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Consequences of selection for improving production traits on the frequency of deleterious alleles for fitness[1]

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ABSTRACT: In this study the effect of artificial selection on BLUP EBV for production traits on the allele frequencies of a pleiotropic QTL affecting both production and disease susceptibility was investigated. Stochastic simulations were used to model artificial selection on a production trait that is controlled, in part, by a biallelic QTL that also controls susceptibility to disease. The QTL allele increasing production also increased susceptibility to disease. Different modes of action and proportions of variation accounted for by the QTL were assessed for the production trait. The main results indicated that alleles that confer susceptibility to the disease could be maintained in the population over a long period, depending on the mode of action of the QTL. In addition, the results of the study indicate that, under various conditions, it is possible to find pleiotropic QTL that control 2 traits despite these traits appearing to be uncorrelated. Therefore, in practice, an estimate of the genetic correlation between 2 traits may be misleading when the presence of such a QTL exists. The results of this study have implications for breeding programs. For example, if a pleiotropic QTL exists that favors heterozygotes for a production trait, it would be very difficult to remove disease susceptibility alleles via traditional selection methods.

Key words: fitness, health-related trait, pleiotropy, quantitative trait locus, selection

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INTRODUCTION

In domestic livestock species, improving health-related traits has become increasingly important (Bishop et al., 2002). To evaluate the benefits of including health-related traits in the breeding objective, it is necessary to know their genetic relationships with other traits of importance such as production traits. It is generally accepted that if the estimated additive genetic correlation between production and disease susceptibility is zero, improvement in production traits can be accomplished without adversely affecting the disease trait (Falconer and Mackay, 1996).

Most QTL mapping experiments have focused on production traits, although QTL for health-related traits may offer more benefits (e.g., Dekkers, 2004). Mapping studies aimed at finding QTL for these low heritability traits could easily have production data available, allowing the search for pleiotropic QTL to be used in marker-assisted selection programs.

One particular study looking at pleiotropic QTL is that of Navarro et al. (2006b). Their analysis suggested the existence of a QTL segregating at intermediate frequencies that had negative effects on ascites resistance and positive effects on production despite the fact that the estimated additive genetic correlation between both traits was zero (Navarro et al., 2006a). The QTL had a dominant effect on disease resistance and an overdominant effect on production. This mode of action might explain why a gene with negative effects on a fitness trait is still segregating in populations undergoing artificial selection to improve production traits. Even if disease resistance were included in the breeding objective, it would be difficult to remove susceptible alleles by conventional selection that ignores information on genetic markers.

The main objective of this study was to investigate the effect of artificial selection to improve production traits on the evolution of the allele frequencies of a pleiotropic QTL affecting both production and disease susceptibility.

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Table 1. Summary of additive (a_1 and a_2) and dominant values (d_1 and d_2), corresponding genotypic values, and percentage of the total variation (θ) accounted for by the QTL for the production trait and for disease susceptibility

	Genotypic value[1]			
Model	AA	AB	BB	θ
Production				
$a_1 = 0.2,\ d_1 = 0.0$	0.2	0.0	−0.2	4
$a_1 = 0.3,\ d_1 = 0.0$	0.3	0.0	−0.3	8
$a_1 = 0.5,\ d_1 = 0.0$	0.5	0.0	−0.5	20
$a_1 = 0.2,\ d_1 = 0.2$	0.2	0.2	−0.2	6
$a_1 = 0.3,\ d_1 = 0.3$	0.3	0.3	−0.3	12
$a_1 = 0.5,\ d_1 = 0.5$	0.5	0.5	−0.5	27
$a_1 = 0.0,\ d_1 = 0.9$	0.0	0.9	0.0	28
$a_1 = 0.2,\ d_1 = 0.9$	0.2	0.9	−0.2	31
$a_1 = 0.5,\ d_1 = 0.9$	0.5	0.9	−0.5	27
Disease susceptibility				
$a_2 = 0.9,\ d_2 = 0.9$	0.9	−0.9	−0.9	85

[1]Allele A increases production and disease susceptibility; allele B decreases production and disease susceptibility.

MATERIALS AND METHODS

Stochastic simulations were used to model artificial selection on a production-type trait affected by a QTL that was also affecting disease susceptibility, so no institutional Animal Care and Use Committee approval was required. Animals for which the phenotype for disease susceptibility exceeded a given threshold were culled (i.e., natural selection was assumed to be acting on the disease trait). The expected changes in allele frequencies for the QTL under different genetic models were monitored. A total of 100 replicates were run for each simulation. Results presented are the averages over all replicates.

Genetic and Population Models

The 2 traits were assumed to be controlled by additive polygenes, a biallelic pleiotropic QTL (alleles A and B) and an environmental component. It was assumed that the A allele increased production, but also increased susceptibility to disease, and the B allele decreased production and reduced susceptibility to disease. The total genetic value of an individual i for each trait was $g_i = v_i + u_i$, where v_i is the genotypic value due to the QTL and u_i is the polygenic value. The polygenic heritabilities were 0.5 and 0.1 for production and disease susceptibility, respectively, and the polygenic correlation between the 2 traits was zero. The genotypic values due to the QTL for trait j were a_j, d_j, and $-a_j$ (for individuals with genotypes AA, AB, and BB, respectively), where $\boldsymbol{a_j}$ is the additive effect defined as half the difference between the 2 homozygotes, and $\boldsymbol{d_j}$ is the dominance effect defined as the difference between the heterozygote and the average of the 2 homozygotes (Falconer and Mackay, 1996).

