Proc. Assoc. Advmt. Anim. Breed. Genet. Vol 12

IMPROVING A TRAIT INFLUENCED BY A MAJOR GENE (QTL) AND MANY GENES WITH SMALL EFFECTS

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SUMMARY

Most economically important traits are influenced by the environment and by many genes. Such traits can be improved by selecting as parents those individuals with above-average genetic merit as assessed from phenotypic information. Methods for predicting genetic merit have assumed genotypes are determined by a large number of genes, each gene having a small effect. In reality, genes likely differ in the size of their effects, and some may account for differences in performance between individuals of up to 1 genetic standard deviation. Well-designed genome searches provide good chances of determining the sizes of quantitative trait loci (QTL) and locating their approximate chromosomal positions. Several options are available for using this knowledge. One could select animals on the basis of marker genotypes, irrespective of polygenic merit, to rapidly increase QTL frequency. Alternatively, one could incorporate marker knowledge in genotype prediction and rank animals on aggregate merit combining polygenic effects with the average effects of QTL. The benefits of these approaches are of interest, relative to selection in ignorance of the presence and size of QTL. In practice, utilising knowledge of QTL to increase their gene frequency can, in the short term, reduce selection available to exploit polygenic variation. Selecting QTL can increase genetic advance to the next generation relative to strategies that more slowly increase QTL frequency but may result in average merit being overtaken in subsequent generations. The reasons for these long-term "losses" are described and some guidance provided as to the circumstances where such losses may be minimised.

Keywords: Selection response, marker-assisted selection

INTRODUCTION

Over the last century, paradigms used to explain animal performance progressed from oligogenic (or even monogenic) inheritance through to polygenic inheritance with an infinite number of small genes. Over the last decade, the availability of microsatellite markers has contributed to improved linkage maps, with sufficient resolution to undertake genome-wide searches for QTL. Genotyping throughput (and cost) and the availability of family material with appropriate pedigree and performance information are the major limitations to detection of QTL. Some interesting chromosomal regions have already been detected in major plant and animal species of laboratory and economic interest (see for example reviews by Haley 1995; Stuber 1995). In some cases (e.g., Drosophila) the inheritance patterns that seemed adequately described by the infinitesimal model now appear to result from a small number of genes with quite large and in some cases interacting (epistatic) effects (Mackay 1995).

Some chromosomal regions of current interest will prove to be the result of Type I errors, but there is little doubt that other QTL will be verified as real. Such genes offer opportunity for exploitation in at least three manners. First, these QTL could be moved between breeds or lines of individuals through marker-assisted introgression (MAI). This technique may allow, for example, fine wool genes to be transferred from merinos into dual-purpose sheep breeds, or marbling genes to be transferred from Jersey cattle into beef breeds, without carrying along undesirable genes. The efficiency of introgression of desirable genes during backcrossing has been shown to be considerably improved by the presence of flanking molecular markers (Soller and Plotkin-Hazan 1977). Second, some QTL will eventually be fine-mapped, allowing base-pair polymorphisms to be identified and the physiological basis for differences in performance that result from alternative alleles to be described. Such discoveries will be of considerable biological significance, and may give rise to non-genetic delivery of improved performance, such as through vaccines or other treatments. Third, knowledge of QTL will allow marker-assisted selection (MAS) whereby markers flanking the QTL will provide additional information to assess the likely QTL genotypes of offspring. The best case scenario would involve highly polymorphic markers located very close to the QTL, allowing across-family selection. In these conditions, Gibson (1994) and Spelman and Garrick (1997) have shown that genetic merit at fixed points in the long term can be reduced by prior selection for QTL. This paper presents a simple model that displays this phenomenon, explains the cause of this apparent anomaly, and identifies some factors that contribute to the magnitude of such losses.

