

Challenges of application of marker assisted selection – a review

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In the past 15 years, the major effort in animal breeding has changed from quantitative to molecular genetics with emphasis on quantitative trait loci (QTL) identification and marker assisted selection (MAS). However, results have been modest. This has been due to several factors including difficulty in gene identification and simplified assumptions in the pattern of inheritance. The move to MAS has resulted in exodus of scientists from the field of quantitative genetics, which is currently responsible for almost all the genetics progress in breeding companies. At the same time, emerging problems in the animal industry of declining fitness as the results of too strong emphasis on production have not been addressed appropriately; there is a shortage of well trained scientists in this area. The future of animal breeding lies in the merge of quantitative and molecular genetics, with quantitative genetics being a crucial component currently.

KEY WORDS: animal breeding / marker assisted selection / quantitative genetics

Marker assisted selection in animal breeding

Around 1990, the focus of main activities in animal breeding started changing from quantitative to molecular genetics. Activities in the new focus were divided into two steps. The first one was detection of markers associated with QTL. The second step was the use of markers in MAS. The new type of selection opened new

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possibilities. Genotypes could be determined without phenotypes, by typing animals for important markers and then calculating the breeding values by simple addition. One advantage of such selection, aside from the cost, is the possibility of making the selection proprietary as opposed to selection using phenotypic data when, with public ownership of phenotypic data in many species, the results of evaluation have to be made public. Another possibility was greater success with sex limited and low heritability traits.

These ideas generated optimism and enthusiasm. Subsequently, a substantial part of funding in animal breeding moved from quantitative to molecular side. New funding sources became available from both governmental and private sources. Large genome scans were initiated. A number of scientists were trained in new techniques. New insights were generated. For example, many genes were no longer parts of a “black box” but could be assigned to specific locations on specific chromosomes. At a major conference in 1991, M. Georges, a major scientist in the area, claimed that in a few years there would be no need for BLUP, which was a traditional method for selection based on phenotypes.

The possibilities of marker assisted selection (MAS) led to efforts to commercialize the new technologies. Examples are ventures with M. Georges, J. Taylor and M. Bishop as principal scientists. Markers were found almost for any trait. However there was problem with validation as major markers found by some groups were not confirmed by other groups, or the substitution effects were very different. Soon, some companies closed while some others drastically reduced their investment.

A good overview of the situation in QTL and MAS could be assessed at the 2002 World Congress on Genetics as Applied to Livestock production. This congress meets every four years and provides an overview of progress in animal breeding over the previous four years. As opposed to the congress held in 1998, the enthusiasm was much reduced and only a few papers addressed practical applications. Spelman *et al.* [2002] presented results of MAS from New Zealand from a project that was collaborative with some of the best scientists and companies in the Netherlands and Belgium. A marker was identified (DGAT1) that increased fat but reduced protein yield; such a marker has approximately zero value in many pricing systems (Weller, personal comm.). Work to incorporate this marker resulted in losses due to testing fewer bulls. A paper on a large QTL project from France by Boichard *et al.* [2002] described only steps in the data collection, stating indirectly that no publishable results existed at that time. A paper on plants by Hospital *et al.* [2002] described an identification of markers but then selection was in the wrong direction as the linkage phase was misidentified. Thus, MAS was not as successful as expected.

Around that time, Quaas *et al.* [2002] gave a talk on gene called Genestar that increased marbling. That gene exhibited uncertain mode of inheritance causing fears that its application on a large scale may also lead to uncertain results. The effect of this gene was a small fraction of the phenotypic SD, and its claimed commercial feasibility was due to increasing the grade of carcass by one when the average was

very close to the grade boundary. In pigs, Noguera *et al.* [2003] looked at the ESR marker that was previously identified as a gene that increased the number of piglets by 1. In this study, ESR was identified as a marker that had only a minimal effect in European populations.

Attitude towards MAS/QTLs

The MAS/QTL revolution generated different types of attitudes in different circles. At universities, there was a great deal of optimism in groups that greatly benefited from large funding. However, in many places, the enthusiasm was only expressed officially while doubts were expressed unofficially, especially among scientists with good knowledge of quantitative genetics. This optimism seems to decline as funding for QTL research declines and is being substituted towards funding in gene expression, proteomics, etc.

The response is mixed in companies. There is an official optimism in companies whose main purpose is commercializing markers (e.g., see proceedings of 2003 BIF workshop). However, there is disillusionment in divisions of breeding companies or breed associations that are responsible for genetic selection as MAS involved large expenditures and the important problems were left unsolved.

For example, the main problem in Holsteins worldwide is deteriorating reproduction that earns this breed a reputation of poor and declining fertility (Lawlor, per comm). Following is a threat of importation of other breeds and of crossbreeding. In such a case, the value of Holstein stock decreases thus reducing the values of Holsteins to registered breeders and also decreasing the semen sales of AI companies.

In pigs, a large improvement at the nucleus level brought little or no improvement at the commercial level over the last 10 years (M. Culbertson, pers. comm) while challenges are mounting. These include increased mortality that now can approach 30% at some farms, reduced meat quality, and increased susceptibility to diseases. There are reports that farms and even breeding companies can lose their entire stock to disease. Solutions to these problems would be methodology that would improve animals at the commercial level. This requires data collection at the commercial level for a large number of traits and development of methodologies for the joint evaluation of purebred and crossbred animals.