Models with different values for a_1 and d_1 (production trait) and initial QTL allele frequencies were considered. In all scenarios, the genetic mode of action of the QTL for disease susceptibility was dominant, with the A allele being recessive. For this trait, the genotypic values for the QTL were 0.9, −0.9, and −0.9 for genotypes AA, AB, and BB, respectively. For the production trait, additive, dominant, or overdominant modes of action of the QTL were considered. The specific models assumed are given in Table 1. In most scenarios, the initial frequency of the B allele ($\boldsymbol{q}$) was 0.5, but situations where q was 0.9 and 0.1 were also considered.

One hundred twenty individuals (60 males and 60 females) were simulated in the base generation ($t = 0$). Generation 1 ($t = 1$) was obtained from matings of individuals selected at $t = 0$. The number of selection candidates was constant across generations and the number of generations simulated was 40 or 400 (see below). At $t = 0$ and for each trait j, u_i was obtained from a normal distribution with mean zero and variance $\sigma^2_{u_j}$. For both traits, the phenotypic value for an individual i was obtained by adding g_i to a normally distributed environmental component (e_i) with mean zero and variance $\sigma^2_{e_j}$. The polygenic and environmental variances summed to 1 for each trait.

In subsequent generations ($t > 0$), the polygenic value of the offspring was obtained by adding a random Mendelian sampling term to the average of the polygenic effects of their parents. The Mendelian sampling term was sampled from a normal distribution with mean zero and variance $(\sigma^2_{u_j}/2)(1 - F)$, where F is the average inbreeding coefficient of the parents. The QTL genotype of an offspring was obtained by randomly sampling 1 allele from each parent.

Selection

In each generation, the 30 males and the 30 females with the highest EBV for the production trait were selected (i.e., standard truncation selection). The EBV were obtained from a BLUP animal model using PEST4 (Groeneveld and Kovac, 1990). The BLUP evaluation used the base population total additive variance ($\sigma^2_{u_1} + \sigma^2_{a_1}$, where $\sigma^2_{a_1}$ is the QTL additive variance for trait 1) and the phenotypic values uncorrected for the effects of the QTL (i.e., it was assumed that no information on the QTL was available). Before selection on production, animals were discarded based on the disease phenotype, modeling natural selection. That is, individuals whose phenotypic value for disease susceptibility exceeded a particular threshold (high positive value, because susceptible animals have, according to the definition of the disease model, high positive phenotypic values) were culled. Two different thresholds were chosen corresponding to a disease incidence of 5 and 20% in the initial generation. In subsequent genera-

tions, the threshold values were kept constant and equal to the initial values; however, the disease incidence varied because of the combined effects of natural selection acting to remove affected individuals from the population and artificial selection on the production trait.

The main objective of this study was to investigate the effect of selection based on BLUP EBV for the production trait on QTL allele frequencies. Selection schemes were run for 40 generations. In addition, some schemes were run for 400 generations of selection on the production trait; in these cases, simple phenotypic selection was used to reduce computation time. In these scenarios, selection was based on the phenotypic records for production, also uncorrected for the QTL effect.

Estimation of Genetic Parameters

Restricted maximum likelihood using the (co)variance component estimation program VCE5 (Neumaier and Groeneveld, 1998) was used to estimate genetic variances and the genetic covariance and correlation between the traits. The phenotypic values for both traits were uncorrected for the effects of the QTL. The correlation obtained in this way would correspond to that estimated in practice when no prior knowledge of the QTL is available. To reduce computation time, the correlations were estimated every 5 generations. Offspring and parent generations at a particular time were considered to obtain the estimates. The estimate of genetic correlation ($\hat{\boldsymbol{\rho}}$) was compared with the true additive polygenic correlation ($\boldsymbol{\rho_u}$) and with the true total correlation ($\boldsymbol{\rho_t}$). The true additive polygenic correlation was calculated as $\rho_u = \text{cov}(u_1, u_2) / \sigma_{u_1}\sigma_{u_2}$ and the total true correlation was calculated as $\rho_t = \text{cov}(g_1, g_2) / \sigma_{g_1}\sigma_{g_2}$, where $\sigma^2_{g_j}$ is the total genetic variance for trait j.

RESULTS

Additive QTL for the Production Trait

Figures 1a and 1b show the change in frequency of the allele reducing disease susceptibility and production (i.e., q) when the QTL had an additive effect for production (i.e., $d_1 = 0$) and artificial selection was based on BLUP EBV. Different proportions of the variation for production accounted by the QTL and different initial disease incidences (i.e., the proportion of animals culled) in the population (20 or 5%) were considered. When the initial incidence was 5%, q decreased over time. When the initial incidence was 20%, q also decreased but only after an initial increase. The greater the proportion of variation the QTL accounted for in production ($a_1 = 0.5$ vs. $a_1 = 0.3$ vs. $a_1 = 0.2$), the faster q decreased.

The increase in q in the initial generations (first 10 to 20 generations, depending on the value of a_1) when the initial incidence was 20% was due to the fact that animals with the favorable allele for production were culled because of natural selection (as this allele also increases disease susceptibility). The net effect was that more animals with the allele that reduced disease susceptibility were selected and q increased. After 10 to 20 generations, as the animals with high production became less susceptible to disease (because the genetic mean for disease susceptibility decreased due to natural selection, see below), there was more scope for selection on production, and, therefore, the frequency of the A allele ($\boldsymbol{p}$) increased (and q decreased). After the initial increase in q, changes in frequency were small when the effect of the QTL was either $a_1 = 0.2$ or 0.3, and, at generation 40, q was still at intermediate values ($q = 0.73$ for $a_1 = 0.2$ and $q = 0.60$ for $a_1 = 0.3$). When the disease incidence in the initial generation was 5%, the scope for selection on production was high from the start of the selection process; therefore, q decreased across the whole selection period. The B allele was lost more rapidly the greater the effect on production of the QTL (Figure 1b).

