A Genome Scan for Quantitative Trait Locus by Environment Interactions for Production Traits

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ABSTRACT

Genotype by environment interactions between milk production traits and production level have often been observed. To increase the power of quantitative trait loci (QTL) detection, QTL by environment interaction was included in QTL analyses for the milk, protein, and fat yields. The aim of the study was to detect QTL with interaction effects with the production environment. The QTL effects were modeled through random regression models for within-herd production level. All autosomes except *Bos taurus* autosome 6 were included in the analysis. A more detailed study of chromosome 6 is planned. For milk yield, 5 QTL were observed, 2 of which had interaction effects with production level (suggestive linkage). For protein yield, 5 QTL were observed, 3 of which had interaction effects (suggestive linkage). For fat yield, 3 QTL were observed, none of which had interaction effects with the environment (suggestive linkage). Thus, some QTL with interaction effects seemingly exist for milk yield and protein yield. For such QTL, estimated correlations between slope and intercept of the effect (close to 1 or -1) indicated that only 2 alleles were segregating. The study indicates that QTL by environment interactions exist, and that random regression models that describe the environment as herd production level can detect this interaction.

Key words: quantitative trait loci, random regression, autosome, genotype by environment interaction

INTRODUCTION

Many studies have been published on interactions between breeding values (BV) for different traits in

dairy cattle and a wide range of environmental variables (e.g., Calus and Veerkamp, 2003; Fikse et al., 2003; Zwald et al., 2003). Within-herd production level, measured as average production of the herd (Kolmodin et al., 2002; Berry et al., 2003) or as a herd-year-season effect (Calus et al., 2002), is an example environmental descriptor that has been reported to cause genotype by environment interactions (G×E). Because herd production level is a continuous variable, random regression models have been used to describe the BV as a function of the production level in the herd (Kolmodin et al., 2002). The alternative is to group the herds in classes according to their production levels and assume that production in different herd classes are different traits (Berry et al., 2003). If the genetic correlation between productions in the different environments is significantly different from 1, it is defined as G×E (Falconer and Mackay, 1996). However, the multiple-trait approach has some drawbacks. First, environmental variation within each environmental class is lost (Calus and Veerkamp, 2003). Second, there are many environmental classes so that many parameters have to be estimated (variance within each class and the covariances between them; Fikse et al., 2003). Finally, if the G×E is caused only by scaling effects, the correlation between BV in different environments will still be 1 (Fikse et al., 2003).

The third point explains a major difference between using a multiple-trait approach and using random regression to describe G×E. When using the correlation between environments as the test-statistic for interaction, as is done by the multiple-trait model, only reranking of effects between environments is defined as G×E. The random regression model searches for differences in slope between the different genotypes. There can be a large difference in slope even though the genotype effects do not show reranking within the environmental range considered. This situation, referred to as “scaling effects”, is defined as G×E when a random

Received December 12, 2006.

Accepted March 20, 2007.

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regression model is used, but not when a multiple-trait model is used.

When random regression models have been used to describe sires' BV as a function of the production level in the herd, the function (or reaction norm) has often been reported to be linear (Kolmodin et al., 2002). High correlations between the intercept and slope of the genetic effect has been reported for protein yield (Calus et al., 2002; Kolmodin et al., 2002), indicating that there are some genes affecting both slope and intercept of the trait. When the same genes affect the average effect and the environmental sensitivity of a trait, selecting for increased average production will also change the environmental sensitivity in the population.

When searching for QTL, possible interactions with the environment have usually not been taken into account (e.g., Olsen et al., 2004; Jiang and De et al., 2005; Szyda et al., 2005). Including interaction between QTL effect and environment might increase the power of QTL detection (Lund et al., 2002; Lillehammer et al., 2007). However, as in prediction of BV, a multiple-trait model or a random regression model can be used in QTL analysis. When the environmental value is a continuous variable, such as production level, a random regression model has the previously described benefits over a multiple-trait model.

