EAAP 2009
60th Annual Meeting of the European Federation of Animal Science
Fira de Barcelona. Barcelona, Spain. August 24-27, 2009

Future trends in Animal Breeding due to new genetic technologies

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The Darwin theory of evolution by natural selection is based in three principles

1. **The principle of variation** (individuals differ from each other for particular characteristics)

2. **The principle of inheritance** (related individuals resemble more that unrelated individuals)

3. **The principle of natural selection** (individuals with different characteristics differentially survive and leave offspring to the next generation)

Variation: The Raw Materials of Evolution

Mutation (new variation) and recombination (shuffling of existing variation) provide the raw material for continued evolution

Recently, other forms of variation are becoming increasingly important

- variation in copy number (CVN)

- microRNAs (miRNA)

Variation in copy number (CNV)

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

approximately 0.4% of the genomes of unrelated people differ with respect to copy number

Humans: lung cancer, susceptibility to HIV, autism, shizophrenia

Pigs: coat colour in pigs (KIT locus)

Cattle: 100 CNV regions have been detected in dairy cattle related to inmunity and metabolism

MicroRNAs (miRNA)

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

- ***miRNAs are encoded by genes from whose DNA are transcribed but are not translated into protein***

- ***mature miRNA molecules are complementary to one segments of messenger RNA and their function is to down-regulate gene expression***

MicroRNAs (miRNA)

Humans: **875 miRNAs**

- **Linked to some types of cancer**
- **Important in heart development and heart diseases**

Livestock:

Pigs: **95 miRNAs**

Cattle: **334 miRNAs**

Chicken: **518 miRNAs**

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

2. The principle of inheritance

There was a deep flaw in Darwin’s theory: it lacks a theory of heredity

Evolution does not work with blending inheritance: the new variants would rapidly be lost through mating with the common form

The modern theory of evolution should be called not *“Darwinism”* but *“Darwin-Wallace-Mendelism”*

Non-mendelian inheritance: Epigenetic effects

Heritable traits in the phenotype (or gene expression) that are not caused by changes to the underlying DNA sequence

- In humans the paternal granddaughters of women who experienced famine while in the womb lived shorter lives

Genomic imprinting

About >1% of genes in human and mouse are imprinted: only the copy coming from the father or the mother is expressed

3.The principle of natural selection

Is the key idea in Darwin thought

ADAPTATION IS THE RESULT OF NATURAL SELECTION ACTING ON MENDELIAN VARIATION

Natural selection acts on fitness that it is an aggregate of several traits

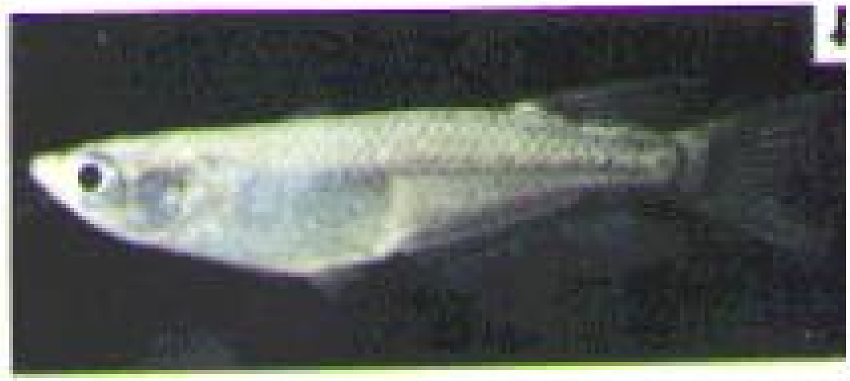
For example, it is thought that transgenes, being essentially macro-mutations, are unlikely to spread throughout a population because they typically have reduced viability

BUT

A reduction in viability can easily be offset by increased mating advantage

2. The principle of natural selection

In the worse-case scenario, the Trojan gene hypothesis, the transgene spreads as a result of increased mating advantage, but its lower viability can cause local extinction of a population



Using data japanese medaka the model predicts the eventual extinction of both natural and transgenic populations

(Muir&Howard, 1999)

Selection for social traits

The presence of altruistic traits in the behavior of some species, including the human species, poses an important theoretical challenge to the evolutionary theory

Altruism = behavioral traits that increase the fitness of other individuals at the expense of one’s own fitness

How natural selection could favour altruistic behaviors ?