MATERIALS AND METHODS

Model. A deterministic model was used to predict responses to selection for a trait influenced by a single additive bi-allelic locus plus many genes with small effects (additive infinitesimal model). The population consisted of three subpopulations, corresponding to the three possible genotypes for the bi-allelic locus (++, Q+, QQ). The initial population was formulated by defining the QTL frequency (and therefore the relative sizes of the three subpopulations assuming Hardy-Weinberg equilibrium) and QTL size (each Q allele increased breeding value by a units). True breeding values from these initial subpopulations followed normal distributions with means $[-2a(1-p), -a(1-2p), +2pa]$ for p = freq(Q) and unit genetic variances for background polygenic effects. Estimated breeding values for each subpopulation followed normal distributions with variances equal to the square of the correlation between true and estimated breeding value (r_{TI}^2) for background polygenic effects. The value assumed for r_{TI}^2 was the within subpopulation heritability, taken to be 0.30, equivalent to the accuracy obtained from a single phenotypic observation adjusted for fixed effects. Truncation selection was applied to estimated breeding values from discrete generations with equal selection intensities imposed on each sex. The subpopulation means for the subsequent generation were calculated for random mating of selected parents using calculated frequencies and average polygenic merits of Q and + gametes, accounting for the two sources of each gamete. That is, both QQ and Q+ parents contribute Q gametes, and Q+ and ++ parents contribute + gametes. Gametes contributed from Q+ parents segregate in merit according to the presence or absence of the favourable QTL allele.

Selection in ignorance of the QTL presence. The usual strategies for estimating breeding values involve adjusting observations for fixed effects and weighting (i.e. *regressing*) the resultant

The intensity of selection applied to background polygenic effects is different for each subpopulation of the three QTL genotypes, as a direct result of truncation selection causing differential preference among these classes. A greater proportion of available QQ individuals are selected as parents than is the case of Q+ or ++ genotypes. Accordingly, the within subpopulation selection intensity for background polygenic effects is least in the QQ class and greatest in the ++ class. This has the effect of advancing polygenic merit in + gametes to a greater extent than the advance in polygenic merit among Q gametes. As a result, a single cycle of selection leads to the differentials between the three subpopulations (previously *a*), shrinking to a lesser amount. The differential will continue to shrink for several cycles of selection (e.g., 1.0*a*, 0.89*a*,..., 0.81*a*) at which point it will stabilise, provided selection is maintained. On cessation of selection, the differential will progressively recover its original value. This phenomenon (Bumer 1971) is variously known as linkage disequilibrium, gametic phase disequilibrium, or the Bulmer effect. Note that it is occurring in this context even though the bi-allelic QTL is physically "unlinked" to polygenic background effects. The development of gametic phase disequilibrium following selection tends to bring the three subpopulations closer together, and therefore reduces the extent to which QQ individuals are preferred over the other genotypes. This reduces the disparity in background selection between the three subpopulations, and reduces the extent to which selection favours Q gametes.

The maximum polygenic advance occurs when equal intensity of selection is applied in each of the three subpopulations. Polygenic advance is compromised by differential selection among subpopulations. This can be demonstrated in general with any two subpopulations. Unequal selection intensities will increase advance in one at the expense of the other, and the pooled selection advance across the subpopulations will be reduced in comparison with equal intensities. As a result of the shape of the normal distribution, this reduction is greatest when 50% candidate individuals are selected and less important when selection is very intense. Figure 2 shows the effect of selection intensity on the reduction in pooled selection differential (i-bar) that results from selection disparity across two equally-sized subpopulations.

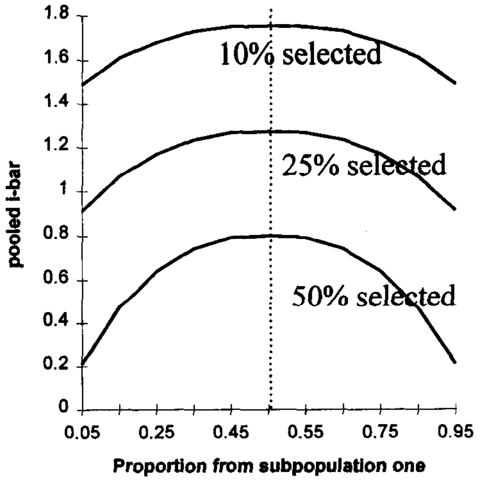

Figure 2. The impact of disproportionate selection from two subpopulations on pooled selection differentials (i-bar) for 10%, 25% and 50% individuals chosen to be parents.