Problems with MAS/QTL

Problems with MAS lead to a question whether these are due to insufficient attention to details or due to too simplistic assumptions. During informal discussion at a Congress of Genetics in 1993, well known British geneticists – W. Hill and R. Thompson – said that if 100 QTLs were responsible for a trait and they acted additively, animal breeders would soon be doing simple counting. However, if interactions exist among QTLs, the QTL model becomes intractable.

Problems of QTL/MAS selection were a focus in a symposium called Molecular Genetics: Lessons from Past/New Directions held in 2003 at the annual meeting of ADSA and ASAS. The current status in MAS/QTL was presented by Dekkers [2004]. He stated that there are three types of markers: genes, linkage equilibrium (LE), which are located very close to the gene, and linkage disequilibrium (LD), which are located farther from the gene. LD markers are easiest to find but hard to use. In selection, LE markers are markedly inferior to genes. There were no markers for low heritability traits as these require a large amount of data for estimation. Finally, benefits from commercial applications were hard to assess. Pomp and Wesolowski [2004] focused on molecular genetics of mice. They stated that, for growth, all regions in a genome were identified, but not a single gene. Genes are expressed in a complex and nonlinear fashion. In particular, epistasis is important. Some insight can be obtained by studies in microarrays, however, there is a long time horizon for potential applications. The future of molecular genetics in animal breeding was addressed by Walsh and Henderson [2004]. They said that it would take a long time before classical selection becomes obsolete. Studies involving microarray data are potentially useful; in the end, one may be able to select on gene networks. However, caution should be exercised as gene expression is tissue dependent and biochemical pathways involve genes in complex ways, involving branches and loops.

Other issues

In QTL studies, it is usually assumed that an allele has a certain substitution value. However, some traits (e.g. fertility) are not well defined, and it impossible to search for markers for an undefined trait or until this trait is well understood. Traits change over time, and also genetic correlations among traits change over time [Tsuruta *et al.* 2002]. When there is a genotype x environment interaction, the substitution value of a gene or gene combinations are not constant but dependent on the environment. Finally, even if a major gene is identified for a trait with a large economic value, it is also necessary to find a value of this gene for secondary traits as such a gene may have a negative impact on fitness. Long term selection on production seemed to have resulted in decreased fertility and increased mortality in many species [Waaij 2004].

Educational issues

Students and industry are easily excited by promises of QTL/MAS, which on the surface seem very simple to implement. However, almost all benefits of breeding are currently derived from classical selection, which requires considerable skills to practice. Large appeal of MAS results in few Ph.D. students entering programs relevant to genetic evaluation. Subsequently, the influx of talent into the field of genetic evaluation has slowed down dramatically, and the industry is already facing a shortage of qualified scientists. The reversal of this trend requires increased funding.

Success stories of molecular genetics in animal production

This article does not try to minimize successes of molecular genetics. This field provides reliable tests for many recessive genes. Several major genes have been identified. Genetic markers are useful for animal identification. This can be used for determining the parental identity, for example in multiple sire systems. The identification can also be useful for tracing animals in the food chain or as a help in animal thefts. MAS is likely to eventually become viable when more progress is made in gene typing and when the path from genotype to phenotype is understood better.

It remains to be seen whether MAS may become successful commercially. The best gauge may be in observing viability of large, well funded groups that at the same time are financially accountable. Perhaps the largest effort in MAS occurs in the pig area in Monsanto in a group led by M. Lohuis. This group employs about 15 Ph.D., and it has access to consulting by major scientists. Monsanto has a track record of funding successful projects and eliminating unsuccessful ones. A successful product from this group would indicate a breakthrough in successful implementation. Similarly, an elimination of this group would indicate that MAS is not likely to be profitable in the near future.

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Wyzwania związane z selekcją wspomaganą markerami – artykuł przeglądowy

Streszczenie

W ciągu ostatnich 15 lat główny nacisk w badaniach genetycznych zwierząt został przeniesiony z genetyki populacji na genetykę molekularną ze szczególnym uwzględnieniem identyfikacji *loci* cech ilościowych (QTL) i selekcji wspomaganą markerami (MAS). Do tej pory wyniki zmiany podejścia są skromne. Jest to wynikiem kilku czynników obejmujących m.in. trudność identyfikacji genów i uproszczone założenia dotyczące sposobu dziedziczenia. Zwrócenie się w kierunku MAS spowodowało odejście pracowników naukowych od genetyki populacji, odpowiedzialnej niemal całkowicie za dotychczasowy postęp genetyczny uzyskiwany przez firmy hodowlane. Jednocześnie problemy związane z pogorszeniem zdolności adaptacyjnych, wynikłe ze zbyt intensywnej selekcji na cechy produkcyjne, nie znajdują odpowiedniego zainteresowania – brak dobrze przygotowanych naukowców w tej dziedzinie. Przyszłość hodowli zwierząt zależy od związku genetyki populacji i genetyki molekularnej. Genetyka populacji jest obecnie krytycznym składnikiem tego aliansu.