The use of a random regression model to detect QTL with an environmental interaction effect requires observations on the same QTL allele over a range of different environments. The most common design for QTL detection in dairy cattle is the granddaughter design (Freyer et al., 2003). The data consists of marker information on grandsires and their sons and phenotypic information on daughters of genotyped sires. A daughter yield deviation is calculated per son as an average of precorrected records from the son's daughters. As a result of averaging over environments, the environmental effects are lost. Thus, G×E studies are based on analysis of individual cow records. Lillehammer et al. (2007) presented a method in which individual cow records were used in the QTL analyses and applied it to simulated data.

The aim of this study was to search for QTL by environment interactions in Norwegian Red cattle using random regression models. In these models, an environmental gradient is defined as the random herd-year effect, predicted in an initial analysis. The search was performed on all the autosomes except *Bos taurus* autosome 6 (BTA6). Several QTL for milk production have been reported on BTA6 (Khatkar et al., 2005), and a more detailed study of BTA6 is planned with a dense marker map; thus, BTA6 was dropped from the current study.

MATERIALS AND METHODS

All animals in the study were of the Norwegian Red dairy breed. Genotypes from 20 grandsires and their 718 sons were obtained, and their pedigree was traced back for 5 generations. Phenotypic data were obtained from the daughters of the genotyped bulls.

Phenotypic Data

Lactation records of milk ($\text{kg} \times 10^3$ per 305-d lactation), protein (kg per 305-d lactation), and fat yields (kg per 305-d lactation) in first lactation were obtained from the GENO Breeding and AI Association (Ås, Norway). The phenotypes were precorrected for heterogeneous variance due to parity and age within parity. Corrected yields were analyzed with the official repeatability animal model, including the fixed effects of age × parity, month of calving × parity, days open × parity, and year of calving and for the random effects of herd × year, animal (genetic effect) and permanent environment of the cow. Yields from 3 lactations were included in the repeatability model analysis. Records for the subsequent QTL mapping analyses were obtained from the repeatability model by subtracting fixed and random effects from the corrected yield:

$$Y = cy - age \times par - cm \times par - do \times par \\ - year - hy - pe,$$

where Y is used as the record in the QTL mapping analyses, cy is the precorrected yield (milk, fat or protein), $age \times par$ is the fixed effect of age × parity, $cm \times par$ is the fixed effect of calving month × parity, $do \times par$ is the fixed effect of days open × parity, $year$ is the fixed effect of year of calving, hy is the random effect of herd × year, and pe is the random effect of permanent environment.

The random herd-year solution predicted by the repeatability model was used as the variable describing the production level of the herd in the subsequent QTL mapping analyses. The phenotypic data included first-lactation records on 468,565 daughters from 738 genotyped sires. Each sire had between 108 and 8,586 daughters.

Marker Data

The DNA from each animal was extracted from frozen semen samples. The IOBT730 microsatellite was chosen from the BOVMAP database (<http://locus.jouy.inra.fr/cgi-bin/lgbc/mapping/common/main.pl?BASE=cattle>; accessed 2004) Web site, and the remaining markers were chosen from the USDA MARC database

Table 1. Bovine linkage map for *Bos taurus* autosomes (except BTA6)

