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Economic benefit of using a major gene in a nucleus selection programme with limits on inbreeding

P.R. AMER[1] AND B. VILLANUEVA[2]

[1]AgResearch Invermay, PB50034, Mosgiel, New Zealand.

ABSTRACT

This study investigates the commercial benefit of including information on an identified major gene in the estimation of breeding values for a breeding nucleus. Two types of selection (dynamic selection to maximise response with controlled inbreeding versus standard truncation selection) and two types of breeding value estimation (using versus ignoring information on a major gene) were compared over 15 generations. Selection strategies based on dynamic rules were commercially superior to strategies using truncation selection under comparable circumstances. Correction of the breeding values of selection candidates for the major gene resulted in extra genotype testing but was commercially superior to ignoring the major gene unless only small numbers of commercial males were sold. Small commercial breeding schemes adopting major gene selection will benefit from the application of selection algorithms that control inbreeding.

Keywords: major gene; inbreeding; nucleus; net present value.

INTRODUCTION

Much research effort is currently being targeted towards gene discovery research in farmed livestock species. It is anticipated that at least a proportion of the benefits of this research will result from the acceleration of genetic response in traits having a direct impact on farm profitability (e.g., Amer *et al*., 1998; Bass *et al*., 1999). Studies on the use of major genes in selection schemes indicate that initial increases in selection response using major genes can be followed by reductions in long-term response (e.g., Gibson, 1994). In breeding programmes with small numbers of animals, the use of the major gene information can also accelerate inbreeding (Villanueva *et al*. 1999), especially when major genes are initially introduced to the population via a small number of animals. Much discussion among population geneticists on the merits of selection programmes using major genes has ensued.

Economic assessment of commercial merits of using major genes has to evaluate the trade-off among breeding programme costs, short-term increases in response to selection, and much more modest increases or even reductions in long-term selection responses. Selection decision rules are also available to maximize genetic progress while controlling rates of inbreeding in small selected populations (e.g., Grundy *et al*., 1998) and these might enhance commercial benefits from breeding programmes using information on major genes. The objective of this study was to investigate the commercial benefits of including information on an identified major gene in the estimation of breeding values for a small nucleus breeding programme. Published simulation results, which consider two types of selection (optimised genetic contributions to maximise response with controlled inbreeding versus standard truncation selection) and two types of breeding value estimation (using versus ignoring information on the major gene), formed the basis of the economic assessment.

METHODS

Results from Monte Carlo simulations carried out by Villanueva *et al*. (1999) were compared under alternative economic assessment criteria. In the study of Villanueva *et al*. (1999), selection candidates were assessed using Best Linear Unbiased Prediction methodology for a single trait affected by a major gene and polygenes. The initial frequency of the favorable allele was 0.15 for all simulations. Selection strategies considered were: 1) dynamic selection with restrictions on inbreeding and correction of breeding values for known effects of an additive major gene of large effect (2 phenotypic standard deviations); 2) dynamic selection with restrictions on inbreeding but without correction of breeding values for major gene effects; 3) truncation selection with correction of breeding values for major gene effects and; 4) truncation selection without correction of breeding values for major gene effects. With truncation selection, a fixed number of males (10) and females (20) with the highest estimated breeding values were selected to be parents of the next generation. Dynamic selection differed from truncation selection in that the contribution of genes from each selection candidate was chosen so as to maximise genetic response per generation subject to a constraint on the total amount of co-ancestry among selected parents. In this way, the rate of inbreeding per generation was restricted to 3%.

In this study, it was assumed that the objective of the commercial breeding company would be to maximise the Net Present Value (NPV) of returns from sale of breeding males net of genotyping costs. Units of all financial variables including NPV were taken as phenotypic standard deviations of polygenic breeding merit. This facilitated wider interpretation of results than might be achieved using currency units relevant to a single species. The numbers of selection candidates produced each generation (60 males and 60 females) were those used in the study of Villanueva *et al.* (1999). An additional number, *n*, of commercial breeding males was assumed to be bred and sold from the scheme each generation. These animals were never considered as selection candidates under the assumption of limitations to testing resources. Surplus untested females were assumed to have a constant salvage value, irrespective of their major gene genotype or polygenic breeding merit, and were, therefore, ignored in the calculations. Prices of

2 Scottish Agricultural College, West Mains Road, Edinburgh, EH9 3JG, Scotland, UK.

commercially sold breeding males were assumed to depend on the major gene genotype, and the average polygenic breeding merit of all males of the same generation.