Dominant QTL for the Production Trait

Figures 1c and 1d show the change in q when the mode of action of the QTL was dominant for production. The trends are similar to those observed when the QTL was additive, but allele frequencies changed at a slower rate. For example, with $a_1 = 0.5$, the allele reducing disease susceptibility was lost after 13 generations when the initial disease incidence was 5% and the QTL acted additively (Figure 1b), but was still segregating after 40 generations when the QTL was dominant (Figure 1d). As with the additive case, there was an initial increase in q when the initial disease incidence was high (20%), but this increase was less drastic when the QTL was dominant. Importantly, with $a_1 = 0.2$ and a high disease incidence, after the initial increase, q stayed almost constant for many generations before it started to decrease slowly. Given these rates of change, 40 generations of selection were not enough to know if, in some scenarios, the frequency would stabilize at an intermediate value.

Overdominant QTL for the Production Trait

When the mode of action of the QTL production trait was overdominant, there was little change in gene frequency after the initial generations of selection (Figures 1e and 1f). In most overdominant scenarios investigated, the frequency of the allele approached equilibrium after as little as 5 generations. The initial disease incidence had relatively little effect on the equilibrium value of q.

Selection for 400 Generations

In the scenarios where the QTL had an additive or dominant effect on the production trait, the evolution of the QTL frequency after 40 generations of selection was unclear (Figure 1). To investigate the trend after

generation 40, simulations were run applying artificial phenotypic selection on production for 400 generations assuming an initial disease incidence of 20%. Figure 2 shows that for the additive and dominant models, q continued to decline across generations and thus the expectation is that the allele reducing disease susceptibility will eventually be lost. This allele was lost more quickly when the mode of action of the QTL on

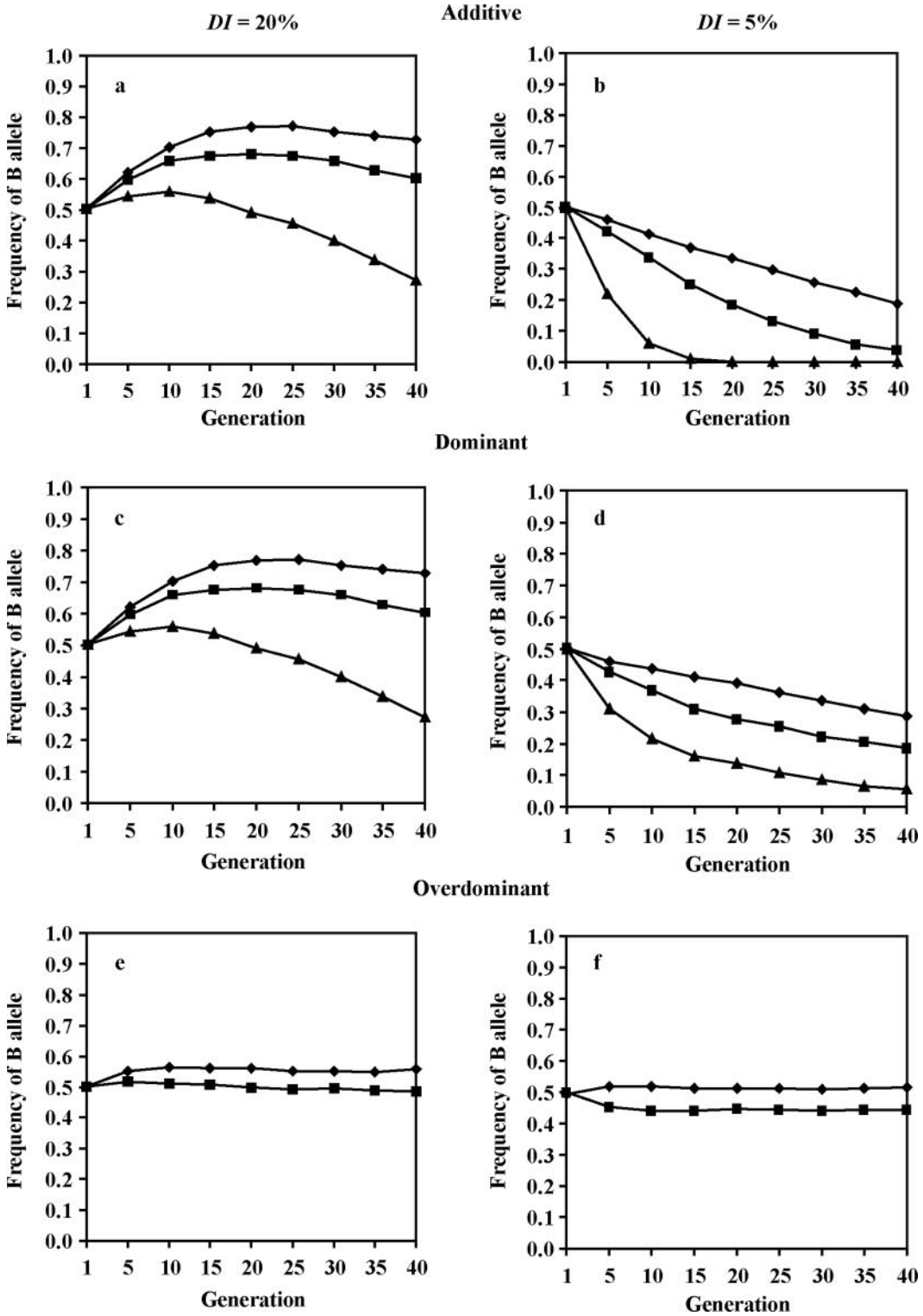

Figure 1. Change in frequency of the allele reducing disease susceptibility (allele B) resulting from artificial selection on BLUP EBV for the production trait when the QTL had an additive (a and b), dominant (c and d), or overdominant (e and f) effect on the production trait and the initial disease incidence (*DI*) in the population was 20% (left panels) or 5% (right panels). In the additive model, the QTL additive values (a_1) for the production trait were 0.2 (◆), 0.3 (■), or 0.5 (▲). In the dominant model, the QTL additive and dominant (d_1) values for the production trait were $a_1 = d_1 = 0.2$ (◆), $a_1 = d_1 = 0.3$ (■), or $a_1 = d_1 = 0.5$ (▲). In the overdominant model, a_1 was 0.0 (◆) or 0.2 (■) and d_1 was 0.9. Standard errors ranged from 0.04 to 0.08.

