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# Challenges in livestock genomics

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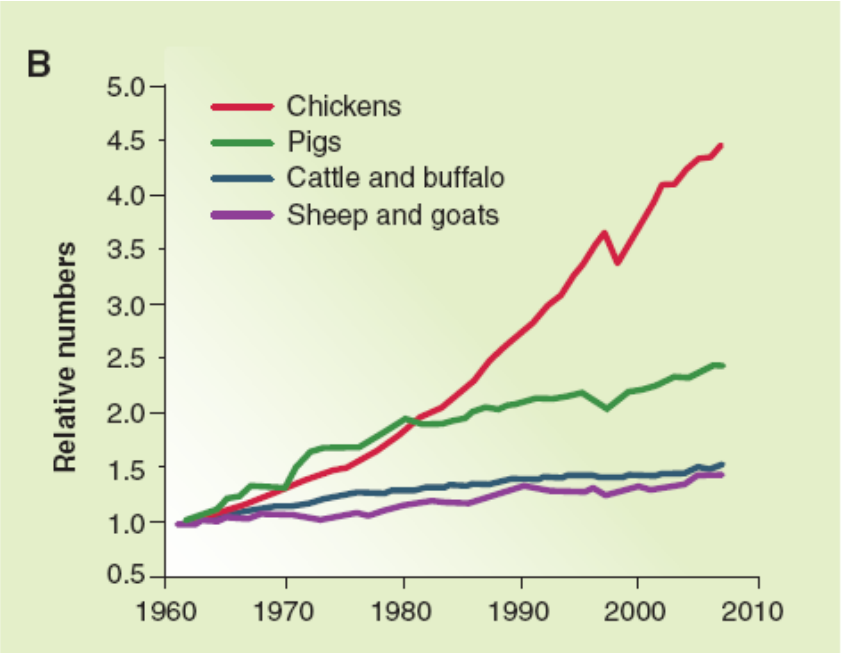
# Livestock production is faced with an enormous challenge

