

Dr. Benjamin Tycko

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Physiological Functions of Imprinted Genes

Ben Tycko, Columbia University ICG



Epigenetics Cell Memory



Rainbow Cat



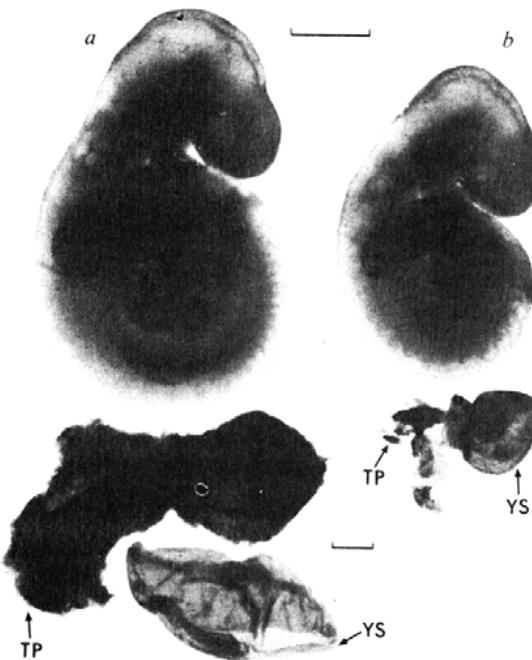
Copy Cat

Genomic Imprinting

"Development of reconstituted mouse eggs suggests imprinting of the genome during gametogenesis"

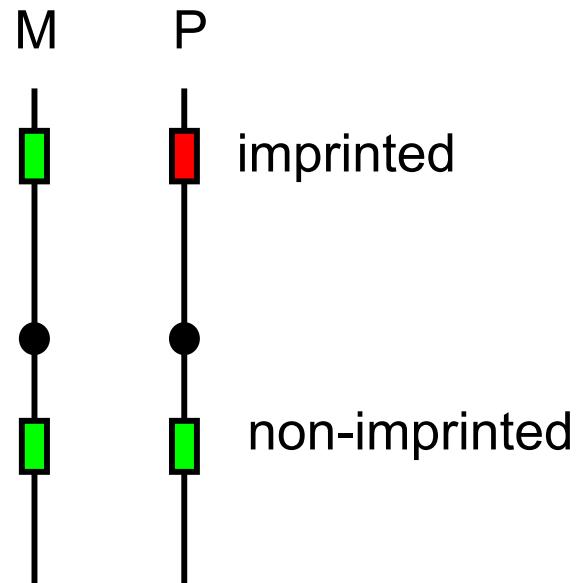
Surani, Barton & Norris, Nature 308, 548-550 (1984)

control most advanced
gynogenetic embryo



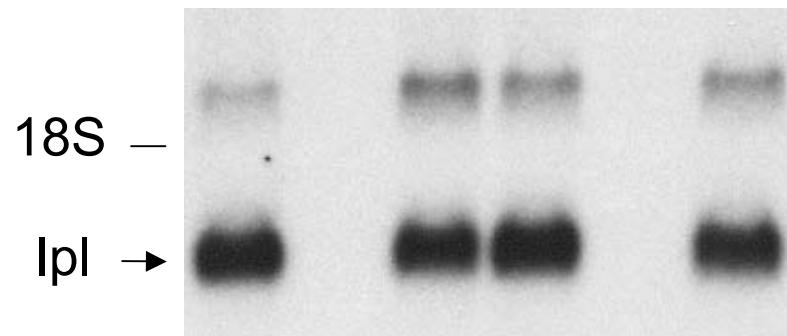
"Our model implies that the paternal and/or maternal genome (whole or in part) are somehow conditioned/altered during gametogenesis and that this conditioning is completely reversible (as is the case for the X chromosome)."

McGrath & Solter, Cell 37, 179-183 (1984)

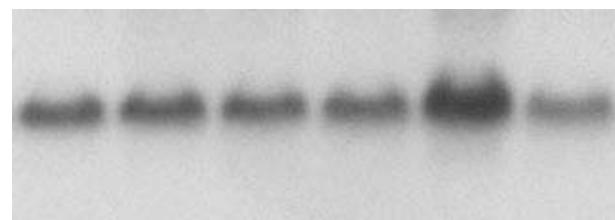


Genomic Imprinting: Gene Dosage

Genotype: $+|+$ $+|-$ ^{mat} $+|-$ ^{pat} $-|+$ $-|-$ $+|+$



Ipl (imprinted gene)



Actin probe

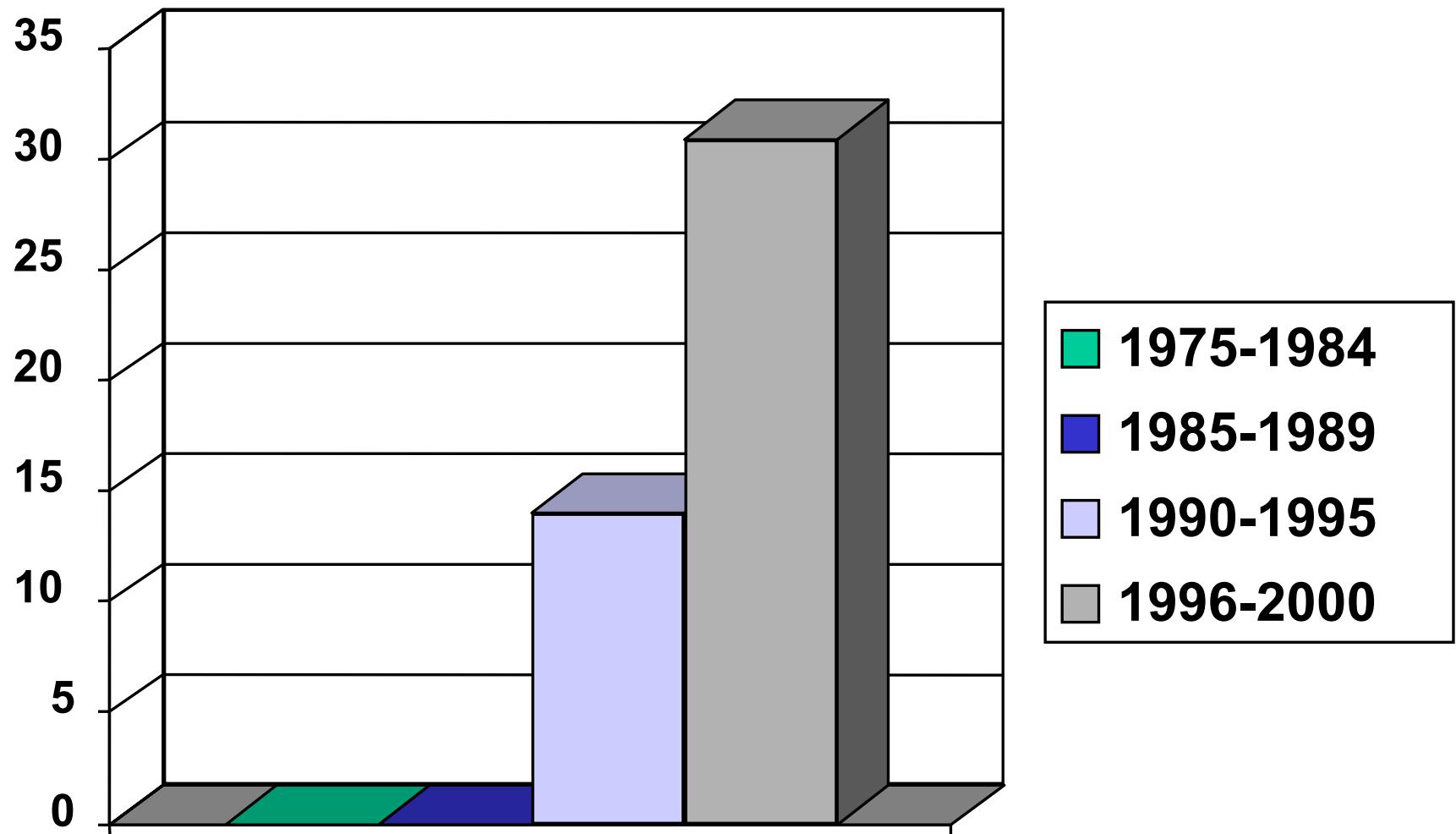
Theories of Imprinting

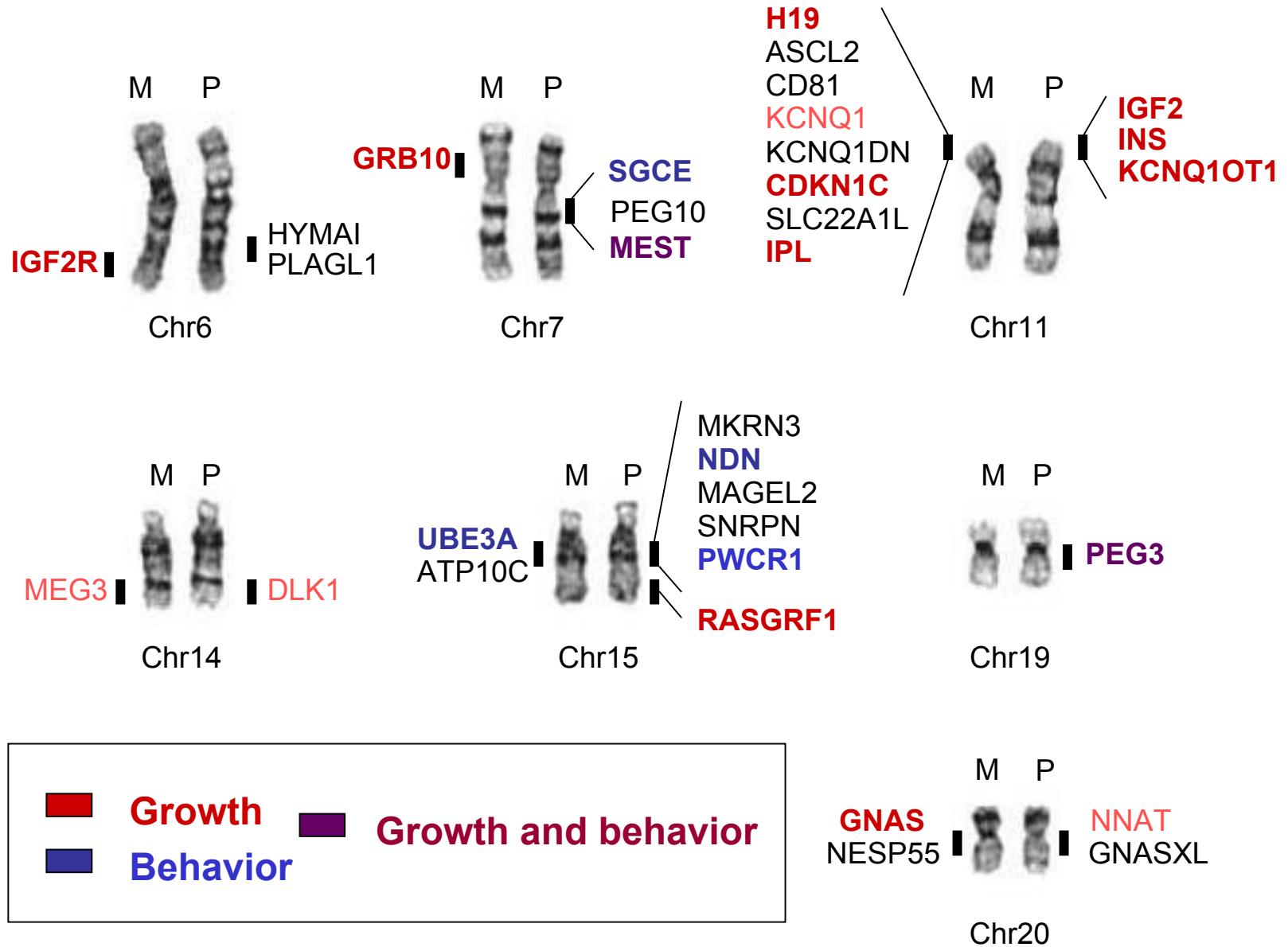
- Mechanism: locations of imprinted domains dictated by DNA methylation and regional chromatin structure in gametogenesis
 - *multiple imprinted genes clustered in megabase-scale regions*
 - *imprinting determined by allele-specific DNA methylation at critical sites*