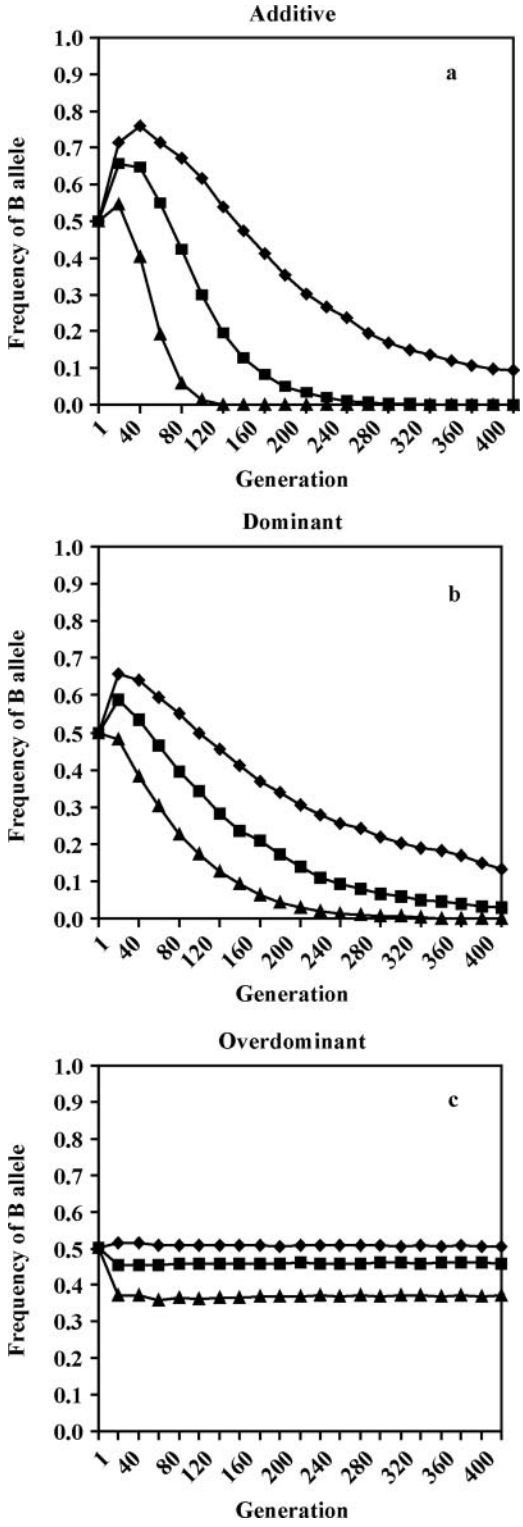

Figure 2. Change in frequency of the allele reducing disease susceptibility (allele B) resulting from artificial selection on phenotypes for the production trait when the QTL had an additive (a), dominant (b), or overdominant effect (c) on production and selection was for 400 generations. The initial disease incidence was 20%. In the additive model, the QTL additive values (a_1) for the production trait were 0.2 (◆), 0.3 (■), or 0.5 (▲). In the dominant model, the QTL additive and dominant (d_1) values for the production trait were $a_1 = d_1 = 0.2$ (◆), $a_1 = d_1 = 0.3$ (■), or $a_1 = d_1 = 0.5$ (▲). In the overdominant model, a_1 was 0.0 (◆), 0.2 (■), or 0.5 (▲) and d_1 was 0.9. Standard errors ranged from 0.04 to 0.08.

production was additive compared with when it was dominant. Also, the greater the effect of the QTL on production, the faster the allele favorable for production was fixed. When the mode of action of the QTL on production was overdominant, the frequency remained constant after reaching an equilibrium value in the initial generations.

Effect of Initial Starting Frequency

Figure 3 shows the changes in allele frequencies when the initial q was very high (0.95, and consequently p was very low), modeling a situation where B was the only QTL allele in the population and a new mutation (the A allele) favorable for production arose in that population. The reverse situation [i.e., when the initial q was very low (0.05)] was also considered, but results are only shown for the overdominant model, because A was quickly fixed in the population when the mode of action was additive or dominant.

When the mode of action was additive (Figure 3a) and the QTL effect on the production trait was either 0.3 or 0.5, q appeared to reach a low (but nonzero) equilibrium value around generation 200 or generation 100, respectively. This also occurred when $a_1 = 0.2$, but only after 600 generations (results not shown). This nonzero equilibrium value was a consequence of the fact that in some of the replicates (10 to 15) the B allele became fixed within this period when its initial frequency at generation $t = 0$ was high. In comparison, when the starting frequency was 0.5, the allele was lost in all of the replicates. When the mode of action was dominant, allele B was lost within 400 generations when $a_1 = 0.5$ (Figure 3b). The allele was also lost when $a_1 = 0.2$, and 0.3, but only after 400 generations (results not shown). When the mode of action was overdominant, the allele frequency reached equilibrium at an intermediate frequency, regardless of the starting frequency of the QTL or the a_1 and d_1 values (only $a_1 = 0.2$ and $d_1 = 0.9$ shown, Figure 3c). In this case, the equilibrium value did reflect the fact that, in all populations simulated, the frequency after 400 generations was still intermediate.

