Marker-assisted Selection 17

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Introduction

Marker-assisted selection (MAS) has been suggested as an improvement to the use of phenotypic records for genetic change of cattle populations. The appeal of an approach that looks directly at genes rather than inferring genotype from phenotype has always been obvious, but only recently have techniques for low-cost and comprehensive genotyping been available. Efforts to map quantitative trait loci (QTL) have begun and will continue. In this chapter, the assumption will be made that loci with major effects on performance have been mapped to chromosomal location and that accurate tracking of segregation of chromosomal segments containing these loci can be done by using the

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causative loci themselves or brackets of linked anonymous markers. Use of this information for cattle improvement is the next step.

The first utilization of these techniques was in the detection of recessive genetic diseases, such as bovine leucocyte adhesion deficiency (BLAD) (Kehrli *et al.*, 1992) and deficiency of uridine monophosphate synthetase (DUMPS) Shanks *et al.*, 1987; Schoeber *et al.*, 1993). Other single-gene traits, such as polled (Georges *et al.*, 1993; Harlizius *et al.*, 1997) and coat colour (Klungland *et al.*, 1995), are also being improved, using molecular testing, but selection for improving economic traits, such as muscling, growth, reproduction, meat and milk quality and health, is just beginning (Cowan *et al.*, 1997).

Breeders and scientists are incorporating molecular data in a number of ways, but optimum strategies are still under investigation. The term itself, marker-assisted selection, implies the most likely use of molecular data as additional information on the genetic value of animals. Combinations of phenotypic records and molecular genotypes into an index for selection will be the most likely implementation. The relative weight placed on phenotype or genotype for optimal efficiency will depend on many factors. The most limiting of these is the size of the effect of a major locus on economic merit. Contributions of major loci to genetic variance are likely to be small to moderate (Smith and Simpson, 1986). Even if a major contribution to genetic variance is due to a few loci, these loci may not be accurately mapped or characterized in every case. With some major loci tracked with molecular data and other untracked loci distributed across the genome, the most efficient index will combine all available molecular and phenotypical information.

In general, cattle breeding uses a hierarchical structure, with élite animals of high genetic value concentrated in pedigreed populations and commercial animals benefiting from advances made at the élite level. Improved genetics are distributed using natural breeding and reproductive technologies such as artificial insemination and embryo transfer, with the potential for technologies such as cloning (Wilmut *et al.*, 1992; Bishop *et al.*, 1995). Use of molecular data at various parts of this infrastructure will have different cost–benefit ratios (Beckmann and Soller, 1983).

Previous studies have indicated that genotyping costs could be balanced by improvements in élite populations (Brascamp *et al.*, 1993). Rapid changes in genotyping technologies have dropped the cost on a per-animal basis and high-throughput strategies are likely to accelerate this trend. Even commercial herds might utilize molecular data profitably in some instances. Strategies for MAS depend on the population structure, state of knowledge of genetic associations, traits of interest and comparison with alternative strategies. Selection at different stages in the life cycle may differ in the contributions that could be made by adding markers to existing improvement schemes, since accuracy of selection differs according to the phenotypical records available.

Theoretical Background to Mendelian Sampling

Use of MAS depends on the correlation of molecular genotypes with genetic value for trait differences. Translation of molecular data into additive genetic value in diploid species is based on the additive value of the two alleles of an individual for a given trait. In order to use a consistent approach to assigning value, Falconer (1989) utilized a notation where the additive breeding value of an individual for a given locus was the sum of the additive effects of each of two alleles carried on homologous chromosomes. These additive effects were indicated as α_1 and α_2 for individual alleles on each chromosome of a homologous pair. Subscripts refer to the two chromosomes, which may carry identical or different alleles. Additive genetic value is based on the value of substitution of one allele for another in a given population and may include the average effect of both additive and dominant gene actions. This notation can be used to illustrate the relationship between alleles in parents and offspring, using the following arguments.

