

NC STATE
125 YEARS

Epigenetics and Fetal Programming and its Phenotypic Consequences

...not everything that is inherited is genetic
Boris Ephrussi, 1958

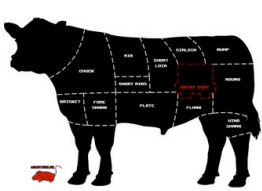
David Threadgill
Department of Genetics
North Carolina State University

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Bos mus musculus

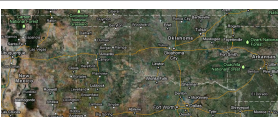
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Nucleic Acids Research, Vol. 18, No. 23 6935

Genomic analysis of the major bovine milk protein genes

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Received August 27, 1990; Revised and Accepted October 16, 1990

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Science

Between genes Gene

SNP difference

AAC(S)TCGAGGATCGTCTAG
TTG(C)AGCTCCTAGCAGATC

Allelic difference

AAC(A)TCGAGGATCGGTTAG
TTG(T)AGCTCCTAGC(AATC

Livestock Decoded

MAAS

GENESEEK
a Illumina Company





Epigenetics
epi = above/upon - genetics

Conrad Waddington, 1942
"... the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being."

The study of heritable changes in gene function that occur without a change in the DNA sequence.

Types of epigenetic regulation:

1. X-Chromosome inactivation in eutherian females
2. Parent-of-origin phenotypes (imprinting)
3. Heritable developmental or environmental effects ('epigenetics')

Each cattle cell has greater than 2 m (~6 feet) of DNA if stretched out linearly

How does DNA compact to fit within one of 60 cattle chromosomes in each cell?

Each muscle cell is 50 mm (~0.002 inch) in diameter

Chromosome

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Histones

Chromosome

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Epigenetic Modifications

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.

Histones

Chromosome

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Regulation of Epigenetic Marks