Chromosome	Linkage map ¹
BTA1	BMS574 - 22.3 - BM4307 - 25.5 - BMS527 - 12.4 - BMS4008 - 51.1 - BMS1170 - 19.3 - CSSM19 - 17.8 - BMS599 - 15.1 - URB14
BTA2	TGLA44 - 22.3 - TEXAN2 - 43.4 - BMS1126 - 36.7 - BMS1866 - 15.1 - BM1223 - 16.4 - BM2113 - 20.8 - FCB11
BTA3	BMS871-12.4 - INRA6 - 4.2 - BMS482 - 30.8 - INRA3 - 23.9 - IOBT250 - 15.1 - BMS2145 - 11.2 - BR4502 - 29.0 - IDVGA27
BTA4	BMC1410 - 27.2 - BMS827 - 22.3 - MAF70 - 12.4 - INRA72 - 20.8 - BMS1074 - 15.1 - BMS648 - 19.3 - BR6303
BTA5	BMS1095 - 13.7 - BMS610 - 13.7 - RM103 - 20.8 - BL4 - 34.7 - BMS1248 - 41.0 - MB006
BTA7	BMS713 - 22.3 - BM6105 - 32.7 - BM6117 - 12.4 - INRA112 - 43.4 - OARAE129 - 22.3 - ILSTS6 - 25.5 - BL1043
BTA8	BMS1864 - 11.2 - BM3419 - 34.7 - BMS678 - 19.3 - INRA122 - 7.5 - MCM64 - 25.5 - BM711 - 27.2 - CSSM47
BTA9	ETH225 - 67.4 - UWCA9 - 8.7 - BMC701 - 8.7 - BM6436 - 23.9 - URB24 - 15.1 - BMS1967
BTA10	BM3033 6.4 - CSSM38 - 30.8 - BRN - 43.4 - BMS419 - 15.1 - BMS1620 - 23.9 - BMS614 - 1.0 - CSSM46
BTA11	BM9067 - 22.3 - INRA177 - 13.7 - BMS1716 - 20.8 - CSSM52 - 15.1 - BMS989 - 19.3 - BMS607 - 5.3 - HEL13
BTA12	BMS410 - 53.9 - RM094 - 8.7 - BM6404 - 19.3 - BM4028 - 19.3 - ILSTS033
BTA13	BMS1742 - 30.8 - BMS1352 - 16.4 - URB7 - 6.4 - RM327 - 34.7 - AGLA232
BTA14	CSSM066 - 6.4 - BMS1747 - 32.7 - RM011 - 41.0 - BM4513 - 13.7 - BM6425
BTA15	BR3510 - 27.2 - JAB1 - 6.4 - INRA050 - 11.2 - IDVGA10 - 19.3 - BMS812 - 30.8 - BMS429
BTA16	TGLA245 - 29.0 - BM121 - 29.0 - BR6504 - 38.8 - BM1706 - 9.9 - BMS462
BTA17	BMS1825 - 19.3 - CSSM9 - 16.4 - ETH185 - 36.7 - BM1862 - 13.7 - BM1233
BTA18	IDVGA31 - 11.2 - BR4206 - 25.5 - INRA121 - 20.8 - BM7109 - 9.9 - ILSTS002 - 41.0 - TGLA227
BTA19	BMS9202 - 13.7 - HEL10 - 36.7 - BMS2142 - 11.2 - BMS650 - 32.7 - IDVGA44
BTA20	HEL12 - 20.8 - BMS1282 - 25.5 - BMS2361 - 29.0 - BM5004 - 8.7 - UWCA26
BTA21	BM8115 - 7.5 - HEL5 - 25.5 - ETH131 - 11.2 - BMS868 - 16.4 - TGLA122 - 0.01 - BMS2382
BTA22	CSSM26 - 23.9 - INRA194 - 23.9 - BM2613 - 9.9 - BMS875 - 15.1 - BM4102
BTA23	INRA64 - 16.4 - BM1815 - 12.4 - CYP21 - 13.7 - BM1818 - 27.2 - BM1443
BTA24	BMS2526 - 17.8 - AGLA269 - 11.2 - BMS66 - 27.2 - BMS1926
BTA25	BMC4216 - 15.1 - INRA206 - 25.5 - BM737 - 13.7 - BMS1353
BTA26	BMS651 - 2.0 - NOR06 - 34.7 - BM4505 - 8.7 - IOBT730 - 27.2 - MAF36
BTA27	BM3507 - 20.8 - BMS641 - 9.9 - CSSM43 - 6.4 - INRA134 - 19.3 - BM203
BTA28	BMS2060 - 11.2 - IDVGA29 - 12.4 - BMS510 - 22.3 - BMS1714
BTA29	BM1857 - 6.4 - BMS764 - 13.7 - BMS1600 - 34.7 - BL1100 - 7.5 - BMS1948

¹The distance (cM) between the markers is indicated.

