

ANIMAL SCIENCE

Title: Optimizing Selection on Major Genes in Swine - **NPB #98-062**

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I. ABSTRACT

Current advances in molecular genetics are leading to the discovery of individual genes for traits of economic importance (major genes or marked QTL). Examples are the halothane gene, the ESR gene and the RN gene. The use of such genes in selection has the potential to substantially enhance rates of genetic improvement, especially for traits with low heritability (e.g. litter size) and traits that are difficult to measure (e.g. meat quality). Identified major genes or markers can be powerful tools that will enhance rates of genetic improvement if they are used properly. At the same time, however, improper use of these powerful selection tools can result in undesirable effects and in less than optimal genetic improvement. Guidelines and strategies on how to best incorporate major genes in selection programs are needed. The aim of this research was to develop such strategies.

To this end, methods were developed to optimize simultaneous selection on a major gene and as well as other (unidentified) genes that affect the trait, through a selection index of major genotype and regular EBV. The latter is derived from phenotype and estimates the value of all the other genes that affect the trait. Index selection strategies were compared to other selection strategies, including a two-stage selection strategy in which selection was first on the major gene and secondly on EBV among selected individuals with the poorest major genotype. As an example, results were applied to selection for litter size using the estrogen receptor gene (ESR). Results showed that, although the two-stage selection strategy led to the fastest fixation of ESR, it resulted in less response in litter size than index selection strategies. This was caused by the lower response in the other (unidentified) genes that contribute to litter size with two-stage selection. These results clearly showed the importance of balancing emphasis on the major gene against emphasis on the other genes that affect the trait through a selection index. Results also showed that response to selection can be further enhanced by optimizing the emphasis on the major gene in the index through the methods developed in this study. Although further work is needed to fine-tune the optimal strategies, their

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application will ensure that greatest benefit is obtained from the information obtained from molecular genetics.

II. 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'. Current advances in molecular genetics are, however, leading to the discovery of individual genes for traits of economic importance (major genes) or of markers linked to such genes. Examples are the halothane gene, the ESR gene and the RN gene. Other examples are just around the corner.

The use of identified genes in breeding programs through marker-assisted selection has the potential to substantially enhance rates of genetic improvement. However, recent research (Gibson, 1994) has shown that strategies for marker-assisted selection that are currently available do not increase genetic improvement to the extent that is possible and may in fact result in less improvement than regular selection on EBV, in particular when considering selection over several generations. Guidelines and strategies on how to best incorporate major genes in selection programs are needed. The aim of this research was to develop such strategies.

III. OBJECTIVES

In previous research, we (Dekkers and van Arendonk, 1998) developed strategies for selection on an identified gene for a simplified breeding program with equal selection among males and females. The objectives of this research were:

1. To extend methods developed by Dekkers and van Arendonk (1998) to optimizing selection on major genes in swine breeding programs.
2. To compare improved strategies for selection on major genes with current selection strategies.
3. To provide guidelines to the industry for selection on major genes.

IV. PROCEDURES

Mathematical models for optimization of selection on a major gene developed by Dekkers and van Arendonk (1998) were extended to include some of the complexities of swine breeding programs. A computer program was developed to optimize selection on a major gene under these more general circumstances. In these procedures, optimal selection maximized the cumulative response to selection after a specified number of generations.

Methods to optimize selection on a major gene were based on a deterministic model that did not incorporate the effect of selection on genetic variance. To further evaluate the strategies for optimal selection, a stochastic model was developed which does incorporate the effects of selection on genetic variance. Although the stochastic model used here was limited to equal selection in males and females and to selection based

on own phenotype, along with major gene information, it did enable evaluation of the optimal strategies developed by the deterministic model.

