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Random model approach for QTL mapping in half-sib families

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Abstract – An interval mapping procedure based on the random model approach was applied to investigate its appropriateness and robustness for QTL mapping in populations with prevailing half-sib family structures. Under a random model, QTL location and variance components were estimated using maximum likelihood techniques. The estimation of parameters was based on the sib-pair approach. The proportion of genes identical-by-descent (IBD) at the QTL was estimated from the IBD at two flanking marker loci. Estimates for QTL parameters (location and variance components) and power were obtained using simulated data, and varying the number of families, heritability of the trait, proportion of QTL variance, number of marker alleles and number of alleles at QTL. The most important factors influencing the estimates of QTL parameters and power were heritability of the trait and the proportion of genetic variance due to QTL. The number of QTL alleles neither influenced the estimates of QTL parameters nor the power of QTL detection. With a higher heritability, confounding between QTL and the polygenic component was observed. Given a sufficient number of families and informative polyallelic markers, the random model approach can detect a QTL that explains at least 15 % of the genetic variance with high power and provides accurate estimates of the QTL position. For fine QTL mapping and proper estimation of QTL variance, more sophisticated methods are, however, required. © Inra/Elsevier, Paris

QTL / random model / interval mapping / sib-pair method

Résumé – Approche en modèle aléatoire pour la détection de QTL des familles de demi-frères (sœurs). Une procédure de cartographie basée sur l'approche en modèle aléatoire a été appliquée de manière à examiner sa pertinence et sa robustesse pour la détection de QTLs dans les populations où prévaut la structure en familles de demi-frères. Dans un modèle aléatoire, la position du QTL et les composantes de variance ont été estimées en utilisant les techniques de maximum de vraisemblance.

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L'estimation des paramètres a été basée sur l'approche par les paires d'apparentés. La proportion de gènes identiques par descendance (IBD) au QTL a été estimée à partir de l'IBD à deux loci de marqueurs flanquants. Les estimées des paramètres pour le QTL (position et composante de variance) et la puissance ont été obtenus en utilisant des données simulées et en faisant varier le nombre de familles, l'héritabilité du caractère, la proportion de variance au QTL, le nombre d'allèles au marqueur et le nombre d'allèles au QTL. Les facteurs les plus importants influençant les estimées de paramètres au QTL et la puissance ont été l'héritabilité du caractère et la proportion de variance génétique due au QTL. Le nombre d'allèles au QTL n'a influencé ni les estimées des paramètres au QTL ni la puissance de détection du QTL. À une héritabilité élevée, on a observé une confusion entre la composante QTL et la composante polygénique. S'il y a un nombre suffisant de familles et de marqueurs polyallèliques informatifs, l'approche du modèle aléatoire permet de détecter avec une puissance élevée un QTL qui explique au moins 15 % de la variance génétique et d'estimer précisément la position de ce QTL. Pour une détection précise et une estimation correcte de la variance au QTL, des méthodes plus sophistiquées sont cependant nécessaires.

QTL / modèle aléatoire / cartographie par intervalle / méthode des paires d'apparentés

1. INTRODUCTION

The development of linkage maps with large numbers of molecular markers has stimulated the search for methods to map genes involved in quantitative traits. The search for QTL has been most successful in plants and laboratory animals for which data are available for backcross and F_2 generation from inbred lines. With such data, the parental genotypes, the linkage phases of the loci, and the number of alleles at the putative QTL are known precisely. Additionally, data from designed experiments can be considered as one large family, because all individuals share the same parental genotypes. As a result, the effect of QTL substitution and dominance can be directly estimated [14, 18, 24].

In most livestock species, especially in dairy cattle, data from inbred lines and their crosses are not available. An outbred population is assumed to be in linkage equilibrium. In the absence of linkage disequilibrium, the linkage phase between the QTL and the markers will differ from family to family, and, therefore, the analysis of the marker–QTL linkage has to be made within a family [17]. The family size, however, is usually not large enough to enable accurate analysis within a single pedigree. Additionally, the number of QTLs affecting traits of interest is uncertain, as well as the number of alleles at each QTL. With the presence of a biallelic QTL with codominant inheritance, the distribution of genotypic values is a mixture of three normal distributions. But, with more alleles at the QTL, the number of possible genotypes increases and the analysis becomes complicated and tedious. With an unknown number of QTL alleles it is impossible to determine the exact number of genotypes, i.e. the number of normal distributions that build up the overall distribution of genotypic values. In such situations, the detection of linkage relationships between a putative QTL and the marker loci can only be based on robust model-free (non-parametric) and computationally rapid linkage methods, such as the random model approach [3].

The random model approach is based on the phenotypic similarity (or covariance) between genetically related individuals. The covariance between two relatives comprises a polygenic and a QTL component. The polygenic component depends on the genetic relationship between animals, whereas the QTL component depends on the proportion of alleles identical-by-descent (IBD) that two individuals share at the QTL. The polygenic component consists of many genes with small effects. Thus, it is assumed that the average proportion of alleles IBD shared by two individuals equals the genetic relationship coefficient between the relatives, i.e. 1/2 for full-sibs and 1/4 for half-sibs. For the same kind of relationship, however, the IBD proportion at the QTL differs from one pair of relatives to another. Because the actual proportion of alleles IBD at the QTL is not observable, the proportion of alleles IBD at the QTL shared by two relatives (π_q) must be inferred from the observed genotypes at linked marker loci.