**The world will need 70 to 100% more food by 2050**

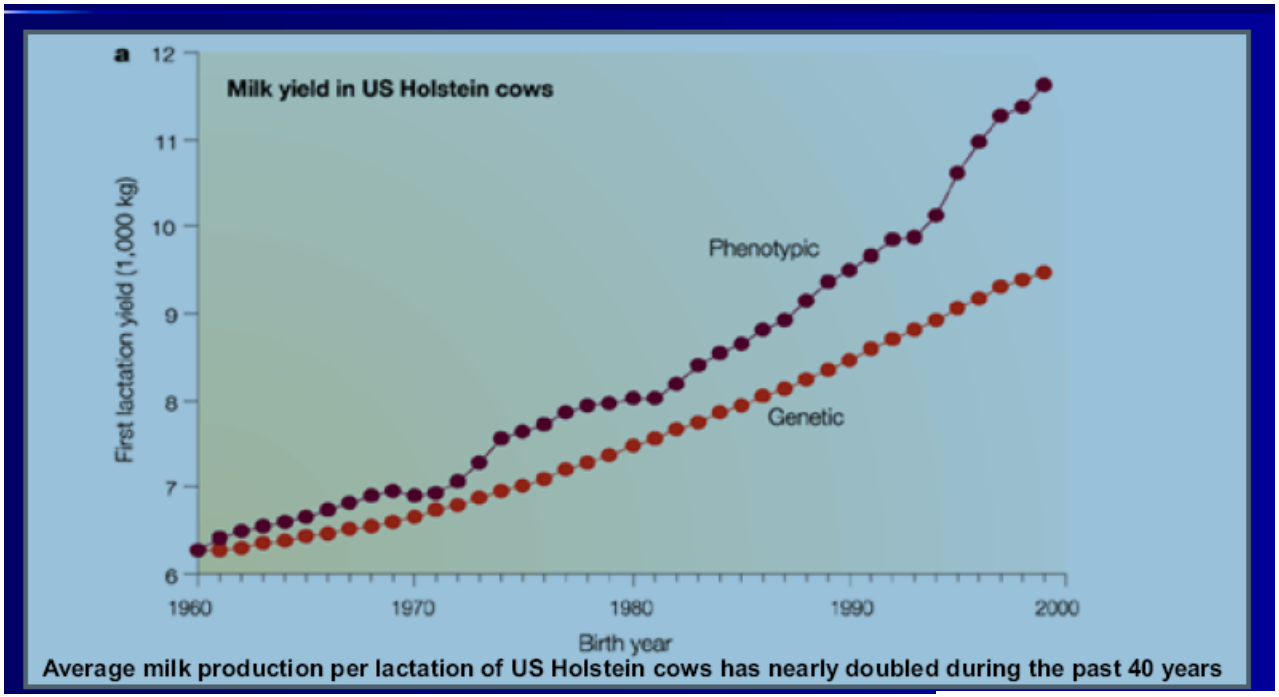



**Aquatic products provides nearly 3 billion people with at least 15% of their animal protein intake**

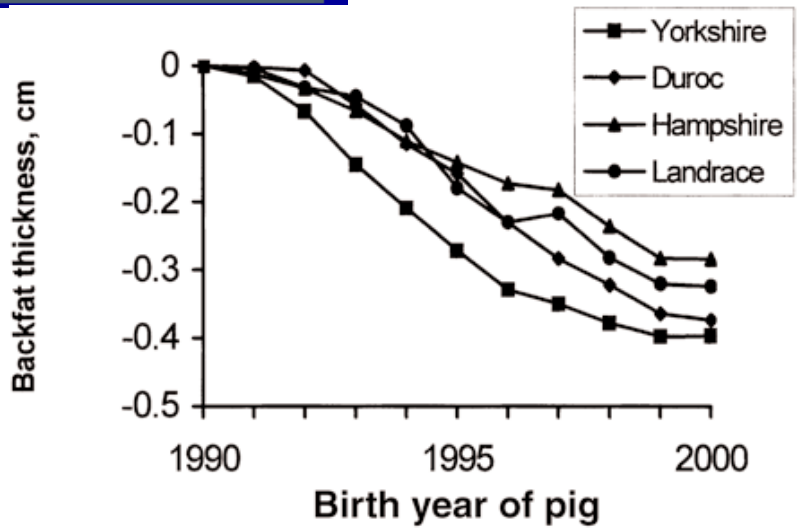
**Together with**

- ***agriculture sustainability***
- ***animal well-being***
- ***environmental concerns***

# Traditional animal breeding can be very successful



Average milk production per lactation of US Holstein cows has nearly doubled during the past 40 years



# *The advances in animal nutrition have also been quit important*

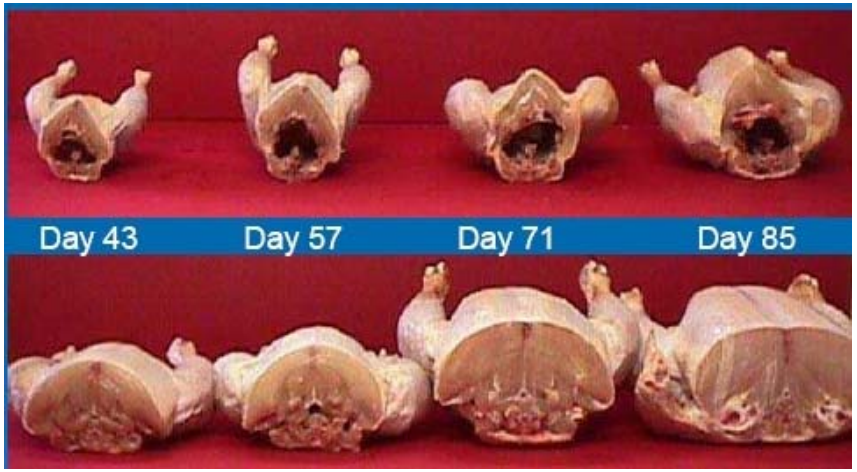
| | *Diet 1957* | *Diet 2001* |
|---|---|---|
| ***Strain 1957*** | **1715** | **1907** |
| ***Strain 2001*** | **4661** | **5958** |

**Diet increases body weight by 5-10%**

**Genetics increases body weight by 150-200 %**

1957

2001



# The genome era

**The molecular genetics revolution in the 1980s and 1990s led to the emergence of a new scientific discipline, genomics, resulting from the convergence of**

**Genetics**

**Molecular biology**

**Bioinformatics**

# *The "Omics" Era:*

- **Genetics** → ***Genomics***
- **Transcription** → ***Transcriptomics***
- **Protein** → ***Proteomics***
- **Metabolite** → ***Metabolomics***
- **Epigenetics** → ***Epigenomics***
- **Nutrition** → ***Nutrigenomics***

# The Human Genome Project

**All 3 billion base pairs of human DNA have been sequenced**

***What have we learned?***

- ***Human genome encodes for ~20,000 genes***
- ***Only 2% of our genome codes for proteins***
- ***We only know the function of ½ of our genes***
- ***99.9% of bases in DNA are alike between humans***