Genetic Gain

Table 2 shows the average polygenic and total (i.e., sum of polygenic and QTL means) genetic means over 40 generations for both traits when artificial selection was based on BLUP EBV for production. The results are shown for the scenarios $a_1 = 0.2$ and $d_1 = 0.0$ (additive), $a_1 = 0.2$ and $d_1 = 0.2$ (dominant), and $a_1 = 0.2$ and $d_1 = 0.9$ (overdominant). Results for corresponding models with different a_1 and d_1 values were similar. For each of the models, the polygenic and total mean for production was greater at each generation when the initial culling in the population was 5% versus 20%. The overdominant model had the lowest accumulated polygenic and total gains after 40 generations. Artifi-

cial selection was on production only, but there was a decrease in disease susceptibility because of natural selection imposed through the culling of affected animals. For all of the models the polygenic and total means were lower (i.e., less negative) for disease susceptibility when the initial incidence was 5%, which means that, after 40 generations, a population with greater initial disease incidence will, on average, be healthier than a population with lower initial incidence. When the initial incidence in the population was 20%, disease susceptibility was reduced most in the additive model, followed by the dominant model, with the overdominant model having the least gain. However, this order was reversed when the initial disease incidence in the population was 5%. This can be explained by the changes in q during the 40 generations of selection on production. When the initial incidence was 20%, q was highest at generation 40 for the additive model compared with the other 2 models (Figures 1a, 1c, and 1e), but q was lowest at generation 40 for the additive model when the initial incidence in the population is 5% (Figures 1b, 1d, and 1f).

Disease Incidence

Table 2 also shows the proportion of animals culled based on the disease phenotype (i.e., disease incidence). When the initial disease incidence was 20%, only 6 and 8% of the population was culled by $t = 40$ under the additive and dominant models, respectively. Under the overdominant model the reduction in the total mean for disease susceptibility (-0.99 at $t = 40$) was smaller than under the additive and dominant models, and, therefore, the disease incidence in the population was greater (10% at $t = 40$). When the initial incidence in the population was 5%, the tendency was for the incidence to increase in the additive and dominant models, because of the allele reducing disease susceptibility going toward zero (Figures 1b and 1d). Under the overdominant model, the disease incidence remained stable through the generations.

Genetic Correlations

Table 3 shows the true additive polygenic (ρ_u), true total (ρ_t), and estimated ($\hat{\rho}$) genetic correlations between the 2 traits. For clarity purposes, one example of each of the additive, dominant, and overdominant models is shown; however, similar trends were obtained for the other scenarios investigated. As expected in the initial population, ρ_u was not significantly different from zero and remained at this value throughout each generation of selection. The estimated genetic correlation ($\hat{\rho}$) differed from ρ_u as the 2 traits were truly correlated due to the QTL, and the estimation method used phenotypes uncorrected for the QTL effect. When the QTL had an additive mode of action on production, $\hat{\rho}$ and ρ_t were of the same sign and of similar magnitude. This would suggest that when the information on the

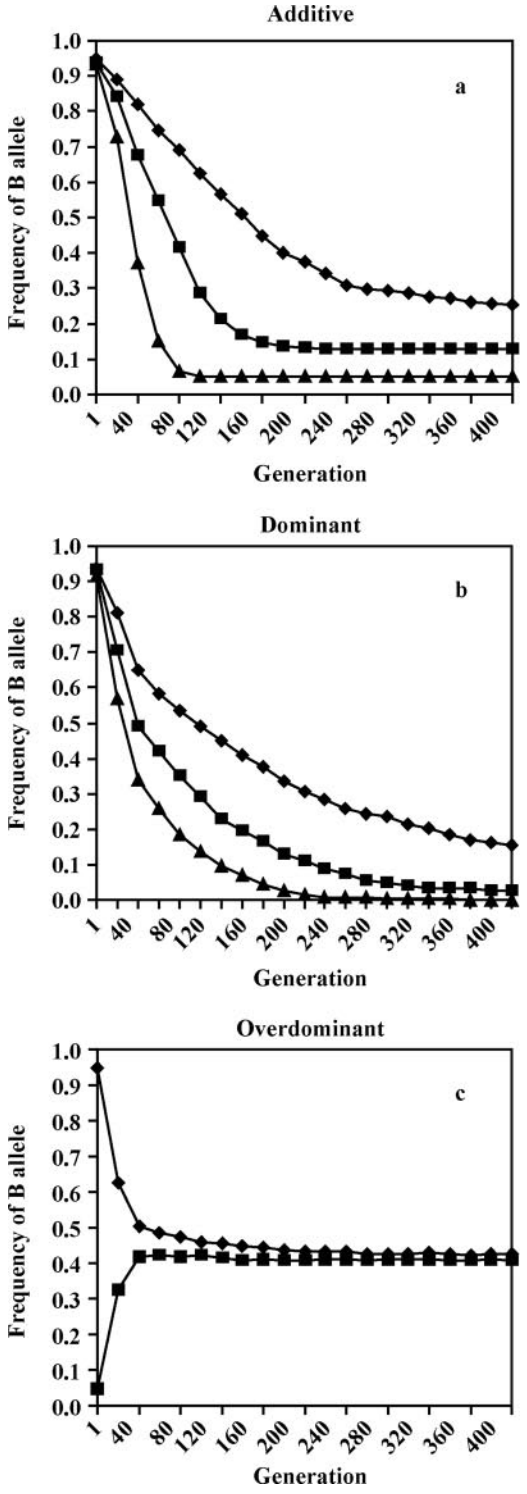

Figure 3. Effect of a different initial starting frequency of the allele favorable for reducing disease susceptibility (allele B) when the QTL had an additive (a), a dominant (b), or an overdominant (c) effect on the production trait and the initial culling level in the population was 5%. In the additive model, the QTL additive values (a_1) for the production trait were 0.2 (◆), 0.3 (■), or 0.5 (▲). In the dominant model, the QTL additive and dominant (d_1) values for the production trait were $a_1 = d_1 = 0.2$ (◆), $a_1 = d_1 = 0.3$ (■), or $a_1 = d_1 = 0.5$ (▲). In the overdominant model, a_1 was 0.2 and d_1 was 0.9 and 2 initial frequencies are shown.

