Epigenetic marks in extra-embryonic tissues

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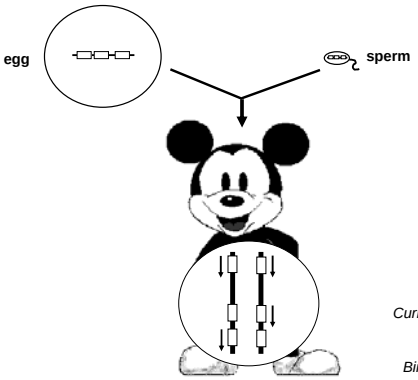
Genomic Imprinting

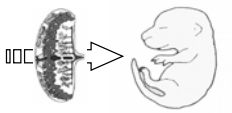


Feil and Berger,
Trends Genet 2007

Katia Delaval et al.
Curr Opin Dev Genet 2004

Arnaud & Feil
Birth Defects Res. 2005

Imprinted genes influence nutrient transfer and behaviour in placental mammals



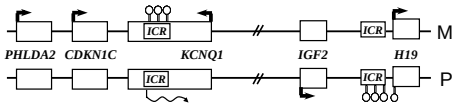
Placental development and function

Fetal growth control

Postnatal fitness

Postnatal behaviour

KCNQ1 and IGF2-H19 domains: deregulated in BWS and SRS growth syndromes and in cancer



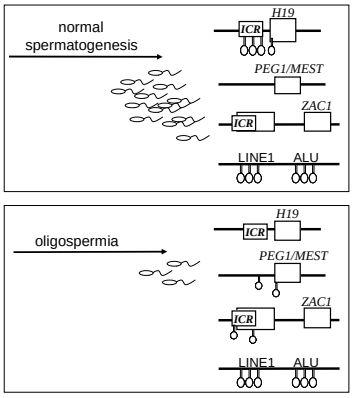
***KCNQ1* domain** ***IGF2-H19* domain**

ICR = 'imprinting control region'

Imprinting Control Regions (ICRs)

CH3 CH3 CH3 CH3 CH3 CH3

Deregulation of imprints during spermatogenesis



Marques *et al.* 2004, 2008
Kobayashi *et al.* 2007

Epigenetic deregulation *in vitro*

*** Derivation and culture of cells**	Dean *et al.* 1998; Humpherys *et al.* 2001; Pantoja *et al.* 2005
*** Pre-implantation embryo culture**	Khosla *et al.* 2001; Young *et al.* 2001; Mann *et al.* 2004
*** Somatic cell nuclear transfer**	Humpherys *et al.* 2001; Young *et al*. 2003; Mann *et al.* 2003
•Assisted reproduction	DeBaun *et al.* 2003; Cox et al. 2003; Maher *et al.* 2003; Örstavik *et al.* 2003; Halliday *et al.* 2004; Arnaud & Feil, 2005, Fortier et al. 2008

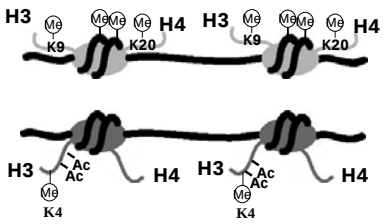
Imprinting is relatively labile in the extra-embryonic lineage

- Superovulation effects on imprinted genes in placenta (Fortier *et al.* 2008)
- *In vitro* embryo culture often affects imprinting in the placenta (Mann *et al.* 2004; Rivera et al. 2008)
- * Somatic cell nuclear transfer has dramatic effects on extra-embryonic lineage and imprinting.

Maintenance of differential methylation at ICRs ??

CH3 CH3 CH3 CH3 CH3 CH3

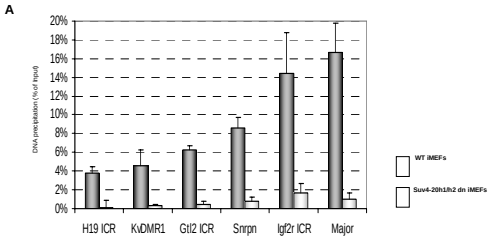
Role and regulation of allelic histone methylation at ICRs?



Katia Delaval *et al.* *EMBO J.* 2007.