# *Genome sequencing of domestic species*

2004

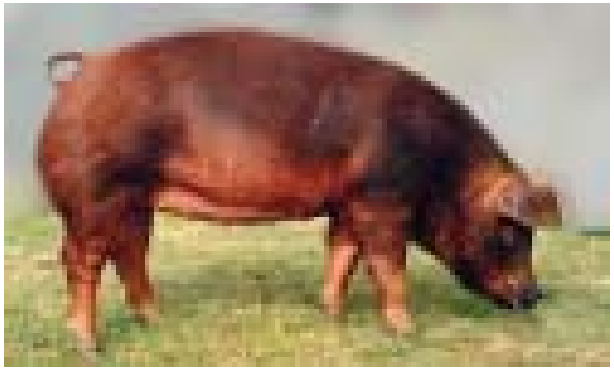

2005


2007

2009


2009

2010



# Molecular Biology has influenced Animal Breeding

- Providing genetic maps of domestic species

- Finding some individual genes with effect on production traits

- Facilitating QTL detection

# QTL detection in domestic species

**In the 90 starts the QTL detection experiments in pigs,cattle, chicken and sheep initially from crosses between divergent lines and afterwards in commercial populations**

**This activity has been very successful**

# QTL detection has been highly successful

PigQTLdb — **6,344 QTLs representing 593 traits**

CattleQTLdb — **4,682 QTLs representing 376 traits**

ChickenQTLdb — **2,451 QTLs representing 248 traits**

SheepQTLdb — **454 QTLs representing 152 traits**

**http://www.animalgenome.org/QTLdb/**

*July, 2011*

# Major Quantitative Trait Loci Affect Resistance to Infectious Pancreatic Necrosis in Atlantic Salmon (*Salmo salar*)

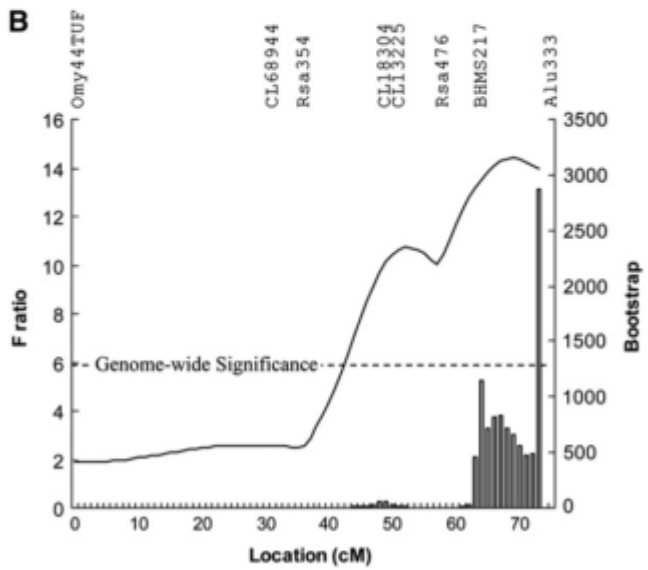




FIGURE 1.—The likelihood profile for linkage group 21 following the sire-based genome scan (A) and the dam-based QTL positioning with additional markers (B).

## *Differences in IPN mortality (%) between QTL genotypes*

| | *Sire QTL haplotype* | |
|---|---|---|
| *Dam QTL haplotype* | **Resistant** | **Susceptible** |
| **Resistant** | **9** | **62** |
| **Susceptible** | **22** | **84** |

# After detecting a QTL the next task is to locate the gene responsible (causal mutation)

**In QTL detection studies we can locate one QTL in a chromosome as a region of about 20-40 cM (200-400 genes)**

# However, although is easy to find QTLs to locate the responsible gene is a formidable task

***There has been some succesful stories***

**DGAT1**

***ABCG2*** } ***milk composition in cattle***

**IGF2** ***muscle mass in pigs***

**MSTN** ***muscle mass in sheep***

# To locate the resposible gene is a formidable task

**Example**

**The first QTL reported in livestock was FAT1 QTL located in swine chromosome 4 (Andersson et al.,1994)**

**However, its causal mutation is still unknow**

**In pigs >6000 QTLs but <10 causative mutations**

# One of the main motivations for QTL detection in domestic animals is Marker Assisted Selection (MAS)

*The usual way of thinking of Marker Assisted Selection*

**Detect one or several QTLs**

⇩

**Find the gene responsible (causal mutation)**

⇩

**Increase the frequency of the favorable allele**

***-selection -introgression***

# The impact of Marker Assisted Selection in livestock breeding programmes has been modest

- many QTL affect a typical quantitative trait

- the known causal polymorphisms explain only a small proportion of genetic variance of the breeding objective