The cumulative Net Present Value of returns net of genotyping costs was calculated as follows:

$$NPV = n \cdot \sum_{t=1+y}^{h} \frac{\left(R_{t-y}^{AA} + R_{t-y}^{AB} + R_{t-y}^{BB} + p^{u} \cdot u_{t-y}\right)}{(1+r)^{t}} - \sum_{t=1}^{h-y} \frac{C_t}{(1+r)^{t}} - FC$$

where r and h are the discount rate (per generation) and planning horizon (in generations) for commercial investments by the company respectively, u^t is the average polygenic merit of animals in generation t and p^u is the price premium per unit of polygenic merit per commercial breeding male sold. Discount rate and planning horizon time units are considered in generations, rather than years, to make interpretation of results more general. Fixed costs (*FC*) for the breeding programme and the lag *y* between the time animals are genotyped and the time the revenue from sale of commercial breeding males is retained were ignored in this study by setting their values to zero. Per animal revenue at generation *t* (R_t^x) from sale of commercial breeding males of genotype *x* (either homozygous absent, *x* = AA, heterozygous, *x* = AB, or homozygous present, *x* = BB, for the favorable allele) for the major gene, was calculated as $R_t^x = Po(x) \cdot p_M^x$ where $Po(x)$ is the proportion of offspring of genotype *x* born in generation *t*, and p_M^x is the sale sprice premium of a commercial breeding male of genotype *x*.

Total genotyping costs for all animals born in generation *t* (C_t) were calculated as

$$C_t = (n+120) \cdot p_G \cdot \left[Pm(AB)_t + Pf(AB)_t - Pm(AB)_t \cdot Pf(AB)_t\right]$$

for *t*=2 to *h* and where p_G is the genotyping cost, *n* is the number of commercial breeding males sold each generation (n is set to zero for situations where breeding values of selection candidates are not corrected for the major gene effect), there are 120 selection candidates, and $Pm(AB)$ and $Pf(AB)$ are the proportions of male and female parents of animals born at generation *t*, which are heterozygous for the major gene. Thus, it was assumed that only those animals with one or both parents heterozygous are genotyped. For generation *t*=1, it was assumed that all selection candidates must be genotyped. Table 1 shows base values, and ranges of alternative values, used for calculations of NPV. The base sale price premium animals homozygous for the major gene was assumed to be equivalent to the value of four phenotypic standard deviations of polygenic merit. This value is quite high relative to our expectation of the size of many major gene effects, so values 50% and 200% the size of the base value were also used in the calculations (Table 1). The costs of genotyping individuals for the major gene were also doubled and tripled relative to a base value equal to two phenotypic standard deviations of polygenic merit.

TABLE 1. Base values and alternative values for parameters used in the calculations of Net Present Values of different breeding strategies[1].

Variable	Abbreviation	Base values	Alternative Values
Number of commercial males sold	N	500	100, 300, 700
Planning horizon (generations)	H	15	-
Discount rate (per generation)	R	0.15	0.00 to 0.20
Sale price of homozygous AA male	p_M^{AA}	0	-
Sale price of heterozygous male	p_M^{AB}	1	0, 0.5, 1.5, 2
Sale price of homozygous BB male	p_M^{BB}	4	2, 6
Price premium per unit of u[2]	p^u	1	-
Genotyping cost (per animal)	p_G	2	4, 6

[1] Units of prices and costs are phenotypic standard deviations of polygenic breeding merit.
[2] u = polygenic breeding merit

RESULTS

Table 2 shows changes in cumulative net present value and the proportion of offspring homozygous for the favorable gene after alternative numbers of generations of selection for the four different selection strategies. For each strategy, fixation of the major gene occurred within the first five generations of selection, and NPV became positive after three generations. From generation two onwards, dynamic selection gave superior cumulative NPV than the corresponding truncation selection scheme.

TABLE 2. Cumulative Net Present Values (NPV in discounted phenotypic standard deviation units) of four alternative breeding strategies in the presence of a major gene with additive genetic effect equal to 2 polygenic phenotypic standard deviations. Simulation results from Villanueva et al. (1999) showing the proportion of offspring that are homozygous for the favorable allele of the major gene (OBB) up to 15 generations[1].

	Dynamic-corrected[2]		Dynamic-uncorrected[3]		Truncation-corrected[4]		Truncation uncorrected[5]	
Gen.	NPV	OBB	NPV	OBB	NPV	OBB	NPV	OBB
0	-927	0.023	-719	0.023	-928	0.023	-719	0.023
1	-1023	0.290	-855	0.190	-955	0.319	-773	0.247
2	391	0.999	165	0.812	190	0.970	-49	0.740
3	1698	1.000	1471	0.997	1460	1.000	1180	0.988
4	2902	1.000	2679	1.000	2632	1.000	2341	1.000
5	4007	1.000	3785	1.000	3703	1.000	3403	1.000
10	8196	1.000	7941	1.000	7743	1.000	7399	1.000
15	10695	1.000	10390	1.000	10110	1.000	9758	1.000

[1] Base assumptions for the breeding strategies are described in Table 1.
[2] Dynamic corrected – Dynamic selection for maximizing response at constrained inbreeding with breeding values corrected for the major gene effects.
[3] Dynamic uncorrected – Dynamic selection for maximizing response at constrained inbreeding ignoring presence of the major gene (selection candidates are not genotyped).
[4] Truncation corrected – Truncation selection with breeding values corrected for the major gene effects.
[5] Truncation uncorrected –Truncation selection ignoring presence of the major gene (selection candidates are not genotyped).