Writing

Acetylases, methylases, phosphorylases

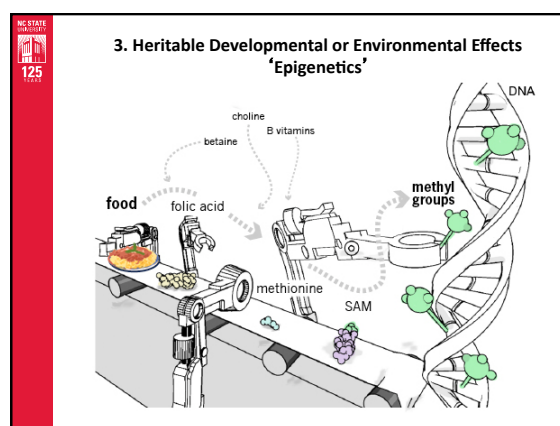
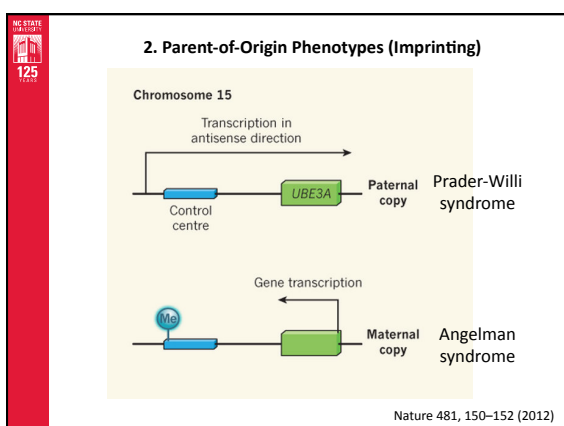
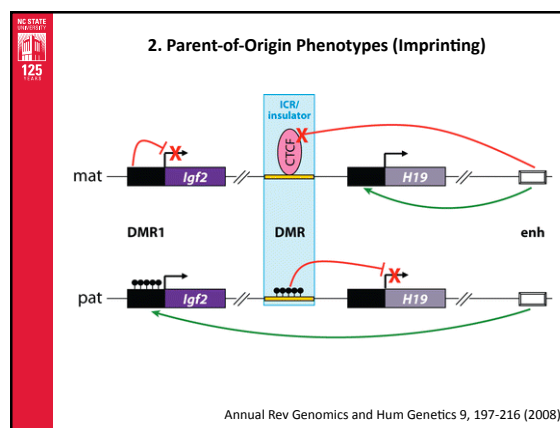
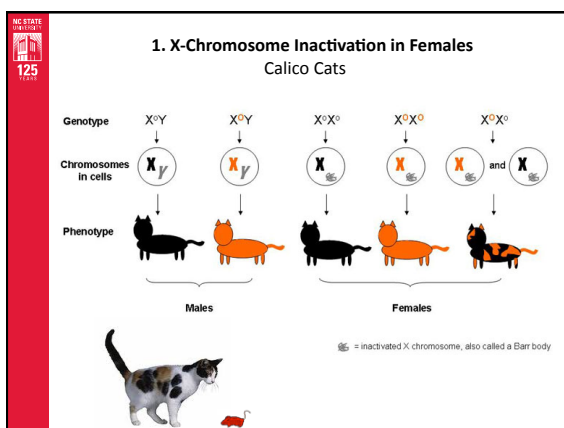
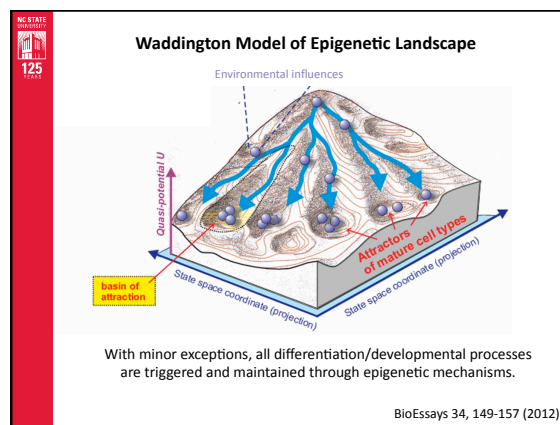
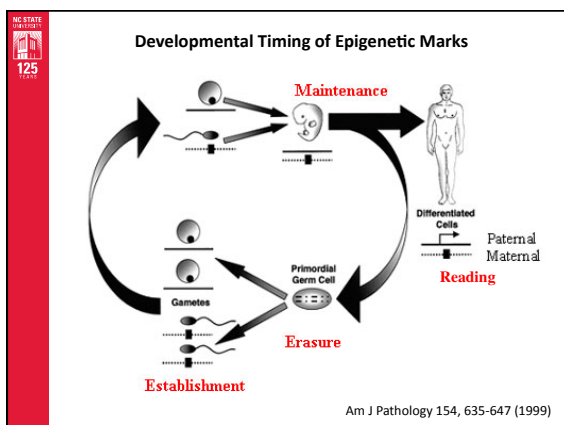
Erasing

Deacetylases, demethylases, phosphatases

Reading

Bromodomain, chromodomain, PHD finger, WD40 repeat

Nature Immunology 11, 565–568 (2010)



Epigenetic Changes at the Agouti Coat Color Gene

PNAS 104, 13056-13061 (2007)

Coat Color Serves as a Sensor for the Degree of Methylation Present at the Agouti Locus

Genetically identical, epigenetically different

Nature Genetics 23, 314-318 (1999)

Maternal Diet Can Cause Changes Lasting Into Adulthood of Offspring (Epimutation)

These Two Mice are Genetically Identical and the Same Age

The mother of this mouse received a normal mouse diet

The mother of this mouse received a diet supplemented with choline, folic acid, betaine and vitamin B12

Mol Cell Biol 23, 5293-5300 (2003)

Maternal Diet Can Cause Changes Lasting Into Adulthood of Offspring AND the Next Generation

PNAS 103, 17308-17312 (2006)

Humans also Show Diet-Induced Epigenetic Effects that Last Two Generations

WW II-related famine in the Netherlands (Nov, 1944-May, 1945) where some pregnant women received less than 1,000 calories/day.