Haseman and Elston [16] proposed a robust sib-pair approach based on simple linear regression of squared phenotypic differences between two sibs within a family on the proportion of alleles IBD shared by the two sibs at the QTL. The Haseman-Elston sib-pair method has been proved to be robust against a variety of distributions of data and independent of the actual genetic model of the QTL. However, this method is limited, because the genetic effect of the QTL and the recombination fraction between the QTL and a marker locus are confounded. It can only detect linkage between a marker and a QTL, but cannot estimate whether this is due to a QTL with a large effect at a large distance, or to a QTL with a small effect closely linked to the marker.

Fulker and Cardon [8] developed a sib-pair interval mapping procedure using two markers to separate the location of a QTL from its effect and to estimate the specific position of a QTL on a chromosome. This results in a higher statistical power, but it is still a least-square-based method and, therefore, does not optimally utilize all information that could be extracted from the distribution of the specific data, as a maximum likelihood (ML) method would do.

Goldgar [10] developed a multipoint IBD method based on the ML approach to estimate the genetic variance explained by a particular chromosomal region. This method has been extended by Schork [19] to simultaneously estimate variances of several chromosomal regions and the common environmental effect shared by all sibs. Both methods take advantage of the distributional properties of the data and, therefore, are more powerful than the Haseman-Elston method. However, they only estimate variance of QTL and not the exact QTL position.

Xu and Atchley [22] extended the Goldgar's ML method to interval mapping. They developed an efficient general QTL mapping procedure, assuming a single normal distribution of QTL genotypic values and fitting a QTL as a random effect along with a polygenic component. They showed that, using the random model approach, a QTL can be successfully mapped and its variance estimated in full-sib families.

The ML-based random model approach for QTL mapping using the sib-pair method has been well established for linkage analysis in humans [3, 22] and multiparious livestock species [15]. For dairy cattle populations with prevailing half-sib family structure this approach is, however, not directly applicable. Therefore, the objectives of this paper were:

a) to extend the random model approach for QTL mapping based on a sib-pair method to half-sib families;

b) to test the appropriateness and robustness of a random model approach for QTL mapping in half-sib families with different sample sizes, heritabilities of the trait, QTL variances, number of alleles at marker loci and number of alleles at the QTL using stochastic simulation.

2. THEORY

2.1. Estimating the proportion of IBD in half-sib families

If the markers are fully informative, the proportion of alleles IBD (π_i) shared by two sibs at a locus can be 0, 1/2 or 1 if they share zero, one or two parental alleles, respectively. For half-sibs, the proportion of alleles IBD at a locus can be either 0 or 1/2, since they only have one common parent and therefore, assuming unrelated dams, they can share either zero or one parental allele.

If the markers are not fully informative, the $\pi_i s$ at the markers cannot be observed and must be replaced by their expected values conditional on marker information available on sibs and their parents. Haseman and Elston [16] proposed a simple method to calculate π_i as

$$\widehat{\pi}_i = f_{i2} + 1/2\, f_{i1} \tag{1}$$

where f_{i2} and f_{i1} are the probabilities that the sibs share two or one allele at a locus, respectively, conditional on observed genotypes of the sibs and their parents. Analogously, $\widehat{\pi}_i$ for two half-sibs can be estimated as

$$\widehat{\pi}_i = 1/2\, f_{i1} \tag{2}$$

The proportions of alleles IBD at marker loci are used to calculate the proportion of alleles IBD at the QTL, because two offspring that receive the same marker allele are likely to receive the same allele at a linked QTL.

Haseman and Elston [16] showed that the expected proportion of IBD at one locus is a linear function of the proportion of IBD at another locus. Fulker and Cardon [8] used the proportions of IBD at two flanking markers to calculate the conditional mean of the proportion of IBD at the QTL (π_q), which is also a linear function of πs at two flanking markers:

$$\widehat{\pi}_q = E(\pi_q|\pi_1\, \pi_2) = \alpha + \beta_1\, \pi_1 + \beta_2 \pi_2 \tag{3}$$

where π_1 and π_2 are IBD values for two flanking markers.