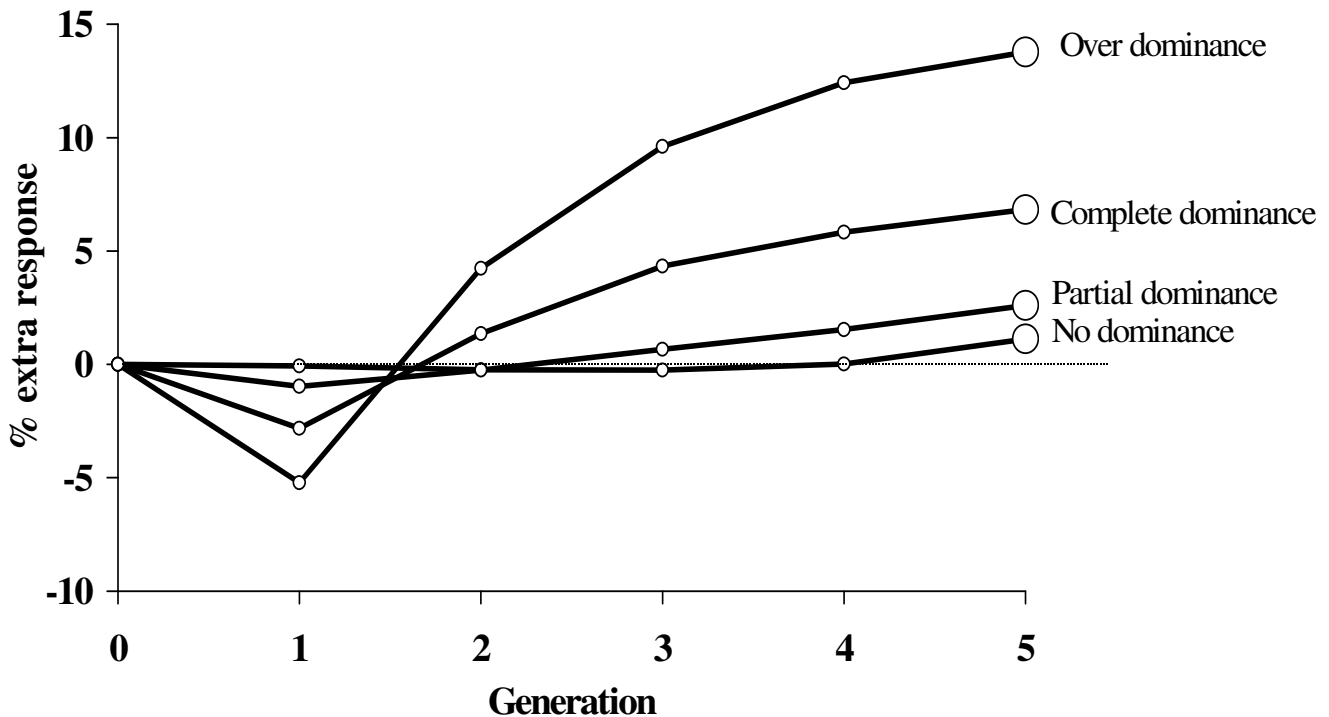
Methods were applied to selection for litter size using the Estrogen Receptor Gene (Rothschild et al. 1991)

V. RESULTS

Objective 1.

Figure 1 illustrates the effect of dominance at the major gene on the extra benefit that can be expected from optimizing selection on the major gene. Cumulative response to optimal selection is expressed as a % of response to standard index selection on a major gene. With standard selection on the major gene, selection is on the simple sum of the effect of the major gene plus the animal's EBV for the collective effect of all other genes (polygenes), which is estimated from phenotype. Results show that with dominance, the extra benefit that can be expected from optimizing selection is substantially greater in the final generation (i.e. generation 5) than for a major gene with additive effects. For example, for the major gene with overdominance, which means that the heterozygote is better than either homozygote, over 10% greater response to selection can be expected after 5 generations when selection on the major gene is optimized.

Figure 1. Extra response from optimal versus standard selection on a major gene with varying degrees of dominance. Optimal selection maximizes response over 5 generations. Heritability of the trait is 25%. The additive effect of the major gene is equal to .25 phenotypic standard deviations. The top 20% of males and females are



Objective 2.