Consider an individual offspring with a sire and dam. At a given locus, let the sire have alleles S_1 and S_2, where the allele designated S_1 is the allele transmitted by Mendelian sampling to the offspring and the allele S_2 is the allele not transmitted to this particular offspring. Similarly, the dam carries alleles D_1 (that was transmitted) and D_2 (not transmitted to this offspring). Then the breeding value of the sire is $\alpha_{S1} + \alpha_{S2}$, the breeding value of the dam is $\alpha_{D1} + \alpha_{D2}$ and the breeding value of the offspring is $\alpha_{S1} + \alpha_{D1}$.

An interesting parameterization involves expressing the breeding value (BV) of the offspring in the following way. Starting with:

$$\text{BV of offspring} = \alpha_{S1} + \alpha_{D1} \quad (1)$$

Adding and subtracting the same quantity in two places (no net change):

$$\text{BV of offspring} = \alpha_{S1} + \left(\frac{\alpha_{S2}}{2} - \frac{\alpha_{S2}}{2}\right) + \alpha_{D1} + \left(\frac{\alpha_{D2}}{2} - \frac{\alpha_{D2}}{2}\right) \quad (2)$$

Rearranging:

$$\text{BV of offspring} = \underbrace{\frac{\alpha_{S1} + \alpha_{S2}}{2}}_{\text{term 1}} + \underbrace{\frac{\alpha_{S1} - \alpha_{S2}}{2}}_{\text{term 2}} + \underbrace{\frac{\alpha_{D1} + \alpha_{D2}}{2}}_{\text{term 3}} + \underbrace{\frac{\alpha_{D1} - \alpha_{D2}}{2}}_{\text{term 4}} \quad (3)$$

In this parameterization, the breeding value of an individual is expressed in four terms. The first and third terms represent the breeding values of the sire and dam of the individual. Thus the sum of the first and third terms is the pedigree contribution to any offspring of these two parents. The second and fourth terms are the Mendelian sampling terms, representing the deviation of this individual from the parental average due to the particular set of alleles passed to this offspring.

Note that this parameterization has an interesting property; the additive value of the offspring is expressed as a function of all the parental alleles, not just those passed to this offspring. In particular, Mendelian sampling terms are expressed as differences in the value of the parental alleles. This difference in

alleles is termed by Falconer the average effect of gene substitution. Given today's technology, with the opportunity to do exchanges of genetic material even between species, gene substitution could be interpreted in several ways. Perhaps a preferable term for Falconer's concept would be average effect of allele substitution. Mendelian sampling terms are one-half of this effect, representing the deviation of this offspring inheriting one allele from the average of all offspring.

This theory can be extended to more than one locus affecting the trait of interest. In the simplest case of independent additive gene action, loci from separate chromosomes segregate independently and effects can be summed. For loci linked in clusters, the effects are similar but need to be adjusted for physical linkage in phase relationships of alleles and for potential recombinations between loci. Even with an infinitesimal model of many loci with small effect, a single marker can have a substitution effect for an entire linked chromosome segment (Dekkers and Dentine, 1991).

Variances of the four terms are equal (each one-quarter of additive genetic variance) if no covariances exist between additive values of alleles in parents or offspring (for instance, in the absence of inbreeding or assortative mating). In these situations, half of the variance of breeding values in the population is due to the variances of the pedigree values and half to Mendelian segregations (Dekkers and Dentine, 1991).

In using molecular information about alleles present in individuals, prediction of these four terms is affected differently based on stage of life cycle and availability of phenotypical information. For planned matings, the prediction of offspring is limited to the prediction of the pedigree merit (terms 1 and 3), since the segregation terms are not yet determined. After the zygote has been formed, prediction of breeding value could include prediction of the Mendelian sampling terms if molecular data are used for the offspring or if phenotypic data are available on the offspring itself or its progeny. Thus the portion of the genotype that can be inferred with phenotype only may vary. For calves too young for phenotypes or offspring, family records (phenotypes or genotypes) can only address the pedigree terms; for animals with their own records and/or records on progeny, phenotypes and genotypes contribute to estimation of all four terms.