The β weights are given by the normal equation:

$$\begin{bmatrix} \mathrm{Cov}(\pi_1,\, \pi_q) \\ \mathrm{Cov}(\pi_2,\, \pi_q) \end{bmatrix} = \begin{bmatrix} V(\pi_1) & \mathrm{Cov}(\pi_1,\, \pi_2) \\ \mathrm{Cov}(\pi_1,\, \pi_2) & V(\pi_2) \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} \tag{4}$$

Defining θ_{12}, θ_{1q} and θ_{q2} as recombination fraction between two flanking markers, between the marker 1 and the putative QTL, and between the marker

2 and the putative QTL, respectively, replacing all πs with 1/4, all variances ($V(\pi_i)$) with 1/16, and all covariances ($\mathrm{Cov}(\pi_i, \pi_j)$) with $(1 - 2\theta_{ij})^2/16$, and solving (4), the estimates of β values can be obtained as follows [2, 7, 8]:

$$\widehat{\beta}_1 = [(1 - 2\theta_{1q})^2 - (1 - 2\theta_{q2})^2(1 - 2\theta_{12})^2]/[1 - (1 - 2\theta_{12})^4] \tag{5}$$

$$\widehat{\beta}_2 = [(1 - 2\theta_{q2})^2 - (1 - 2\theta_{1q})^2(1 - 2\theta_{12})^2]/[1 - (1 - 2\theta_{12})^4] \tag{6}$$

and

$$\widehat{\alpha} = (1 - \widehat{\beta}_1 - \widehat{\beta}_2)/4 \tag{7}$$

2.2. Mapping procedure under the random model

A general form of the random model has been defined by Goldgar [10] as

$$y_{ij} = \mu + g_{ij} + a_{ij} + e_{ij}$$

where y_{ij} is the phenotypic value of the trait in the jth offspring of the ith half-sib family; μ is the population mean; g_{ij} is the random additive genetic effect of the QTL with mean = 0 and variance = σ_g^2; a_{ij} is the random additive polygenic effect with mean = 0 and variance = σ_a^2; e_{ij} is the random environmental deviation with mean = 0 and variance = σ_e^2.

All random effects in the model are assumed to be normally distributed. However, if σ_a^2 and σ_e^2 are large enough to make the distribution of the data normal, the normal distribution of the QTL effects is not absolutely required.

In a half-sib family, the variance of y_{ij} assuming a linkage equilibrium is:

$$\mathrm{Var}(y_{ij}) = \sigma^2 = \sigma_a^2 + \sigma_g^2 + \sigma_e^2 \tag{8}$$

and a covariance between two non-inbred half-sibs j and j' is:

$$\mathrm{Cov}(y_{ij}, y_{ij'}) = \pi_q \sigma_g^2 + 1/4\sigma_a^2 \tag{9}$$

with π_q = the proportion of alleles IBD at the putative QTL shared by two half-sibs.

The coefficient of the polygenic variance is 1/4 because, by expectation, two non-inbred half-sibs share 1/4 alleles IBD. The proportion of IBD at the QTL (π_q) will be different for each half-sib pair. π_q is a variable that ranges from 0 to 1/2 in half-sib families.

For the estimation of variance components, π_q in equation (9) is replaced by its estimated value $\widehat{\pi}_q$ from equation (3).

The covariance between two half-sibs j and j' within a family i is:

$$V_i = \mathrm{Var}\begin{bmatrix} y_{ij} \\ y_{ij'} \end{bmatrix} = \sigma^2 C_i \tag{10}$$

with

$$\mathbf{C}_i = \begin{bmatrix} 1 & r_i \\ r_i & 1 \end{bmatrix} \tag{11}$$

and

$$r_i = \widehat{\pi}_q h_g^2 + 1/4\, h_a^2 \tag{12}$$

With k sibs in each family, $\mathbf{C}_i$ is a $k \times k$ matrix.

We define $h_g^2 = \sigma_g^2/\sigma^2$ as the heritability of a putative QTL, $h_a^2 = \sigma_a^2/\sigma^2$ as the heritability of a polygenic component, and $h_t^2 = (\sigma_g^2 + \sigma_a^2)/\sigma^2$ as the total heritability. Assuming a multivariate normal distribution of the data (y_{ij}), we have a joint density function of the observations within a half-sib family:

$$f(\mathbf{y}_i) = \frac{1}{(2\Pi\sigma^2)^{k/2}|\mathbf{C}_i|^{1/2}} * \exp\left\{-\frac{1}{2\sigma^2}(\mathbf{y}_i - \mathbf{1}\mu)'\mathbf{C}_i^{-1}(\mathbf{y}_i - \mathbf{1}\mu)\right\} \qquad (13)$$

where $\mathbf{y}_i = [y_{i1}\, y_{i2}\, y_{i3} \ldots y_{ik}]'$ is a $k \times 1$ vector of observed phenotypic values for k half-sibs within the ith family, and $\mathbf{1} = k \times 1$ vector with all entries equal to 1.

The overall log likelihood for n independent families is

$$L = \sum_{i=1}^{n} \log[f(\mathbf{y}_i)] \qquad (14)$$

The likelihood function relates to the position of the QTL flanked by two markers through r_i. The unknown parameters that have to be estimated are μ, σ^2, h_g^2, h_a^2 and θ_{1q}. In maximizing L, the common practice in the interval mapping procedure is to treat the recombination fraction between the first marker and a putative QTL (θ_{1q}) first as a known constant, then gradually increase θ_{1q} and decrease the distance between the QTL and the right marker (θ_{q2}) throughout the entire interval between the flanking markers, and repeat the procedure in every interval until, eventually, the whole genome is screened. The maximum likelihood estimate of the QTL position is determined by the value of θ_{1q} in the appropriate interval that maximizes L through the entire chromosome.