Table 1 illustrates results from the evaluation of derived optimal strategies under the stochastic model. The stochastic model more closely models selection in a population than the model that was used to derive the optimal strategies.

Initially, our evaluations were based on simulating an unselected population as the starting generation. Under this situation (results not shown), the optimal strategies did not perform well under the stochastic model, in particular for short planning horizons. We expected that this was caused by the reduction in genetic variance that takes place in the stochastic model in the initial generations of selection. We subsequently adapted both the deterministic and stochastic models to account for the effects of prior selection on genetic variance. For the stochastic model, this was accomplished by simply simulating phenotypic selection for 4 to 5 generations and then switching to selection using the major gene. In the deterministic model, the effects of prior selection were incorporated by using the genetic variance and related parameters that were obtained in the stochastic model after 4 or 5 generations of phenotypic selection.

Table 1. Evaluation of optimal strategies for selection on a major gene based on the stochastic simulation model. Extra response to phenotypic (Phen) or optimal (Opt) selection is shown as a % of response to standard index selection on a major gene for various generations of selection that correspond to strategies that optimize selection after 1, 2, 3, 5, and 10 generations of selection and for various parameters of the major gene. Heritability of the trait was 30% and 20% of males and females were selected each generation. Initial gene frequency was 5%. Populations that had been under prior phenotypic selection were simulated.

		Generations of Selection and selection strategy (phenotypic or optimal)									
Gene effects	Simulation model used	1		2		3		5		10	
		Phen	Opt	Phen	Opt	Phen	Opt	Phen	Opt	Phen	Opt
Additive a=0.25	Stochastic	-2.7	0	-3.2	+0.4	-3.5	+0.2	-3.1	+0.2	+0.56	+1.6
	Deterministic	-4.2	0	-3.8	+0.3	-2.6	+0.8	-1.9	+2.1	+2.1	+3.1
Complete Dominance a=d=0.25	Stochastic	-0.8	+0.2	+0.4	+2.0	+4.2	+4.2	+8.1	+7.2	+7.6	+5.2
	Deterministic	-5.4	+0.34	-3.3	+1.9	-0.1	+4.1	+3.8	+5.8	+4.5	+5.1
Negative Dominance a=.25, d=-a	Stochastic	+0.5	0.0	+0.5	-0.3	+0.3	-0.2	+0.3	-0.3	+0.1	-1.1
	Deterministic	-0.1	0.0	-0.1	0.0	-0.1	0.0	-0.1	0.0	-0.2	+7.1
Over Dominance a=.25 d=0.375	Stochastic	-2.5	-0.2	+0.3	+2.5	+8.4	+9.2	+14.7	+12.9	+10.2	+7.3
	Deterministic	-6.3	+0.2	-3.8	+2.5	+0.9	+5.7	+5.8	+7.7	+5.3	+6.5

Table 1 shows that the results from the stochastic model agreed reasonably well with results from the deterministic model with regard to extra response from optimized

relative to standardized selection on the major gene. For example, for a major gene with complete dominance, the deterministic model predicted 4.1% greater response from optimal selection after 3 generations, whereas the stochastic model found 4.2%. An exception was a major gene with negative dominance for selection over 10 generations.

Comparing responses to optimal versus phenotypic selection under the stochastic model, however, showed that optimal selection did not always result in greater responses than phenotypic selection, which ignores the major gene, for the longer planning horizons (5 or 10 generations). This indicates that further research is needed to refine the optimal strategies to selection.

Objective 3.