Opportunities for Marker-assisted Selection

For various traits, phenotypical data provide more or less information for estimating breeding value, depending on heritability. Low-heritability traits use family information more heavily and, until extensive records on individual and progeny are available, correlations of actual additive genetic value and estimated breeding values remain low. In these situations, MAS will have more advantages. High-heritability traits leave little to be improved and MAS will provide fewer advances for these traits unless the traits are sex-limited or phenotypes are difficult to obtain. Carcass traits, longevity, disease resistance and

reproduction are traits where MAS may have unique advantages (Sellier, 1994; Ruane and Colleau, 1996).

In cattle, most selection schemes utilize phenotypical information on individuals and their relatives in complete animal models, using best linear unbiased prediction (BLUP) or some approximation to this selection-index approach. These methods work most efficiently when accurate and complete pedigree information is known and when large numbers of phenotypical records are available. For some cattle-improvement schemes, pedigrees may be unavailable or uncertain. The utilization of molecular information on individuals has different contributions to make in these various schemes. Clearly, when family information is unavailable and heritability from individual records is low, molecular data can provide additional selection tools. If pedigrees are known, loci with direct effects and loci with known linkages within families can be used. If pedigrees are not known, only those loci with causative effects or those in population disequilibrium with known markers could be used.

Adult selection

For cattle populations using progeny-test schemes with many offspring records, little additional information can be obtained from genotyping of élite sires (Dentine, 1992). Correlations of estimated breeding value with true breeding value are already close to 1, and molecular data cannot improve these estimates for the sires themselves. At the other extreme, animals with no pedigree information and no performance records might benefit most from molecular testing, since MAS would provide the only estimate of breeding value. Selection of grade animals, verification of parentage in pasture-bred herds and identification of homozygotes for favourable qualitative traits, such as polled, would be most enhanced by MAS for adult cattle.

Juvenile selection

Young animals present a unique opportunity for MAS. Estimates of breeding values for parents, regardless of the records used in the estimation technique, can only predict the pedigree terms (terms 1 and 3 in equation 3). Even sib data only contribute to the accuracy of the prediction of pedigree terms. The Mendelian sampling terms are not available, regardless of the extent of phenotypical records on parents or sibs. Thus the maximum correlation of estimated breeding value with true additive genetic merit is limited. The 'effective heritability', the squared correlation between the criteria for selection and actual additive breeding value, is limited to 50% if no records on self or progeny are included.

Molecular data can be obtained on young calves or even embryos to assist in the prediction of the breeding values for terms 2 and 4. Thus MAS has a particular role for juvenile selections where reproductive technologies allow early

selections and no other records are available. Molecular data may be the only selection criteria with very rapid generation turnovers (e.g. velogenetics; Georges and Massey, 1991) or may be followed by phenotypical or progeny testing. Early molecular testing has been used to sex embryos (Colleau, 1991), and young dairy bulls are currently screened for a number of genetic defects prior to progeny testing.

Multistage selection

Artificial insemination bulls

Selection of bulls for artificial insemination is a very large contributor to decisions affecting genetic progress in current dairy-cattle schemes (Van Vleck, 1977). Investments in bulls due to testing costs can be high and the opportunity to improve the accuracy of selection is very attractive. In addition to using the molecular data to predict the value of young bull calves, molecular data may also be an additional tool used to evaluate the genetic superiority of the parents. Genotyping of élite progeny-tested sires may not be efficient, due to the high accuracy with which their breeding value is estimated, but questions about the superiority of bull dams could be addressed. Bull dams are highly selected, but may have lower accuracy of selection than bull sires. Bull dams are often young to shorten the generation interval and have limited phenotypical records. In addition, preferential treatment of élite cows may not allow for dependable estimates of their additive breeding values.