The null hypothesis is that $h_g^2 = 0$, i.e. that no QTL is present in the tested interval. The ML under null hypothesis is denoted by L_0. The likelihood ratio (LR) test statistics is

$$\mathrm{LR} = -2(L_0 - L) \qquad (15)$$

The LR statistics under H_0 follows the χ^2 distribution with a number of degrees of freedom (df) between 1 and 2. With a single QTL, one df is due to fitting h_g^2 and the remaining df for fitting the QTL position. The remaining df depends on the distance between two markers and is less than one because we search for the QTL only within an interval, rather than in the entire genome (chromosome). If the H_0 is that no QTL is present in the whole genome (chromosome) covered by the markers, the df under H_0 is $=\sim 2$ [22].

3. SIMULATION AND ANALYSES

The Monte Carlo simulation technique was used to generate genotypic and phenotypic data. Mapping QTL were considered in a 100 cM long chromosomal segment covered by six markers, equally distributed along the chromosome at a 20 cM distance. All markers had an equal number of alleles with the

same frequency. A single QTL with several codominant alleles with the same frequency and additive effects was simulated in the middle of the chromosomal segment (i.e. at 50 cM).

Parents were generated by the random allocation of genotypes at each locus assuming a Hardy-Weinberg equilibrium. Parental linkage phases were assumed unknown. Offspring were generated assuming no interference, so that a recombination event in one interval does not affect the occurrence of a recombination event in an adjacent interval. Recombination fractions for each locus were calculated using the Haldane map function [13].

Normally distributed phenotypic data with mean = 0 and variance = 1 were generated according to the following model:

$$y_{ij} = \mu + q_{ij} + 1/2(s_i + d_{ij}) + \phi_{ij} + e_{ij}$$

where y_{ij} is the phenotypic value of the individual j in the half-sib family i; μ is the population mean; q_{ij} is the effect of the QTL genotype of individual j; s_i is the sire's contribution to the polygenic value; d_{ij} the dam's contribution to the polygenic value; ϕ_{ij} is the effect of Mendelian sampling on the polygenic value; and e_{ij} the residual error.

Phenotypic values were assumed pre-corrected for fixed environmental effects. Family structure was chosen to accommodate a typical situation in a commercial dairy population. For simplicity, sires were assumed to be unrelated. Each sire was mated to 25 randomly chosen unrelated dams to produce one offspring per mating.

The values of the simulated parameters varied depending on the major purpose of the simulation.

To test the behavior of the random model approach under different heritabilities of the trait and different proportions of variance explained by the QTL (i.e. different size of the QTL), seven different values of heritability were assumed: the heritability of the trait was varied from 0.10 to 0.70 in steps of 0.10. The total genetic variance consisted of a QTL component and an unlinked polygenic component. The additive allelic effect of the QTL was set so that the QTL variance accounted for 10, 50 and 100 % of the total genetic variance. The number of alleles at the QTL was 5. All of the six markers had six alleles with the same frequency.

To test the influence of marker polymorphism on the performance of the random model approach, each of six marker loci was assumed to have two, four, six or ten alleles with an equal frequency. Two different heritabilities of the trait were considered: 0.10 and 0.50. The number of alleles at the QTL was five. The total genetic variance was accounted for by the QTL, i.e. no polygenic component was simulated.

To test the robustness of the random model approach against the number of alleles at the QTL, the QTL was simulated with two, five or nine equally frequent alleles with additive effects. Again, the phenotypic trait was simulated assuming two different heritabilities: 0.10 and 0.50, with the complete genetic variance due to the QTL. Each of six marker loci had six equally frequent alleles.

In each simulation two different sample sizes were considered: 50 and 100 sire families with 25 offspring each.

The ML interval mapping procedure was applied to the simulated data. The chromosome was searched in steps of 2 cM from the left to the right end. Unknown parameters h_g^2, h_a^2 and σ^2 were estimated simultaneously. The likelihood function was maximized with respect to these parameters using the simplex algorithm provided by Xu (pers. comm.). The test position with the highest LR was accepted as the most likely position of the QTL. For each parameter combination the simulation and analysis were repeated 100 times. The accuracy of estimation was judged according to an empirical 95 % symmetric confidence interval, estimated from the observed between-replicate variation and calculated as $2t_{\alpha/2,99}$ times the empirical standard error.

The empirical distribution of the LR test statistics was generated in the same manner for each parameter combination under the null hypothesis, i.e. assuming no QTL in the entire segment. A significance level of 0.95 was chosen for all analyses. The empirical threshold value was defined as the 95th percentile of the empirical distribution of the LR test statistics under H_0. The power was defined as a percentage of replications in which the null hypothesis was rejected at the 5 % significance level. The distribution of the maximum LR values obtained under H_0 for heritability of the trait 0.10 and 0.50 is illustrated in *figure 1*.

