Estimation of Genetic Parameters for Quantitative Trait Loci for Dairy Traits in the French Holstein Population

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ABSTRACT

A marker-assisted selection program (MAS) has been implemented in dairy cattle in France. The efficiency of such a selection program depends on the use of correct genetic parameters for the marked quantitative trait loci (QTL). Therefore, the objective of this study was to estimate the proportion of genetic variance explained by 4 QTL described in previous studies (these QTL are segregating on chromosomes 6, 14, 20, and 26). Genotypes for 11 markers were available for 3,974 bulls grouped within 54 sire families of the French Holstein population undergoing MAS. The parameters were estimated for 4 QTL and 5 dairy traits: milk, fat and protein yields, and fat and protein percentages. The proportion of genetic variance explained by the QTL ranged from as low as 0.03 to 0.36%. Both lack of marker informativity and poor monitoring of QTL transmission might limit the accuracy of estimation. The QTL explained a larger proportion of genetic variance for milk composition traits. The QTL on chromosome 14 and chromosomes 6 and 20 have their largest influence on fat and protein percentages, respectively. The overall proportions of genetic variance explained by the QTL were 27.0, 30.7, 24.1, 48.2, and 33.6% for milk, fat and protein yields, and fat and protein percentages, respectively. These results clearly indicated that a large part of the genetic variance is explained by a small number of QTL and that their use in MAS might be beneficial for dairy cattle breeding programs.

Key words: genetic parameter, quantitative trait locus, dairy trait, marker-assisted selection

INTRODUCTION

In dairy cattle, selection of traits of economic value historically has relied on the collection and use of phenotypic and pedigree data. More recently, advances in molecular genetics have made it possible to map genes

affecting traits of economic importance. As a result, many studies have investigated the association between traits in the breeding goal and genetic markers (Georges et al., 1995; Zhang et al., 1998; Boichard et al., 2003). The first detection of several QTL was carried out with granddaughter designs (Georges et al., 1995; Boichard et al., 2003). Further studies were conducted to increase the knowledge about the most significant QTL detected, such as on chromosome 6 (Spelman et al., 1996; Ron et al., 2001; Cohen-Zinder et al., 2005; Olsen et al., 2005; Schnabel et al., 2005), 14 (Grisart et al., 2001; Looft et al., 2001), 20 (Blott et al., 2003), or 26 (Gautier et al., 2005). For example, QTL have been assigned to the gene encoding acyl coenzyme A:diacylglycerol acyltransferase (**DGAT1**; Grisart et al., 2001) on chromosome 14 or to the **ABCG2** gene (Cohen-Zinder et al., 2005) on chromosome 6. Blott et al. (2003) found tight linkage between the QTL on chromosome 20 and the growth hormone receptor (**GHR**). The resulting QTL information is now available to improve selection through the use of genetic markers via marker-assisted selection (**MAS**). In addition, statistical methods were also developed to implement MAS. Fernando and Grossman (1989) showed how to incorporate genetic markers associated with QTL into mixed models. Goddard (1992), Wang et al. (1995), and Pong-Wong et al. (2001) proposed methods to estimate the genetic covariance between individuals at a specific position within the genome through genetic markers.

Kashi et al. (1990) and Boichard et al. (2003) stated that MAS could be particularly valuable in dairy cattle for several reasons. Most traits of interest are sex-limited, the generation interval is long, and the progeny test is a long and costly step. Furthermore, breeding companies often select bull dams based on pedigree information only (Boichard et al., 2002). Finally, functional traits with low heritabilities are gaining emphasis in the breeding goal.

