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Efficiency of Incorporating Genotypes of Small-Effect Genes in Dairy Cattle Breeding Schemes

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Abstract: Development of genotyping technology is leading to detect more quantitative effect loci (QTL) involving small effect on trait. A dairy cattle population involving an open nucleus breeding scheme was simulated for twenty years of selection. Two QTL-assisted schemes were simulated and compared with conventional QTL-free scheme. First, a breeding scheme assuming one large effect QTL information (1QAS) and second, 4QAS, which involves information of four small effect QTLs. Genotypes of QTL(s) were incorporated as fixed effects in animal model for estimating breeding values. Indeed, QTL-Free selection runs were made with QTL simulated but not fitted in model (1QFS and 4QFS). Despite of significant differences for short term response, the present study showed that, if genotypes of four QTLs with relatively small effect were incorporated in conventional animal models as fixed effects, QAS could not improve conventional schemes, in the long term. This fact suggests the other strategies might be required.

Key words: Breeding scheme · Quantitative trait loci · Progeny test · Animal model

INTRODUCTION

Numerous studies have demonstrated that the incorporation of major genes in BLUP of BV's, lead to effectively increasing of genetic response in the short term [1-3]. Development of cheap and high-density marker maps would move the selection based on polygenes plus individual loci to effective total genomic selection [4]. Meuwissen *et al*. (2001) developed the analytical framework to compute total genomic values given high-density marker maps and showed that with one polymorphic marker per centimorgan and a half sib structure with 100 offspring per sire, genomic selection yields an accuracy of selection of 0.73, which was due to more accurate evaluation of marker effects [5]. Since the early work of Meuwissen *et al*. (2001), others have proposed different methods of computing marker effects and consequently more marker effects were detected significant, although most of them could not be detectable using previous QTL analysis methods. As not all animals can be genotyped, the estimated marker effects are currently implemented in a multistep breeding strategy. For example, an implementation for US dairy cattle [6, 7] requires three steps: a regular evaluation by the animal model, b) estimation of genomic effect for a relatively small number of genotyped animals and c) estimation of genomic breeding values by a selection index. Since the number of genotyped animals has been dramatically increasing, it is expected that causative mutations including novel large and small genes would have been detected by near future. Advantages of Gene Assisted Selection (GAS) programs could sustain in the long term if useful new gene markers continually be discovered. These new genes might have smaller effect, because the larger effect genes have been more likely detected or moved to be fixed via the forces of conventional selection. The objective of this study was to compare two selection schemes using different numbers of genes in selection strategies. Although these two schemes were different in gene numbers, the sum of genotypic effects due to major genes were similar for both schemes.

MATERIALS AND METHODS

Stochastic simulation of dairy cattle populations with selection practices, structures and parameters similar to the Holstein populations was implemented. Base

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population consisted of 50 and 10000 unrelated and unselected males and females, respectively. The simulated population included an open nucleus and a commercial herd, with overlapping generations and a four-pathway structure involving progeny testing. Selection for the milk yield was modeled using heritability, total phenotypic variance (σ^2_p) and population mean of 0.27, 1300[2] and 6500 respectively. In addition, four fixed effects affected the individual's record: Herd, Year, Season and Parity. Twenty herds were simulated. Herd effects were sampled from a normal distribution $N\sim(0, 0.15\ \sigma^2_p)$. Six seasons were considered in the simulation model. Each two consecutive months starting with January constituted the six season levels, which their values in kilograms were 179, 68, -158, -318, 43 and 187 respectively. For the parity effect, a value of -249 kilograms was added to first-parity record and a value of 249 kilograms to each next record. Year effects were sampled from a normal distribution $N\sim(0, 0.04\ \sigma^2_p)$. Two populations were simulated, first with one known QTL (1Q) and the second one with four known QTL (4Q). Although, the number of QTLs were different for populations, sum of genotypic effects of four QTLs in 4Q was equal to genotypic effect of one QTL in 1Q. An infinitesimal model was used to simulate polygenic part of an individual's breeding value (PgBV). Model (1) and model (2) were used to simulate breeding values of base and following generations, respectively.