Young bulls

For young bulls, MAS provides early information on Mendelian sampling (Kashi *et al.*, 1990). In particular, molecular data provide the only data on inheritance of major qualitative loci, such as genetic defects or exact genotypes for desired qualitative traits. For quantitative traits, MAS applied within families allows some discrimination between full-sibs with identical pedigrees or between half-sibs with similar dams.

Another strategy that might benefit from MAS is the sequential selection decisions based on traits expressed at different times throughout life. If traits are expressed late in life, early molecular testing might allow prescreening of individuals at an earlier age to avoid the expenses of testing for all individuals. Lifetime reproductive performance, longevity or freedom from arthritis might be traits that could benefit from knowledge of loci associated with these late performance traits. Given the expense of progeny testing, a prescreening of candidates to identify those with more potential will be an important use of molecular data.

Utility of Marker Data

Parentage and species verification

The ability to track segregation of alleles from parent to offspring and the uniqueness of genotypes for individuals allow use of molecular data directly in cattle improvement. Even if loci are not linked to genetic disease or major trait effects, knowledge of a deoxyribonucleic acid (DNA) pattern, or fingerprint, can be used to improve cattle. Animals and carcasses can be positively identified to connect animals to phenotypes such as meat quality and other post-mortem measurements. Identification of species or an individual can prevent fraud in meats (Meyer *et al.*, 1995) or be used in potential theft cases (Wagner *et al.*, 1994). Parentage can be verified for cases of pasture breeding by multiple bulls or to improve accuracy of progeny testing.

Qualitative traits

A number of qualitative traits can also be managed more easily with identification of heterozygotes as carriers of genetic disease or to distinguish homozygotes from heterozygotes for favourable single alleles, such as polled. In addition to checking for undesirable alleles in young bulls entering progeny testing, homozygous normal heifers or embryos might bring a premium price. Coat colour has economic value in some markets and matings could be made based on knowledge of genotype to ensure that offspring would have the most desirable phenotypes. Sexing of embryos would also add value to embryos and would contribute efficiencies to herd replacement operations (Colleau, 1991).

Although molecular data will help eliminate undesirable alleles and increase favourable alleles, there are costs associated with testing. At very low frequencies of undesirable alleles, the cost of testing would not be balanced by the potential gains from knowing genotype. Thus, undesirable alleles would probably not be eliminated completely by testing. If testing is stopped, based on the small potential gain, but some undesirable alleles rise again in frequency to the point where the impact rises to previous levels, molecular testing could be resumed.

Quantitative traits

Additive variation

Use of marker data to improve selection for continuous quantitative traits has been of great interest. Although most scientists agree that a combination of marker information and phenotypic records is superior to either alone, the weighting of the two sources of data is still under investigation. Clearly the maximum use of additive genetics for the subsequent generation would result

from estimation of combined breeding value for major genes and other genetics in a single value. Methods for this estimation have been proposed by Fernando and Grossman (1989) but have not been utilized, due to computational and logistic difficulties. With only a few individuals genotyped, reluctance of genotyping organizations to make data public and reliance on linked markers for genotyping, the complete approach is unlikely to be utilized. Various other indices of merit have been proposed and used in simulations to investigate the likely results of utilizing these methods (Larzul *et al.*, 1997). A few general conclusions can be drawn as a result of these studies.

1. Modest improvements in genetic progress are likely under selection on a combined index of molecular and phenotypical data, as contrasted with the use of predictions from phenotypical records alone.
2. Putting too much emphasis on a few major loci can result in lower overall progress than using phenotypical data alone.
3. Greater progress is possible under low initial frequency of favourable alleles, more accurate estimates of major gene effects, larger effects from fewer loci, shorter time horizons, traits of lower heritability, traits that are not measured on every individual (sex-limited, carcass traits, etc.) and instances where family relationships are unknown, incomplete or misidentified.
4. Although increases in selection accuracy may be modest, changes in generation interval may also occur if marker information is used for earlier decisions (Edwards and Page, 1994). Most studies have assumed selection decisions occurring at the same time in two alternative schemes. With genotypic information available much earlier than most phenotypical records, strategies that shorten the generations may accelerate genetic progress primarily through increasing the turnover of generations.
5. Advantages of MAS for a single major locus are realized fairly quickly (Fournet *et al.*, 1997) and continued progress depends on continued discovery of QTL with major trait effects (Meuwissen and Goddard, 1996).