Two mechanisms:

1. ***Group selection***
2. ***Kin-selection***

1) Group selection

There can be no doubt that a tribe including many members who, from possessing in a high degree the spirit of patriotism, fidelity, obedience, courage, and sympathy, were always ready to give aid to each other and to sacrifice themselves for the common good, would be victorious over other tribes; and this would be natural selection (Darwin 1871, **The descent of Man**)

Probably, group selection is not important in natural populations

2) Kin-selection

A gene that causes altruistic behavior can increase in frequency if the recipient of altruism is a relative

***The competition and selection among families thus introduced could make selection favor any genes which tend to cause their possessor to sacrifice himself* for his deme, *provided the sacrifice promotes the biological welfare of his relatives (some of whom will have some of the gene he has) enough to more than compensate for the genes lost in his own sacrifice* (**J.L. Lush, 1951, **The Genetics of Populations)**

2) Kin-selection

In more formal terms : Hamilton rule (1964)

$$c / b < r$$

An altruistic behavior will be favored by natural selecion if the ratio of the loss of fitness of the altruist (c) to the gain in fitness of the relative (b) is less that the coefficient of relationship (r)

Social interactions of individuals living in group could affect livestock production traits

Examples: Cannibalism in fish, pecking in chickens, aggression in pigs

The phenotype P_i of a particular individual i included in a group of n other interacting individuals can be decomposed into a direct effect $P_{D,i}$ from individual i plus the sum of all of the associate effectss $P_{A,j}$ of others in its group

$$P_i = P_{D,i} + \Sigma P_{A,j}$$

Final phenotype

(Griffing, 1967; Muir, 1982; Bijma, 2007)

Canibalistic pecking behavior in chickens:

$$P_i = P_{D,i} + \Sigma P_{A,j}$$

-*direct effect* ***of an individual indicates its ability to survive by avoiding being pecked***

-***associate effects*** ***indicates the effect of its own pecking behavior on survival of its cage members***

(Bijma et al., 2007)

Important points

- Individual selection (for example, body weight) when individuals live in groups may result in little (or even negative) response in the trait because an increase in aggressivity or competition

- Group or kin-selection could be tried in such cases

- *It has an impact on animal welfare*

Canibalistic pecking behavior in chickens:

Example: survival in chickens, data from Hendrix Genetics

Expected responses from:

Classic individual selection:

increase of 7.8 days in survival

Selection on groups of random individuals:

increase of 11 days in survival

Selection on groups of full-sibs:

increase of 23 days in survival

(Bijma et al, 2007)

Kin-selection can explain some intriguing phenomenon as genomic imprinting from an evolutionary point of view

About 50% of genes in human and mouse are imprinted: only the copy coming from the father or the mother is expressed

-many imprinted genes have a growth-related function

-paternally expressed genes tend to increase growth

-maternally expressed genes tend to decrease growth

-Callipyge muscular hypertrophy in sheep

-IGF2 in pigs

Kin-selection can explain some intriguing phenomenon as genomic imprinting from an evolutionary point of view

Evolutionary conflict:

-Paternal alleles are selected more strongly to increase the growth of individual offspring

-Kin-selection acts on maternal alleles to mitigate excessive competition on the mother and on other siblings

Molecular Biology has transformed research in Evolutionary Biology

- Providing powerful new techniques

- Establishing the phylogenetic relation between species

- Understanding the evolution of development

Molecular Biology has also 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	**1,831** QTLs representing **316** traits
CattleQTLdb	**1,123** QTLs representing **101** traits
ChickenQTLdb	**657** QTLs representing **112** traits
SheepQTLdb	**84** QTLs representing **30** traits