Comparative progress for selection with and without knowledge of the QTL. Knowledge of the QTL prevents the bias or "shrinkage" in EBVs that occurs when major genes go undetected. Accordingly, the degree to which QQ and Q+ subpopulations are preferred in comparison to ++ is greater when QTL are known than was the case in ignorance. This has the effect of placing greater deviations towards the population mean. Applying this technique across subpopulations, in ignorance of the presence of the QTL, will bias EBVs towards the population mean. That is, ++ genotypes will tend to be overevaluated and QQ genotypes underevaluated, with Q+ individuals under- or over-evaluated depending upon QTL frequency. The actual bias will vary with generation as QTL frequency changes, and gametic disequilibrium develops. The proportion of individuals chosen as parents from each of the three subpopulations was determined by calculating the truncation point of these biased EBVs across the three QTL genotypes, using arithmetic techniques as in Ducrocq and Quaas (1988). Knowledge of the average true breeding values for the selected proportion within each subpopulation was then used to determine gametic merits.

Selection with knowledge of the QTL genotype. Truncation selection was applied to EBVs across subpopulations, but given knowledge of the QTL genotypes the EBVs are unbiased as deviations would be regressed towards relevant subpopulation means rather than towards the overall population mean.

General framework for selection. Selection can be applied to change QTL frequency, to advance background polygenic merit, or both. Such partitioning can be considered from the perspective of a selection objective. The goal is to increase phenotypic performance, the "traits" in the objective represent the QTL effect and background polygenic effects. Given knowledge of the QTL, the breeder can control the relative emphasis to apply to each component.

Index = v_1 × QTL BV + v_2 × polygenic EBV

Selection on EBV in ignorance of the QTL amounts to selection using $v_1 = h^2$ and $v_2 = 1$, whereas selection with knowledge of the QTL uses $v_1 = v_2 = 1$ and is not the longterm optimal weighting. These represent two scenarios from a continuum of strategies. Given a timeframe for benefits from the improvement, and costs of genotyping, the optimum relative emphasis for QTL effects can be derived. Determining optimum emphasis across multiple generations will not be considered in this paper.

RESULTS AND DISCUSSION

Selection in ignorance. Truncation selection across the (biased) EBVs for the three subpopulations will result in a preference order favouring QQ > Q+ > ++ individuals. The extent of preference for individuals carrying one or more copies of the QTL depends upon the degree of bias in EBV prediction, the selection intensity and the magnitude of *a*, the additive QTL effect. Figure 1 shows QTL frequency by generation for three different sized QTL. Larger QTL will be fixed more rapidly than smaller-sized QTL. Fixation will be more rapid when selection intensity is increased.

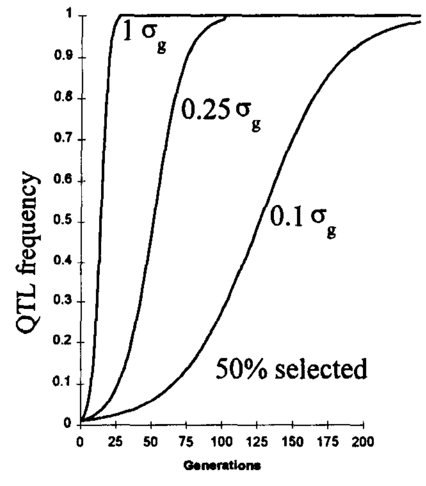

Figure 1. QTL frequencies for mass selection of a trait influenced by polygenic effects and a bi-allelic additive QTL of 0.1, 0.25 or 1.0 genetic standard deviations in a population with 50% individuals selected as parents each generation.

selection emphasis on an increase in QTL frequency and further increases the disparity between background polygenic advance in Q compared to + gametes. In an extreme situation, all QQ individuals may be selected as parents such that polygenic advance in Q gametes will only occur if there is selection among Q+ parents. In this situation, the increase in QTL frequency could occur at the expense of about one generation of selection on background polygenic effects. Given selection in ignorance, the QTL frequency will increase but without as much reduction in background selection. Accordingly, when we compare these strategies over timeframes such that selection in ignorance leads to QTL fixation, this strategy will be superior to selection with knowledge, as the degree of background "loss" in early generations was reduced.

