technical brief

"Gene Marker Technology Update"

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Background

Only a few traits are controlled by a single gene sequence, eg Pompe's disease. The expression of these genes is independent of environment.

Most of the commercially important production traits are influenced by many genes (mutli-gene traits) eg; growth, carcase traits, fertility etc. The expression of these multiple genes is influenced by environment.

Breedplan EBVs are calculated from phenotypic differences between individual animals, and reflect the sum effect of all the genes influencing a given trait in a given environment. For some traits that are hard/impossible to measure in the live animal, eg marbling, the EBV is calculated from a "correlated trait" that has a known genetic association with the target trait, eg, scan IMF%. Often phenotypic measurements are only available when the animal is yearling age or older.

Gene markers identify individual genes that contribute to, and influence a trait. In isolation they provide only a small part of the information about a trait. A significant advantage of gene markers is that they can identify genetic merit for traits that are hard to measure on the live animal, eg marbling, and they can be measured early in life eg, at birth, and they are not reliant on phenotypic expression for measurement.

There is potential to include DNA information with phenotypic information to calculate marker-assisted EBVs, (thereby increasing the accuracy of traditional EBVs calculated using only phenotypic measurements), or by providing marker-only EBVs for difficult to measure traits such as NFI.

The present – gene marker technology

Development of gene markers to date has been based on the assumption that mutli-gene traits were influenced by a small number of genes(5-10) that had a major effect on expression of the trait, together with a large number of genes that collectively only had a small effect.

Current DNA marker technology has been directed towards finding those genes of major effect for a small number of traits.

At present, 4 markers each for Marbling, NFI and Tenderness are being marketed to Australian cattle breeders by Catapult Genetics.

Validation of the effect of markers at present have generally been conducted by the discoverer or commercialized and the results often not published for scientific scrutiny.

Independent analysis of effects of some available gene markers on phenotypic performance are only now becoming available, and some reports of little or no effect for some markers have been made.

The discovery and commercialization of gene markers, gene by gene, is ongoing however there is a growing realization that much larger panels are required to account for a reasonable phenotypic effect.

Catapult is reported to be releasing a further 10-12 unspecified markers in the near future, whilst Merial is reportedly preparing to market a 100 marker panel to the Australian industry once validation against the CRC reference database is completed.

The Merial marker panel is expected to code for NFI, wean wt; carcase wt; EMA; fat depth; marbling ; tenderness and yield & quality grade.

The future – whole genome scans

With the release of the bovine genome in 2006, the "few genes of major effect" theory is clearly an oversimplified, although a very marketable, logic.

The cattle genome sequence has an estimated 30,000+ genes. The genome project has discovered some 3,000,000 SNPs (Single Nucleotide Polymorphisms – DNA sequence variations - pronounce SNIP), and that it takes 100's if not 1000's of snips to explain 50% of the genetic variance for a single trait, with each gene accounting for only a small effect on trait expression.

New marker technology has developed assay panels (SNP chips) of up to 50,000 markers that will code for genes across a wide range of traits. This information will be able to be used independently or incorporated into EBVs via a prediction equation.

SNP chips accommodating up to 300,000 markers are expected to be available within the next few years.

This “whole genome scan” technology is rapidly changing the way DNA markers will be developed, marketed and used across the industry.

Information derived from this technology will be used for estimating/increasing the accuracy of breeding values for seed-stock animals (marker assisted EBVs) as well as for estimating phenotypic performance (EPP’s) of commercial animals, eg; for predicting the marbling performance of feeder steers under different feeding/market systems; inclusion in the MSA model etc.

More sophisticated equipment and many more animals are now required to discover (1000), confirm (1000) and validate (5000) “whole genome” marker panels making genomic research and validation more costly.

For genome-wide marker testing to be successful, a national genomic database and reference population will need to be established, and validation and quality control procedures put in place if industry trust and confidence is to be gained.

At the present stage of R&D, it is feasible that the 50K+ chips will be used as a research tool, and that 1400 marker chips) and 100 marker chips would be developed for the seed stock and feedlot industries respectively.

When developed and validated, whole genome marker panels will effectively account for multiple DNA markers (each of small effect) for multiple traits.

Such marker panels will allow multi-trait genetic profiling of an animal at a similar level of accuracy as a progeny test – but the information will be available at birth, and at much lower cost.

It is likely that marker panels could be breed specific – if so, then it also likely that such panels would be first developed for major-market breeds such as Angus and Brahman at the exclusion of smaller-market breeds.