Starvation during third trimester of pregnancy resulted in dramatic decline in birth weight.

Starvation during the second trimester of pregnancy resulted in increased incidence of schizophrenia.

An effect on birth weight and perinatal mortality was also observed in children of their daughters', but only on those daughters malnourished in the first or second trimesters of their own fetal development (and who were not underweight at birth).

Paediatr Perinat Epidemiol 6, 240-253 (1992)

Potential Epigenetic Effects of Stress


The stress hormone cortisol is involved in response to stress. Low levels detected in the saliva are associated with difficulties coping with stressful events, which may induce a Post Traumatic Stress Disorder (PTSD).

Pregnant women in their third trimester of pregnancy at the time of the attacks on the Twin Towers and who suffered with PTSD not only had low levels of cortisol but also their children were born with lower than normal levels of cortisol in their saliva as well.

This indicated that events during third trimester of pregnancy can change offspring's ability to cope with stress. Presumed, but not confirmed that this was an epigenetic change.

Journal of Clin Endocrin and Metab 90, 4115-4118 (2005)

Don't Count Out the Importance of Dad (Sire)



The remote Swedish town of Overkalix has an extensive archive of population records, including all births and deaths of people who have lived there and, crucially, annual harvest information going back hundreds of years.

An analysis of hundreds of years of these records showed that food availability between the ages of 9 and 12 for the paternal grandfather affected the lifespan of his grandchildren. Surprisingly, shortage of food for the grandfather was associated with extended lifespan of his grandchildren.

Food abundance, on the other hand, was associated with a greatly shortened lifespan of the grandchildren. Early deaths were the result of either diabetes or heart disease.

Eur J Hum Genet 14,159-166 (2006)

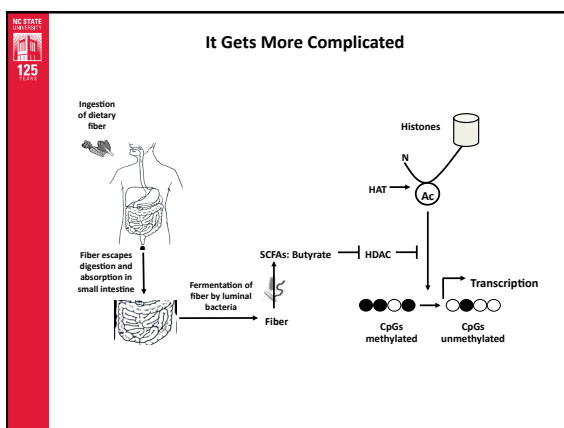
Sci Transl Med 15 September 2010;
Vol. 2, Issue 49, p. 49ra67
Sci. Transl. Med. DOI: 10.1126/scitranslmed.3001262

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RESEARCH ARTICLE

EPIGENETICS
Personalized Epigenomic Signatures That Are Stable Over Time and Covary with Body Mass Index

Andrew P. Feinberg^{1,2,3,4}, Rafael A. Irizarry^{1,3,5}, Delphine Fradin^{1,2,3,4}, Martin J. Aryee^{1,4}, Peter Murakami^{1,2}, Thor Aspelund^{5,6}, Gudny Eiriksdottir⁵, Tamara B. Harris⁷, Lenore Launer⁷, Vilundur Gudnason^{5,6} and M. Daniele Fallin^{1,4,8}



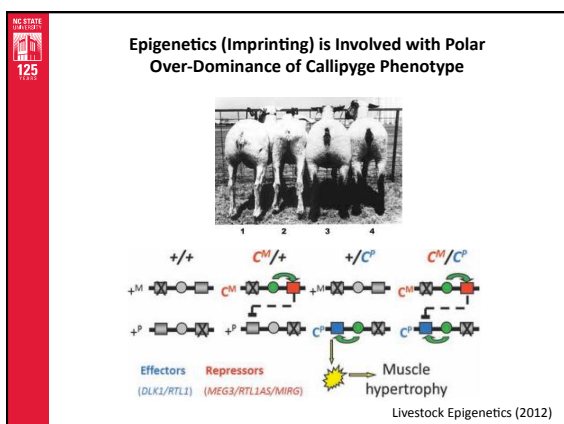
Is Epigenetics Relevant to Livestock?

