Marker / Genotypic Assisted Selection

Gene251/351 Lecture 11
Overview of selection strategies

- Phenotypic selection
- Corrected phenotype
- EBVs from index (*multiple phenotypic sources*)
- EBVs from BLUP (*index + more*)

- What are the main advantages of selection on BLUP EBVs?
Information sources used in calculation of EBVs

- These can include
  - own phenotype
  - information from relatives
  - information from correlated traits

- Plus ??
Information sources used in calculation of EBVs

These can include:
- own phenotype
- information from relatives
- information from correlated traits

Plus *Information from DNA*
- termed ‘gene markers’
\[ P = G + E \]

polygenic + major gene

Genes of smaller effect  
Gene of larger effect

Also termed QTL for quantitative trait locus
Technologies

- Marker assisted selection (MAS)
  - select on a molecular marker linked to the gene of interest \(\rightarrow\) indirect marker

- Genotypic assisted selection (GAS)
  - select directly on the gene of interest \(\rightarrow\) direct marker
Molecular markers include

- Restriction fragment length polymorphisms (RFLPs)
  - presence / absence of restriction enzyme recognition sequences

- Microsatellites
  - variable numbers of short tandem repeats
  - high number of alleles

- Single nucleotide polymorphisms (SNPs)
  - single base pair substitutions at appreciable frequency
The basis of selecting on gene markers
Quantitative traits are controlled by many genes
… which differ in terms of size of effect.
Finding the actual genes is difficult
… so in the first instance markers linked to genes (generally those of larger effect) may be identified
Marker assisted selection

-8

Marked gene from sire

Other genes from sire

Genes from dam

-2

?
‘Indirect marker = gene marker linked to a gene with a significant effect on a production trait (QTL)’
Although if recombination between the marker and gene occurs …..

Ram

Marked gene from sire

Genes from dam

Other genes from sire

Although if recombination between the marker and gene occurs …..

Progeny

Progeny

+8

-2

?
If gene identification has been successful, the causative mutation is used as a marker.
Progeny

Ram

Genotypic assisted selection

Recombination is irrelevant

Marked gene from sire
-2

Other genes from sire

Genes from dam

+8

??
Some points about MAS

- MAS is less accurate than GAS
  - what is accuracy of MAS dependant on?
If the marker (M) is linked to the QTL (Q), r = 5%, what is the frequency of the 4 progeny genotypes?
If the marker (M) is linked to the QTL (Q), \( r = 20\% \), what is the frequency of the 4 progeny genotypes?
Some points about MAS

- MAS is less accurate than GAS
  - dependant on recombination frequency (linkage distance) between QTL and marker
  - results in *probabilities* of inheriting certain genotypes
- MAS requires progeny testing to determine linkage phase of QTL and marker in each family
Some points about GAS

- Marker is the causative mutation
  - Thus *certainty* of inheriting a particular genotype

- Identifying the gene and causative mutation can take many years
  - More difficult for quantitative rather than discrete traits

- Causative mutation is population wide
  - Thus do not need to re-establish linkage phase in each family
Use of gene markers
Traits for gene markers

Gene markers are most beneficial for traits are difficult to improve under traditional selection

- Require slaughter to measure
  - Carcase traits
  - e.g. meat pH, tenderness, colour

- Are measured on one sex only
  - Milk Production

- Are measured late in life
  - Lifetime fecundity

- Are difficult or expensive to measure
  - Disease resistance
Breeding scheme structures can also be altered to accommodate markers

For example, progeny testing in dairy:

Candidate young sires to progeny test

Determine marker (and thus QTL) genotypes

Only progeny test those that have promising genotypes
Response

- Relative advantage of MAS/GAS over traditional selection is higher if
  - trait heritability is low.
  - the QTL is of large effect
  - the favourable allele is initially rare.
  - QTL and marker are closely linked
  - mode of gene action is non-additive
Short and long term effects of Marker Assisted Selection

- **Marker assisted selection**
- **Normal selection**

**Short-term benefits**: 2% to 60%

**Year**

- 0
- 5
- 10
- 15
- 20
- 25
- 30

**Response**
Industry implementation

- Emerging technology
  - QTL detection experiments underway in all major livestock species

- Some industry use
  - Most advanced probably breeding companies

- Research underway to incorporate QTL information into genetic evaluation systems
Examples of direct markers in sheep: from Australian sheep gene mapping website

Fecundity

Inverdale fecundity (FecX)  The Inverdale mutation causes increased fecundity in heterozygous ewes and sterility in homozygous ewes. The causative mutation for Inverdale fecundity has been identified within the BMP15 gene on the X chromosome (Galloway et al., 2000).

Booroola fecundity (FecB)  The Booroola mutation causes increased fecundity in heterozygous ewes with a further increase in fecundity in homozygous ewes. The causative mutation for Booroola fecundity has been identified within the BMPR1B gene on chromosome 6 (Wilson et al., 2001; Mulsant et al., 2001; Souza et al., 2001).