Total numbers of animals genotyped for the major gene locus were 1236, 1125, 1402 and 1285 for dynamic-corrected, dynamic-uncorrected, truncation-corrected and truncation-uncorrected strategies, respectively. The amount of genotyping for each strategy is influenced by two factors. Firstly, with uncorrected selection, it is not necessary to genotype selection candidates, only those progeny that are put up for sale. Secondly, genotyping is unnecessary once the QTL is fixed, and so the faster the rate of reduction of heterozygous parents as fixation is approached, the less

genotyping required. For both dynamic selection and truncation selection situations simulated in Table 2, the genotyping costs from correcting for the major gene in selection candidates were not fully offset by savings in genotyping costs of sold males resulting from faster fixation of the gene. However, the faster fixation has benefits because more males homozygous for the favorable allele of the major gene are sold. Thus, correction of breeding values for the major gene gave superior cumulative NPV relative to corresponding schemes in which the major gene was ignored.

Changes in the discount rate resulted in similar proportional reductions to each strategy (results not shown) and, therefore, had no effect on ranking of strategies. Decreasing the number of males sold favored selection strategies with no correction of breeding values for the major gene. However, this only a small influence on the relative ranking of schemes except when numbers of males sold was very low (100, relative to base value of 500). Selection strategies with no correction of breeding values for the major gene were also favoured (Table 3) when the genotyping cost was increased by a factor of 2 or 3 and when the price premium for commercial males homozygous for the favourable allele at the major gene was reduced by a factor of 0.5. Despite the large range tested for these values, no re-ranking of schemes was observed. Modification to the assumed price for heterozygous animals sold had only small effects on the comparisons of strategies (results not shown).

TABLE 3. Cumulative Net Present Values (in discounted phenotypic standard deviation units) of 4 different breeding strategies after 5 generations of selection with alternative numbers of commercial males sold annually, price premiums for sold males, and genotyping costs.

	Strategy			
Males sold	Dynamic-corrected	Dynamic-uncorrected	Truncation-corrected	Truncation-uncorrected
Base[1]	**4007**	**3785**	**3703**	**3403**
Males sold				
100	634	757	574	681
300	2321	2271	2138	2042
700	5693	5299	5268	4764
Price of homozygous males sold				
2	1610	1588	1303	1216
6	6404	5982	6103	5590
Genotype cost				
4	2178	2005	1701	1415
6	349	225	-302	-572

[1]For the base situation, the number of males sold was 500, the price of homozygous males sold and the genotype cost were 4 and 2 phenotypic standard deviation units of polygenic breeding merit respectively.

DISCUSSION

There was only one instance in which truncation selection was superior to dynamic selection over all of the simulations carried out for a major gene with an additive genetic effect of 2. This was with a very low (100) number of commercial males sold, resulting in truncation selection with no major gene correction being superior to dynamic selection with genotyping of selection candidates and selection on the major gene. Villanueva *et al.* (1999), found that dynamic selection was always better than truncation selection when attempting to maximise long-term selection response at a constrained level of inbreeding in the presence of a major gene. Application of dynamic selection rules for control of inbreeding is a relatively low-cost procedure and should, therefore, be commercially effective for small breeding populations, irrespective, of whether or not a major gene is segregating.

The commercial value of testing for major genes and using the information in selection has been shown to depend on the relativity between genotyping costs and the sale value of animals carrying one or two copies of the favorable allele of the major gene. In some situations in which genotyping costs are high, and the animals sold are few or gain insufficient premium from having a desirable major gene genotype, it may not be cost-effective to genotype selection candidates. Note that this conclusion only applies when the trait affected by the major gene is recorded in selection candidates prior to the age at which selection takes place, and for a co-dominant major gene effect on phenotype, as used in the simulations.

The population structures and mode of testing simulated in this study are quite specific, and may not be expected to apply across livestock breeding programmes in general. For example, in dairy breeding programmes in which genetic progress is currently based on progeny testing, a different population structure should be simulated. The structure used in this study corresponds closely to an aquaculture breeding programme, where testing for individuals or families may be limited by costs, but in which large numbers of untested individuals with selected parents could be sold. Potential breeding programmes incorporating new biotechnologies such as *in vitro* reproduction technologies for sale of large numbers of normal or cloned embryos are also similar. For these situations, it is conceivable that the major gene could be a result of genetic modification technology.

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