Table 2. Polygenic (G_u) and total (G_t) genetic means for the production trait and for disease susceptibility, and disease incidence (*DI*, proportion of animals culled based on phenotypes for the disease trait) across generations (*gen*) when the QTL had an additive ($a_1 = 0.2$; $d_1 = 0.0$), dominant ($a_1 = 0.2$; $d_1 = 0.2$), or overdominant ($a_1 = 0.2$; $d_1 = 0.9$) effect on production, and the initial *DI* at $t = 0$ was 20 or 5%[1]

	Initial *DI* = 20%					Initial *DI* = 5%				
	Production		Susceptibility			Production		Susceptibility		
Effect/*gen*[2]	G_u	G_t	G_u	G_t	*DI*	G_u	G_t	G_u	G_t	*DI*
Additive										
1	0.32	0.30	−0.02	−0.56	0.18	0.40	0.40	−0.01	−0.43	0.05
3	0.91	0.86	−0.05	−0.72	0.12	1.05	1.07	−0.03	−0.38	0.06
5	1.52	1.45	−0.09	−0.80	0.10	1.68	1.71	−0.04	−0.34	0.06
10	2.73	2.64	−0.13	−0.89	0.08	2.93	2.97	−0.08	−0.29	0.06
40	11.02	10.93	−0.40	−1.14	0.06	11.19	11.32	−0.37	−0.01	0.07
Dominant										
1	0.32	0.40	−0.02	−0.56	0.17	0.39	0.50	−0.01	−0.42	0.05
3	0.90	0.95	−0.06	−0.69	0.12	1.04	1.15	−0.03	−0.39	0.05
5	1.50	1.53	−0.09	−0.75	0.11	1.68	1.80	−0.05	−0.39	0.05
10	2.68	2.69	−0.14	−0.85	0.09	2.92	3.05	−0.08	−0.37	0.06
40	10.76	10.80	−0.42	−1.06	0.08	11.26	11.42	−0.33	−0.26	0.05
Overdominant										
1	0.29	0.73	−0.02	−0.53	0.17	0.36	0.82	−0.01	−0.42	0.05
3	0.83	1.24	−0.06	−0.62	0.15	0.99	1.45	−0.03	−0.41	0.05
5	1.37	1.77	−0.09	−0.66	0.13	1.58	2.04	−0.05	−0.43	0.05
10	2.42	2.83	−0.16	−0.73	0.12	2.77	3.23	−0.08	−0.42	0.05
40	9.63	10.06	−0.50	−0.99	0.10	10.61	11.08	−0.24	−0.54	0.04

[1]Standard errors ranged from 0.01 to 0.05 for both G_u and G_t.

[2]At *gen* = 0, G_u and G_t were zero except for disease susceptibility under all models ($G_t = -0.45$) and for the production trait under the dominant ($G_t = 0.10$) and overdominant ($G_t = 0.45$) models.

QTL is ignored, $\hat{\rho}$ is a good estimate of the actual underlying total genetic correlation. When the mode of action of the QTL on the production trait was dominant, $\hat{\rho}$ was of the same sign, but clearly overestimated ρ_t. Last, when the mode of action was overdominant, $\hat{\rho}$ and ρ_t were very different and even had opposite signs. This indicates that in certain situations the estimated correlation between 2 traits that are affected by a single QTL can be very inaccurate. The inaccurate estimates may even suggest that the 2 traits are controlled independently when they are not. For instance, when the mode of action of the QTL on production was overdominant and $a_1 = 0$, $\hat{\rho}$ was not significantly different from zero (results not shown), indicating that the 2 traits are controlled independently, despite the fact that the pleiotropic QTL was segregating in the population.

DISCUSSION

This study investigated the evolution of allele frequencies for a QTL with pleiotropic effects on production and disease susceptibility when artificial selection is applied to increase production. Navarro et al. (2006a,b) suggested that 2 traits that seemed to be uncorrelated based on the estimates of genetic parameters obtained using standard animal models may be controlled by

Table 3. Effect of the mode of action of the QTL for production on the true polygenic (ρ_u), true total (ρ_t), and estimated ($\hat{\rho}$) genetic correlations between the production trait and disease susceptibility over generations (*gen*)[1]

	Additive $a_1 = 0.5$, $d_1 = 0.0$			Dominant $a_1 = 0.5$, $d_1 = 0.5$			Overdominant $a_1 = 0.2$, $d_1 = 0.9$		
gen	ρ_u	ρ_t	$\hat{\rho}$	ρ_u	ρ_t	$\hat{\rho}$	ρ_u	ρ_t	$\hat{\rho}$
1	0.02	0.36	0.47	0.00	0.19	0.48	0.01	−0.16	0.21
5	0.02	0.31	0.30	−0.01	0.13	0.28	0.00	−0.18	0.08
10	0.02	0.31	0.26	0.00	0.13	0.30	0.01	−0.20	0.15
15	0.02	0.33	0.30	0.01	0.13	0.32	0.00	−0.22	0.05
20	0.02	0.34	0.36	0.00	0.13	0.27	0.00	−0.23	0.16
25	0.01	0.35	0.34	0.00	0.14	0.31	−0.03	−0.24	0.15
30	0.00	0.37	0.39	−0.01	0.14	0.32	−0.03	−0.27	0.09
35	0.00	0.36	0.36	−0.01	0.14	0.35	0.01	−0.27	0.08
40	0.02	0.32	0.32	0.00	0.12	0.25	0.01	−0.29	0.18