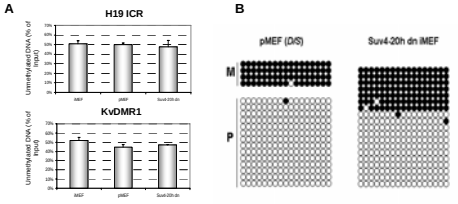
- Similarities with pericentric heterochromatin and telomeres
- Protection against loss of DNA methylation
- Protection against *de novo* methylation (via H3K4me2/3?)
- Role for RNA?

Suv4-20h1/2 and PrSet7 control H4K20me3 at ICRs and pericentric heterochromatin

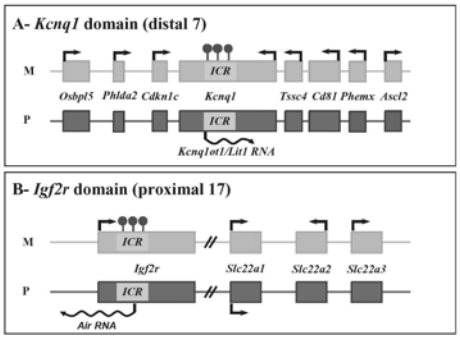


Maëlle Pannetier *et al.*, submitted

Loss of H4K20me3 does not affect allelic DNA methylation at ICRs



Imprinting in the mouse placenta



Alexandre Wagschal *et al.* *Cytogenet Genome Res 2006*

Difficult to determine the imprinting status of genes in human placentas: example of Chr. 10q21-22

Comparison between hydatidiform moles and normal placentas:

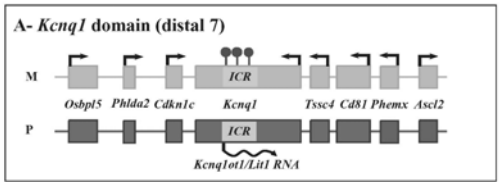
van Dijk *et al.* *Nat. Genet.* 2005

Oudejans *et al. 2004*

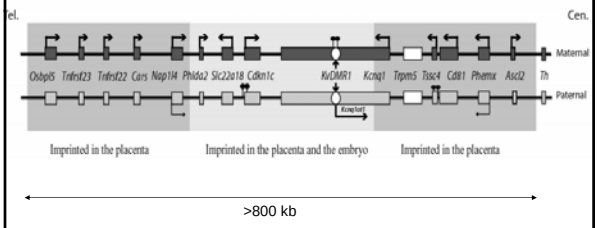
Use of SNPs to study normal placentas:

Iglesias-Platas *et al.* *Nat. Genet.* 2007

The *Kcnq1* domain: ICR-mediated repression *in cis* via a non-coding RNA

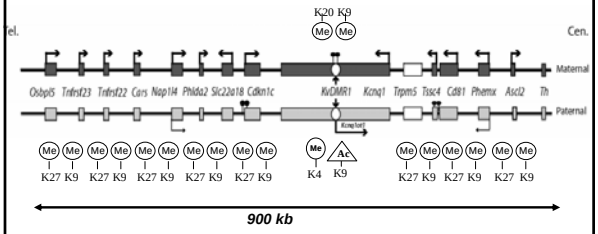


The *Kcnq1* domain: placenta-specific imprinting at proximal and distal genes



(NB: Placenta-specific imprinting is maintained in *Dnmt1*-/- conceptuses)

The repressed paternal chromosome is marked by H3K9me2 and H3K27me3



David Umlauf *et al.* Nature Genet 2004
Annabel Lewis *et al.* Nature Genet 2004

SET domain proteins G9a and Ezh2 are involved

G9a Histone methyltransferase (HMT)

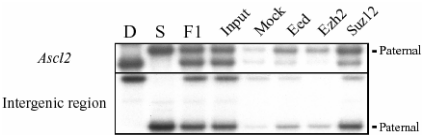
K9 **K27** **Histone H3**

Ezh2 Histone methyltransferase (HMT)

David Umlauf *et al. Nature Genet* 2004
Alexandre Wagschal *et al. Mol Cell Biol* 2008