Theories of Imprinting

- Mechanism: locations of imprinted domains dictated by DNA methylation and regional chromatin structure in gametogenesis
 - *multiple imprinted genes clustered in megabase-scale regions*
 - *imprinting determined by allele-specific DNA methylation at critical sites*
- Biological Function: conflict between maternal and paternal “drives” for reproductive success.
paternally silenced genes retard growth of the conceptus; maternally silenced genes promote growth and increase nutritional demands on the mother

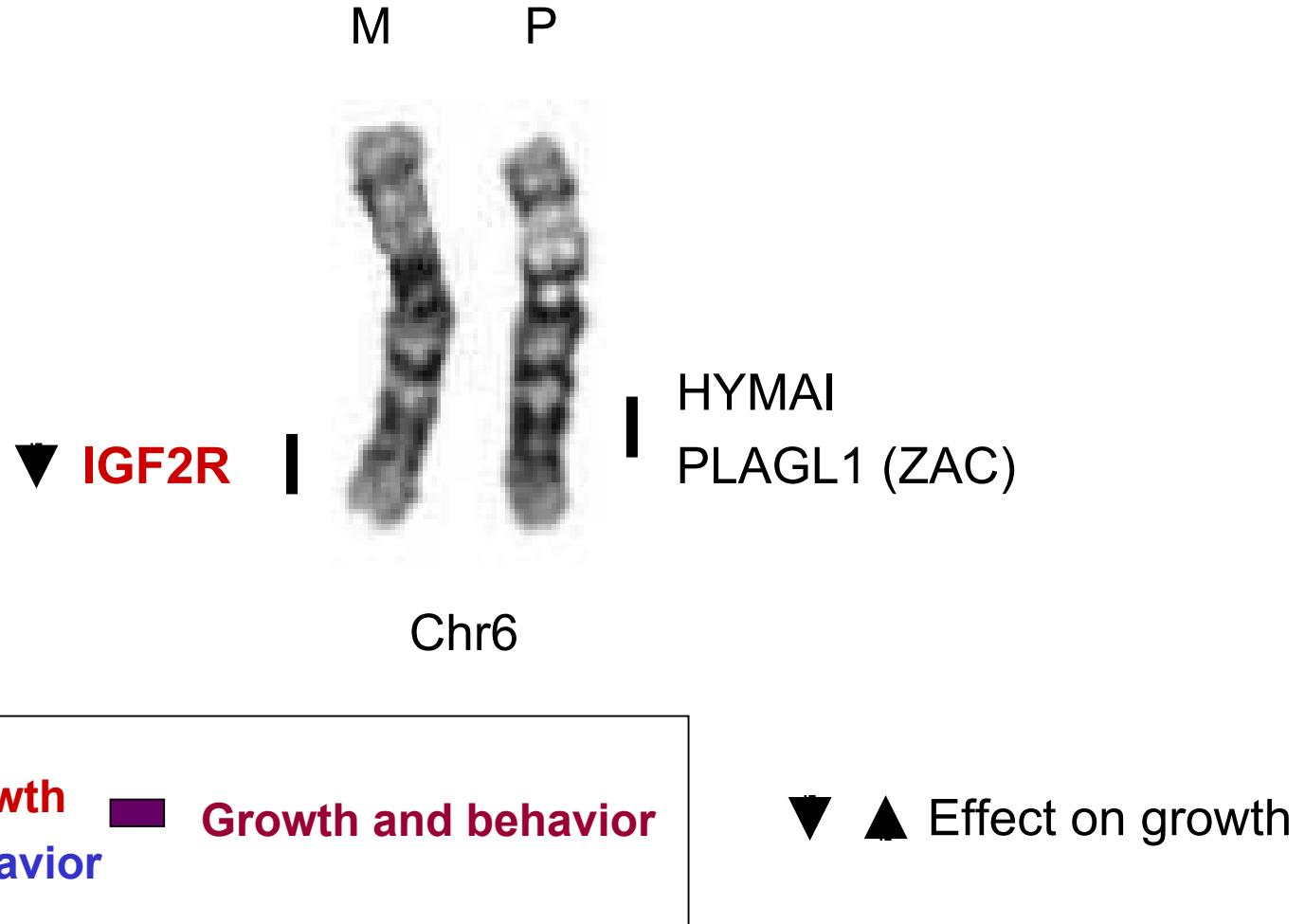
Imprinted Genes



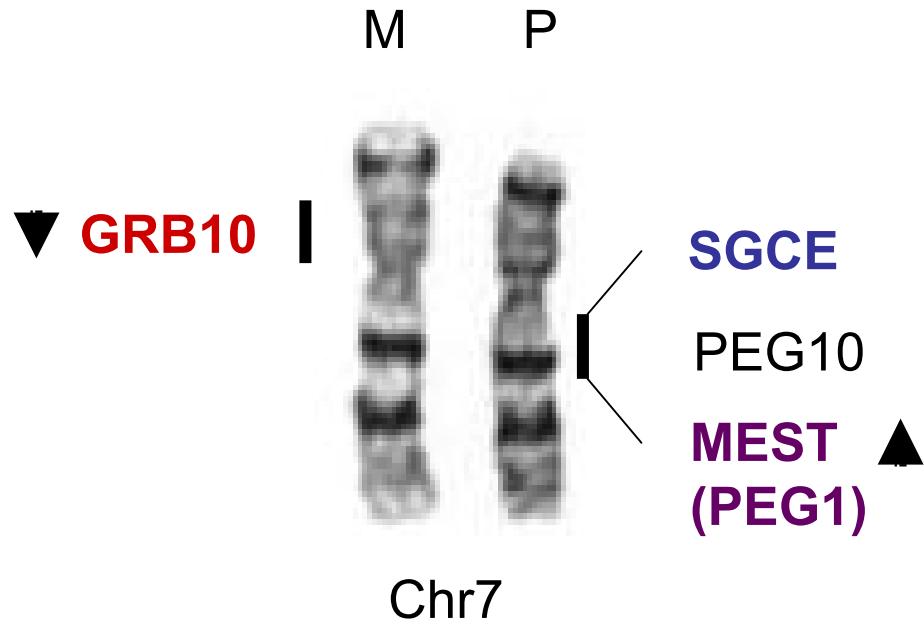


Tycko and Morrison, J Cell Physiol, 2002

Imprinted genes on Mm17/Hs6



Imprinted genes on Mm11/Hs7



▼ ▲ Effect on growth

Imprinted Genes on Hs19q/Mm7

M P

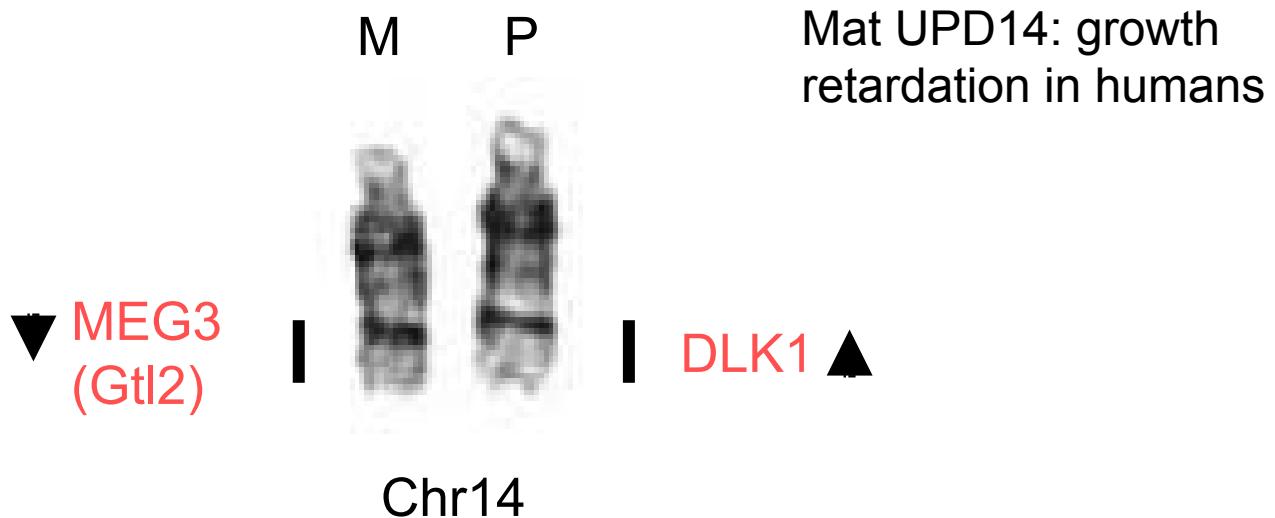


Chr19



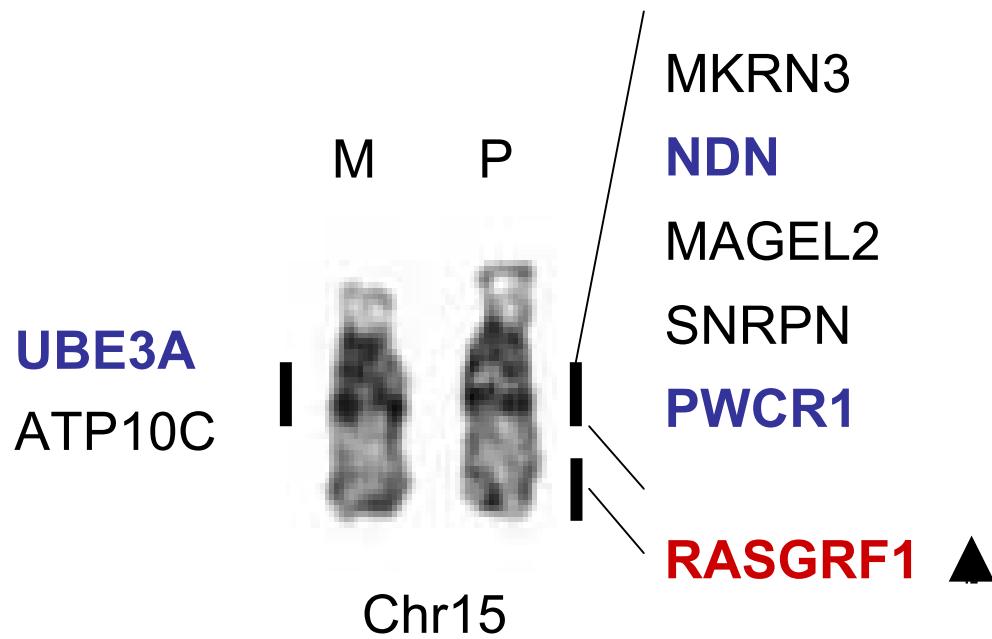
▼ ▲ Effect on growth

Imprinted Genes on Hs14q32/Mm12



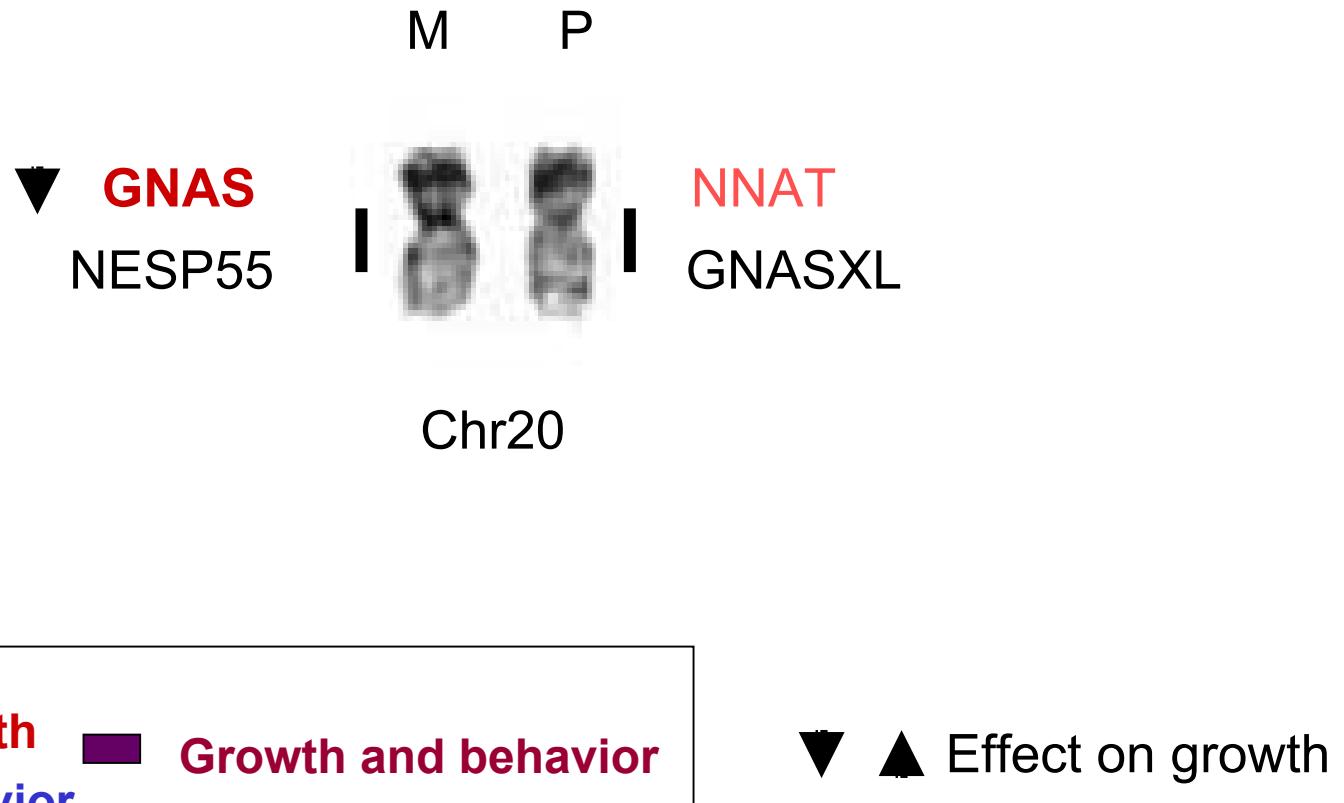
▼ ▲ Effect on growth

Imprinted Genes on Hs15q/Mm7

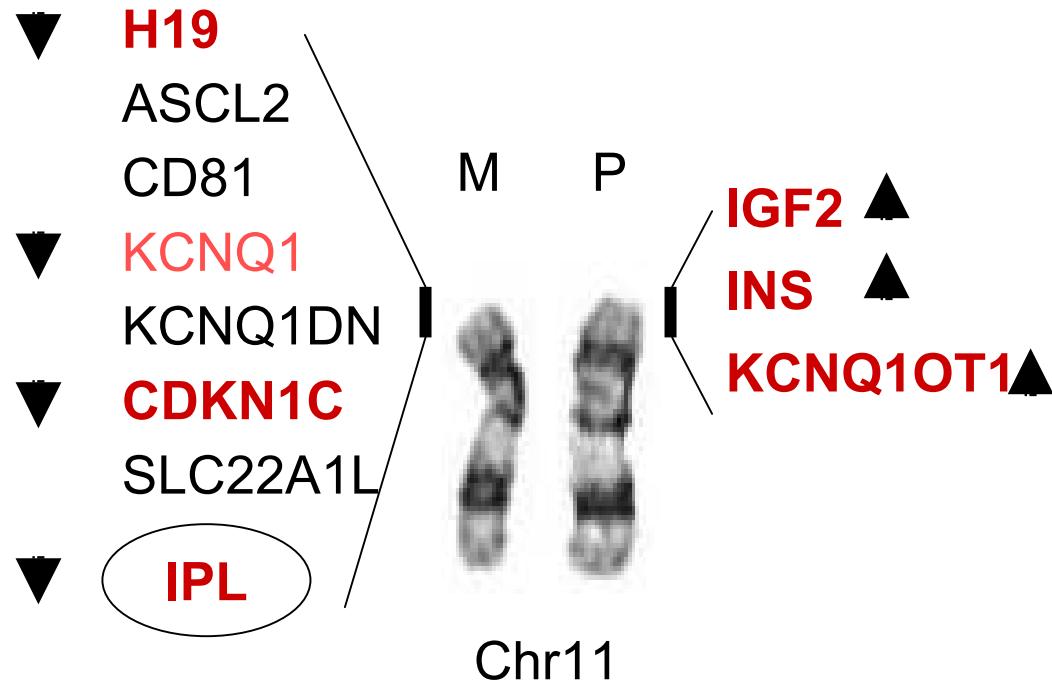