At the end of the year 2000, a MAS program was implemented in France (Boichard et al., 2002) to take full benefit of these advantages. The efficiency of the implementation of MAS is dependent on the accuracy of the information about the QTL. After 4 yr of implementation of MAS, a large number of sire families has

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Table 1. Number of markers, information content, number of noninformative sire families, and mean polymorphism information content (PIC) of markers for QTL used in marker-assisted selection affecting dairy traits

Chromosome on which the QTL is located	Position (in cM) of the QTL ¹	Number of markers	Information content measured as $ 1 - 2p $	Number of noninformative sire families ²	Mean PIC
6	50	3	0.79	3	0.54
14	0	2	0.70	11	0.59
20	43	4	0.60	5	0.43
26	14	2	0.38	21	0.26

¹Positions are defined on the map of Ihara et al. (2004).²Out of 54 families available.

been genotyped, which offers the opportunity to increase our knowledge of QTL. The objective of this study was to use this accumulated information for estimating the proportions of genetic variance of dairy traits explained by the QTL associated with DGAT1 (Grisart et al., 2001), GHR (Blott et al., 2003), the ABCG2 gene (Cohen-Zinder et al., 2005), and the QTL located on chromosome 26 fine-mapped by Gautier et al. (2005).

MATERIALS AND METHODS

Materials

French MAS began at the end of 2000 and its main characteristics were presented by Boichard et al. (2002). All young bulls and a proportion of candidates for bull dams were genotyped. In addition to these animals, relatives (dams or other ancestors) and first-crop daughters of bulls were proposed for genotyping (Boichard et al., 2002). In February 2005, more than 25,000 Holstein animals had been genotyped for MAS using 45 markers for 14 QTL. Transmission of the 4 QTL located on chromosomes 6, 14, 20, and 26 was followed through 11 markers. The positions of these QTL were determined by previous fine-mapping studies: Grisart et al. (2001) for DGAT1, Blott et al. (2003) for GHR, Cohen-Zinder et al. (2005) for the ABCG2 gene, and Gautier et al. (2005) for the QTL on chromosome 26. These positions and marker positions were defined on the map of Ihara et al. (2004; see Table 1 for QTL positions). In the present study, only sire families with at least 30 progeny-tested young bulls were selected, and 3,974 genotyped bulls from 54 families were extracted. The full pedigree file consisted of 6,718 animals. The 54 sire families spanned over 4 generations and the pedigree file included 3,944 tested bulls, 2,720 dams of these bulls, and 54 sires of sires. Thirty of these 54 sires of sires were included as a progeny in different sire families. Only dams and genotyped animals were kept in the pedigree to avoid having a great proportion of animals in the pedigree with no genotypes. For these

animals that were not genotyped, the probability of QTL allele transmission would be equal to the additive genetic relationship (0.5); consequently, they would not be informative for estimating the gametic variance.

Phenotypic records were daughter yield deviation (DYD; VanRaden and Wiggans, 1991) computed for milk, fat and protein yields, and fat and protein percentages, pooled from the first 3 lactations jointly as in VanRaden and Wiggans (1991). These records were obtained from the official genetic evaluation of February 2005 (Robert-Granié et al., 1999). The genetic parameters were estimated for the 4 QTL presented in Table 1 and for all milk production and composition traits.

Method

The model used in this study was a single-trait and single-QTL model (Fernando and Grossman, 1989):

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{u} + \mathbf{Z}_v\mathbf{v} + \mathbf{e} \quad [1]$$

where $\mathbf{y}$ is a vector containing DYD for bulls, β is a vector of fixed effects (the mean), $\mathbf{u}$ is a vector of random polygenic effects, $\mathbf{v}$ is a vector of random gametic effects, and $\mathbf{e}$ is a vector of random residual terms. $\mathbf{X}$, $\mathbf{Z}$, and $\mathbf{Z}_v$ are known design matrices relating results to fixed and random polygenic and gametic effects, respectively.