$$PgBV_i = Z \times PgS_A \qquad \text{Model (1)}$$

$$PgBV_i = \frac{PgBV_{Sire} + PgBV_{Dam}}{2} + Z \times MS \qquad \text{Model (2)}$$

$$MS = \sqrt{\frac{2 - INBSire - INBDam}{4}} \times SA \qquad \text{Model (3)}$$

$$BV_i = PgBV_i + MgBV_i \qquad \text{Model (4)}$$

Where Z is a random number sampled from a standard normal distribution. PgSA and MS represent standard deviation of PgBV and Mendelian sampling, respectively and INB is the inbreeding coefficient of parents. A finite locus model used to simulate individual's genotype assuming no linkage. For the base population it was assumed that all loci have two alleles with favorable allele frequencies of 0.2. The major gene part of the individual's breeding value (MgBV) was simulated based on the individual's genotypes and average allele substitutions effects which were calculated in base population and were used for following generations. Covariance between major genes and polygens in the base population was ignored. Complete breeding value was the sum of the PgBV and MgBV (Model 4).

$$P_{ij} = \mu + FixEff_{ij} + PgBV_i + MgBV_i + Z \times Se \quad \text{Model (5)}$$

Model (5) was used to simulate phenotypic records. Fixed effects were simulated by adding a constant to individuals BV that corresponded to its levels of fixed factors. In this model P_{ij}, μ, $FixEff_{ij}$ and Se are j^{th} record of i^{th} individual, population mean, sum of fixed effects related to j^{th} record of i^{th} individual and standard deviation of error, respectively. Two separate selection schemes were simulated for each of 1Q and 4Q. First, QTL Assisted Selection schemes, in which genotypes of the simulated major gene(s) were accounted for in the animal model as a fixed effect (1QAS and 4QAS) and second, QTL Free Selection scheme, which was similar to the first but information of major gene(s) were ignored (1QFS and 4QFS).

$$y = Xb + Gg + Zu + e \qquad \text{Model (6)}$$

$$y = Xb + Zu + e \qquad \text{Model (7)}$$

A Single trait animal model was used to predict breeding values. Mixed models (6) and (7) of the above were used for estimating breeding values in QAS and QFS, respectively. In these models, b is a vector of fixed effects, a is a vector of random additive effects, g is a vector of genotype effects, X, Z and G are incidence matrices relating the records to fixed effects, genotypes (also as a fixed factor) and random effects respectively. Three years of random mating were simulated to provide suitable data structure before selection strategies were practiced. Gauss-Seidel iteration with 10^{-6} convergence criteria was used to obtain solution. Twenty years of selection were practiced. For each year ten and two percent of top active sires and all commercial dams were selected respectively in order to identify bull sires and bull dams. Young bulls were included in a progeny-testing program. Proved young bulls replaced twenty percent of active sires annually that was started from fifth year.

RESULTS AND DISCUSSION

Fiftieth replications for different procedures were conducted to compare strategies.

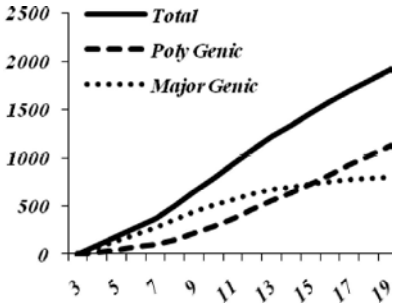


Fig. 1: Response to selection for 1QAS.

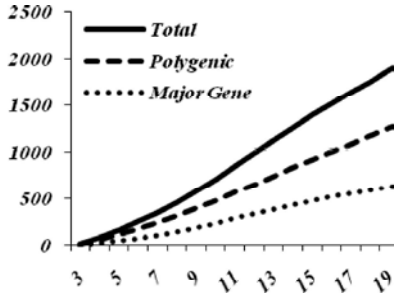


Fig. 2: Response to selection for 1QFS.