# *However, now large panels of SNPs in domestic species are available*

Change in one nucleotide of the DNA sequence

Alelo A **a a a c c a g t c a a c t a c t a g.....**

Alelo B **a a a c c g g t c a a c t a c t a g.....**

**High-density SNP (commercial) platforms**

| | |
|---|---|
| **Cattle** | **50,000 (800,000)** |
| **Sheep** | **56,000** |
| **Goat** | **50,000** |
| **Pigs** | **60,000** |
| **Horses** | **55,000** |
| **Dogs** | **125,000** |
| **Chicken** | **60,000** |
| **Salmon** | **15,000** |
| **Human** | **1 000,000** |

***Cost: 100-200 $ /chip***

# A more radical proposal: GENOMIC SELECTION

**Two-step process**

**1)** ***Estimate the effects of markers (>50000 SNPs) in a reference (training) populations*** **that has been phenotyped and genotyped**

**2)** ***Use this information to predict the breeding value of candidates to selection*** **in a testing (evaluation) population that has been only genotyped (>50000 SNPs)**

# GENOMIC SELECTION

**Difference with MAS**

**1)** ***MAS concentrates on few QTLs with well verified association with markers***

**2)** ***Genomic selection uses a genome-wide panel of dense markers so that all QTLs are in LD with at least one marker***

# GENOMIC SELECTION has met with a lot of enthusiasm and some breeding companies are re-designing the breeding program

- **With genomic selection, we can potentially predict the breeding values with an accuracy of 0.8 for selection candidates at birth**

- **Consequently we can select animals at an early age**

**GENOMIC SELECTION is expected to double the rate of genetic improvement per year**

# Dairy cattle

**Until now many bulls have been genotyped.**

- ***> 16.000 from Eurogenomics (FR+DE+NL+DK)***
- ***> 10.000 from CAN+US***

**In January 2009, US produce the first official genetic evaluation including genomic data**

**Nowdays, there are oficial genomic evaluations in FR, NL, DE, DK, NZ..**

# Dairy cattle

## Future potential applications

***-selection of replacement heifers on farms that use sexed semen***

***-genomic screening of young bulls or potential bull dams***

***-optimal mate selection***

***-genome based management protocols***

## Beef cattle

-it could be important for traits that are difficult to record (behaviour, longevity, meat quality..)

-there are problems for creating a reference population

## Poultry breeding

-increased accuracies of EBV up to two-fold for selection in layers at an early age and by up to 88% for selection at a later age

## Pig breeding

-genetic gain increased by 23% - 91% for maternal traits

## Fish breeding

-no dense marker maps available

-important for traits that are tested on the sibs of the candidates (disease resistance)

# Genomic selection for new objectives

*- a quick adaptation to a climatic change scenario where dairy faming may be more dependent on pasture instead of grain (select bulls to generate daughters that will be productive at low levels of feeding)*

*- select for lower GHG (green-house gas) emissions in species, but especially in cattle and sheep where feed efficiency is not currently measured*

# *Problems in genomic selection*

1) **How to combine genomic and traditional breeding values when many animals are not genotyped?**

2) **Which is the best statistical methodology ?**

**GBLUP**

**Bayes A, B, C,...**

**Lasso, Bayesian Lasso,..**

**Semiparametric methods,..**

**Maching-learning methods,**

# *Problems in genomic selection*

**3) How to deal with non additive effects?**

***allocate matings that profit from non-additive gene effects***

**4) and GxE interactions?**

***create genotypes optimized for specific environments***

**5) Which type of genetic variability affect phenotypic traits?**

## *For higher accuracies in genomic selection:*

**-many more SNPs are needed**

- **denser SNP panels (DNA sequences in the future) will include causal mutations**
- **to produce prediction equations that work across generations and across breeds**
- **to mitigate the decay of associations under selection**

## *For higher accuracies in genomic selection:*

**-many more phenotypes are needed (phenomic gap)**

- **cooperation between breeders and competing companies (Interbull) ?**
- **difficult to measure traits: resistance to disease and stress, adaptability, longevity, nutrition efficiency, heat tolerance…**
- **‘Animal Trait Ontology’ inititiative to make the of phenotypic information more easy**