Challenges such as finding useful markers that have a proven effect, developing prediction equations for inclusion of markers into EBVs, developing and maintaining genomic databases, and using marker information for prediction across breeds will undoubtedly occupy geneticists for the next few years.

It is inevitable that numerous “whole genome” marker panels will be on the market within the next few years.

These panels could well have different combinations of markers coding for different combinations of traits. Some component markers may be well known, published, and validated; other markers may be proprietary markers having no independent validation and having an effect known only to the developer and/or commercialize.

It could be argued that the greater number of undisclosed markers in a panel, the greater the speculative element when using the panels be as a genetic evaluation tool.

Breeders may well be confused, if not overwhelmed, by the promises on offer.

It will be very much a case of “buyer beware” or more preferably “buyer be informed”. Investment in gene marker technology at the farm level will need to be made on the basis of likely cost-benefits, risks and likely effects.

Whilst it would be desirable for all marker effects to be independently validated against reference populations, the high cost of doing so for a large number of traits would be prohibitive, and hold back the release of markers.

After initial validation, further, on-going validation and “proof of effect” will come from analysis of the phenotype information being recorded on marker identified animals, much as Breedplan EBVs are recalculated as more performance information becomes available. However, very few phenotypes will be routinely collected for difficult to measure traits, eg. tenderness or NFI, and proof of effect will need to be planned in purposely set up and recorded herds – ie. information nucleus.

The CRC is presently developing a DNA Marker commercialization strategy that is likely to include non-exclusive release of their markers, minimum standards for validation on some 5000 animals before release and possible trade-marking as a QA measure.
The CRC strategy is a responsible approach to marker commercialization, but other marker discoverers and/or developers/commercialisers would not be bound by the CRC commercialization plan.

Marker-assisted EBVs

Where a significant gene effect is validated, this information will be included in the calculation of EBVs using procedures currently being developed by AGBU. These EBVs will be known as marker assisted EBVs. The first MA- EBV, for tenderness, is expected to be released by mid-year

To avoid markers of unknown effect influencing the calculation of marker-assisted EBVs, unvalidated markers would get zero estimated effect in the prediction equation until credible validation information becomes available.

Markers with known effect will get a commensurate effect value in the equation model.

The risk factors – should Shorthorn breeders invest in DNA technologies?

1 - Farm-level investment in gene markers that have not been independently validated as to their effect on phenotypic performance must be considered a cost-benefit risk proposition.

2 - Whilst the size of effect is an important aspect in deciding whether or not a gene marker is of value, so is the frequency of the gene in the population – for example, if frequency of the favourable gene is extremely high or extremely low, opportunity to select better animals is very limited.

3 - Given the potential for DNA technology to change genotypes of cattle populations with increased speed and accuracy, several issues are of concern;

* there is no published research that demonstrates progeny benefits derived from parent populations selected using gene markers. In fact the reverse applies – validation is based on resident genes being identified in populations selected on phenotypic performance.

* there is no published research that investigates possible correlated effects between marker selected and unselected traits ; for example, could selection for tenderness in the Brahman breed be negatively associated with fitness traits such as tick resistance ?

* the "whole genome scan" approach assumes "linkage disequlibrium" between markers and genes ie genes stay linked from one generation to the next, whereas genes in linkage equilibrium segregate independently from one generation to the next

If linkage disequilibrium is not a correct assumption then the genes could be in a different association in the next generation and we may find that we should be selecting for the opposite form of the gene rather than what we currently think is the favourable form.

<u>Considerations for deciding to use the currently available DNA tests</u>

- Questions remain about the effectiveness and cost-benefit of currently available tests, and these questions will not be answered until independaent validation results are published.

  If not convinced, adopt a "wait but be prepared" policy, by collecting and storing tail hairs on important animals in the pedigree (eg. AI sires or all sires) and test when the effectiveness of the tests are validated to your satisfaction

- Always check the frequency of the genes in the population – gene frequencies around 50% present the best selection opportunities

- Marker assisted EBVs will be the 'best' form in which to use validated DNA results

<u>Considerations for genome-wide scans (SNP chips)</u>

- Many unknowns still remain

- Interpretation will be difficult so only use as part of marker assisted EBVs

- Storing tail hairs will keep options open

- Continue a sound performance recording system because it may be necessary in future to determine the best way to use the SNP chip information