(<http://www.marc.usda.gov/genome/genome.html>; accessed 2004). Genotypes for the 160 microsatellites were determined using the GeneMapper program, version 4.0 (Applied Biosystems, Foster City, CA). Linkage maps (Table 1) were constructed using the CRI-MAP program, version 2.4 (Green et al., 1990) and the Hal-dane map function.

Statistical Methods

The midpoint of each marker bracket was regarded as a putative QTL position. The marker phases of the bulls were determined and for each putative QTL position, renumbered haplotypes and their identical by descent (IBD) matrices were estimated with combined linkage disequilibrium and linkage analysis (Meuwissen et al., 2002). Effective population size for Norwegian Red breed was assumed to be 250 and the number of generations since mutation was assumed to be 100 (Meuwissen et al., 2002). Two different models (models [2] and [3]) were used to test for the presence of a QTL and for a possible interaction effect with the environment. A reduced model (model [1]) assuming no QTL effect was used in likelihood ratio testing for the statistical significance of the QTL. The models are described below.

$$Y_{jkl} = \mu + b \times hy_l + sire_j + \beta_j \times hy_l + e_{jkl}, \quad [1]$$

where Y_{jkl} = the yield deviation of milk, protein, or fat yield for daughter k of sire j , in herd-year class l , μ = the overall mean, b = overall fixed regression coefficient on hy_l , hy_l = random solution for herd-year class l for either milk, protein, or fat yield, $sire_j$ = random effect of sire j (intercept), which assumed that the effect comes from a $N(0, \mathbf{A}\sigma_{sire}^2)$ distribution, β_j = random regression coefficient on hy_l , nested within sire j ; the effect was assumed to come from a $N(0, \mathbf{A}\sigma_{\beta}^2)$ distribution. The covariance between $sire$ and β effect was modeled as: $\text{Cov}(sire, \beta) = \mathbf{A}\sigma_{sire, \beta}$, and e_{jkl} = random residual.

The model with a QTL that does not interact with the environment was

$$Y_{ijkl} = \mu + b \times hy_l + sire_j + \beta_l \times hy_l + h_{i1} + h_{i2} + e_{ijkl}, \quad [2]$$

where h_{i1} and h_{i2} are the random effects of the paternal and maternal haplotypes of sire j , respectively, which assumed that the effect comes from a $N(0, \mathbf{G}\sigma_h^2)$ distribution, where $\mathbf{G}$ is the IBD matrix between the haplotypes and σ_h^2 is the haplotype variance for intercept.

The model with a QTL that interacts with the environment was

$$Y_{ijkl} = \mu + b \times hy_l + sire_j + \beta_I \times hy_l + h_{i1} + h_{i2} + \lambda_{i1} \times hy_l + \lambda_{i2} \times hy_l + e_{ijkl}, \quad [3]$$

where h_{i1} and h_{i2} describe the random effects of sire j 's haplotypes on the intercept of the trait, λ_{i1} and λ_{i2} describe the random regression coefficients on hy_l , nested within each sire's paternal and maternal haplotypes respectively, and λ_{i1} and λ_{i2} were assumed to come from a $N(0, \mathbf{G}\sigma_\lambda^2)$ distribution, where $\mathbf{G}$ is the IBD matrix between the haplotypes and σ_λ^2 is the haplotype variance for slope. The covariance between the intercept and slope of the QTL effect was modeled a $\text{Cov}(h, \lambda) = \mathbf{G}\sigma_{h,\lambda}$.

Statistical analyses were performed with the AS-REML software (Gilmour et al., 2001). Paternal and maternal haplotypes were assumed to be different classes within the same random effect.