▼ ▲ Effect on growth

Imprinted Genes on Hs20q/Mm2

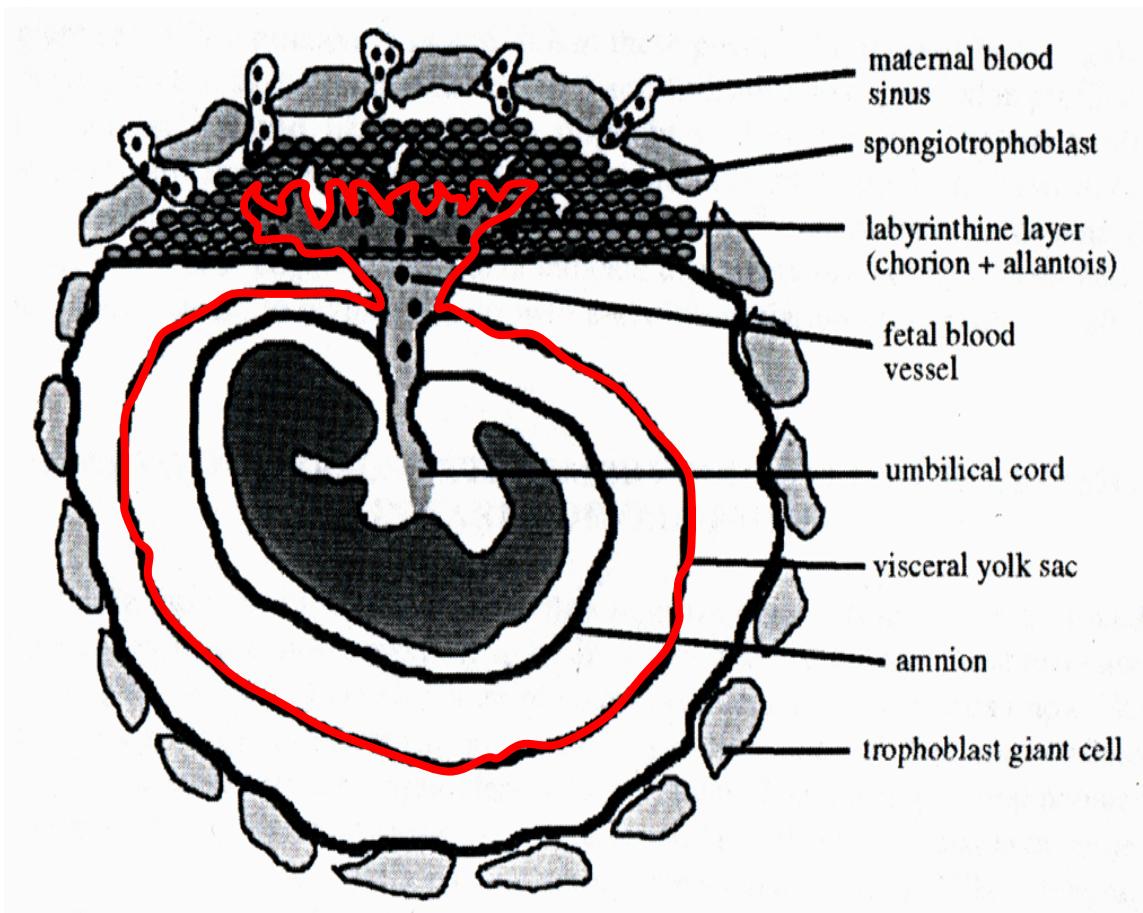


Imprinted Genes on Hs11p15/Mm7



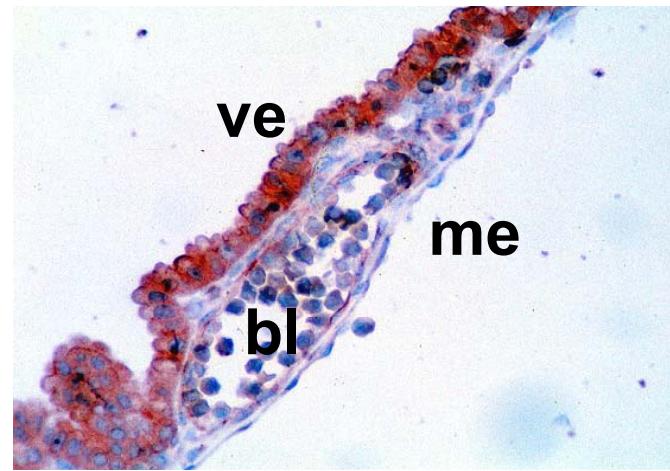
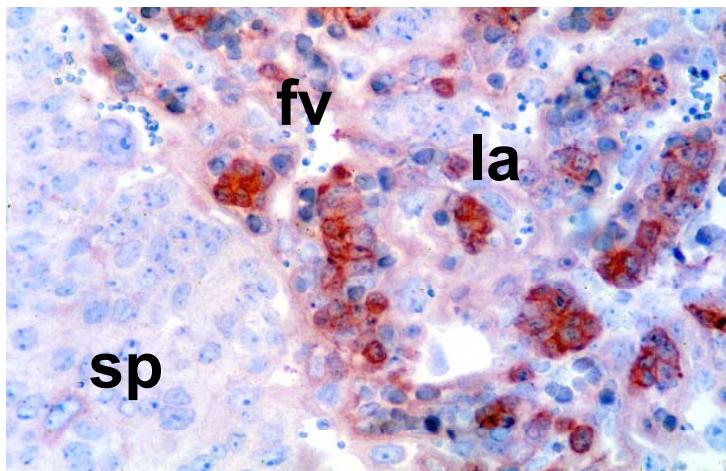
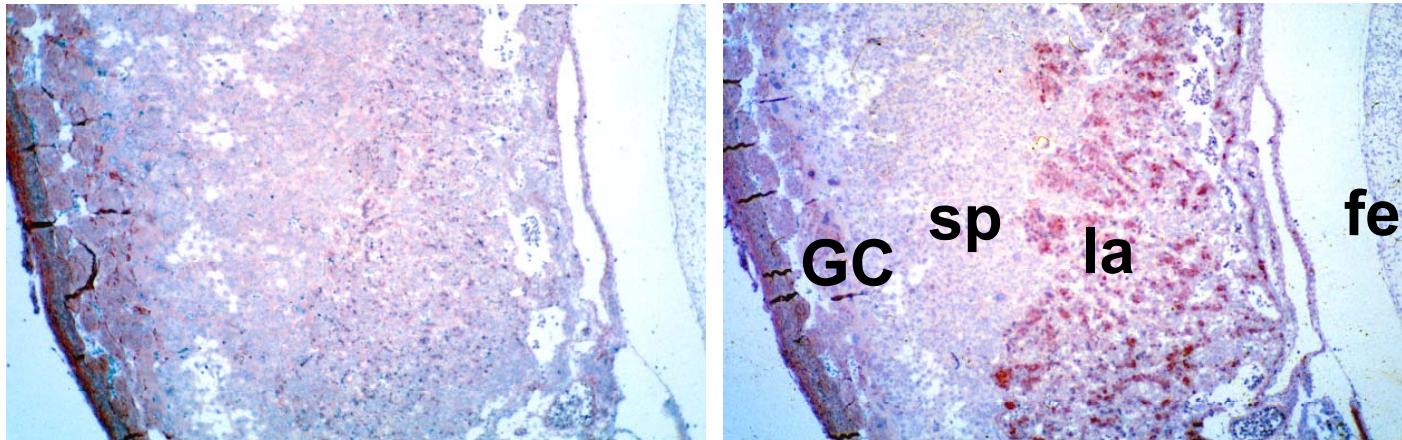
▼ ▲ Effect on growth

Feto-Maternal Interaction: Extraembryonic Tissues

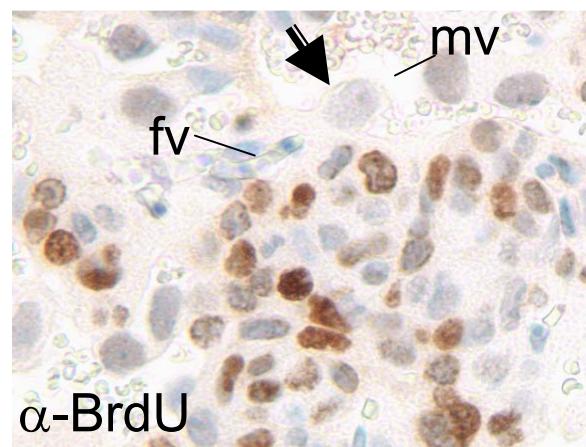
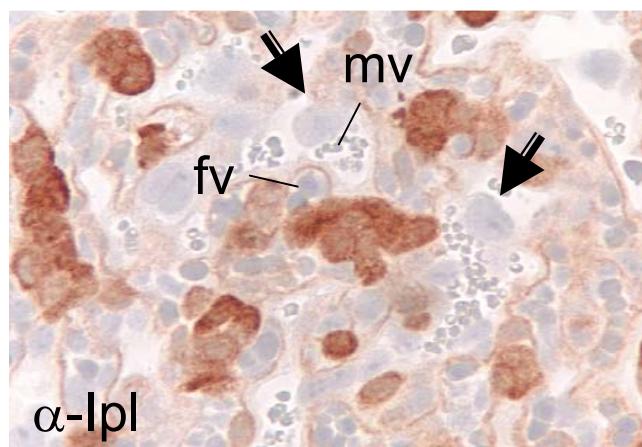
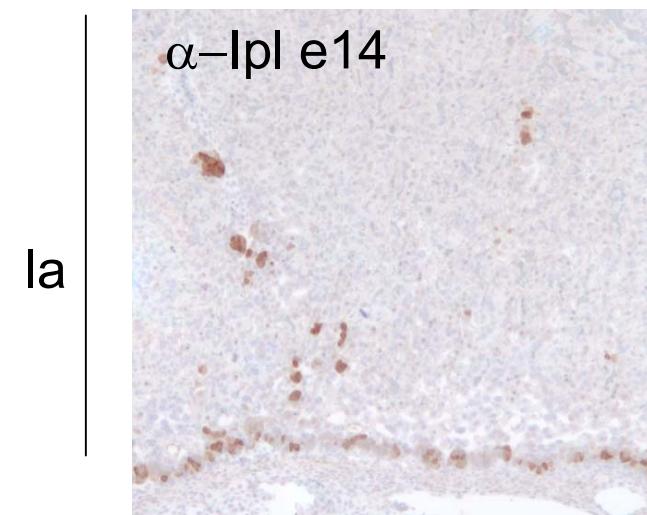
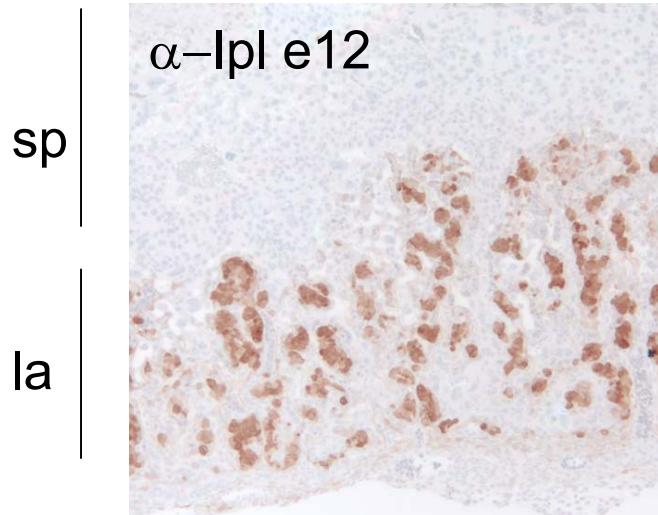


[Cross, J.C., Annals NY Acad Sci]