[1]Standard errors ranged from 0.004 to 0.015 for both ρ_u and ρ_t and from 0.03 to 0.07 for $\hat{\rho}$.

a pleiotropic QTL (dominant for disease susceptibility and overdominant for production), and, as a result, the disease susceptibility allele could be segregating at intermediate frequencies in a commercial population under artificial selection for production. Here, we show that it is possible to find such QTL segregating for a variety of genetic modes of action. The changes in frequency of the QTL over time clearly depend on the mode of action of the QTL on production; however, regardless of this, we showed that the QTL could still be segregating in the population after 40 generations of selection. In fact, under certain scenarios, the QTL alleles remained at intermediate frequencies for all 40 generations. The maintenance of segregation due to the conflict between artificial and natural selection was also described by Verghese (1974), Minvielle (1980), and Nicholas and Robertson (1980), who showed that plateaus in artificial selection experiments can result from this conflict rather than from a loss of additive genetic variance. More recently, Thompson et al. (2006) showed that assuming a single locus model and an infinite population, a lethal recessive allele will tend toward a stable equilibrium frequency if there is a selective advantage of the heterozygote.

In the case of the additive and dominant models, the QTL favorable for production was eventually fixed in most scenarios ($p = 1$), but this did not happen for several hundreds of generations. This is highly relevant for practical breeding programs because, even with a generation interval as short as 1 yr, fixation will not occur for a long time, highlighting the importance of detecting pleiotropic QTL and using molecular information to control their allele frequencies. When the mode of action of the QTL on the production trait was overdominant, an intermediate equilibrium frequency was reached, and the QTL remained at this frequency throughout the generations.

The amount of variation accounted for by the QTL for disease susceptibility was assumed to be large (85%). In scenarios where this allele is lost, this would happen more quickly when the QTL has a smaller effect on susceptibility. In circumstances in which the QTL explains all of the genetic variation in disease susceptibility, there is no opportunity for evolution of the background polygenic resistance to disease, and the QTL would be expected to remain segregating in the population for a longer period. As expected, the changes in the QTL allele frequency depend on the amount of variation the QTL explains for each of the traits. Under the additive and dominant models for the production trait, the greater the proportion of variation explained by the QTL, the faster the allele favorable for the production trait was fixed, and the allele reducing disease susceptibility was lost. Under these models, when the initial disease incidence in the population was 20%, there was an initial decrease in the disease susceptibility allele as the high-production animals, with the AA genotype, were culled. However, as the high-production animals were improved genetically for disease susceptibility (via the background polygenes), more of these animals with the favorable QTL allele for production were selected and the frequency of the A allele increased. This contrasts with what is expected when assuming that i) both traits are controlled by a single QTL (and there are no polygenes); ii) the population size is infinite; and iii) fitness is constant over time for a particular genotype. Under these assumptions, a population with any given initial frequency $0 < q < 1$ is predicted to converge monotonically toward the equilibrium frequency, which is determined by the selection coefficients for both traits (see Appendix).

In this study, we simulated a situation in which selection on disease resistance occurred through natural culling of affected animals. The parameters were based on those for ascites and its indicator trait, blood oxygen saturation (Navarro et al., 2006a,b). In the case of ascites, natural selection can be augmented, possibly substantially, by additional selection on the continuously distributed trait blood oxygen saturation. Selection against low blood oxygen saturation can potentially eliminate birds carrying alleles for increased susceptibility to ascites, but that would not actually develop the disease. Although a model with selection for a continuously distributed indicator of disease differs from that utilized in this study, the outcomes are likely to be similar, with the potential for long-term maintenance of disease susceptibility alleles under some models of gene action.

Accurate estimation of the genetic correlations among traits in the selection objective is an integral part of any breeding program. Such correlations will help to determine whether or not we can expect correlated responses when selecting for a particular trait or for a combination of traits. Here, we simulated a polygenic genetic correlation of zero between the 2 traits. When the pleiotropic QTL was segregating, the 2 traits were correlated to some degree because of the QTL. Here we show that the mode of action of the QTL on the production trait had an effect on the estimated genetic correlation and that under some circumstances this correlation can be very different from the true correlation. When the QTL had an additive effect on the production trait, the estimated correlation was a good indication of the total genetic correlation. However, under the nonadditive models the estimated correlation was far from the true value, and, in the case of the overdominant model, the estimated and true correlations even had opposite signs. This has implications in terms of selection in a breeding program because, traditionally, a single genetic correlation assumed to be caused by additive polygenes is estimated in the absence of information on QTL. When the phenotypic values were corrected for the QTL, the estimated genetic correlations did not differ significantly from zero (results not shown). This is expected as the polygenic genetic correlation simulated was zero and the effects of the QTL have been accounted for, thereby removing the correlation that had been generated by the QTL.

Originally, QTL mapping experiments focused on single traits. However, the ability to simultaneously record many traits and the advances in statistical methodology to detect QTL has led to attempts in detecting pleiotropic QTL (Freyer et al., 2003; Varona et al., 2004). This information is very important in the context of designing breeding programs, which usually aim to improve several traits simultaneously, such as production and disease-type traits. Examples of pleiotropic or closely linked QTL found in livestock species include QTL for milk component traits in dairy cattle (Schrooten and Bovenhuis, 2002; Freyer et al., 2003), and lean meat and susceptibility to stress in pigs (Nicholas, 1996). Here, we utilize estimates of QTL effects that were generated from a study of ascites in chickens (Navarro et al., 2006b). Nevertheless, the scenarios could be typical of any livestock species in which production traits have been artificially selected for, for many generations.