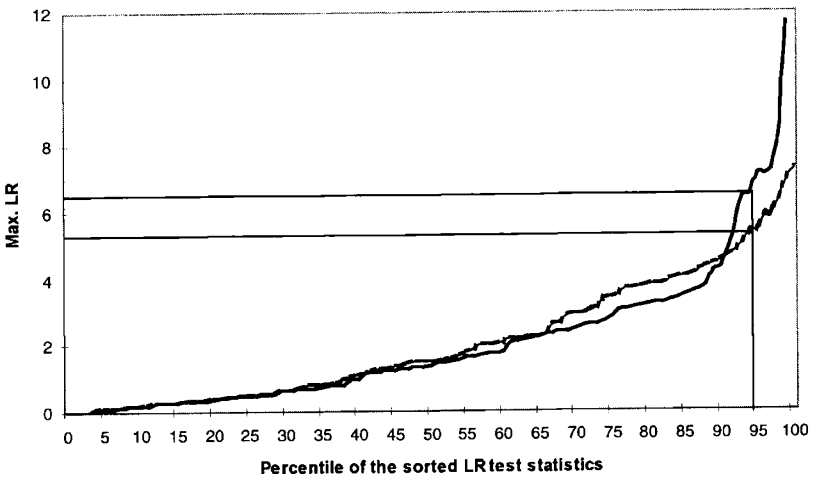

Figure 1. Maximum likelihood ratio values under H_0 for the heritability of the trait = 0.10 (- - - - -) and heritability of the trait = 50 % (——) for parameter combinations with 50 families. The 95 % empirical threshold values for heritability of the trait of 0.10 and 0.50 are 5.47 and 6.42, respectively.

4. NUMERICAL RESULTS

4.1. Heritability of the trait and proportion of QTL variance

Estimates for the QTL location, averaged over 100 replicates, with corresponding confidence intervals for different heritabilities of the trait, proportions of genetic variance due to QTL, and sample sizes are summarized in *table I*.

Table I. Effect of sample size, heritability of the trait and proportion of genetic variance due to QTL on estimates and the confidence interval for QTL location, averaged over 100 replicates.

N	h^2	Proportion of genetic variance due to QTL (%)					
		100		50		10	
		cM_A	CI	cM_A	CI	cM_A	CI
50	0.10	47.4	10.9	43.4	11.8	41.4	13.4
	0.20	49.6	6.3	47.0	9.3	44.8	13.1
	0.30	50.6	4.4	50.1	7.2	45.8	12.4
	0.40	50.3	4.4	49.6	6.5	53.0	11.8
	0.50	48.9	2.2	50.6	4.7	46.4	11.2
	0.60	49.0	2.1	50.1	3.7	45.6	11.1
	0.70	49.4	1.8	49.7	3.0	48.6	10.3
100	0.10	52.3	7.9	54.8	10.2	52.4	11.8
	0.20	49.3	4.9	54.1	8.1	57.0	11.4
	0.30	49.2	3.8	50.1	5.4	52.4	11.3
	0.40	49.8	1.9	50.1	4.3	50.5	10.2
	0.50	49.9	0.9	49.9	3.7	49.7	10.3
	0.60	49.8	0.7	49.2	2.7	50.2	9.4
	0.70	49.9	0.6	49.6	2.4	49.2	8.8

N, sample size (number of families); h^2, heritability of the trait; cM_A, estimated QTL location (cM); CI, empirical 95 % confidence interval, defined as $2t_{\alpha/2,99}\times$ between-replicate standard error.

When the QTL explained the entire genetic variance, the estimates for the QTL position were close to the true parameter value of 50 cM. When the QTL explained 50 % of the genetic variance, the estimates were close to the true QTL position when the heritability of the trait was 0.30. When the QTL explained only 10 % of the variance, the average estimates were biased and close to the true value only with a very high heritability of the trait and a sample of 100 families.

When the genetic variance is completely due to the QTL, the accuracy of the QTL position estimates, given as a width of the 95 % empirical confidence interval, was strongly influenced by the heritability of the trait and the number of families. When heritability increased from 0.10 to 0.20, the accuracy of the estimates increased by approximately 40 % (the confidence interval decreased from 10.9 to 6.3 cM and from 7.9 to 4.9 cM for 50 and 100 families, respectively). With a further increase in heritability to 0.70, the confidence interval decreased to 1.8 and 0.6 cM for 50 and 100 families, respectively. Relative improvement in accuracy was smaller when the QTL explained a smaller proportion of the genetic variance. When 50 % of the genetic variance was explained by the QTL, the increase in heritability of the trait from 0.10 to 0.20 resulted in a reduction of the confidence interval by 20 %. With a QTL explaining only 10 % of the genetic variance, the improvement in accuracy with increased heritability of the trait was very small, regardless of the sample size. However, generally, more accurate estimates of the QTL position were obtained with large samples.

