# Selection and Biotechnology: the best of both worlds

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## INTRODUCTION

To date, most genetic progress for quantitative traits in livestock has been made by selection on phenotype or on estimates of breeding values (EBV) derived from phenotype, without knowledge of the number of genes that affect the trait or the effects of each gene. In this quantitative genetic approach to genetic improvement, the genetic architecture of traits of interest has essentially been treated as a 'black box'. Despite this, the substantial rates of genetic improvement that have been and continue to be achieved in the main livestock species, is clear evidence of the power of quantitative genetics approaches to selection. In swine, considerable rates of genetic progress have been obtained for, in particular, growth rate and backfat. Both these traits have, however, high heritability and the traits can be measured on all selection candidates (males and females). This is an ideal situation for quantitative selection methods because accurate EBV can be obtained on all animals. Recent results, however, show that even for traits that were thought to be extremely difficult to improve using selection, e.g. littersize (low heritability, only observed on females and only <u>after</u> selection), important progress can be made through the application of BLUP methodology.

The success of quantitative genetic approaches does, however, not mean that genetic progress could not be enhanced if we *could* gain insight into the black box of quantitative traits, in particular for traits that are more difficult to improve using current selection strategies (e.g. littersize and meat quality traits). By being able to study the genetic make-up of individuals at the DNA level, molecular genetics has given us the tools to make those opportunities a reality.

The eventual application of molecular genetics in livestock breeding programs depends on developments in the following four key areas, which jointly culminate in the successful implementation of strategies for marker-assisted selection (MAS):
i. *Molecular genetics*: identification and mapping of genes and genetic polymorphisms
ii. *QTL detection*: detection and estimation of associations of identified genes and genetic markers with economic traits
iii. *Genetic evaluation*: integration of phenotypic and genotypic data in statistical methods to estimate breeding values of individual animals in a breeding population
iv. *Marker-assisted selection*: development of breeding strategies and programs for the use of molecular genetic information in selection and mating programs.
Aspects of each of these areas of research will be reviewed in what follows.

## MOLECULAR GENETICS

Through the use of molecular genetic technology, a large number of genes have been mapped over the past 10 years in the main livestock species. In swine, the number of

genes mapped on published maps approaches 2000. Although some of these genes have a functional role in the animal's physiology (i.e. they contain the genetic code for a protein), most are non-functional or 'neutral' genes. The latter are often referred to as 'genetic markers'. The fact that genetic markers are non-functional does, however, not mean that they are not useful. In particular, genetic markers can be used to identify genes that affect the quantitative trait we are interested in (so-called quantitative trait loci or QTL). The important difference between genetic markers and their 'linked QTL' is that we can determine what genotype an animal has for the genetic marker but not for the QTL. Because the observable genetic marker is linked to the QTL, we can, however, select on the genetic marker to indirectly select for the QTL, which is the concept behind marker-assisted selection.

## QTL DETECTION

Two approaches can be distinguished for finding QTL for the traits we are interested in improving through selection: the candidate gene approach and the genome scan approach (Rothschild and Soller, 1997). In the candidate gene approach knowledge from species that are rich in genome information (e.g., human, mouse) and/or knowledge of the physiological basis of traits is used to identify genes that are thought to play a role in the physiology of the trait. Using this information, the candidate genes are identified in the species of interest and polymorphisms (genetic variants) are identified. It is then determined whether there is an association between the genotype for the candidate gene with the phenotype for the trait. Using this approach, several genes with major effect have been identified, a prime example being the estrogen receptor gene affecting litter size in pigs (Rothschild et al., 1996).

The genome scan approach to QTL detection uses random genetic markers spread over the genome to identify genes affecting quantitative traits. Using statistical methods QTL can then be identified and their position and effect estimated by associating marker data to phenotypic records. The precision of, in particular, estimates of QTL position that can be obtained from these approaches is, however, limited, and large population sizes are needed.

## USE OF GENE OR MARKER INFORMATION IN GENETIC EVALUATION

Although candidate gene and QTL mapping experiments can result in identification of genes of interest that can be used in genetic improvement programs, their implementation will require estimation of QTL effects in commercial breeding populations. In particular with the use of linked markers, marker and QTL effects must be estimated on a within-family basis and re-estimated on a regular basis. This will require routine systems for DNA collection and marker genotyping. Even when the actual gene has been identified, there will be a need to re-estimate gene effects on a regular basis to improve the accuracy and to guard against unfavorable associations with other traits and against epistatic effects with the background genome or environment.

Ideally, estimation of QTL and gene effects will be incorporated in routine animal model genetic evaluations, providing best linear unbiased predictors (BLUP) of EBV for identified QTL and for the collective effect of polygenes.

## USE OF GENE OR MARKER INFORMATION IN SELECTION

One of the approaches to use this QTL in a selection program would be to fix the favorable allele as quickly as possible by selecting only individuals that have one or preferably two copies of the favorable allele. Although this approach would lead to fixation of the gene within a couple of generations, depending on gene frequency and selection intensity, it does not result in greatest response to selection for the trait. This is because the QTL is only one of the genes that affects the trait, albeit a major one, and no selection pressure is applied to the other genes in this selection process. A better approach is to select on an index of QTL and regular EBV, which will be described below.