Expression of *Ipl* in Extraembryonic Tissues

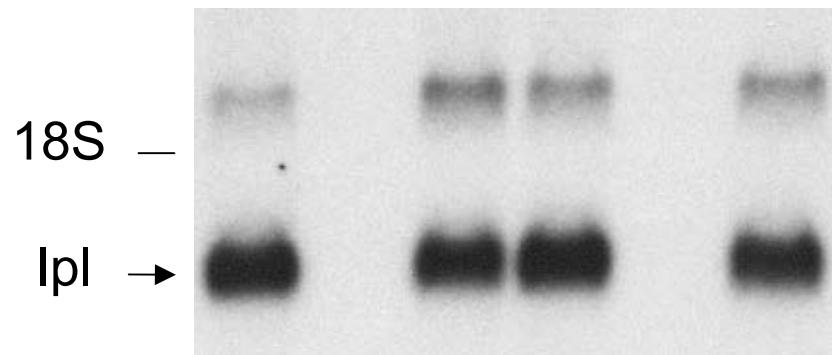


Ipl-positive cells disappear at mid→late gestation

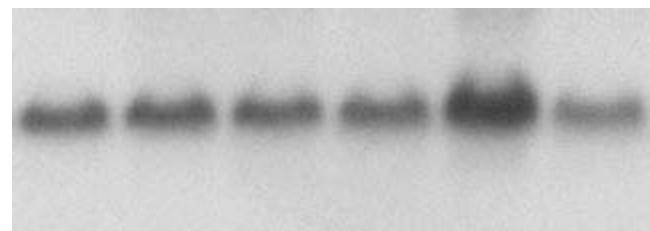


Ipl KO mice

Genotype: $+|+$ $+|-$ ^{mat} $+|-$ ^{pat} $+|+$ $-|+$ $+|+$

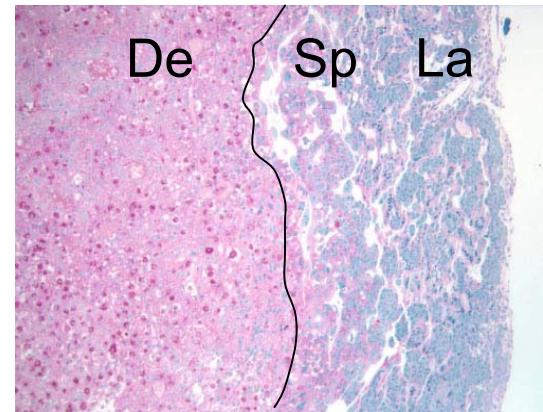
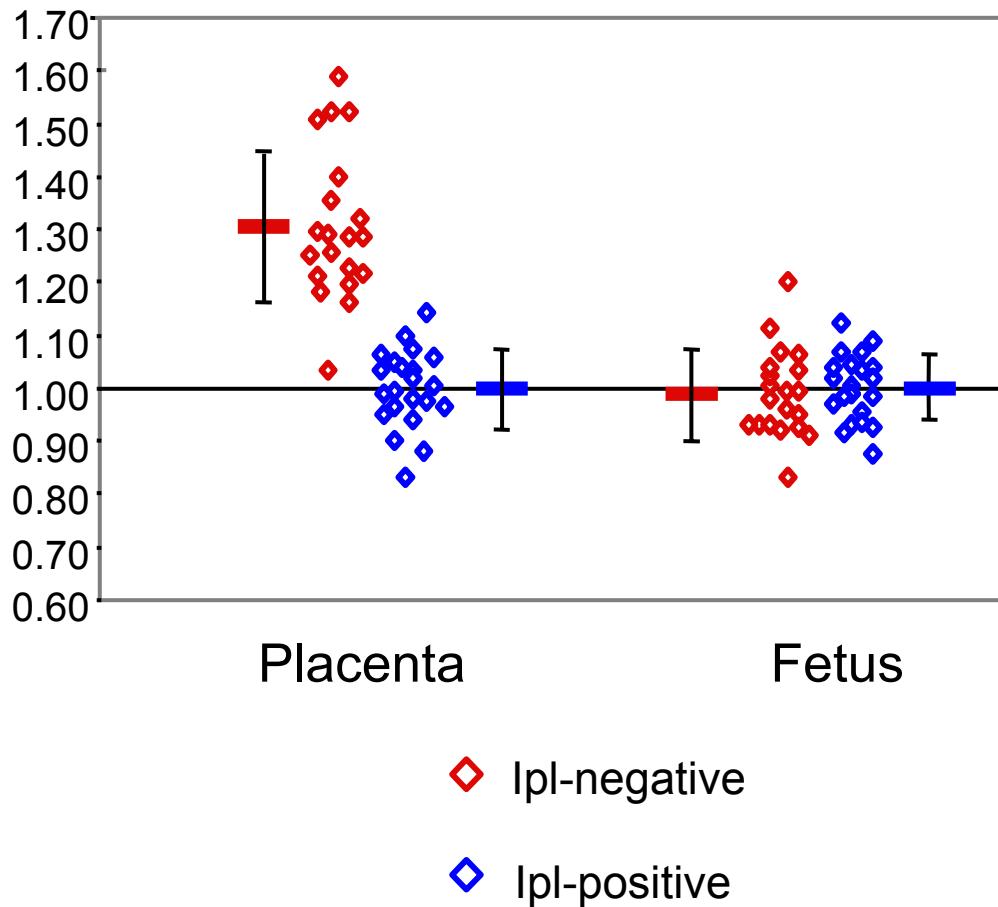


Ipl (imprinted gene): cDNA probe

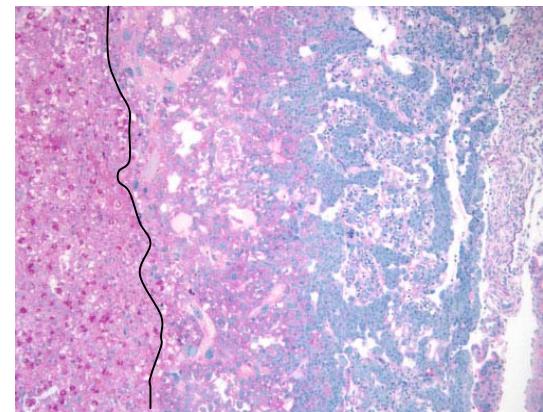


Actin probe

Placental Overgrowth in *Ipl* KO Mice

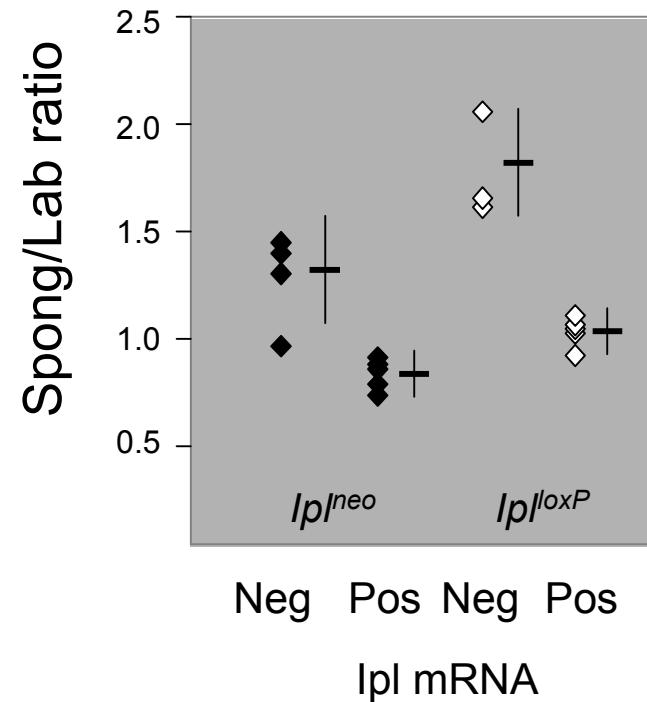
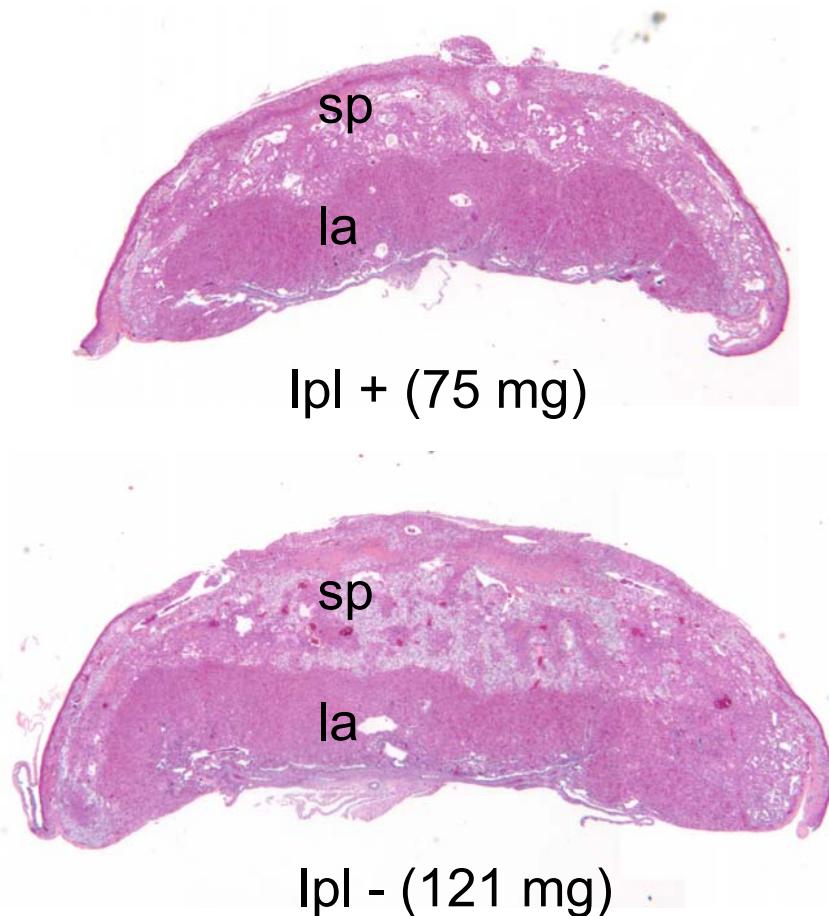