Estimates for QTL (h_g^2), polygenic (h_a^2) and total (h_t^2) heritability are given in *table II*. Estimates for total heritability, which represents a sum of QTL and polygenic heritability, were equal or very close to the true parameter values. When the QTL explained 10 % of the total genetic variance, the estimated h_g^2 was relatively close to the true value or only slightly overestimated for the heritability of the trait = 0.10. With an increase in heritability from 0.10 to 0.40, h_g^2 was overestimated. With further increase in heritability (over 0.40), the bias became smaller, so that the estimated h_g^2 was close to the true value. This pattern is visible in *figure 2a*. When 50 % of the genetic variance was explained by QTL, the estimates of h_g^2 followed a different pattern (*figure 2b*). For low heritability of the trait, 0.10 and 0.20, the estimates were close to the true values of the parameter. With further increase in heritability, the estimates became biased, and finally considerably underestimated when the heritability of the trait reached 0.70. Even more severe downward bias was encountered in the parameter combinations in which QTL accounted for the entire genetic variance (*figure 2c*). As the heritability of the trait increased, the estimated values of h_g^2 became more and more biased. This inability of the random model to 'pick up' a larger QTL variance was observed independently of the sample size.

The empirical power of QTL detection, defined as the percentage of replicates in which the maximal LR exceeded the average empirical threshold

Table II. Effect of sample size, heritability of the trait and proportion of genetic variance due to QTL on estimated values for QTL, polygenic and total heritability, averaged over 100 replicates.

N	h^2	Proportion of genetic variance due to QTL (%)								
		100			50			10		
		h_g^2	h_a^2	h_t^2	h_g^2	h_a^2	h_t^2	h_g^2	h_a^2	h_t^2
50	0.10	0.09	0.02	0.11	0.07	0.03	0.10	0.04	0.06	0.10
	0.20	0.15	0.05	0.20	0.10	0.09	0.19	0.07	0.12	0.19
	0.30	0.20	0.09	0.29	0.13	0.15	0.28	0.08	0.20	0.28
	0.40	0.26	0.13	0.39	0.17	0.20	0.37	0.08	0.27	0.36
	0.50	0.29	0.20	0.49	0.19	0.28	0.47	0.09	0.39	0.48
	0.60	0.32	0.27	0.59	0.20	0.37	0.57	0.09	0.49	0.58
	0.70	0.34	0.36	0.70	0.23	0.45	0.67	0.09	0.59	0.68
100	0.10	0.08	0.02	0.10	0.06	0.03	0.09	0.02	0.07	0.09
	0.20	0.15	0.05	0.20	0.09	0.10	0.19	0.05	0.14	0.19
	0.30	0.20	0.10	0.30	0.12	0.17	0.29	0.06	0.23	0.29
	0.40	0.26	0.14	0.40	0.16	0.23	0.40	0.06	0.33	0.39
	0.50	0.28	0.23	0.51	0.18	0.31	0.49	0.07	0.41	0.48
	0.60	0.31	0.30	0.61	0.20	0.39	0.59	0.07	0.52	0.59
	0.70	0.34	0.38	0.72	0.22	0.47	0.69	0.07	0.61	0.69

N, sample size (number of families); h^2, heritability of the trait; h_g^2, estimated QTL heritability; h_a^2, estimated polygenic heritability; h_t^2, estimated total heritability.

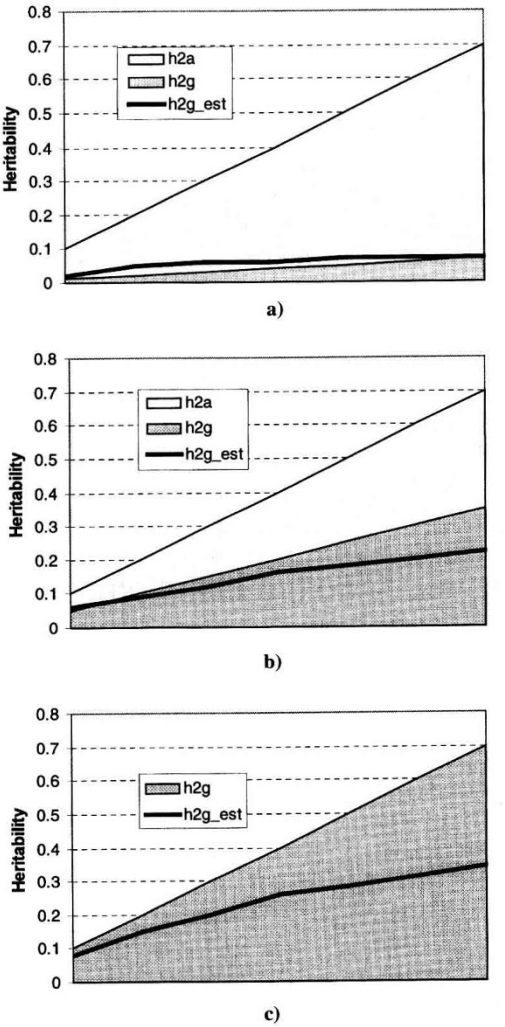

Figure 2. True values of QTL (h_g^2) and polygenic heritability (h_a^2), and estimated QTL heritability (h_g^2_est) with different heritabilities of the trait and a proportion of genetic variance explained by the QTL of: a) 10 %; b) 50 %; c) 100 %.

obtained by data simulation under H_0, is given in *table III*. The power to detect QTL was highly dependent on the heritability of the trait. With a heritability of 0.10, the maximum power was 32 % (with 100 families and the complete genetic variance accounted for by the QTL). With increasing heritability of the trait, the power increased rapidly. A further factor with a strong influence on power was the proportion of genetic variance due to QTL. When the QTL explained only 10 % of the total genetic variance, the power increased from 6 to 27 % and from 6 to 34 % for samples of 50 and 100 families, respectively, as the heritability of the trait increased from 0.10 to 0.70. When the QTL

Table III. Effect of sample size, heritability of the trait and proportion of genetic variance due to QTL on the power of QTL detection.