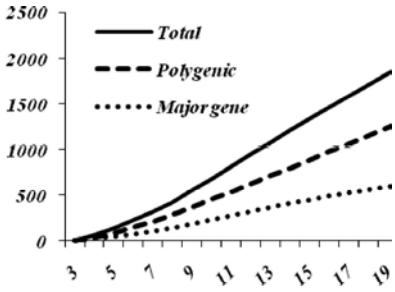


Fig. 3: Response to selection for 4QAS.

1QAS: For first fifteen years, response of major gene part of breeding values was higher than polygenic. After fifteenth year, due to reduction in variation of major genes, polygenic response was comparable than major gens. Figure (1) and figure (2) represent difference in response of selection between 1QAS and 1QFS. Results indicated that response to selection in 1QAS was significantly higher than in 1QFS from ninth to fifteenth years ($P<0.05$). Superiority of response reaches a maximum 9.2%, or 91Kg, for twentieth year. Favorable allele frequencies of single major gene of these two strategies were 0.75 and 0.49 for 1QAS and 1QFS, respectively. For twentieth year, the superiority of 23 kilograms for 1QAS was not significant ($P<0.05$).

4QAS and 4QFS: Figures (3) and (4) show responses to selection for these two schemes. Both of the schemes had higher response for polygenic breeding value.

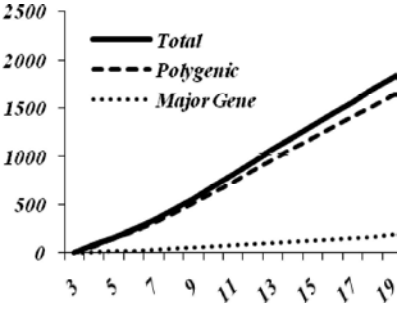


Fig. 4: Response to selection for 4QFS.

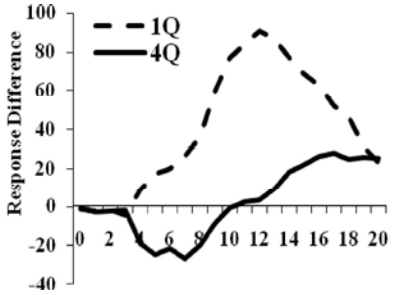
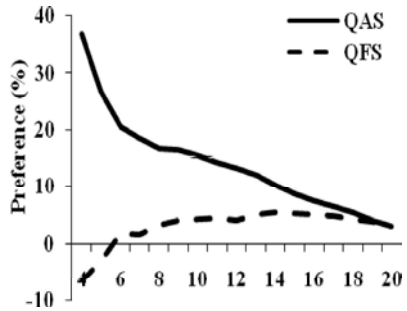


Fig. 5: Superiority of QAS over QFS for response to selection

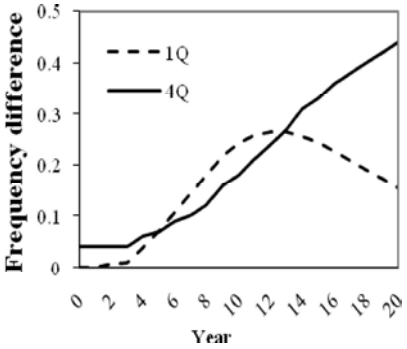


$$\text{Preference}\% = [(1Q_{\text{Res.}} - 4Q_{\text{Res.}}) / (4Q_{\text{Res.}})] \times 100$$

Fig. 6: Preference of 1Q over 4Q

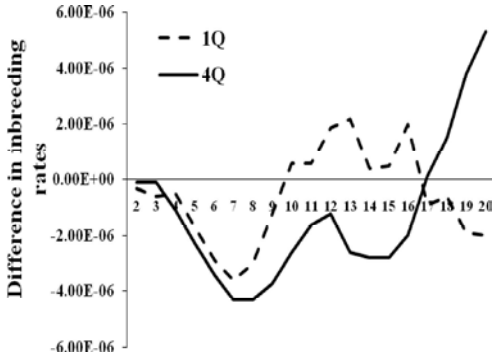
Lower response of major gene occurred because fixation of favorable alleles in four loci was delayed compared to 1Q. Total response was significantly different for fourth and fifth years (Figure 5).

