emailvision

TheScientist

EXPLORING LIFE, INSPIRING INNOVATION

Pregnancy Stress Spans Generations

The stressors a female rat experiences during pregnancy can have repercussions for her granddaughters, a study shows. By Anna Azvolinsky | August 7, 2014

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