# Are there new sources of genetic variation?

1) Variation in copy number (CNV)

2) MicroRNAs (miRNA)

3) Epigenetic effects

# 1) Variation in copy number (CNV)

**Segment of DNA in which copy-number differences have been found by comparison of two or more genomes**

**>1000, 135 and 161 CNV regions detected in cattle, sheep and goat**

- some found in multiples animals
- differences across breeds
- there is overlap between sheep and goat species
- in cattle they are related to immunity, lactation, reproduction, and rumination

**>100 CNV pigs**

- related to sensory perception

**>100 CNV chicken**

-15 related to functional genes

# 2) MicroRNAs (miRNA)

**Single-stranded RNA molecules of 21-23 nucleotides in length, which regulate gene expression**

**Pigs: 120 miRNAs**

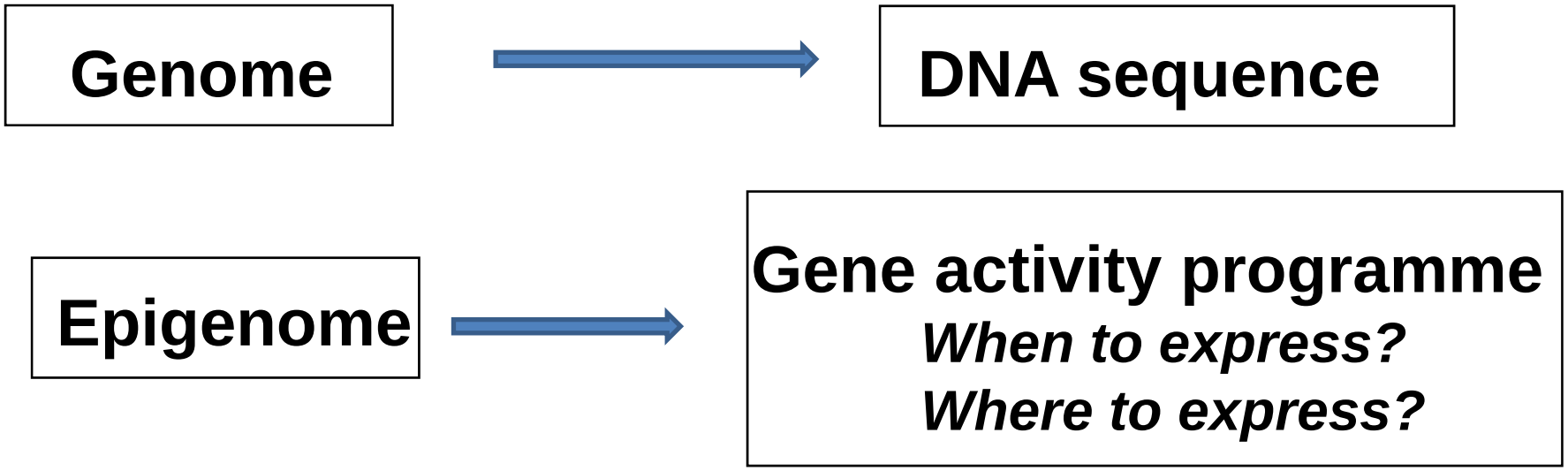
**Cattle: 228 miRNAs**

**Chicken: 609 miRNAs the majority especif of bird especies**

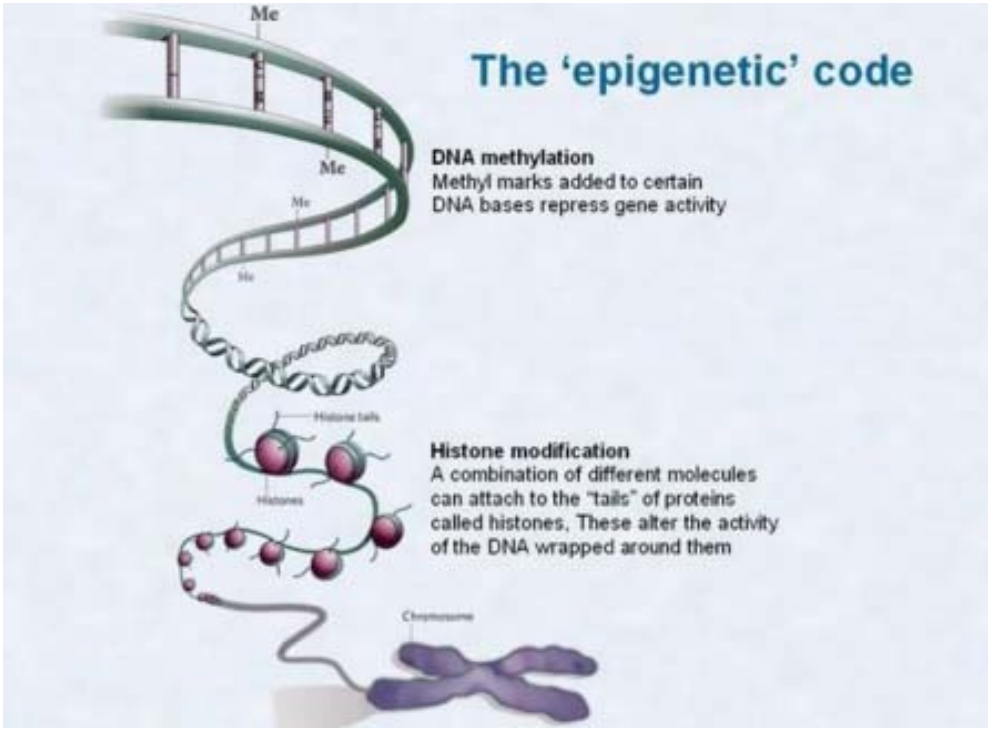
**-skeletal muscle, adipose tissue, reproduction, and feed efficiency**

# 3) Epigenetic effects

**Changes in the phenotype (or gene expression) that are not caused by changes to the underlying DNA sequence and that can be heritable**



# Why the cells of an organism, with the same DNA, are different?

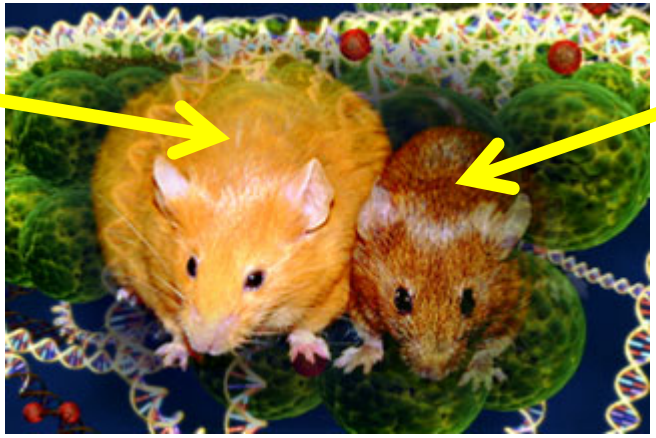