Ipl-positive

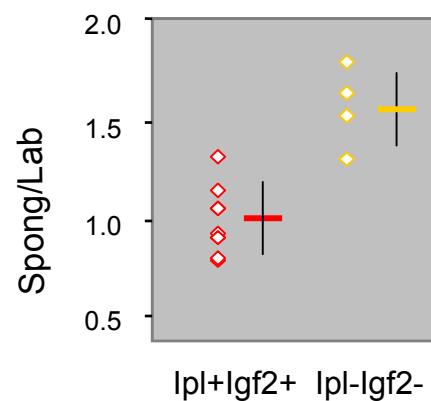
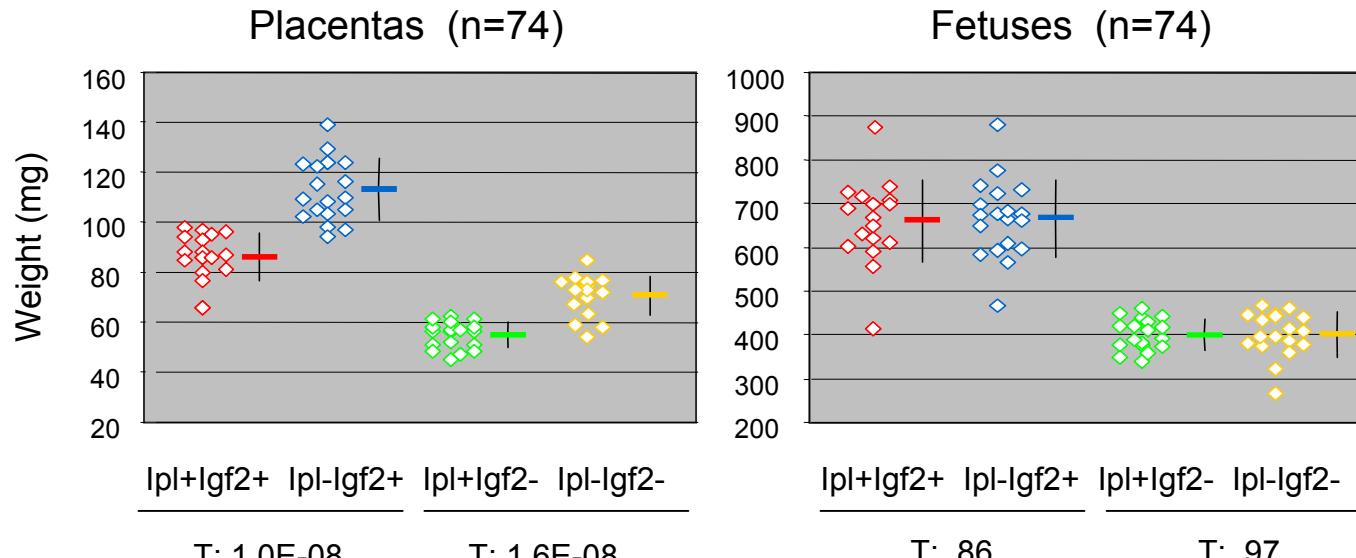


Ipl-negative

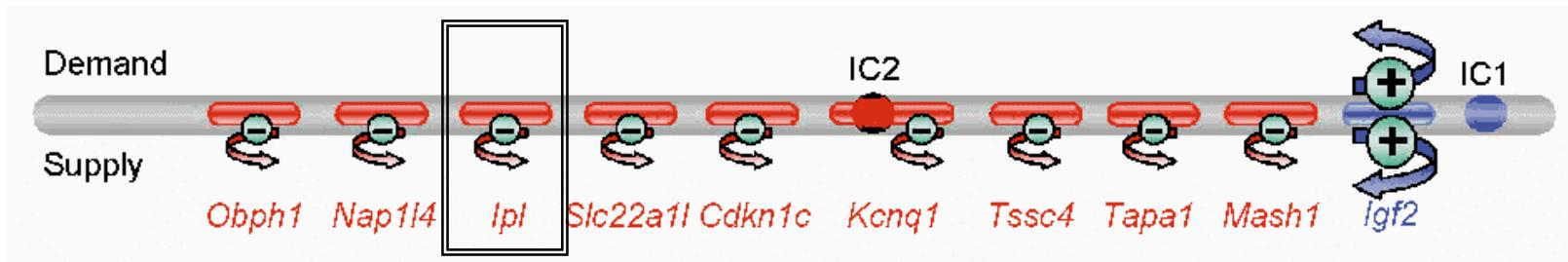
Expansion of Spongiotrophoblast in Ipl-null Placentas



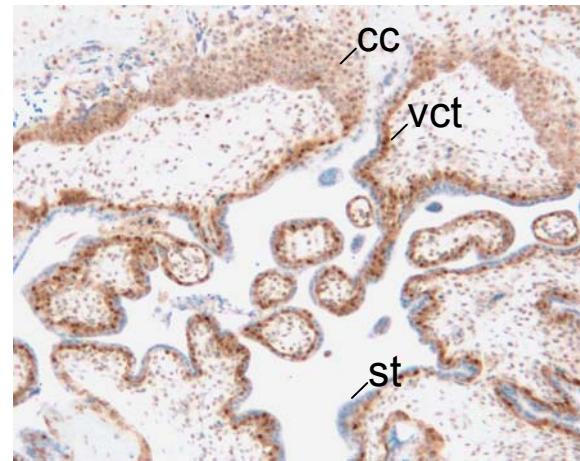
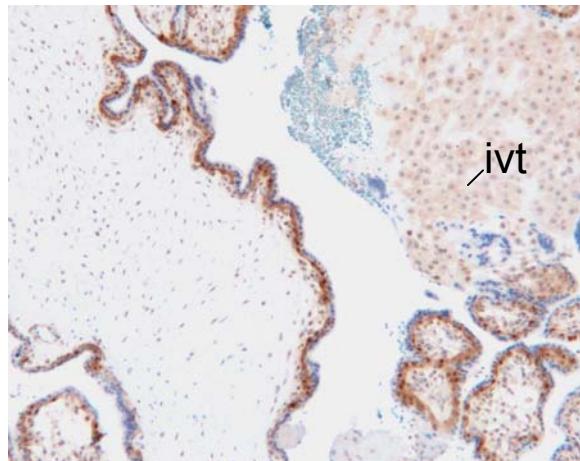
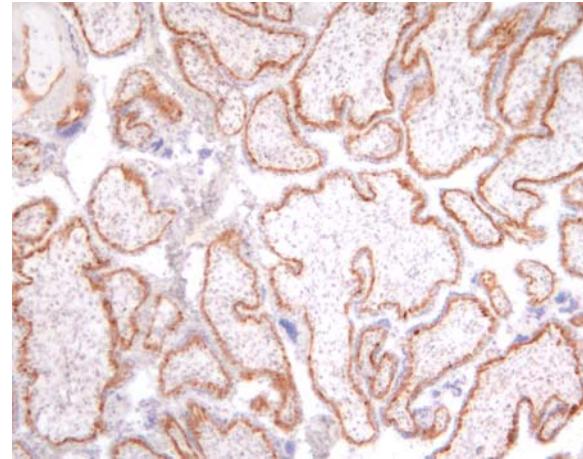
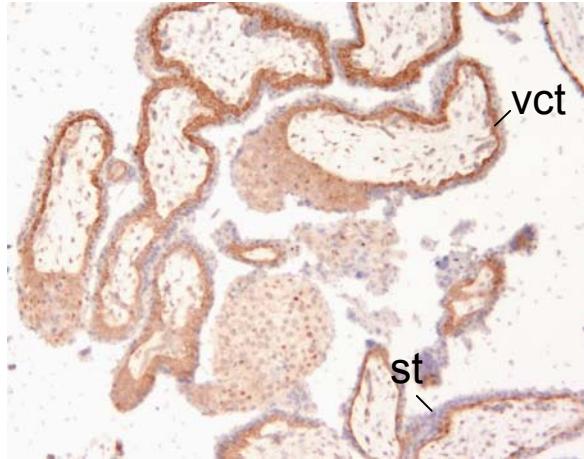
Ipl controls placental size independently of *Igf2*



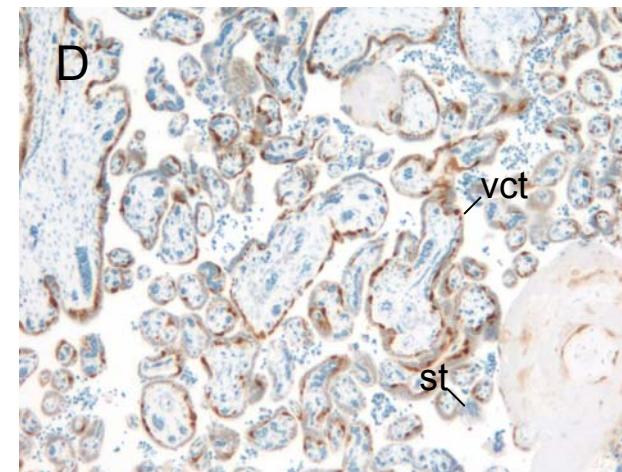
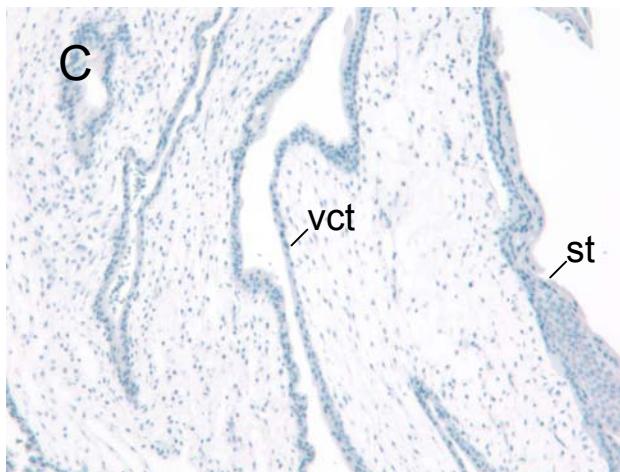
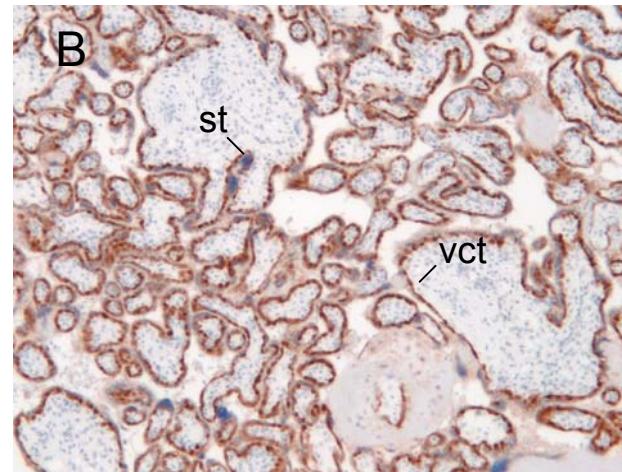
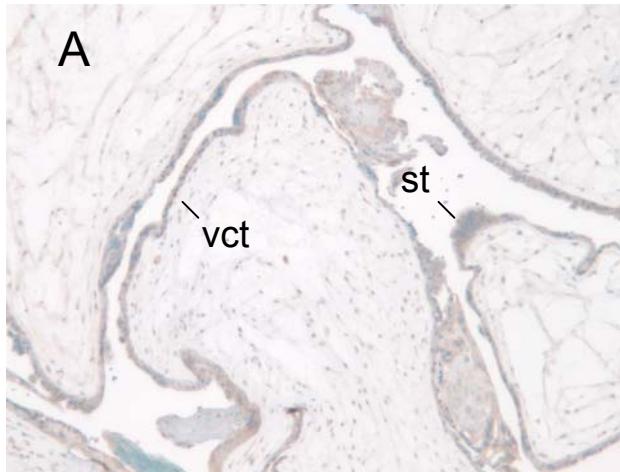
Ipl :maternal expression/paternal repression of a gene that restrains placental growth