Several other strategies could potentially provide genetic improvement through MAS faster than in traditional individual or family-index selection. In the case of multiple trait selection, MAS could utilize individual loci with pleiotropic effects on several traits. Genetic correlations that unfavourably retard desired genetic progress are composed of the joint effects of all loci involved in both traits. But individual loci may not have pleiotropic effects consistent with the average genetic correlations. Individual loci with favourable, or at least less undesirable, joint effects could be used in MAS to make faster progress toward the desired goals.

Non-additive variation

Non-additive variation is also a target for MAS utilizing specific loci. Many QTL detection schemes allow estimation of dominance or epistasis for a set of loci. Schemes that deploy genotypes across a variety of environments could also be used to estimate genotype × environment interactions. Quantitative trait loci that exhibit such interactions could be used to specifically target assignment of

individuals to environments, using marker genotypes. Maintenance of genetic variability and avoidance of inbreeding could also be objectives of MAS (Schoen and Brown, 1993). Mating strategies could incorporate these data to take advantage of non-additive merit for individuals or breeding populations. Finally, selection for heterosis at single locus or as a general index across loci would be possible using molecular data for individual selection.

Specialized uses

Transgenics

Several special cases involve the tracking of introduced alleles into populations. Use of molecular tags on genes introduced by gene insertion or site-directed mutagenesis can track the inheritance of alleles in the offspring of the original (usually hemizygous) founder animals. The insertion of pharmaceutical genes into embryos that originated from ova of cull cows has been suggested. If the original transgenic animal was created from embryos of lesser overall merit relative to the population, the successful transgene insertion must be transferred to a better background genotype to make the resulting transgenic line economically valuable (Cundiff *et al.*, 1993; Hillel *et al.*, 1993).

Introgression

Similarly, superior alleles not currently present in improved breeds can be introduced into populations by conventional breeding and their introgression accelerated if molecular data can track the introduced alleles (Hospital *et al.*, 1992). An additional advantage comes from the ability to discriminate against the other parts of the introduced genome by selection against other introduced (and presumably inferior) alleles (for instance, Markel *et al.*, 1997). Various schemes have been proposed to save the cost of genotyping every individual and the conclusions of several authors favour use of molecular data in early generations and use of phenotypical data on most loci, with genotyping only at the introduced locus.

Marketing

Income from sale of improved genetics is not entirely based on objective measures of genetic merit. Market demand can influence price, based on the reputation of the provider of genetics, popular perceptions of the competitiveness of organizations and enthusiasm for new approaches. In the case of MAS, customer preference for higher accuracies of selection and the ability to market an organization as forward-thinking may create temporary advantages that increase the attractiveness of genotype data. Buyers of cattle, embryos and semen may be willing to pay premium prices for genotyped animals in excess of the true genetic value of the information.

Potential Pitfalls

Timing of selection

Although marker-assisted selection has considerable potential for genetic improvement, some additional considerations must be included. The first is the cost of testing and analysis to determine desirable genotypes. The logistics of getting DNA samples and phenotypical records on appropriate individuals will continue to be difficult in dispersed cattle populations. Original estimates of costs of molecular testing were based on Southern hybridization techniques (Beckmann and Soller, 1983) and are overestimates under current polymerase chain reaction technology. More advanced laboratory techniques, such as the DNA chip technologies, clever statistical designs and improved software for analyses are likely to decrease costs even further. Cost–benefit analyses will still need to be included in choice of strategies for employing MAS but may not be limiting factors.