The (co)variance structure was:

$$\text{var} \begin{bmatrix} \mathbf{u} \\ \mathbf{v} \\ \mathbf{e} \end{bmatrix} = \begin{bmatrix} \mathbf{A}\sigma_a^2 & 0 & 0 \\ 0 & \mathbf{G}_v\sigma_v^2 & 0 \\ 0 & 0 & \mathbf{R} \end{bmatrix} \quad [2]$$

where $\mathbf{A}$ is the additive relationship matrix and σ_a^2 is the variance associated with the random polygenic effects. $\mathbf{G}_v$ is the relationship matrix among QTL allelic effects estimated from relationships and marker information (Fernando and Grossman, 1989). The method of calculating the identity-by-descent matrix was similar to that of Pong-Wong et al. (2001). The variances of

paternal and maternal alleles were assumed to be equal, and a single parameter was estimated (σ_v^2) as in Grignola et al. (1996). Variance associated with the QTL (QTL allelic variance) was then twice σ_v^2 . The proportion of total genetic variance due to the QTL was

$$\frac{2\sigma_v^2}{\sigma_a^2 + 2\sigma_v^2} \quad [3]$$

R is a diagonal matrix containing the residual variance (σ_e^2) divided by the weight of the corresponding DYD. These weights were daughter equivalent and were estimated as in VanRaden and Wiggans (1991), with a correction for number of cows in each herd.

Genetic parameters were estimated after maximizing likelihoods with an AI-REML approach (Jensen et al., 1996). The software of Misztal et al. (2002) was modified to incorporate relationship matrices among QTL allelic effects.

The likelihood ratio test statistic considered variance components as parameters and was used to confirm whether a QTL was present at the position used in MAS (George et al., 2000):

$$\lambda = -2\ln \frac{L(H_0)}{L(H_1)} \quad [4]$$

where $L(H_0)$ and $L(H_1)$ are the maximum values of the likelihood functions estimated by REML under a polygenic model with no QTL fitted and with a one-QTL model (Equation 1), respectively:

$$\begin{aligned} -2\ln L(H_1) = & \text{const} + \ln |\mathbf{V}_1| \\ & + \ln |\mathbf{X}'\mathbf{V}_1^{-1}\mathbf{X}| + \mathbf{y}'\mathbf{P}_1\mathbf{y} \end{aligned} \quad [5]$$

where $\mathbf{V}_0 = \mathbf{Z}(\mathbf{A}\sigma_v^2)\mathbf{Z}' + \mathbf{R}$, $\mathbf{V}_1 = \mathbf{Z}(\mathbf{A}\sigma_v^2)\mathbf{Z}' + \mathbf{Z}_v(\mathbf{G}_v\sigma_v^2)\mathbf{Z}_v' + \mathbf{R}$ and $\mathbf{P}_1 = \mathbf{V}_1^{-1} - \mathbf{V}_1^{-1}\mathbf{X}(\mathbf{X}'\mathbf{V}_1^{-1}\mathbf{X})^{-1}\mathbf{X}'\mathbf{V}_1^{-1}$ (Jensen et al., 1996).

The distribution of the test (Equation 4) is not known but can be obtained by permutation of data within family (Churchill and Doerge, 1996). With a complex pedigree, it is no longer possible to permute the data because families are no longer independent. An alternative would be to generate gametic relationship matrices at random with the same informativity as the real data set. For each QTL and trait separately, the distribution of the test was obtained through 5,000 simulated gametic relationship matrices corresponding to the null hypothesis (no QTL). These were obtained by randomly changing the origin of the parental alleles. For instance, the QTL allele received by a progeny from its sire (paternal or maternal) can change at each simulation, and

the link between QTL genotype and phenotype is broken. With data permutation, within sire families, repartition of animals in 2 groups according to the allele they received from their sire remains the same but performances change at each permutation. Here, animals always keep the same performance but the repartition of the 2 groups changes at each simulation. Therefore, the relationship between additive polygenic effects and the data is not broken and the polygenic effect remains estimated properly. To keep the same informativity, for each animal the value of the probabilities of transmission (p) of a parental allele was switched to $1 - p$ or kept constant, depending on whether the parental origin changed or did not change, respectively.