The scenario simulated (artificial selection for a production trait when no information is known about a pleiotropic QTL that affects both production and disease susceptibility) would be representative of animal breeding schemes over the last several decades. The findings of this study have important implications for practical breeding programs. For example, if a pleiotropic QTL existed that favored the heterozygotes for a production trait (i.e., overdominant), then it would be very difficult to remove the disease susceptibility allele via traditional selection methods. In such situations, the use of QTL information could be of great benefit to increase accuracy of selection and obtain unbiased estimates of genetic parameters by correcting for QTL effects, and to optimize breeding decisions.

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APPENDIX

Changes in Allele Frequency for a Pleiotropic Locus Under Antagonistic Selection

Changes in allele frequencies for a single biallelic QTL (alleles A and B) with pleiotropic effect on 2 traits can be obtained using the framework of Falconer and Mackay (1996; chapter 2). This framework is based on the calculation of gametic contributions of different genotypes to the offspring generation and assumes i) a single QTL controlling both traits; ii) an infinite population size; and iii) constant fitness over time for a particular genotype. A single QTL mode of action (dominant) is considered for disease resistance, but 3 different QTL modes of action (additive, dominant, and overdominant) are considered for the production trait. Table A1 shows gametic contributions for the 3 genotypes when assuming different modes of QTL action.

Additive QTL for the Production Trait

Let A be the allele that increases production and reduces disease resistance and B the allele that decreases production and increases resistance. Then, for the production trait, genotype AA is the most favored and its contribution is taken to be 1. Genotype BB is selected against and its contribution is $1 - s_1$, where s_1 is the coefficient of selection (i.e., the proportionate reduction in gametic contribution of this genotype compared with AA) for production. Under the additive model, the selective value for the heterozygous genotype is simply $1 - 1/2\ s_1$. For disease resistance (complete dominance), genotypes BB and AB are the most favored, and their contributions with respect to this trait are taken to be 1, whereas genotype AA is selected against and its contribution is $1 - s_2$, where s_2 is the coefficient of selection for disease resistance. Overall selective values are the product of selective values for both traits. Let q_n be

the frequency of allele B at generation n. Then, summing the gametic contributions of individual genotypes (Table A1), the total gametic contribution of generation n toward generation $n + 1$ is $1 - s_1 q_n - s_2(1 - q_n)^2$.

The frequency of the B allele in generation $n + 1$ is the gametic contribution of genotype BB plus half of the gametic contribution of genotype AB relative to the total; that is,

$$q_{n+1} = q_n \frac{1-(1/2)s_1(1+q_n)}{1-s_1q_n-s_2(1-q_n)^2}. \quad [1]$$

Equation [1] provides the conditions for changes in allele frequency. In particular, allele frequencies are stable if $q_{n+1} = q_n$; that is,

$$\frac{1-(1/2)s_1(1+q_n)}{1-s_1q_n-s_2(1-q_n)^2} = 1, \quad [2]$$

which, after solving for q_n, leads to the necessary conditions:

$$q_n = 1 \text{ or } q_n = [s_2 - (1/2)s_1]/s_2.$$

Similarly, the frequency of allele B increases from one generation to the next (i.e., $q_{n+1} > q_n$) if the left hand side of Eq. [2] is greater than 1; that is, if $q_n < [s_2 - (1/2)s_1]/s_2$, and decreases if $1 > q_n > [s_2 - (1/2)s_1]/s_2$.

Dominant QTL for the Production Trait

Table A1 also shows gametic contributions for the 3 genotypes when assuming that the QTL is dominant for the production trait. The frequency of the B allele in generation $n + 1$ under this model is

$$q_{n+1} = q_n \frac{1-s_1q_n}{1-s_1q_n^2-s_2(1-q_n)^2},$$

which, as before, provides the conditions for changes in allele frequency. Under this model, the frequency of allele B is stable if $q_n = 1$ or $q_n = s_2/(s_1 + s_2)$, increases from one generation to the next if $q_n < s_2/(s_1 + s_2)$, and decreases if $1 > q_n > s_2/(s_1 + s_2)$.

Overdominant QTL for the Production Trait

Under the overdominant model the frequency of the B allele in generation $n + 1$ is

$$q_{n+1} = q_n \frac{1-s_1q_n}{1-s_1q_n^2-(1-q_n)^2(s_1+s_2-s_1s_2)},$$

and therefore, the frequency of allele B is stable if $q_n = 1$ or $q_n = (s_1 + s_2 - s_1s_2)/(2s_1 + s_2 - s_1s_2)$, increases from one generation to the next if $q_n < (s_1 + s_2 - s_1s_2)/(2s_1 + s_2 - s_1s_2)$, and decreases if $1 > q_n > (s_1 + s_2 - s_1s_2)/(2s_1 + s_2 - s_1s_2)$.

Table A1. Genotypic frequencies at generation n, selective values for production (S_P) and disease resistance (S_R), and gametic contributions (C) for the 3 genotypes assuming an additive, dominant, or overdominant model for the production trait and a dominant model for disease resistance[1]

	QTL genotype		
Item	AA	AB	BB
Frequency	$(1 - q_n)^2$	$2(1 - q_n)q_n$	q_n^2
S_R	$1 - s_2$	1	1
Additive			
S_P	1	$1 - (1/2)s_1$	$1 - s_1$
C	$(1 - s_2)(1 - q_n)^2$	$2[1 - (1/2)s_1]\,(1 - q_n)q_n$	$(1 - s_1)\,q_n^2$
Dominant			
S_P	1	1	$1 - s_1$
C	$(1 - s_2)(1 - q_n)^2$	$2(1 - q_n)q_n$	$(1 - s_1)\,q_n^2$
Overdominant			
S_P	$1 - s_1$	1	$1 - s_1$
C	$(1 - s_1)\,(1 - s_2)(1 - q_n)^2$	$2(1 - q_n)q_n$	$(1 - s_1)\,q_n^2$

[1] q_n is the frequency of allele B at generation n, s_1 is the coefficient of selection for production, and s_2 is the coefficient of selection for disease resistance.