A comparison of these two strategies is shown in Figure 3. Knowledge of the QTL resulted in superior performance for the first three generations whereas selection in ignorance was superior thereafter. Results shown in this study are in agreement with findings of Gibson (1994). However, Gibson expressed responses as the superiority relative to a selected population without the QTL segregating. Results of both studies should not be misinterpreted to imply that annual genetic gains in the long-term are compromised by selection for QTL. In this model, gains per year are identical in the long-term for all selection strategies once QTL fixation has occurred. Some researchers (e.g. van der Beek and van Arendonk 1996) have implied that reduced polygenic response following QTL selection results from the negative covariance between QTL and polygenic merit. Ruane and Colleau (1995) rightly point out that this is not the case, citing the fact that there is loss of polygenic response in the first cycle of selection, before a negative covariance has established. Ruane and Colleau conclude the effect is due to lower intensity or accuracy of selection of polygenic effects and go on to demonstrate reduced accuracy in evaluation for selection in ignorance relative to selection with knowledge. Based on the study reported in this paper, it is argued that lower intensity of selection for polygenic effects causes the phenomenon.

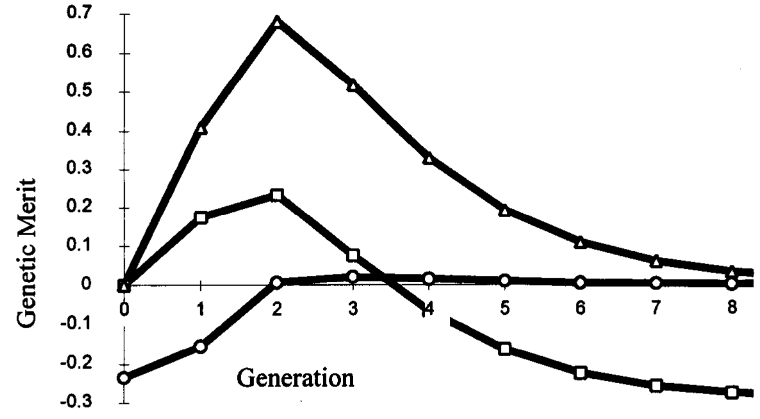

Figure 3. Differences in QTL frequency (triangles), background polygenic selection differential (circles), and performance (squares) between selection with QTL knowledge and selection in ignorance when 25% individuals are selected as parents for a QTL with initial frequency 0.3.

CONCLUSIONS

The results of the deterministic model indicate that QTL will segregate in populations under single-trait selection for many generations. Given that most livestock populations have been selected for multiple traits suggests that if QTL were ever present some are still likely to be segregating.

Long-term losses result from reduction in background polygenic selection that occurs when selection pressure is diverted to change QTL frequencies. Strategies that account for the short- and long-term effects of such compromises will give improved gains. It seems contradictory that additional knowledge (of a QTL) should reduce selection response. However, the usual approach to compare selection strategies involves situations where asymptotic responses are equal to the response from one round of selection. This is not the case when large QTL are involved because selection changes the QTL frequency and introduces gametic disequilibrium.

The development of gametic disequilibrium reduces the differential between subpopulations classified on the basis of their QTL genotypes. The heterozygote Q+ subpopulation produces Q and + gametes that segregate in merit such that their difference in breeding value equals the additive effect of the QTL. Accordingly, the best (and worst) gametes in the whole population arise from the heterozygotes. Selection strategies that can harvest the Q gametes and discard the + gametes from this subpopulation can improve selection responses without achieving longterm losses. Such strategies require the use of reproductive technologies in conjunction with marker assessment. A current challenge is to identify such strategies that can be cost-effectively applied within the context of a particular breeding industry in advance of the detection and verification of useful QTL.

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