**Epigenetic mechanisms typically comprise**

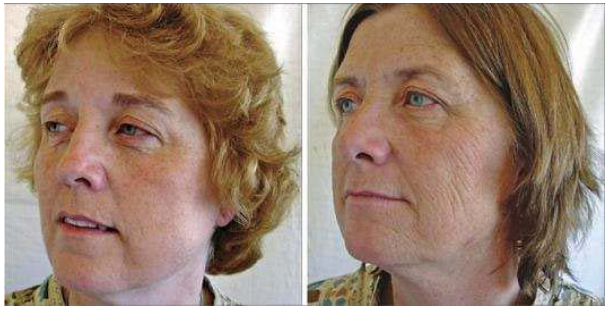
- ***DNA methylation***
- ***Histone modifications***

# Why twins, with the same DNA, are different (or become) different?

**Agouti gene unmethylated** **Agouti gene methylated**



**Identical sisters**



**-Discordant human twins are considered a valuable resource to study common diseases**

**-Cattle twins?**

# *Why individuals, with the same DNA, are completely different?*


***Which is the role of the royal jelly?***

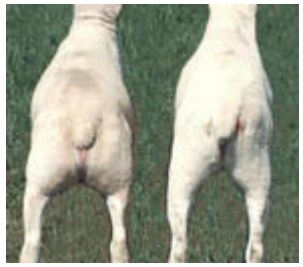
**When the gen DNMT3 (DNA methyl-transferase) is active in larvae the queen genes are silenced and larvae are developed as workers**

**The royal jelly (royalactine protein) silences DNMT3 and the queen genes are active and larvae are developed as queens**

# Why only one of two copies of some genes are expressed in the offspring?

## *Genomic imprinting*

**The ovine callipyge phenotype: only heterozygous animals with the mutation inherited from the sire exhibit the muscular hypertrophy**