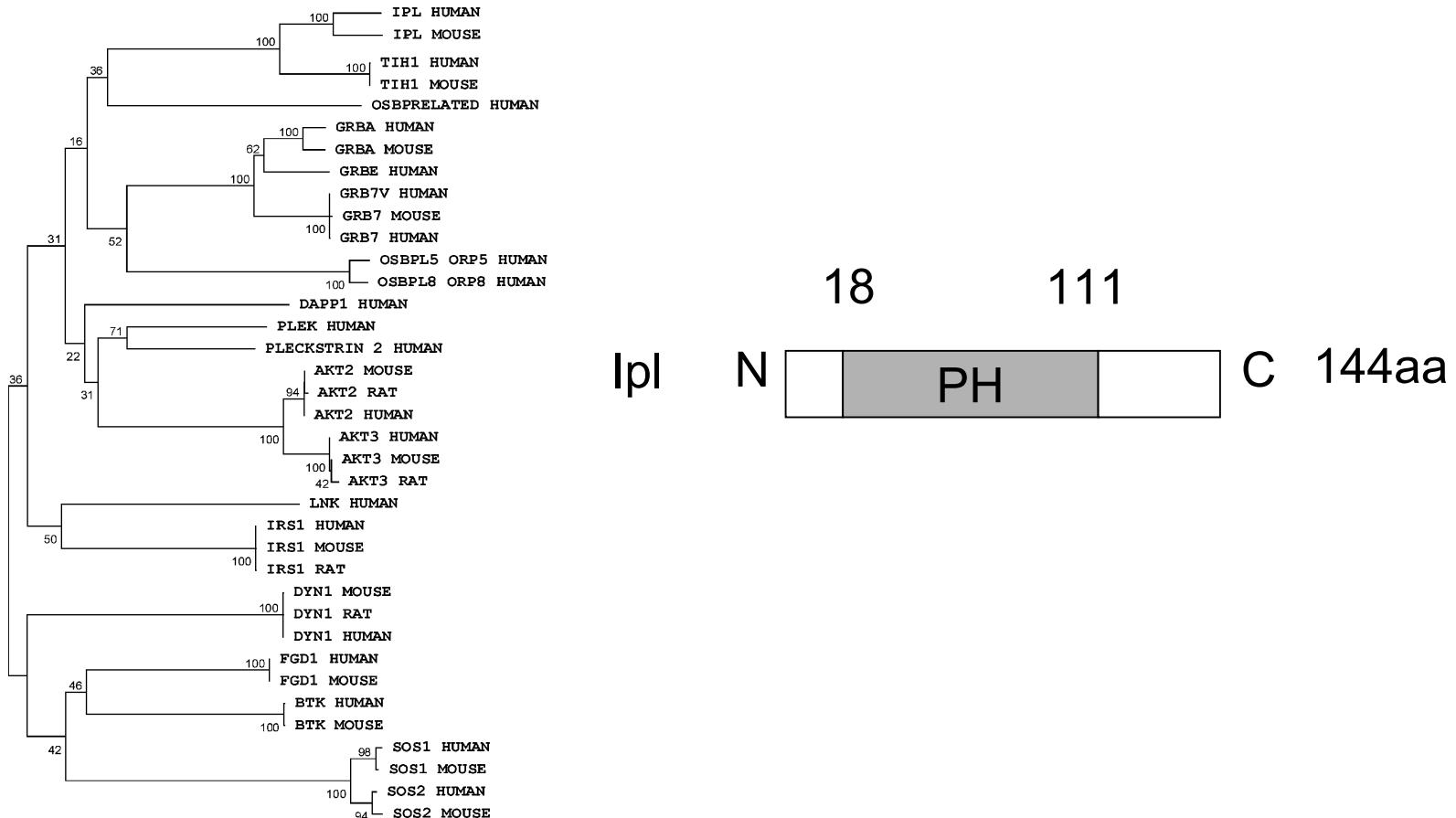
Human IPL marks villous cytotrophoblast



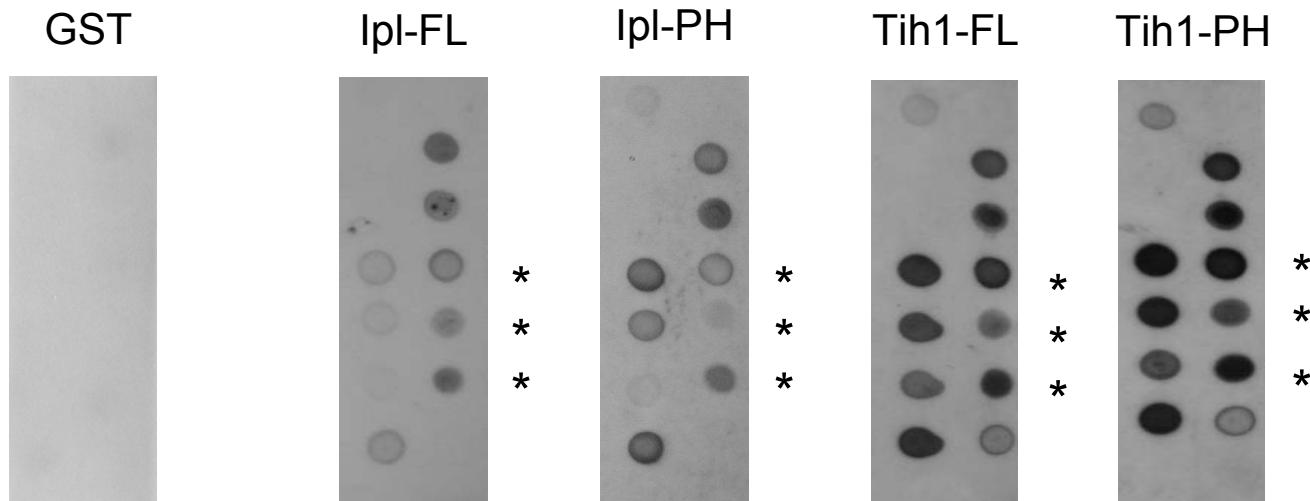
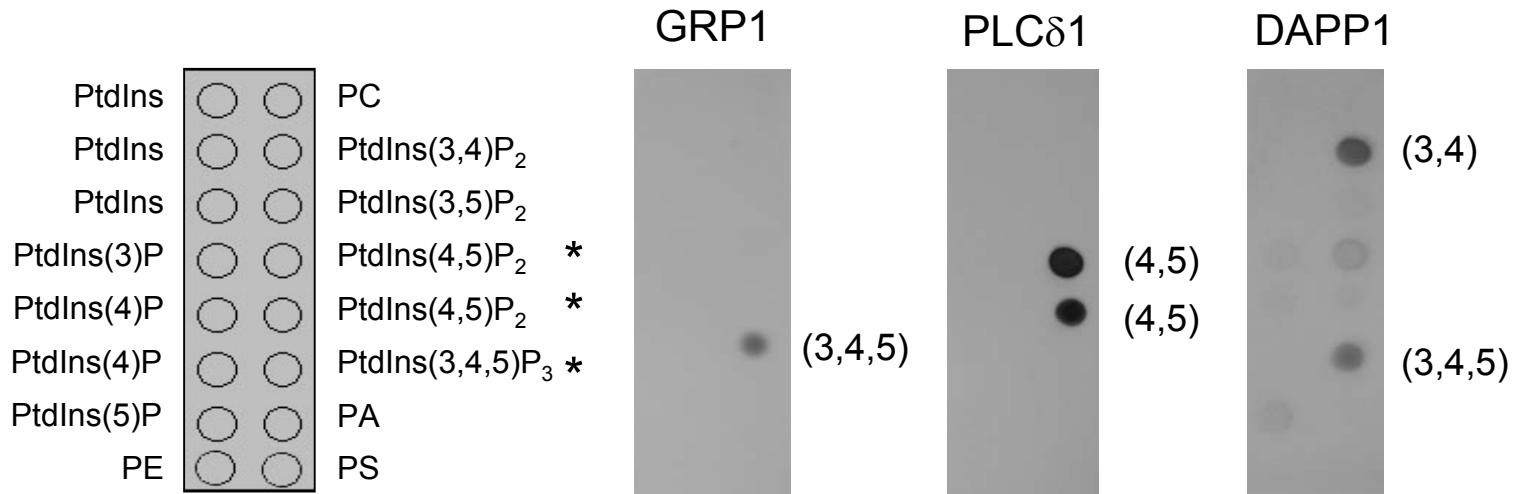
IPL is absent in hydatidiform moles



