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Disruption of Imprinting and Abnormal Growth in Hybrids

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Disruption of Imprinting and Abnormal Growth in Hybrids

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Disruption of Imprinting and Abnormal Growth in Hybrid Mammals

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UNIVERSITY OF MONTANA

Parent-of-origin growth effects

Paternal Genes ⇧ Growth

Maternal Genes ⇩ Growth

Abnormal growth patterns in hybrids are often parent-of-origin specific, such as mules (large, female horse x male donkey) and hinnies (small, female donkey x male horse). This is thought to be caused by a dosage imbalance of growth related genes.

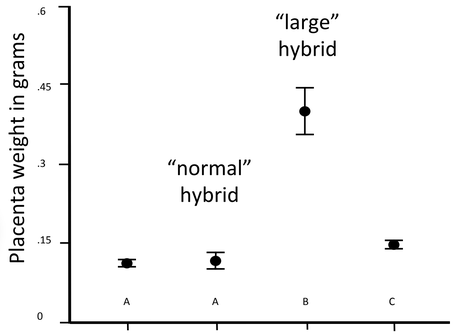
Dwarf Hamster as a Model System

Normal sized embryo and placenta

P. campbelli

Overgrown embryo and placenta

Large hybrid



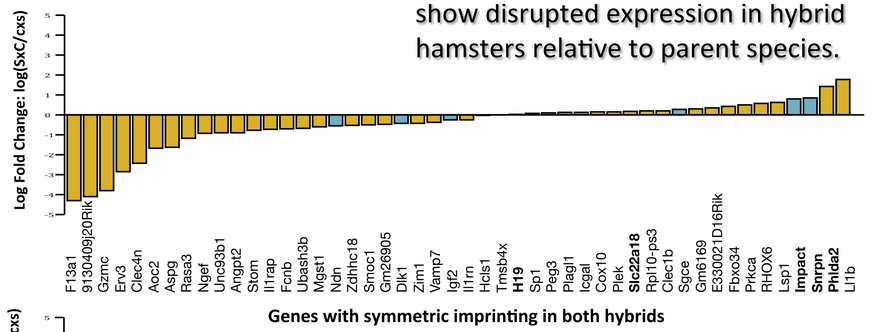
Brekke and Good 2014

Disrupted Imprinting in Hybrids

Maternally expressed genes

Paternally expressed genes

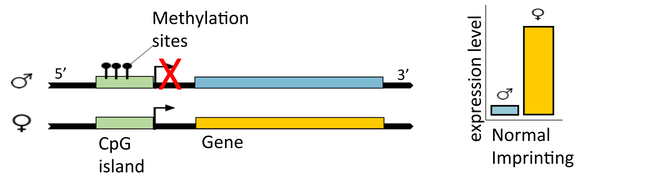
Imprinting causes allele specific expression. 69 of 88 imprinted genes show disrupted expression in hybrid hamsters relative to parent species.



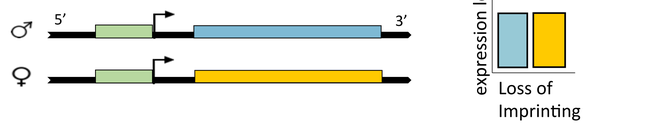
Brekke et al. 2016

Allele-Specific DNA Methylation

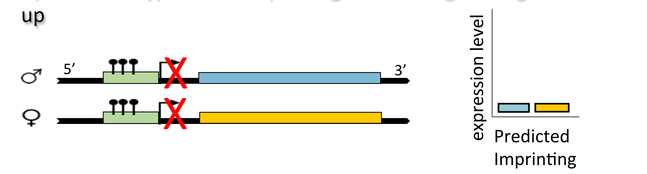
When a 'C' is followed by a 'G' in the genome, it may be methylated. Clusters of methylated 'C's are called CpG islands. These can alter gene expression levels.



A) Normal Imprinting Model: One allele is methylated and silenced



B) Previous Hypothesis: Imprinting is lost and growth genes turned up

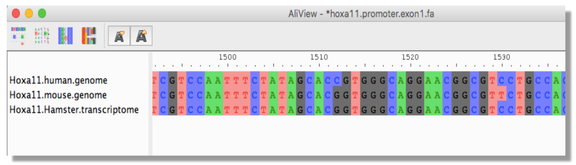


C) Current Prediction: Imprinting is gained on both alleles, silencing growth repressors and causing placental overgrowth

Methods: Testing for Differential Methylation Patterns Between Hybrid hamsters and Parent Species

Candidate Gene Search

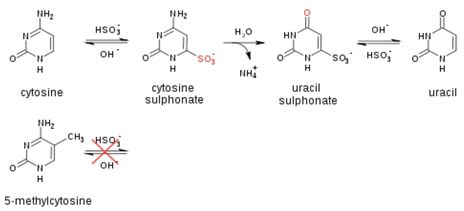
- Searched literature on all disrupted imprinted genes for evidence of CpG islands in other species
- Aligned gene sequences to find conserved regions for primer design



Lab Work

- Extracted DNA from placental tissue of parent species and reciprocal hybrids

- Treated extracted genomic DNA with sodium bisulfite to convert non-methylated 'C's to 'T's



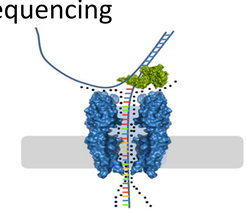
- Designed primers to isolate desired CpG island regions

ATAAA
5′TATUTTGACGTAUAUGTAG3′
ACATC

- Amplifed region using PCR

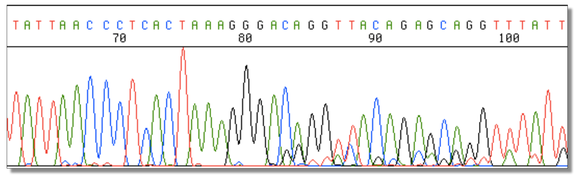
5′TATTTTGACGTATATGTAG3′
5′TATTTTGACGTATATGTAG3′
5′TATTTTGACGTATATGTAG3′
5′TATTTTGACGTATATGTAG3′

- Sequenced amplified regions using PyroMark Sequencing



Analysis

- Aligned sequencing reads of parent species and hybrids to compare differences in methylation status at specific sites (*in progress*)



Implications

Genome Evolution and Speciation

Molecular mechanisms that regulate development may play an important role in mammalian species formation. Imprinting regulation may contribute to postzygotic barriers that lead to speciation.

Human Health

Many of these genes are also found to be miss expressed in various types of cancer. Hybrid growth patterns are very similar to those found in rare but serious growth-related birth defects in humans, such as Beckwith-Weideman Syndrome.

Results/Conclusions

Studying DNA methylation in a non-model species faces many challenges. Nonetheless, my initial results have found several CpG islands around candidate genes that may control imprinting, and I have successfully designed primers for two of these so far.

Acknowledgements:

Erica Larson, Thomas Brekke, the Good lab, Alex Knox, Dan Vanderpool, the Breuner Lab

Funding:

The Tolle-Bekken Family Memorial Research Fund; Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health