**-about 1% of genes in human and mouse are imprinted**

**- Imprinted genes accounts for 8-25% of genetic variance for many traits in beef cattle**

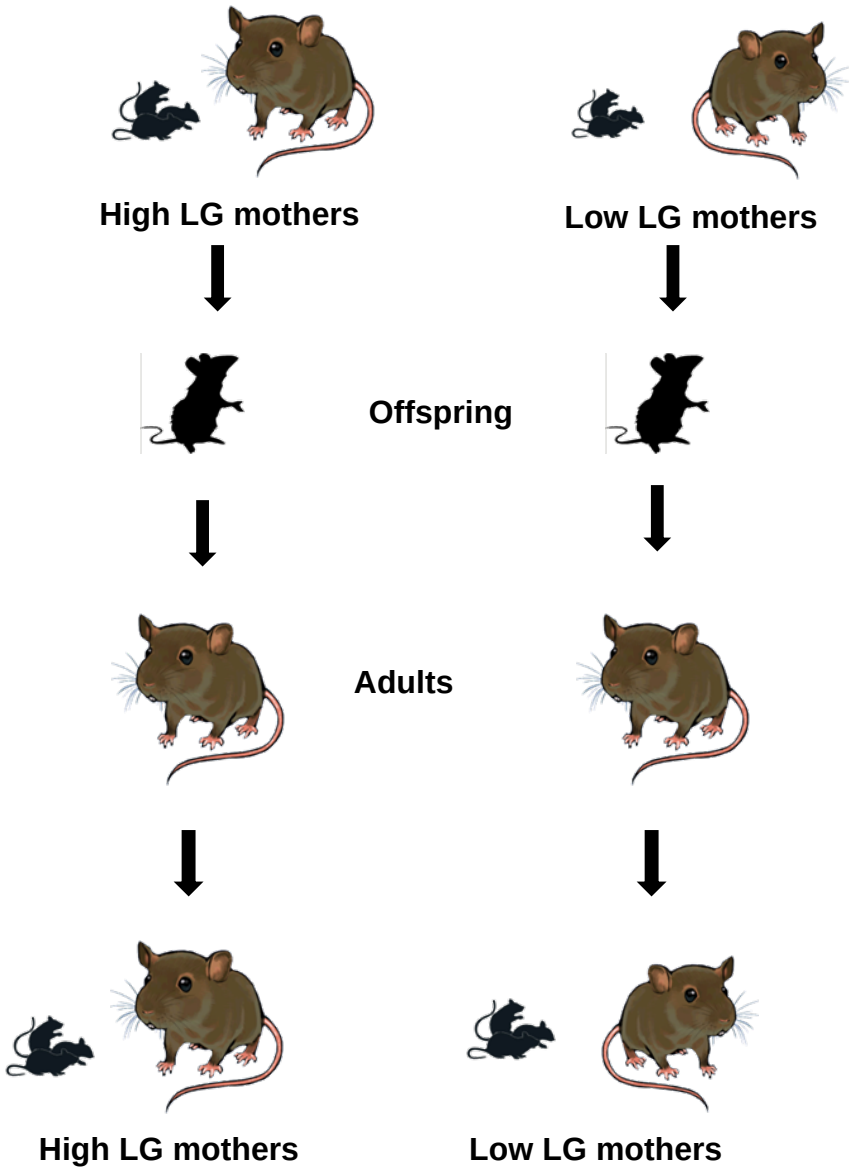
## *In the zygote all epigenetic marks are erased*

**But,**

**sometimes are not (and become heritable for some generations)**

# **But,** sometimes are not (and become heritable for some generations)

Rat mothers that show heritable poor maternal behaviour (pup licking and grooming) due to an epigenetic mark