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

July, 2009

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

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

o refine the position several actions can be taken

To study sucessive generations of crossing (F3, F4...)

ine mapping through linkage disequilibrium

Candidate gene approach'*: to look for known genes that for physiological reasons could be the gene responsible*

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

There has been some succesful stories

DGAT1	***milk composition in cattle***
ABCG2	
IGF2	***muscle mass in pigs***
MSTN	***muscle mass in sheep***

To locate the resposible gene is a formidable task

Example 1

Georges et al. 1995 found a QTL on chromosome 6 with effect on milk production

However, de Koning (2006) discusses which of the two possible genes
OPN (Osteopontina)
ABCG2 protein
is the causal mutation

Example 2

Rothschild et al.1996 show that variation in the ESR in pigs is associated to litter size

However, still it is controversial if the ESR is the responsible gene (Alfonso, 2005)

To locate the resposible gene is a formidable task

Example 3

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 >1800 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

Despite of the great enthusiam for breeding companies to be involved there are very few application of MAS in commercial poultry breeding. They are not convinced about economic feasibility of MAS (de Koning y Hocking, 2007)

Although several useful genes (primarily gene-linked markers) have been identify in pigs, their application has been limited and their success inconsistent (Spotter y Distl, 2006)

The much anticipated benefits of DNA-based tools to routinely guide selection decisions in cattle have not been fully met since the origin of this premise (Sonstegard y van Tassell, 2004)

Although initial expectations for the use of marker assisted selection were high the current attitude is one of cautious optimism (Dekkers, 2004)

A more radical proposal: bypassing QTL detection by GENOMIC SELECTION (Meuwissen et al. 2001)

Two assumptions:

-Panels with ten of thousands of markers will be available together with cost-effective genotyping procedures

-Marker-density will be sufficient for all resposible genes of a trait be in linkage disequilibrium with flanking markers