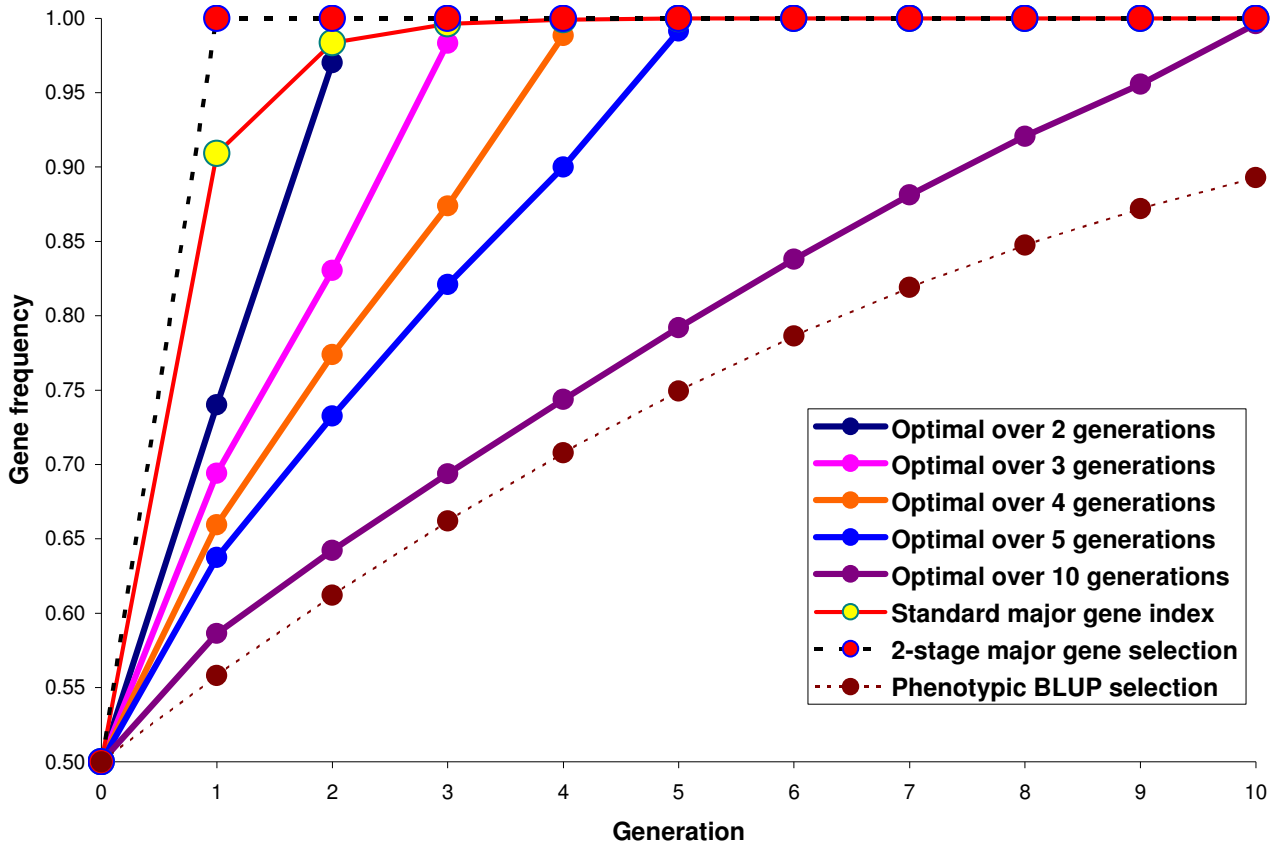
Methods were applied to single-trait selection for litter size using the Estrogen Receptor Gene (Rothschild et al. 1991) along with EBV for litter size based on phenotype. Parameters for the effect and frequency of ESR were taken from Short et al. (1996) based on first parity results, which showed an additive effect of 0.39 and a dominance effect of 0.05 (i.e. BB sows average $2 \times 0.39 = 0.78$ piglets more than AA sows and AB sows average $0.39 + 0.05 = 0.44$ piglets more than AA sows). Estimates of polygenic breeding values were derived from an index of pedigree information (selection was prior to first parity), resulting in an accuracy of polygenic EBV of 0.30 for both males and females. Selected proportions were 10% for boars and 25% for gilts. Initial frequency of the favorable (B) ESR allele was 50%, similar to what was found in commercial Yorkshire lines by Short et al. (1997).