The BLUP-QTL genetic evaluation procedures described in the previous section result in estimates of breeding values for identified QTL and estimates of residual breeding values, which includes the effect of all other genes. An estimate of the total breeding value can then obtained by simply summing the EBV for identified QTL and the EBV for the residual polygenic effects, to give the following total QTL-BLUP EBV: $EBV_{Total} = EBV_{QTL} + EBV_{Polygenes}$. In theory and under additivity, selection on such EBV will maximize performance of progeny, i.e. single-generation response.

Several studies have investigated the extra response to selection that can be achieved with incorporation of marker or gene information in genetic evaluations. Extra responses from MAS depend on the amount of genetic variance explained by the marked QTL, the ability of markers to trace segregation of QTL (linkage and marker informativeness), and the efficiency of selection without marker information. In general, benefits from MAS are greatest in situations where regular selection is limited or inefficient. This includes selection for traits with low heritability and traits with restrictions on phenotypic recording, such as sex limited traits, traits recorded after selection, meat quality traits, and traits that are expensive or difficult to evaluate (Meuwissen and Goddard 1996).

Most studies on MAS show greatest extra responses in early generations, followed by a decline in later generations. Gibson (1994) examined the long-term consequences of MAS using computer simulation of selection on a known major QTL. He found that, although MAS resulted in greater cumulative response to selection in the short term, phenotypic selection achieved greater response in the longer term. Although MAS fixes the QTL more rapidly, this is at a cost of response in polygenes. With MAS, the polygenic response that is lost in the initial generations, as the QTL is selected toward fixation, is never entirely recovered in later generations. The reason for the lower response from MAS is not that QTL information is not useful but that simply summing the EBV for the QTL and polygenes is not the best way to use QTL information. We (Dekkers and van Arendonk, 1998) have developed methods that optimize the use of QTL information and have shown that with optimal use, MAS does give greater response

to selection, in particular for non-additive QTL. Thus, there are selection strategies that use the QTL information in a beneficial way, which result in greater responses to selection than traditional selection methods.

## INTEGRATING MOLECULAR AND REPRODUCTIVE TECHNOLOGIES

The previous section indicates that one of the main challenges for selection on a QTL is that it reduces selection on polygenes and, unless selection on the QTL is properly balanced against lost response in polygenes, QTL selection can be detrimental in the long-term and suboptimal in the short term. In the cases considered, however, QTL selection was incorporated into traditional selection stages, where QTL selection competes with regular selection. Several authors have suggested that the most effective manner to capitalize on QTL information is by incorporating it at stages, where selection was not possible previously.

A prime example is preselection of young dairy bulls for entry into progeny testing (e.g., Kashi *et al*. 1990); with use of multiple ovulation and embryo transfer (MOET) technologies, often more bull calves are produced from superior bull dams than can be entered into progeny testing. Similar cases exist in swine breeding programs. Because the EBV of full brothers is identical when based on pedigree information alone, QTL information allows informative decisions to be made on which full brother should be entered into progeny testing. The effect of this additional QTL selection stage on polygenic response depends on the availability of excess bull calves that is not capitalized on in current selection strategies; if currently the choice of which bull calf from a flush to enter into progeny testing is at random, the QTL selection stage will have minor consequences on polygenic response and there is no need for optimization, apart from consideration of costs.

Opportunities for QTL selection in this manner can be increased through the use of reproductive technologies. The use of MOET in preselection of dairy bulls, as discussed above, is a good example. Other technologies, such as oocyte recovery and in vitro fertilization can be used to further enhance reproductive rates.

In the example of pre-selection of bull calves for progeny testing, QTL selection capitalized on extra selection space that was created within a generation through increased reproductive rates. Georges and Massey (1991) proposed designs they named velogenetics, in which short generations with selection based on QTL information alone are introduced, with generations with regular phenotypic selection alternated by several generations of QTL selection. Without the need to produce phenotypic data on selection candidates for QTL selection, the generations with QTL selection can be very rapid through oocyte recovery from the foetus, in-vitro embryo production and embryo transfer (Georges and Massey 1991). Variations upon velogenetic designs were proposed by Haley and Visscher (1998). Such designs do require optimization of QTL versus polygenic responses, along with costs. An additional challenge in these designs is generation of QTL information which, unless QTL are known, must be re-estimated on a regular and within family basis using phenotypic information generated in the phenotypic

selection generations. Nevertheless, these examples show great opportunities exist for the development of enhanced breeding programs based on integrating molecular and reproductive technologies.

**CONCLUSIONS**

The main conclusion to be drawn from the preceding is that use of molecular genetics in selection can improve responses to selection, but only if it is used judiciously in connection with traditional EBV. Molecular genetics will not replace traditional selection methods but can be used as an additional tool to identify superior animals. The benefit of molecular genetics as a tool to enhance selection can be enhanced in breeding programs that integrate molecular and reproductive technologies.

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