The information content at each QTL was measured as the mean value of $|1 - 2p|$ where p was the probability of transmission of a given paternal QTL allele (Boichard et al., 2003). Sire families for which this mean was null were uninformative: for the corresponding QTL, all p were equal to 0.5 and it was not possible to infer which of its alleles was transmitted by the sire.

The software QTLMAP was used, as in Boichard et al. (2003), to determine whether a sire was heterozygous or not heterozygous for a QTL. Heterozygosity of sires was estimated based on the protein percentage, fat percentage, protein percentage, and fat yield for chromosomes 6, 14, 20, and 26, respectively.

RESULTS

The results of informativity are presented in Table 1. For the QTL on chromosome 26, 21 families were noninformative. This relatively large proportion increased the difficulty of correctly estimating the QTL gametic variance. On this chromosome, the polymorphism information content (**PIC**; Botstein et al., 1980) was low for both microsatellites used. The information content criterion indicated the amount of information available for different QTL. It depended on the distance between markers, on the supposed QTL location, and on the informativity (e.g., **PIC**) of the markers close to the QTL location. For instance, although their numbers of informative families were similar, the QTL on chromosomes 6 and 20 presented different values for information content because of different distances between marker and QTL locations and different informativities of markers indicated by the **PIC** values.

Likelihood ratio tests for the 4 QTL studied are presented in Table 2. These QTL were largely described in other studies (Georges et al., 1995; Spelman et al., 1996; Zhang et al., 1998; Ron et al., 2001; Boichard et al., 2003; Gautier et al., 2005). The QTL on chromosome 14 (Grisart et al., 2001) had high levels of significance for all traits. In all studies, this QTL is the most signifi-

Table 2. Likelihood ratio test of the 4 QTL for milk, fat, protein yields, and fat and protein percentages

Trait	Chromosome on which the QTL is located			
	6	14	20	26
Milk yield	1.45	85.71***	17.05***	7.10**
Fat yield	21.92***	37.31***	10.30**	23.27***
Protein yield	10.42***	42.18***	7.73**	17.86***
Fat percentage	18.03***	310.02***	21.15***	0.31
Protein percentage	49.70***	36.25***	40.94***	0.04

** $P < 0.01$; *** $P < 0.001$.

cant for fat percentage, whereas in some studies (e.g., Zhang et al., 1998; Boichard et al., 2003), it was not detected for protein yield. However, the fine-mapping studies of Grisart et al. (2001) or Looft et al. (2001) found that the QTL affected all yield traits. The QTL on chromosome 20 (Blott et al., 2003) was the most significant for protein percentage but was also significant on most traits. As found by Spelman et al. (1996), Ron et al. (2001), and Olsen et al. (2002, 2005), the QTL on chromosome 6 was detected for protein and fat percentages. Georges et al. (1995), Zhang et al. (1998), and Olsen et al. (2002) found that this QTL also caused a minor effect on milk yield without affecting fat and protein yields. However, in the fine-mapping study of Olsen et al. (2005), the QTL was no longer significant for milk yield, in agreement with Spelman et al. (1996) and Boichard et al. (2003). Ron et al. (2001) and Freyer et al. (2003) detected a possible second QTL on chromosome 6 affecting fat and protein yields. Szyda et al. (2005) described a QTL affecting all yield traits. In our study, the QTL was also significant for fat and protein yields but not for milk yield. This QTL might require further investigation to understand whether 1 or 2 QTL are involved and which traits each is influencing. Finally, despite the low informativity of markers used, the QTL detected on chromosome 26 was significant for fat and protein yields and the level of significance was lower for milk yield; this result was in agreement with that of Boichard et al. (2003).

The proportions of heterozygous sires, estimated as in Boichard et al. (2003), were 20, 57, 19, and 24% for QTL on chromosomes 6, 14, 20, and 26, respectively. The proportions of total genetic variance explained by the QTL studied are presented in Table 3. The proportions explained by the significant QTL ranged from 3 to 36%. All of the QTL reached more than 9% for at least one trait.