The following selection strategies were compared:

- 1) Two-stage selection, with selection on ESR genotype in the first stage, followed by selection on polygenic EBV among selected animals with the poorest ESR genotype among those selected in the first stage.
 - 2) Standard major gene index selection. Selection was on $I = g + EBV$, where g is the breeding value for the ESR gene and EBV an estimated breeding value for polygenic effects.
 - 3) Optimal major gene index selection. Selection was on $I = b g + EBV$, where b is an index weight on the breeding value for ESR. Index weights were derived using the optimization methods developed under objective 1, with the aim to maximize cumulative response after 2, 3, 4, 5 or 10 generations.
 - 4) Phenotypic BLUP selection: selection is on BLUP EBV ignoring ESR genotype
- All comparisons were based on the deterministic model used for optimization.

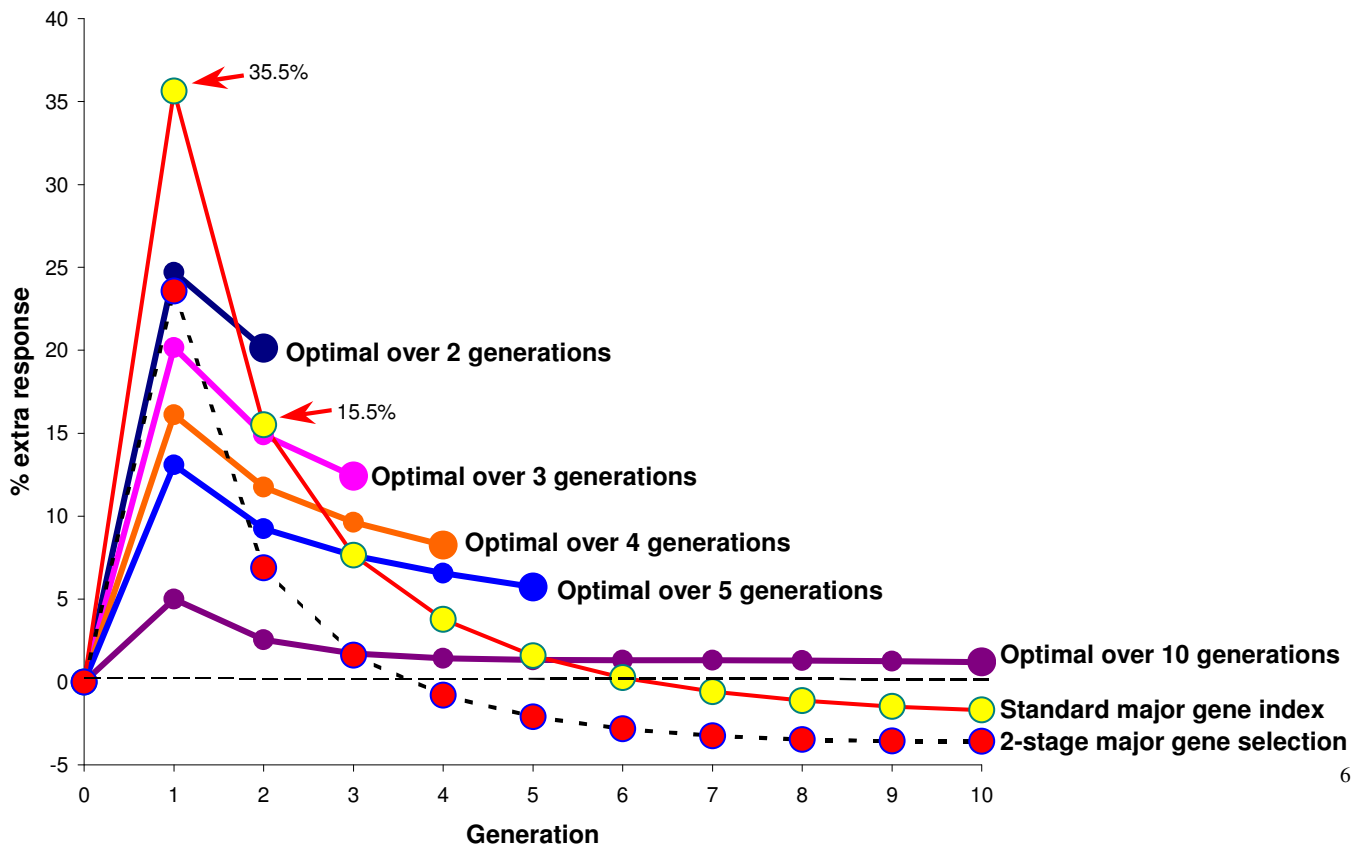
Figure 2 shows the increase in frequency of the favorable ESR allele for the alternative selection strategies. Although phenotypic BLUP selection did not put explicit emphasis on ESR, it did increase the frequency of ESR because animals with favorable ESR genotypes (BB or AB) tend to have greater litter size and, therefore, higher EBV for litter size. The increase in frequency was, however, very gradual and did not reach fixation after 10 generations of selection. With preselection on ESR, the gene frequency was fixed after 1 generation; with a starting frequency of 0.5, the frequency of BB individuals is 0.25. With 10% selection among males, all selected boars were BB, leaving some room for selection on polygenic EBV in the second selection stage. With 25% selection among females, all selected sows were also BB. However, because the frequency of BB was also 25%, this left no room for selection on polygenic EBV among sows.