Likelihood ratio (LR) tests were used to test for significance in 2 steps. First, the log-likelihoods of model [2] were analyzed with model [1] as the reduced model to test whether a significant QTL for intercept of the trait was segregating at the putative QTL position. Second, an LR test of model [3] was performed, with model [2] as the reduced model to test for significant QTL for slope of the trait. Each test was carried out for the position on each chromosome with the highest LR value.

Chromosome-wise thresholds were chosen to obtain a genome-wise suggestive linkage, and one false positive per genome scan was expected (Lander and Kruglyak, 1995). For each test, a chromosome-wise threshold value was calculated by the method of Piepho (2001). For the intercept test, the number of genetic effects of the putative QTL (degrees of freedom of the test) was 1 (an additive effect only). For the slope test, the number of genetic effects of the putative QTL was 2 (additive slope effect and covariance between slope and intercept).

A genome-wise false discovery rate (FDR) was calculated by dividing the number of expected false positives by the number of detected QTL. The test was conducted for 2 models and 3 traits over 28 chromosomes, giving 168 ($2 \times 3 \times 28$) tests. The expected number of false positives was 6 ($2 \text{ models} \times 3 \text{ traits}$).

RESULTS

Eight chromosomes were found to have QTL affecting at least one of the traits studied. The significant QTL found are summarized in Table 2. Model [2] was not able to detect any of the QTL with significant environmental

interactions. A total of 5 QTL were found with a significant interaction term, with 2 affecting milk yield and 3 affecting protein yield. The milk yield QTL with interaction were located in the same bracket as a protein yield with interaction, which indicated 1 QTL affecting both milk and protein yield or 2 closely linked QTL, where one affects milk yield and the other affects protein yield.

A high correlation between slope and intercept of the sire effect implies that the same genes explain a substantial proportion of the variation in both slope and intercept. In this study, the estimated genetic correlations of slope with intercept for the sire effects were 0.6 for milk yield, 0.5 for protein yield, and 0.6 for fat yield. For protein yield, this is lower than reported in other studies (Calus et al., 2002; Kolmodin et al., 2002). The QTL $\times$ environment interactions detected for milk yield had correlations between slope and intercept of QTL effect close to 1 or to -1 (Table 2). This was also the case for 2 of the QTL $\times$ environmental interactions for protein yield, whereas 1 protein yield QTL (on BTA2) had a positive, but weaker, correlation. A correlation between haplotype effects on the slope and intercept close to 1 or -1 indicates the presence of only 2 QTL alleles, or that 2 of the QTL alleles are much more frequent than other alleles (Lillehammer et al., 2007).

Figures 1, 2, and 3 show the haplotype effects of the grandsires for the QTL with significant environmental interactions. Each grandsire is represented by 2 lines in each figure, but 1 line can refer to more than 1 grandsire if they share a haplotype with a probability of more than 0.95 (Meuwissen et al., 2002).

Figure 1 shows the haplotype effects on protein yield found on BTA2, in the marker bracket between BMS1126 and BMS1866. This QTL effect increases with increasing environmental gradient. In addition, the results indicate some reranking of allele effects on both sides of the mean.

Figure 2 shows the haplotype effects found on BTA7, in the bracket between BMS713 and BM6105, for milk yield and protein yield. For milk and protein yield, the estimated correlation between slope and intercept was close to unity (0.999). However, because there is no variance in the random intercept for protein yield (Figure 2), the correlation between slope and intercept is not defined for this trait. All of the haplotype effects cross each other in one single point, indicating that there are 2 QTL alleles.

Figure 3 shows the effects found in the bracket between TGLA254 and BM121 on BTA16. In this bracket significant QTL for milk and protein yield were found. For both traits, correlation between slope and intercept of the QTL effects were <-0.9 .