The largest QTL allelic variances were associated with QTL on chromosomes 14 and 20. The first QTL was identified (Grisart et al., 2001; Looft et al., 2001), whereas Blott et al. (2003) found a strong linkage between the second and GHR. Variance associated with the QTL on chromosome 14 has been estimated by dif-

ferent methods (Zhang et al., 1998; Grisart et al., 2001; Boichard et al., 2003). For the fat percentage, Zhang et al. (1998), Grisart et al. (2001), and Boichard et al. (2003) estimated the ratio of QTL allelic to additive genetic variance at 0.24, 0.64, and 0.40, respectively. Our estimation was 0.36 for fat percentage. In agreement with Zhang et al. (1998) and Boichard et al. (2003), this QTL clearly appeared to be the QTL explaining the largest part of genetic variance. For the protein percentage, the QTL on chromosome 20 explained 13.5% of genetic variance. This value was larger than the percentages of 7.5 and 7% estimated by Zhang et al. (1998) and Boichard et al. (2003), respectively.

Zhang et al. (1998) found that the proportion of genetic variance explained by the QTL on chromosome 6 was larger for fat (11%) and protein percentages (11%) than for milk yield (4%). Olsen et al. (2005) found this QTL to be significant only for fat and protein percentages. Szyda et al. (2005) estimated the genetic parameters for the 3 lactations separately for yield traits. Our results were in agreement with those studies, with the proportion of genetic variance due to this QTL on chromosome 6 ranging from 3 to 11% and maximal for protein percentage. However, Freyer et al. (2002, 2003) estimated much larger variances, which were inconsistent across DYD and EBV. Boichard et al. (2003) also found a larger variance ratio for the protein percentage (0.18).

The proportion of genetic variance explained by the QTL on chromosome 26 for fat yield was relatively low, 9.0%. Boichard et al. (2003) and Gautier et al. (2005)

Table 3. Proportion of genetic variance (in %) explained by the 4 QTL for milk, fat, and protein yields, and percentages of fat and protein

Trait	Chromosome on which the QTL is located			
	6	14	20	26
Milk yield	1.2	14.7	7.0	4.1
Fat yield	5.4	10.3	6.0	9.0
Protein yield	3.3	9.1	4.1	7.6
Fat percentage	4.8	35.5	7.8	0.1
Protein percentage	11.4	8.7	13.5	0.0

estimated this proportion to be 16 and 17%, respectively.

DISCUSSION

Marker informativity is essential to estimate genetic parameters of QTL correctly. Indeed, for all noninformative sires, the probability of identity-by-descent is equal to 0.5, which is identical to the additive relationship. If many animals are noninformative, then the QTL gametic relationship matrix is close to the additive relationship matrix, and separation of polygenic from gametic effects is difficult, leading to poor parameter estimation.

Noninformativity of sire families can result from the fact that a sire is homozygous for all the markers used for a given QTL. The low informativity of some microsatellite markers also has consequences in informative sire families: some progenies might still be noninformative because they have an equal probability of having received the paternal or the maternal allele of the sire conditionally on the marker data. Therefore, the effective family size is reduced and some power is lost.

In complex pedigrees, some families can also be noninformative because it is not possible to infer the paternal and maternal marker haplotypes of a sire. Indeed, if we cannot determine which haplotype is the paternal or maternal haplotype of a sire, neither can we determine whether the paternal or maternal haplotype was transmitted to a progeny. The data set provided by MAS was different from data sets used for QTL detection: the data set was larger and integrated more families and different generations with complex ties among families, but it included fewer markers. In this study, informativity appeared to be low for the QTL on *Bos taurus* autosome (BTA) 26. This was the consequence of a complex pedigree structure, a low number of markers, and low marker informativity. For this QTL, estimation of correct variance components was more difficult. To improve the efficiency of MAS, a new set of more informative microsatellites has been defined for the French MAS and has been in use since January 1, 2005. Changes were oriented toward those QTL with less marker informativity. In addition, the increase in the proportion of genotyped dams of sires will have a positive impact on marker informativity.