The lack of QAS effect over the first three years is a lag associated with overlapping generations. Consequently it could explain why figure (6) started at fourth year. 4QFS superiorities over 4QAS were 30% and 17% for fourth and fifth years, respectively. During the following years this superiority were decreased to zero in eleventh year and continued to be higher for 4QAS. Total response of 4QAS was 25 kilograms higher than 4QFS however this superiority (1.3%) was not significant ($P<0.05$).



$$\text{Difference} = QAS - QFS$$

Fig. 7: Difference in favorable allele frequency. Average allele frequency was used for 4Q.



$$\text{Difference} = INB_{QAS} - INB_{QFS}$$

Fig. 8: Difference in population inbreeding rates.

There was no significant difference between total responses of 1QFS and 4QFS, which it was expectable. Range of difference over twenty years was -6.6% to 5.4%. This preference tended to be zero after fifteenth year. Figure (6) shows preference of 1Q over 4Q. Preference in QAS schemes was different. Although preference in twentieth year (2.9%) was not significant, it was significant from the fourth to seventeenth year.

Preference of 1QAS over 4QAS was 37% in the fourth year but an enormous reduction was occurred over two years later and decreased it to 21%. Afterwards, the preference decreases slowly and reached 6.4% in the seventeenth year.

Inbreeding: Inbreeding rates of 1QAS and 4QAS were not significantly different. Figure (8) displays difference in inbreeding rates of QAS and QFS schemes (INB_{QAS} - INB_{QFS}). Regarding to figure (8), incorporating major gene information in selection schemes could affect inbreeding. The quantity of this effect depended on major gene characteristics. In the sixth and seventh years, inbreeding preferences of 4QAS over 4QFS were -11% and -11.3% and were significant ($P<0.05$). For 1QAS over 1QFS, the preferences of -9.9% and -8.7% were not significant. Results indicated that QFS schemes had larger inbreeding rate than QAS for several first years. By considering figures (7) and (8), the maximum rate of inbreeding difference concurred with the maximum difference in favorable allele frequencies. Maximum difference in allele frequency (0.25%), as well as maximum difference of inbreeding rate was occurred in twelfth year for 1Q scheme. Difference of allele frequency was increasing by twentieth year, which led to increase of difference in inbreeding rates for 4Q scheme.

Muir and Stick (1998) reported that conventional breeding schemes prefer to marker assisted selection for long time response because of lower selection deferential for major genes versus polygenes [9]. Figure (6) support this idea although indicates that superiority could be different for small effect genes.

Comparable emphasis on major gene led to immediately fixation of favorable allele inattention to polygenes, as a result some favorable polygenes could be omitted or drifted therefore long time response that mainly is due to polygenes would have been limited [10-12].

Our study supports the idea that there is still a great deal of doubt about the possibility to find QTL or marked QTL with a very large effect on trait, at low frequency. This study suggests that incorporating information on several genes with small effects into the animal model, can negatively affect short-term response to selection, even if true marker effects are known. Presumably there must be a reason for this negative effect, which needs to be investigated. Our results were contrary to previous concepts, which had suggested to use such additional information. Results of present study indicated that the other selection schemes such as optimized genotypic selection or preselection, must be designed and evaluated for efficiently application of newly detected major genes. It must be kept in mind that a major gene would be useful for increasing response to selection if its favorable allele frequency was low. If a trait in a specific population had been selected for a long time it is expected that all major genes with large effect on it, most probably tended to be fixed and have high favorable allele frequency therefore most newly detected genes have medium or small effect.

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