SNPs: Single Nucleotide polymophisms

Change in one nucleotide of the DNA sequence

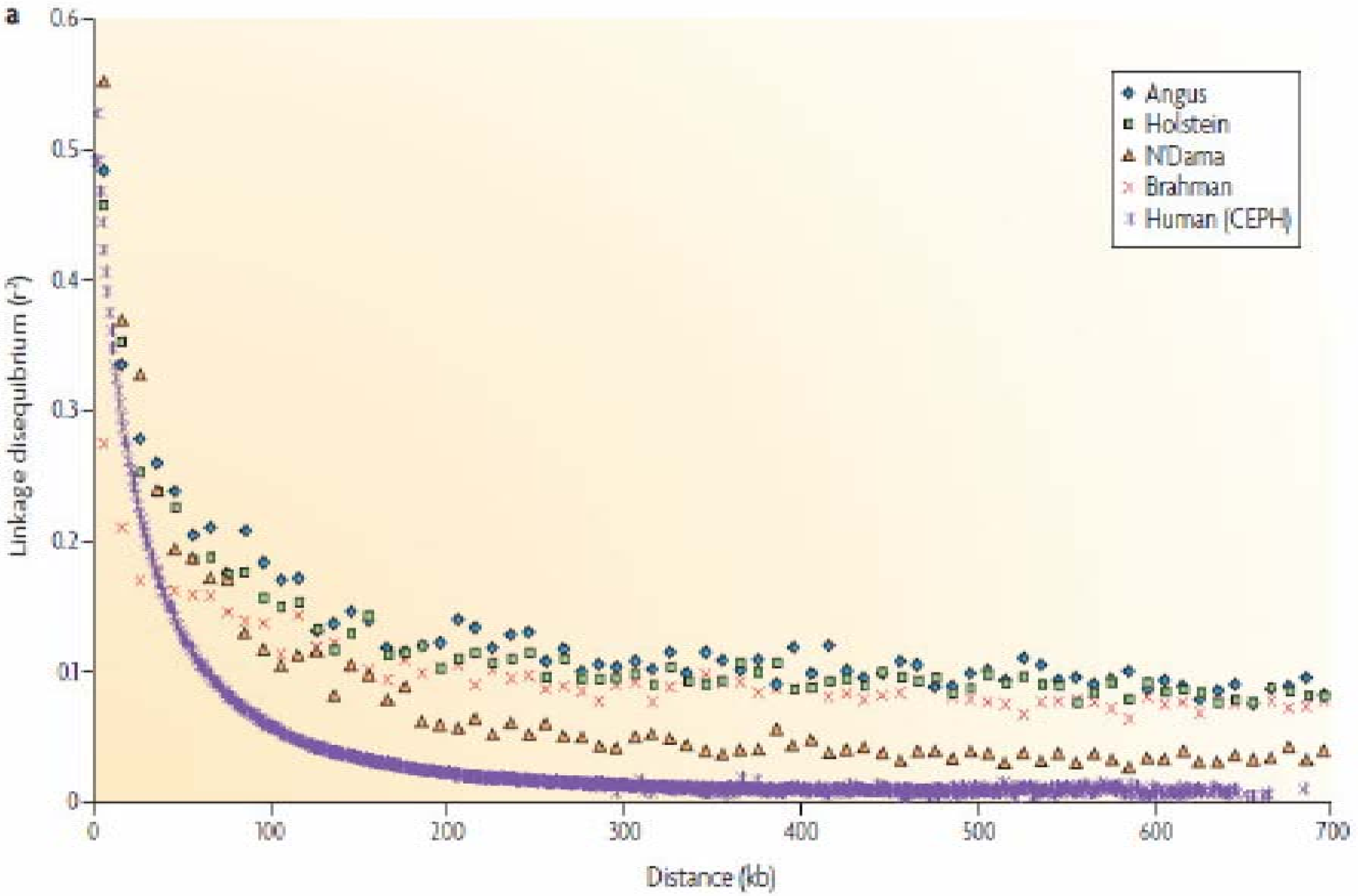
Alelo A	**aaaccagtcaactactag......**
Alelo B	**aaaccggtcaactactag......**

Commercial SNPs chip

Cattle	**50,000**
Sheep	**56,000**
Pigs	**60,000**
Horses	**55,000**
Dogs	**25,000 (250,000)**
Chicken	**60,000**
Human	**1 000,0000**

Cost: 100-200 $ /chip

Linked Disequilibrium (LD) in cattle



Hayes and Goddard, 2009

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 enthusiam 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: optimal breeding design with genomic selection

- Genotype a large number of bull calves from the population
- Calculate GEBVs for these calves
  Accuracy = 0.8 = accuracy of progeny test
- Select team based on GEBV and sell semen from these bulls as soon as they can produce it
- Generation interval reduced from ~4 yrs to ~ 2 yrs

Double rate of genetic gain

Genomic predictions are officially implemented in 2009 resulting in substantially greater reliability of Prediction Transmission Ability for young bulls and heifers

Trait	Gain over parent average reliability (~35)
Net merit	**+23**
Milk	**+23**
Fat	**+33**
Protein	**+22**
Fat (%)	**+43**
Protein (%)	**+34**

VanRaden et al (2009)

Animal Breeding Fiction: synergistic use of GENOMIC SELECTION and germ-line manipulation

Velogenetics

collect, mature and fertilize prepubertal oocytes in vitro and select embryos for implantation based on genomic selection

Whizzogenetics

instead of being reimplanted the development of embryos continue, in vitro meiosis is induced and embryos are formed (GENOMIC SELECTION in the lab!)

(Georges & Massey, 1991; Haley & Visscher, 1998)

Finally, the above research should be complemented by parallel research in animal production

Redefining the nutritional needs of improved genotypes

Adapting management systems to optimize the benefits of selective breeding

THANKS

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GRACIAS

GRÀCIES

The Gaudí Pig