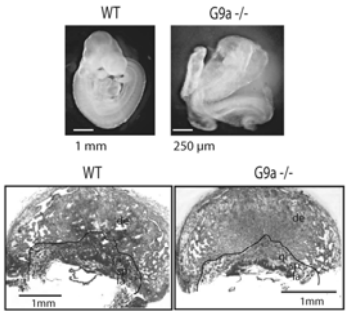
Paternal repression involves recruitment of the PRC2 complex

⇨ The PRC2 complex (Eed, Suz12, Ezh2) → H3K27me3

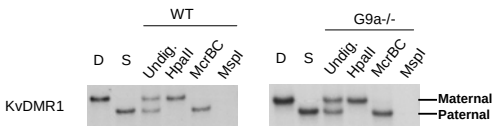


David Umlauf *et al.* 2004

G9a-/- conceptuses

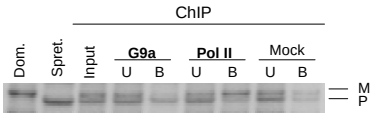


G9a HMT deficiency: unaltered DNA methylation at KvDMR1and *H19 ICRs*



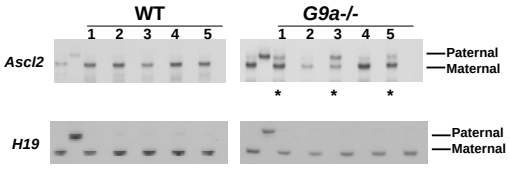
Alexandre Wagschal *et al.* Mol Cell Biol. 2008.

ChIP on cross-linked chromatin: G9a associates with the repressed allele of *Ascl2*

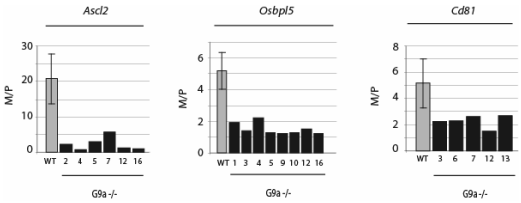


Ascl2

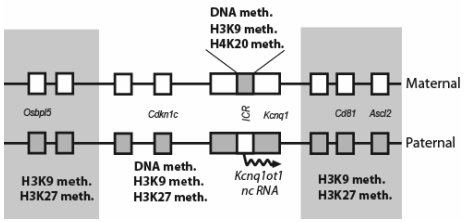
G9a deficiency: relaxation of placental imprinting



G9a deficiency: relaxation of placental imprinting

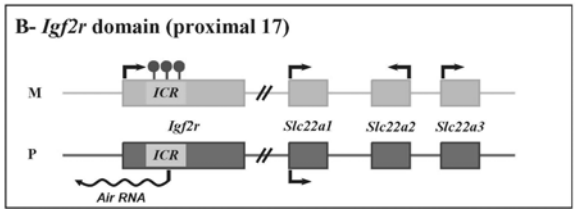


Model for the mouse *Kcnq1* domain



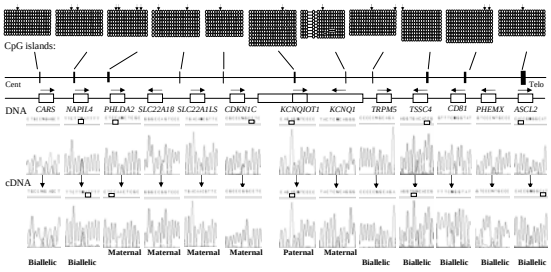
Alexandre Wagschal *et al. Mol Cell Biol.* 2008.

Mechanistic similarities between the Kcnq1 and Igf2r imprinted domains



Polymorphic imprinting at the *IGF2R* domain in humans
David Monk *et al.* PNAS USA 2006

Limited conservation of placental imprinting in humans



David Monk *et al*. PNAS USA 2006

Conclusions

- Imprinted genes play important roles in extra-embryonic tissues
- Some genes are imprinted in the placenta only.
- Imprinting is more labile in the placenta than in the embryo
- Imprinting maintenance relies less on DNA methylation in the placenta than in the embryo
- Involvement of histone lysine methylation in placenta-specific imprinting
- Important to unravel the enzymatic machineries involved, particularly in early conceptuses

"Genomic Imprinting and Development"

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