			Proportion of genetic variance due to QTL (%)		
N	h^2	Thr.	100	50	10
50	0.10	5.47	29	16	6
	0.20	5.39	73	37	10
	0.30	5.28	97	62	15
	0.40	5.58	100	81	14
	0.50	6.42	100	91	15
	0.60	5.63	100	97	26
	0.70	5.59	100	98	27
100	0.10	6.27	32	18	6
	0.20	6.31	93	41	11
	0.30	5.97	100	77	11
	0.40	6.26	100	99	25
	0.50	6.53	100	99	23
	0.60	6.73	100	100	27
	0.70	6.02	100	100	34

N, sample size (number of families); h^2, heritability of the trait; Thr, empirical threshold value, obtained from data simulation under H_0 (no QTL) and defined as the 95th percentile of the empirical distribution of LR test statistics. The power is defined as a percentage of replicates where the H_0 was rejected at a 5 % error rate.

explained 50 % of the total genetic variance, the power increased much faster and reached over 90 % already with a heritability of the trait of 0.40–0.50. Even faster increase in power could be observed in parameter combinations in which the QTL explained the entire genetic variance.

Figure 3 shows the LR profiles averaged over 100 replicates for different proportions of genetic variance due to QTL, heritability of the trait = 0.10 and sample size = 50 families. The LR profiles for different QTL effects with the same parameter combination and heritability of the trait = 0.50 are shown in *figure 4*. Both figures show a flat profile when QTL accounts for only 10 % genetic variance, regardless of the heritability of the trait. With a higher heritability and greater proportion of genetic variance due to the QTL, the LR profile indicates the QTL location very precisely. With the heritability of the trait = 0.10, the location of the QTL is clearly indicated only when the QTL accounts for the complete genetic variation. But, the average LR in this situation did not exceed a value of 2.3, which is far below our empirical threshold value of 5.47.

4.2. Number of alleles at marker loci

The effect of the number of alleles at marker loci on the estimates of the QTL location and the corresponding confidence intervals for different sample

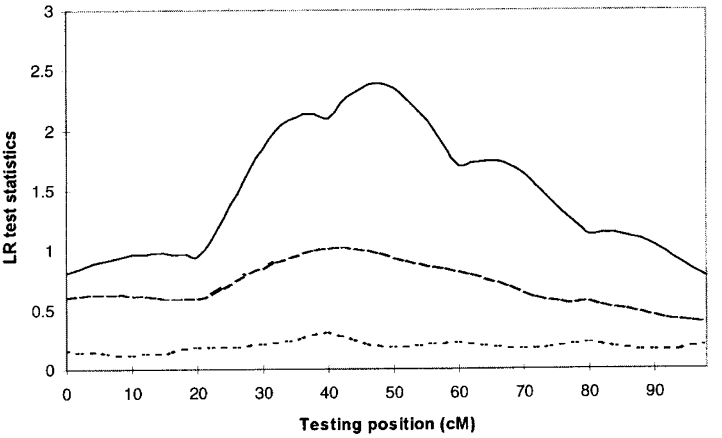

Figure 3. Comparison of LR profiles for different proportions of genetic variance due to QTL, for total heritability = 0.10, number of families = 50 and six alleles at marker loci, averaged over 100 replicates. QTL variance = 100 % (——), QTL variance = 50 % (– – –), QTL variance = 10 % (- - - - -).

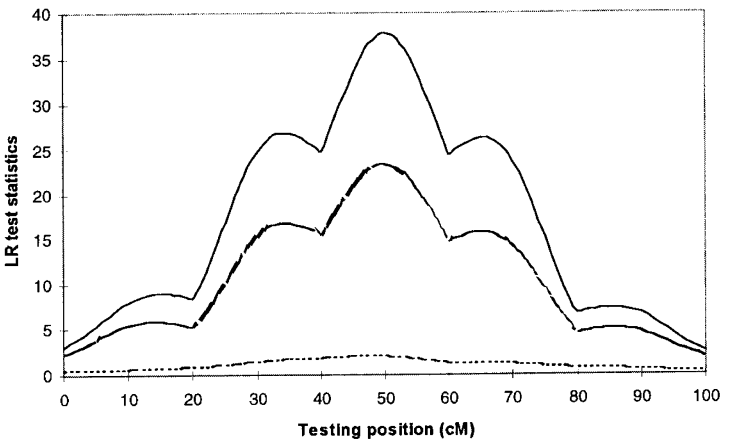

Figure 4. Comparison of LR profiles for different proportions of genetic variance due to QTL, for total heritability = 0.50, number of families = 50 and six alleles at marker loci, averaged over 100 replicates. QTL variance = 100 % (——), QTL variance = 50 % (– – –), QTL variance = 10 % (- - - - -).