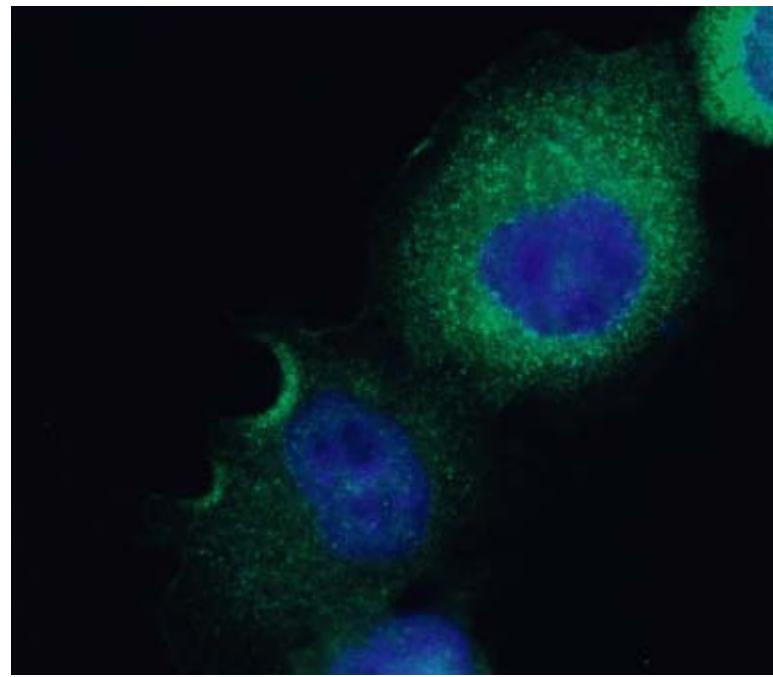
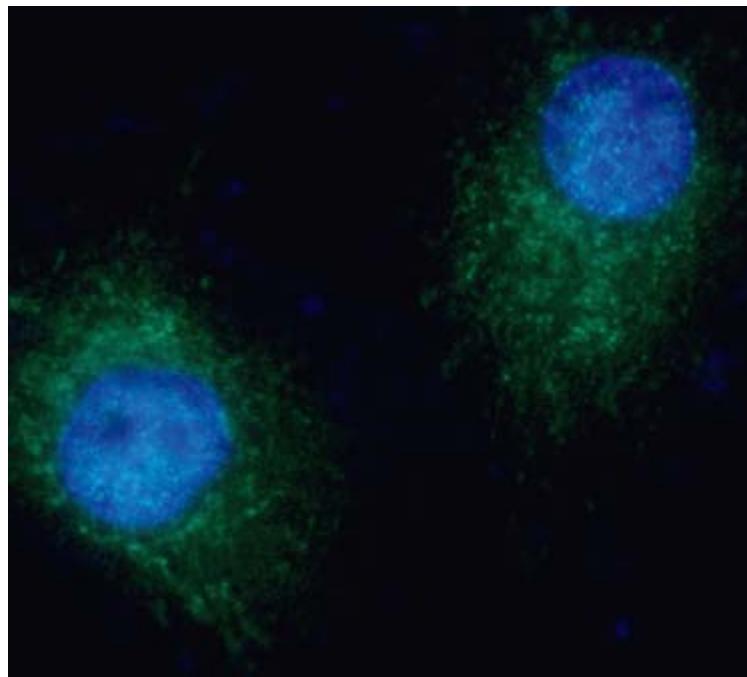
How does IPL inhibit placental growth?



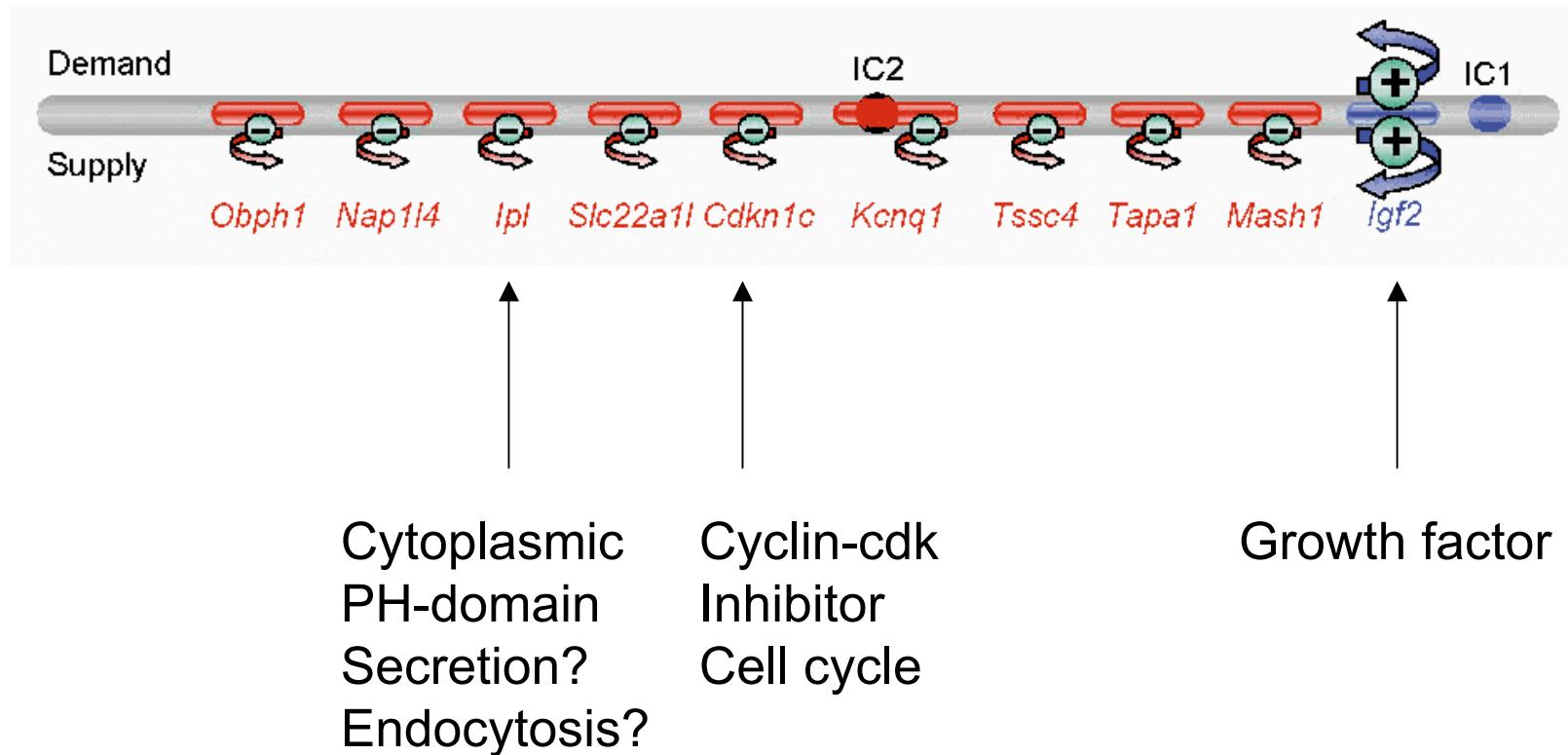
IPL is a bona fide PH-domain protein



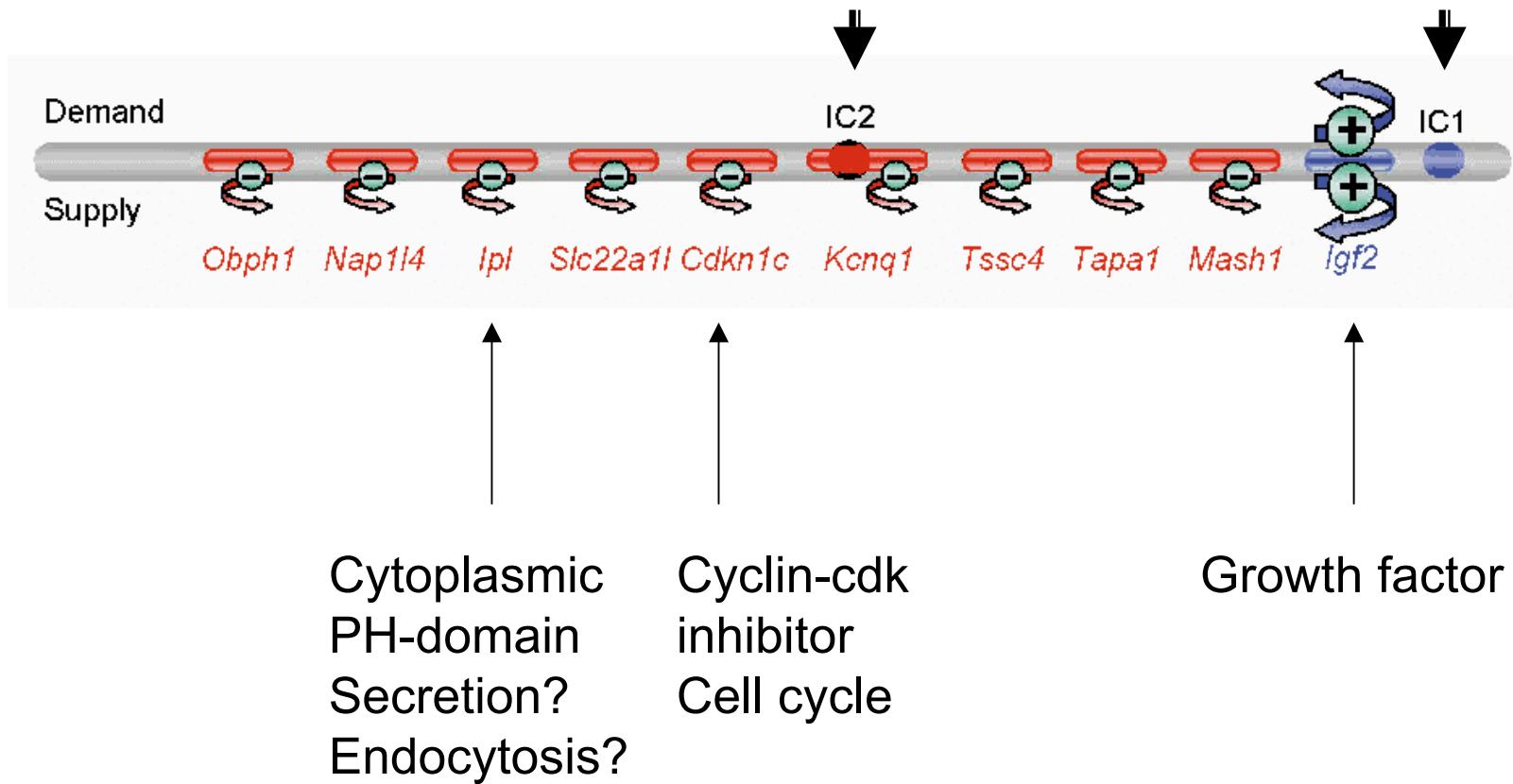
Punctate (vesicular) cytoplasmic distribution of IPL protein



Diverse biochemical pathways control supply and demand for maternal nutrients via imprinting



Q: Imprinting and IUGR?



References

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- Saxena A, Frank D, Panichkul P, Van den Veyver I, Tycko B, Thaker H (2003) The product of the imprinted gene IPL marks human villous cytotrophoblast and is lost in complete hydatidiform mole. *Placenta*, in press.
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