**But, sometimes are not (and become heritable for some generations)**

**Chronic high fat diet in fathers**

**Insuline resistence in daughters**

**An individual's phenotype is the result of complex interaction between his genotype and environment**

$$P = G + E$$

**Dietary intake is a major contributor to environmental effects**

# *Nutrigenomics and Nutrigenetics*

- ***Nutrigenomics:***

  ***The study of how nutrients affect global gene expression and function***

- ***Nutrigenetics:***

  ***The study of how genetic variation alters dietary response or requirements***

# *Nutrigenomics*

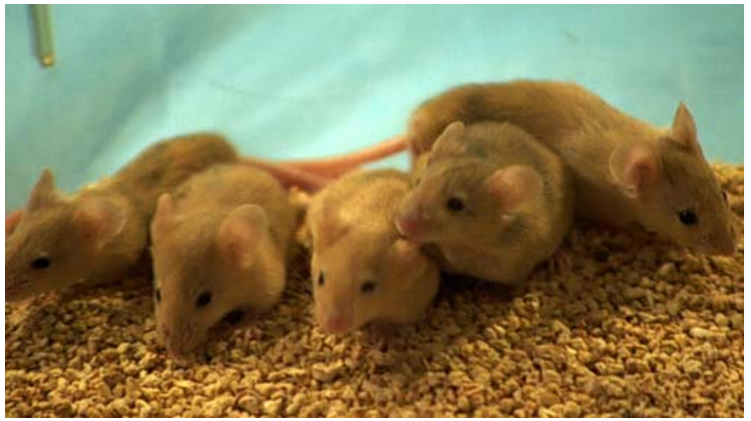
**Pregnant mothers feed with BPA (bisphenol A, plastics)**

⬇

**Decrease DNA methylation**

⬇

**More yellow (agouti), unhealthy offspring**



**But, pregnant mothers feed with BPA + methyl-rich foods (folic acid, soy)**

⬇

**More brown, healthy offspring**

# *Nutrigenomics*

- **Broilers challenged with a diet low in phosphorus for the first 90 hrs post-hatching have increased ability to better utilize phosphorus later in life**

  ***- it is partially explained by an increase in the expression of an intestine-specific sodium/phosphorus cotransporter gene***

- **Expression of Adipose MicroRNAs is sensitive to Dietary Conjugated Linoleic Acid Treatment in Mice**

- **Gene expression of selenoproteins is influenced by selenium deficiency or excess and dietary energy concentration**

# *Nutrigenetics*

- **Some SNPs alter nutrient requirements in a significant portion of the population**

- ***Individuals with the MTHFR 677TT genotype (15–30% of the population ) have higher folate requirements***

- ***Individuals with the rs12325817 PEMT SNP (20–45% of the population) have higher choline requirement***

# *Nutrigenetics*

- **Some SNPs directly alter a metabolic response to a nutrient, rather than changing the requirement for it**

  - ***one SNP in APOA5 modifies the effects of a high fat diet on blood pressure***

**Understanding how nutrients interact with the genome, better dietary regimens may be designed to improve**

***- nutritional utilization***

***- performance***

***- health of animals***

## *Nutrigenomics requires a metagenomic approach:*

***the interplay between three genomes: the food, the host and the gut microbial genome***

- **Microbial communities of intestinal tract maintain a symbiotic relationship with their host and are essential for mammalian health**

  - ***maintains immune homeostasis***

  - ***protects against pathogens***

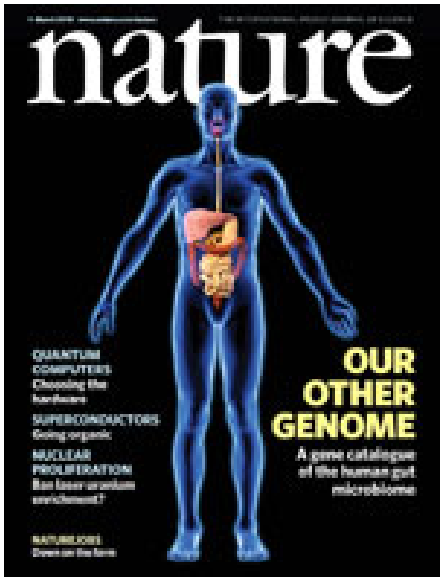
  - ***prevent adverse inflammatory responses to harmless commensal microbes***

***Human genome***

**~20,000 genes**

***Inside a human body (metagenome)***

**> 9,000,000 genes**



# The Human Microbiome Project

***What have we learned?***

**- there is a huge heterogeneity between individuals**

**- factors such as our lifestyle (diet, tobacco usage, alcohol consumption, stress, etc) influence the bacteria hosted by our body**

**- changes of human gut bacterial community is associated with obesity , diabetes and hypertension**

**- there is genetic variation: Inbreed lines of mice harbor distinct gut floras**

# *Knowledge of the rumen microbiome may provide new opportunities*

- **for using roughages and crop residues more effectively**

- **for developing strategies to achieve sustainable decreases in methane production**

- **for better utilization of tree leaves and agro-industrial by-products**

## Over the longer term, genomic tools will create new opportunities to change methods

**in animal breeding**
**food safety and traceability**
**quality of animal products**
**nutrition**
**health**

**However**
**ethical, legal, environmental, consumer concerns with the technology have to be addressed**

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# THANKS FOR YOUR ATTENTION