The QTL variance is a function of QTL allele frequencies and the QTL substitution effect. The proportion of heterozygous sires for QTL also is a function of QTL allele frequencies and therefore directly influences the QTL variance. In consequence, the efficiency of genetic parameter estimation will depend on the efficiency of assessing which sires are heterozygous and which are the QTL effects. If some sires are noninformative, it is

not possible to determine whether they are heterozygous. Therefore, the estimated proportion of heterozygous sires will be underestimated.

Highly informative founder alleles are essential for the estimation of genetic parameters: alleles of sires of sires. In the granddaughter design, the number of sires of sires is relatively limited. In this MAS data set, 54 sires of sires were available. The variance will essentially be estimated by the 108 alleles of these animals.

In addition, estimation of the QTL effect depends on the data structure: a sire must have many informative progeny to correctly estimate the difference between both allelic effects. Finally, correct estimation of the variance also depends on the ability to make a distinction between homozygous sires carrying positive or negative alleles. This is a function of the connection in the population between alleles. Some connections can be relatively weak because they can easily be broken by ungenotyped or noninformative animals. In the case of weak connections, allelic effects of homozygous animals will be regressed toward zero. They will not participate in the estimation of the gametic variance and in the distinction with the polygenic effect.

In summary, the estimation of the genetic parameters is complex because of a nonoptimal data structure and low marker informativity. However, with the MAS program, a very large number of genotyped sire families was available for this study. In addition, marker informativity was good for many QTL. Therefore, estimation of genetic parameters appeared reliable for most QTL.

As expected, QTL on chromosome 14 explained the largest proportion of genetic variance, 36% for fat percentage. Other identified QTL on chromosomes 6 (Olsen et al., 2005) and 20 (Blott et al., 2003) explained more than 10% of genetic variance in protein percentage. The estimated proportions of heterozygous sires were 20, 57, and 19% for the QTL on BTA6, 14, and 20, respectively. These QTL are highly polymorphic in the population and are therefore responsible for large fractions of the genetic variance. The proportion of genetic variance of the QTL on chromosome 26 was 9% for fat yield. As mentioned, marker informativity was poor for BTA 26, and the proportion of variance explained by this QTL might be larger in reality. Indeed, the proportion of heterozygous sires was 24% and Gautier et al. (2005) estimated, with more informative markers, that this QTL explained 17% of genetic variance for fat yield. Previous studies have suggested that there might be 2 QTL on chromosomes 6 (Spelman et al., 1996; Ron et al., 2001; Freyer et al., 2003; Cohen-Zinder et al., 2005) and 26 (Gautier et al., 2005). Correct estimation of genetic parameters of one QTL would require taking into account the second QTL. However, our marker map

covers only one QTL region on each of these chromosomes, and it was therefore not possible to correct properly for the second QTL.

The estimated parameters confirm earlier results: some identified QTL are responsible for a substantial part of genetic variance. The total proportions of genetic variance explained by the studied QTL were 27.0, 30.7, 24.1, 48.2, and 33.6% for milk, fat and protein yields, and fat and protein percentages, respectively. These proportions suggest that a large part of the genetic variation is explained by few QTL and confirm that MAS can be efficient if these QTL have a significant effect on the selection index and if they continue to segregate in the population.

CONCLUSIONS

Estimation of genetic parameters of QTL appeared to be a challenging task because proper separation of genetic variance between polygenic and QTL effects depends on marker informativity and the data structure (connection). However, the proportion of genetic variance explained by these QTL was estimated. A large portion of the genetic variance was explained by a small set of QTL, clearly indicating that use of these QTL in MAS could be beneficial for dairy cattle breeding if they have an impact on the breeding goal.

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