Table 2. Summary of all significant QTL, with the position given as the marker bracket, within the lowest *P*-value for the trait obtained, for either intercept or slope

Chromosome	Trait	Marker bracket	<i>P</i> intercept ¹	<i>P</i> slope ²	Correlation of slope-intercept ³	Intercept variance ⁴ (%)	Slope variance ⁵ (%)
2	Protein	BMS1126–BMS1866	0.994	0.006	0.586	(4.9)	48.7
5	Fat	BL4–BMS1248	0.001	0.720	—	12.2	—
7	Milk	BMS713–BM6105	1	0.009	0.999	(3.3)	32.0
	Protein	BMS713–BM6105	1	0.023	0.999 ⁶	(0.0)	28.1
12	Milk	RM094–BM6404	0.008	1	—	6.2	—
	Protein	BMS410–RM094	0.005	1	—	16.8	—
	Fat	BMS410–RM094	0.010	1	—	15.4	—
14	Milk	BM4513–BM6425	0.028	1	—	6.0	—
15	Protein	IDVGA10–BMS812	0.025	0.388	—	5.3	—
	Fat	IDVGA10–BMS812	<0.001	0.325	—	10.0	—
16	Milk	TGLA254–BM121	0.539	0.014	–0.915	(2.0)	34.7
	Protein	TGLA254–BM121	0.673	0.024	–0.999	(2.3)	33.0
29	Milk	BL1100–BMS1948	0.010	1	—	8.8	—

¹Chromosome-wise *P*-value for an intercept QTL.²Chromosome-wise *P*-value for a slope QTL.³The estimated correlation of the QTL effects of slope with intercept when the slope variance was significant.⁴The QTL variance for intercept, given as percentage of the total sire variance for intercept. The percentage is in parentheses when the QTL did not have a significant interaction term.⁵The QTL variance for slope, given as percentage of the total sire variance for slope. No QTL slope variance is given if the slope effect of the QTL was not significant.⁶The estimated variance for intercept was 0.0, so the correlation between slope and intercept is not defined.

The 2 QTL with a significant interaction effect for milk yield contributed 32.0 and 34.7% of the total sire slope variance, according to their variances (Table 2). The 3 QTL with significant slopes for protein explained 48.7, 28.1, and 33.0% of the total sire slope variance for protein (Table 2). Theoretically, the sum of several QTL can exceed the total genetic variance, because the variance generated by QTL can cancel each other out. However, it is well known that the variance explained by significant QTL is overestimated (Hayes and Goddard, 2001). The large proportions of the genetic variances explained by these detected QTL implies that the model overestimates the QTL variance.

Figure 1. Effect of the grandsires' haplotypes on protein yield on *Bos taurus* autosome 2. Herd-year solution is the herd-year solution for protein yield. The correlation between slope and intercept is 0.586.

To obtain a threshold corresponding to genome-wide suggestive linkage (Lander and Kruglyak, 1995), the chromosome-wise *P*-values could not exceed 0.0357 (1/28). With that criterion, 13 QTL were detected, considering independent QTL effects for the different traits. With an expected number of false significant effects of 6, this gives a FDR of 46%.

DISCUSSION

Including QTL by environment interactions in the QTL detection model gave improved power of detection. In total, 13 QTL were detected (Table 2), of which 8 were detected to have significant effects on intercept (by model [2]) and 5 were detected to have significant effects on slope (by model [3]). Note that improved power was obtained by searching both for QTL with intercept effects and QTL for slope effects, not by exchanging one model with another. The QTL detected with significant slope effects had low average effects; hence, no effect on intercept could be detected. These QTL would not have been detected without taking QTL × environment interactions into account. The strong environmental interaction of these QTL causes them to have large effects in some environments (Figures 1, 2, and 3).