A more biological difficulty is the timing of detection of QTL and utilization. In general, detection of QTL occurs by observing the performance of progeny (or grand-progeny; Weller *et al.*, 1990) and relating this performance to alleles inherited from parents or grandparents. Estimates are relevant to the previous population allele frequencies. With the long generation intervals in cattle, changes in allele frequency or traits of importance may have occurred that change the economic value of the loci. Utilization is most advantageous in young animals and is most likely to occur in an even later generation than those involved in the detection. Thus the long time span between the genetic basis for MAS and the utility of that knowledge will continue to decrease the impact of MAS.

Additionally, designs for detection are most powerful at intermediate frequencies of favourable alleles, but the advantages of MAS are greatest for quickly increasing favourable alleles at low frequency. No doubt some favourable alleles will be detected that are near fixation; in these instances, MAS has little to offer. Some advantages to knowing that such loci have significant effects on traits may still be useful in cases where favourable alleles can be introgressed into other populations or where searches of the locus may discover previously undetected alleles superior to the currently prevalent ones. These loci will also be used in basic biological studies to determine what gene actions are involved in allele superiority.

Accuracy of estimates of allele substitution

Most simulations that have addressed the use of molecular data have presumed that estimates of allelic effects would be known without error, although some have considered losses from recombination. Inaccuracies of estimation, particularly overestimates, will put undue emphasis on molecular data. Uncertainty about size of allelic effects will undoubtedly lower genetic progress

(Spelman and van Arendonk, 1997). The power of detection in most schemes is not able to detect smaller QTL, and efforts to avoid high false-positive rates can bias estimates. Some simulations have looked at risk in MAS strategies and have concluded that risks were not increased by the use of markers (Meuwissen and van Arendonk, 1992). Continued verification of allele substitution effects associated with markers may avoid some of the problems with false-positive identification or inaccurate estimation of size or location (Gimelfarb and Lande, 1994)

Linkage disequilibrium problems

Most uses of marker data will be in populations already under selection for one or more traits. In these populations, some linkage disequilibrium between loci will already exist and further changes to phase disequilibrium will occur with MAS. In some instances, existing unfavourable linkages can be more efficiently handled with marker data. An example is the apparent close linkage of a genetic defect in Brown Swiss and favourable alleles for production traits at one or more loci (Hoeschele and Meinert, 1990). If a cluster of QTL is present in populations, MAS provides a mechanism to select favourable recombinant haplotypes that might otherwise increase in frequency very slowly.

Unlinked QTL can also be in phase disequilibrium from mutation, migration, selection or drift (Hospital and Chevalet, 1996). These relationships may complicate estimates of QTL allele substitution effects in segregating populations (Mackinnon and Georges, 1992). Negative covariances between effects at loci that influence traits could slow genetic progress and reduce genetic variance (Bulmer, 1971). This effect occurs regardless of the method of selection used, but some strategies for MAS could modify the relationships in positive or negative directions.

Short-term versus long-term results

One particular demonstration of this disequilibrium effect on genetic progress is seen in the comparison of short-term and long-term response. Gibson (1994) showed that some strategies for MAS could produce a greater short-term response but lower longer-term gains. This phenomenon also occurs with other methods of selection, such as family index, and is attributable to decreases in genetic variance due to linkage disequilibrium. Dekkers and van Arendonk (1998) showed that MAS could be modified to optimize response at a given planning horizon, with weights that varied with allele frequencies.

Summary

One unifying principle in genetic selection is the importance of using all known information in the selection process. With increasing knowledge of the position and effects of major loci for quantitative variation, modifications of traditional selection procedures based only on phenotypes will be needed. Complications of the use of MAS will require customized strategies to maximize benefits and avoid problems. Although MAS may not be as simple as first proposed, some combinations of molecular and phenotypical data are likely to be used profitably in cattle selection programmes.

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