BMC Developmental Biology


Research article
Aberrant epigenetic changes and gene expression in cloned cattle dying around birth

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* Corresponding author *Equal contribution



Epigenetics Impacts Production Traits



When boars are fed a methyl supplemented diet and are mated with control sows for two generations, their F2 offspring keep a higher level of DNA methylation in their muscle associated with a higher back fat thickness.


Also differences in mRNA levels for muscle, liver and kidney and a trend towards a higher percentage in shoulder and adipose tissue are shown.

Changes in methylation status of *Irf1* (Interferon regulatory factor 1, involved in thyroid hormone production) observed in offspring.

PLoS ONE 7, e30583 (2012)

Overfed Ewes Have Overweight Offspring that Persists for at Least Two Generations

Group of pregnant ewes fed 150 percent of their required diet.



The offspring were predisposed to have a shorter length from rump to crown and increased body fat. While they spent the same amount of time feeding as control sheep, the test sheep ate more food, faster. The offspring of obese sheep had higher glucose levels but more resistance to insulin.

Offspring of the sheep in the first trial were then fed just 100 percent of their required diet, an amount which did not promote obesity. Again, the offspring (third generation) showed differences in body length and body fat.

JAM Preconference Symposium (2011)

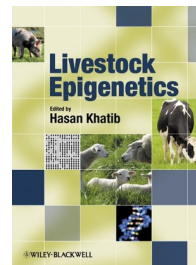
frontiers in GENETICS

OPINION ARTICLE
published: 28 January 2012
doi: 10.3389/fgen.2011.00106

Epigenetics: a new challenge in the post-genomic era of livestock

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*Correspondence: gonzalez.oreico@inia.es




What Are the Potential Impacts on Beef Cattle?

Propagation of epigenetically-influenced enhancements or impairments by sires used as semen donors (probably biggest impact could be in seedstock)

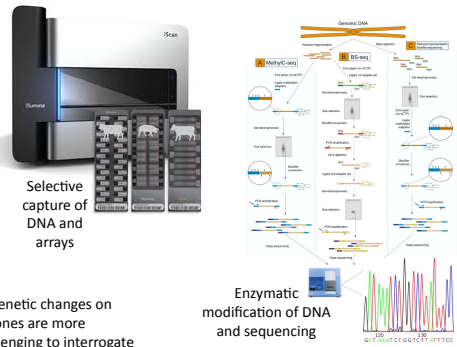
Alteration of calf body composition and feed efficiency by type and quantity of feed eaten by cows

Transgenerational changes in average body composition and feed efficiency in cattle whose sires or dams (or their sires/dams) were under stress (heat, nutritional, physical, behavioral, etc)

Stay tuned-ultimate impact of epigenetics on production has yet to be determined



Technologies for Epigenetic Typing

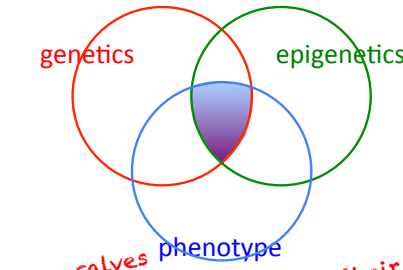


Selective capture of DNA and arrays

Epigenetic changes on histones are more challenging to interrogate

Enzymatic modification of DNA and sequencing

genetics **epigenetics**



phenotype

Your calves *their*

~~You~~ not only inherit genes from ~~your~~ grandparents, but also the consequences of their diet and lifestyle