The calculated FDR of 46% indicates that there is considerable uncertainty attached to the detected QTL in the genome-wide scan conducted here. To validate

Figure 2. Effects of the grandsires' haplotypes on *Bos taurus* autosome 7 for milk yield and protein yield. The correlations of slope with intercept of the haplotype effects were estimated to be 0.999 for both traits. For milk yield, the QTL had a variance for both slope and intercept, but for protein yield, the QTL did not contribute to the intercept variance. The herd-year solution is the herd-year solution for milk yield when explaining haplotype effects on milk yield and for protein yield when explaining the effects for protein yield.

these detected QTL, further research including $G \times E$ is required. Searches for $QTL \times$ environment interactions in other populations would be useful to validate the QTL. Using a dense marker map would not only serve as a validation, but also determine the positions of the QTL more accurately.

The QTL detected with model [3] only are not expected to be highly supported in the existing literature because none of the references included environmental information and interaction in their QTL models. Several of the QTL detected with model [3] only were detected in regions where no QTL have previously been reported for this trait (Khatkar et al., 2005). The possibility of detection of QTL having linear reaction norms, without assuming interactions in the analysis, depends on whether the QTL contribute to genetic variation in the average environments of the animals in the study. If the mean environment is close to the crossing point of the reaction norms, the QTL effects are much harder to detect than if the mean environment is far from the crossing point. In addition, the interaction pattern of

Figure 3. The grandsires' haplotype effects from *Bos taurus* autosome 16. The top panel shows the haplotype effects on milk yield, and the bottom panel shows the haplotype effects on protein yield. The correlations of slope with intercept of the haplotype effects were negative (< -0.9) for both traits.

the QTL might affect the power of detection (Lillehammer et al., 2007).

Reaction norms of BV have shown that considerable scaling effects exist, but little reranking is reported, except in extreme environments (Calus et al., 2002; Kolmodin et al., 2002). For single genes, the situation seems to be different. All the QTL detected with a significant interaction term had reranking of alleles within the environments from which the data originated (Figures 1, 2, and 3), with the crossing point often close to the mean environment. This may explain why these QTL have not been fixed by strong selection for production traits. Lillehammer et al. (2007) found that the random regression method detects QTL with reranking of effects more easily than QTL with scaling effects.

Reranking among alleles makes animal breeding more complicated, because the best allele in one environment is not necessarily the best in another environment. This is a challenge if marker-assisted or gene-assisted selection is performed and the offspring are expected to produce in many different environments. However, it also raises the opportunity to breed animals

especially adapted for production in specific environments.

For the QTL detected for milk and protein yield on BTA7 and BTA16, the correlation between slope and intercept was close to 1 or -1. This confirms that the same gene is affecting both slope and intercept. It also indicates that only 2 alleles are segregating in the population, or at least that 2 alleles are much more frequent than the others (Lillehammer et al., 2007).

Some of the QTL produced an estimated slope variance that could explain a large proportion of the total $G \times E$ (Table 2). The high slope variances reported for the QTL indicate that the model overestimates the $QTL \times$ environment effects. This might happen because of a heterogeneous residual variance. The residual variance itself might change when the environment is changing, and in addition, three-fourths of the genetic variance and three-fourths of the QTL variance are included in the residual variance because a sire-model was used for these 2 terms. A random regression model that accounted for heterogeneous residual variance would be preferable (Kolmodin et al., 2002). The variances of the interaction terms are small compared with the variances in intercept. Slope variances from the genetic and QTL parameters that are included in the residual variance will therefore have little impact on the residuals. Simulations have shown that the sire model used in this study does not give a high proportion of falsely significant interaction terms (Lillehammer et al., 2007). Even though the predicted interaction effects of the QTL might be overestimated, the QTL probably have real interaction effects with the environment.