Woodlands fecundity (FecX2)  The Woodlands fecundity trait is maternally imprinted and has a complex inheritance pattern. This trait has been mapped to a region on chromosome X (Davis et al., 2001).

Meat Traits

Callipyge  "beautiful buttocks"  The callipyge locus causes muscular hypertrophy of buttock muscles in sheep with the hypertrophied muscles being less tender than those in normal sheep. This trait has a complex mode of inheritance (Cockett et al., 1996) and has been mapped to a 400 kb region on chromosome 18 (Berghmans et al., 2001; Charlier et al., 2001). This region influences the expression of the GTL2 gene in hypertrophic muscles (Bidwell et al., 2001).

Carwell  The Carwell locus causes a milder form of muscular hypertrophy than callipyge and maps to a similar region on chromosome 18 (Nicoll et al., 1998, Proc VI World Conf. Genet. Appl. Livest. Prod. 26:529-532). It is likely that Carwell is allelic to callipyge.

Diseases

Spider Lamb Syndrome  Spider Lamb Syndrome is a skeletal disorder that has a recessive mode of inheritance. The causative mutation for Spider Lamb Syndrome has been identified within the FGFR3 gene on chromosome 6 (Cockett et al., 1999). Contact Dr Cynthia Bottema for details about testing for Spider Lamb Syndrome in Australia.

Other

Horns  The Horns locus of Merino sheep has been mapped to a region on chromosome 10 (Montgomery et al., 1996).

Black wool  The recessive self-colour phenotype of Australian Merino sheep has been mapped to a region on chromosome 13 (Parsons et al., 1999, Australian Journal of Agricultural Research 50:1099-1103). The agouti gene is a candidate for the self colour phenotype.
GeneSTAR Marbling

GeneSTAR Marbling is a DNA diagnostic test for a major gene associated with marbling. It is the first gene marker for a production trait in beef cattle. The test enables cattle breeders to select individuals that carry one or two copies of the favourable allele.

GeneSTAR® Results Explanation

GeneSTAR Marbling

0 This animal carries zero copies of the favourable form of the GeneSTAR Marbling gene

★ This animal carries one copy of the favourable form of the GeneSTAR Marbling gene

★★ This animal carries two copies of the favourable form of the GeneSTAR Marbling gene
### Examples of tests on the market

<table>
<thead>
<tr>
<th>Name</th>
<th>Trait</th>
<th>Desired genotype</th>
<th>Company</th>
</tr>
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<tr>
<td>GeneSTAR®</td>
<td>Marbling in beef</td>
<td>**</td>
<td>Genetic Solutions (Aus)</td>
</tr>
<tr>
<td>Igenity-L™</td>
<td>Marbling in beef</td>
<td>TT</td>
<td>Select Sires (USA)</td>
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<tr>
<td>GeneSTAR®</td>
<td>Tenderness in beef</td>
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<tr>
<td>Igenity-ComponentMaker™</td>
<td>Milk composition in dairy</td>
<td></td>
<td>Select Sires (USA)</td>
</tr>
</tbody>
</table>
How are gene markers identified
The basis of mapping experiments

- If a major gene influences a trait (e.g. muscle depth), progeny inheriting the favourable (Q) & unfavourable (q) alleles will have a distribution as follows:
Basis of mapping experiments

- So if marker and QTL are linked, progeny inheriting the marker alleles will have a distribution as follows:

  For $r = 0.20$
  - m is linked to q (40%) & Q (10%)
  - M is linked to Q (40%) & q (10%)
Basis of mapping experiments

If marker and QTL are unlinked, progeny inheriting the marker alleles will have a distribution as follows:

- Marker and QTL are not linked
- m is inherited with q (25%) & Q (25%)
- M is inherited with Q (25%) & q (25%)
Basis of mapping experiment

- For half-sib design and single marker analysis
  - Breed heterozygous (Qq) sire
  - Create 100+ progeny from the sire
  - Type progeny at marker loci
  - Test for different in trait means of animals inheriting M vs m marker alleles

- More powerful mapping designs exist than that described above

- These usually involve identification of markers flanking the QTL
From indirect to direct marker

- ‘Positional candidate’ approach to gene identification is typically used
  - position of QTL is known from mapping experiments (down to say 3 cM, ~30 genes)
  - candidates within this region identified
  - candidate genes sequenced to detect causative mutation
  - this is not straight-forward
    - DGAT1 gene (for milk production) took 7+ years
The type of traits that benefit the least from MAS or GAS are those which

a. Are easily measurable prior to selection
b. Are measurable on one sex only
c. Are difficult or expensive to measure
d. Are measured late in life
Questions

- Should industry implement MAS or GAS?
- What traits should be targeted?
- Who should pay for the research behind the technology?
- How should QTL EBVs be presented to breeders?