Figure 2. Increase in gene frequency for ESR from alternative selection strategies on ESR



With standard major gene index selection, the frequency of ESR also increased rapidly, with fixation in generation 4. For the optimal selection strategies, ESR also reached near fixation by the end of the planning horizon (2, 3, 4, 5 or 10 generations) but the

Figure 3. Extra response (%) relative to phenotypic BLUP selection from alternative selection strategies on ESR



increase in gene frequency was almost linear. This in contrast to standard major gene index selection, which resulted in a very rapid increase in frequency in the first two generations, followed by much smaller increases to reach fixation. Thus, optimal selection resulted in a much more balanced increase in gene frequency than standard index selection and it achieved that by reducing the index weight on the major gene ($b < 1$).

Figure 3 compares cumulative responses to selection for the alternative selection strategies. All responses are expressed relative to response for phenotypic BLUP selection, which is on the zero axis. For example, as indicated by the arrows, the response to standard major gene index selection was 35.5% greater than response to phenotypic BLUP selection after 1 generation and 15.5% greater after 2 generations of selection.

Standard index selection was superior to phenotypic BLUP selection for the first 5 generations. After 6 generations, however, cumulative response with selection ignoring ESR was greater than response from standard index selection. This is similar to results observed by others (e.g. Gibson, 1994) and is due to the reduced selection emphasis on other genes that affect litter size when selection emphasis is placed on the major gene. Standard index selection was, however, superior to two-stage major gene selection for all generations. The reason for this is that two-stage selection on ESR allowed selection of individuals with inferior polygenic EBV which, although they had the favorable ESR genotype, did not have superior overall breeding values for litter size because of their inferior polygenic EBV. Index selection results in a balance between selection on ESR and polygenic EBV, which allows selection of individuals with the unfavorable ESR genotype if the superiority of their polygenic EBV compensates for the unfavorable ESR genotype. This result clearly demonstrates the importance of balancing selection on a major gene with selection on polygenic EBV.

An even better balance between the major gene and polygenic EBV is achieved by the optimal selection strategies. Although the optimal strategies resulted in less response in initial generations than standard index selection (Figure 3), responses were 3 to 5% greater in the final generation of the respective planning horizons. Optimal selection over 10 generations also resulted in slightly greater response to selection than phenotypic BLUP selection.

Although these results clearly show that there is a need to balance and optimize selection on major genes, further work is needed to balance the short and longer-term benefits of optimal selection.

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