When a few genes control a big part of the total variance, marker-assisted selection can be quite efficient, especially, if markers are identified to be in strong linkage disequilibrium with the gene. The question is whether, depending on the environmental sensitivity of the QTL, the QTL represents important characteristics for selection. So far, selection has focused on changing the average production over all environments. The QTL detected with environmental interaction have small average effects and will therefore be bad candidates for selection as long as average production is the measurement for the gene effect. However, it might be desirable to change not only the average production, but also to control production over a range of environments. The QTL with a large $QTL \times$ environment interaction will be very well suited to change the environmental sensitivity in the population. Whether it is desirable to change the environmental sensitivity depends on which environments we expect to appear in the future. Some different breeding strategies are described below.

The production potential of the offspring of the selected parents will be a combination of their genetics,

the environments they are given, and the interactions between genes and environments. If the future environments were known, the future production of the offspring could be predicted from the genotypes of the parents combined with the future environmental information. The situation is more complicated when the future environment is unknown and expected to be highly variable. In the long term, genetic selection for environmental sensitivity can be performed by selecting different lines specialized to different environments (Calus et al., 2005). The QTL by environmental effects detected in this study may facilitate selection for such lines.

The protein yield QTL on BTA2 and the milk QTL on BTA7 had positive correlations between slope and intercept (Table 2). This has the practical consequence that a positive allele will be even more positive if the environment is improved. Selection for the best allele in today's environment will create a population that is not well suited for less-favorable environments. As long as the environment is expected to improve in the future, the allele with a positive slope is a good selection candidate.

The QTL for milk and protein yield on BTA16 have negative correlations between slope and intercept. This means that a positive allele in an average environment will have a lower effect in an improved environment. Hence, assuming environmental improvement over time, a currently unfavorable allele on average may be the best allele in the long term.

The protein yield QTL on BTA7 has no effect in an average environment, and represents a QTL suitable for changing the environmental sensitivity without affecting the average production. The QTL can be of great importance if the environment is changed in one direction or another, even though it seems to have no average effect. However, as environment changes, the average herd-level will change as well, and the QTL might get an average effect. This might be the case over time or when applying the results in other populations or environments than the Norwegian. Before any QTL alleles are selected for, their effects in the expected future environment(s) should be studied.

Historically, production levels have increased from both selection and environmental improvements. Further improvement of the environment will probably continue to increase production in the future. Alleles with positive slope effects will have positive effects in such improved environments. On the other hand, these alleles will make animals sensitive to poor environments. Thus, selecting for alleles with steep reaction norms is a "high risk, high output" approach.

The opposite idea is to select for flatter reaction norms in the population. The environment, as defined here,

produces an average reaction norm of 1 in the population. If a lower average response to environmental changes is obtained, the measured environmental variation decreases, whereas the average reaction norm remains 1. Animals with a lower environmental sensitivity can be desirable if the future environment is uncertain, because such animals will respond less to changes in the environment. The animals having alleles described by a negative environmental sensitivity for the detected QTL will have a lower than average environmental sensitivity. Selecting for these alleles will create animals well suited to tolerate bad environments. This is thus a "low risk, low output" approach. Both the QTL detected on BTA7 and the QTL on BTA16 facilitate selection for a lower environmental sensitivity. However, selecting for the alleles with negative slopes will result in lower production in the highest producing environments. Hence, the strategy is bad if the environment is expected to improve in the future.

A third possibility is to use the information about the G×E to breed specialized animals for certain environments. This can be accomplished either by including different specialized lines in the national breeding scheme, or by making the genotypic information of the bulls available for breeders to select bulls well-suited for their specific farm environments. To establish multiple breeding schemes and select different sires for production in different environments is expensive, and has been found to be disadvantageous (Weigel et al., 1999). Regardless of which strategy is chosen, G×E should be taken into account before a specific allele is selected for.

CONCLUSIONS

Several QTL with environmental interaction were detected by the random regression method. A high FDR implies that further research is required to confirm the detected QTL and to be able to identify the genes responsible for the interaction and understand the biological systems behind G×E.

ACKNOWLEDGMENT

We gratefully acknowledge funding from the Norwegian Research Council, Geno Breeding and AI Association, and Bovibank Ltd.

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