sizes and heritabilities of the trait, assuming the complete genetic variance due to QTL, is shown in *table IV*. The mean estimates for QTL location were consistent for all parameter combinations and close to the true parameter value (50 cM), regardless of the number of marker alleles. The confidence intervals were, however, narrower for polyallelic than for biallelic markers, which indicated more accurate estimates when markers were polymorphic. Increasing the number of alleles from four to six and ten did not affect the confidence interval. The heritabilities of the trait showed a significant influence on the accuracy of estimation. In all parameter combinations, the confidence interval

Table IV. Effect of the heterozygosity of marker loci on the estimates and confidence interval for QTL, averaged over 100 replicates.

N	h^2	Number of marker alleles							
		2		4		6		10	
		cM_A	CI	cM_A	CI	cM_A	CI	cM_A	CI
50	0.10	47.5	12.2	52.1	9.9	47.4	10.9	50.4	10.0
	0.50	51.5	4.5	51.4	3.8	48.9	2.2	51.4	3.2
100	0.10	53.0	10.9	43.8	8.9	52.3	7.9	44.4	7.1
	0.50	49.7	3.8	50.2	1.9	49.9	0.9	50.2	2.2

N, sample size (number of families); h^2, heritability of the trait; cM_A, estimated QTL location (cM); CI, empirical 95 % confidence interval, defined as $2t_{\alpha/2,99}\times$ between-replicates standard error. The genetic variance is completely due to the QTL.

was considerably wider with the low heritability of the trait. Increasing the number of families also resulted in narrower confidence intervals and thus more accurate estimates for the QTL location.

Estimates for QTL, polygenic and total heritability for different numbers of marker alleles, heritability of the trait and sample size are given in *table V*. Estimates for total heritability were close to simulated values for almost all parameter combinations, except for the situations with biallelic markers in which h_t^2 was overestimated. For heritability of the trait = 0.10, estimates for both QTL and polygenic heritability were relatively close to the true values, regardless of the number of marker alleles and other parameters. For heritability of the trait = 0.50, QTL heritability was again severely biased downwards. The estimated polygenic component, although not simulated, accounted for almost 50 % of the estimated total heritability.

Table V. Effect of heterozygosity of marker loci on estimated values for QTL, polygenic and total heritability, averaged over 100 replicates.

N	h^2	Number of marker alleles											
		2			4			6			10		
		h_g^2	h_a^2	h_t^2	h_g^2	h_a^2	h_t^2	h_g^2	h_a^2	h_t^2	h_g^2	h_a^2	h_t^2
50	0.10	0.10	0.03	0.13	0.09	0.02	0.11	0.09	0.02	0.11	0.10	0.03	0.13
	0.50	0.35	0.27	0.62	0.27	0.23	0.50	0.29	0.20	0.49	0.29	0.26	0.55
100	0.10	0.10	0.03	0.13	0.08	0.02	0.10	0.08	0.02	0.10	0.10	0.01	0.11
	0.50	0.33	0.31	0.64	0.27	0.23	0.50	0.28	0.23	0.51	0.29	0.27	0.56

N, sample size (number of families); h^2, heritability of the trait; h_g^2, estimated QTL heritability; h_a^2, estimated polygenic heritability; h_t^2, estimated total heritability. The genetic variance is completely due to the QTL.

The empirical power for the same parameter combinations is given in *table VI*. As expected, the power to detect QTL strongly depended on the heritability of the trait. For a heritability of the trait = 0.50, power was close to 100 for all parameter combinations. Therefore, differences in power to detect QTL caused by parameters other than heritability could be observed only for parameter combinations with heritability of the trait = 0.10. The power mostly increased when the number of marker alleles increased from two to four. With a further increase in the number of marker alleles, the power did not change considerably. Power was also significantly increased with increased sample size. With 100 families, the power was almost twice that with 50 families for all parameter combinations. A drop in power from 42 to 32 % when the number of marker alleles increased from four to six might be due to the higher threshold value obtained for this parameter combination.

Table VI. Effect of heterozygosity of marker loci on the power of QTL detection.

			Number of marker alleles			
N	h^2		2	4	6	10
50	0.10	Thr	6.28	5.09	5.47	4.69
		P	11	25	29	31
	0.50	Thr	6.13	5.76	6.42	6.18
		P	95	100	100	99
100	0.10	Thr	5.98	5.57	6.27	5.62
		P	31	42	32	44
	0.50	Thr	7.21	6.44	6.53	5.58
		P	100	100	100	100

N, sample size (number of families); h^2, heritability of the trait; Thr, empirical threshold value, obtained from data simulation under H_0 (no QTL) and defined as the 95th percentile of the empirical distribution of LR test statistics; P, power, defined as a percentage of replicates where the H_0 was rejected at a 5 % error rate. The genetic variance is completely due to the QTL.

Figures 5 and *6* show the LR profile averaged over 100 replicates for two, four and ten marker alleles, sample size of 50 families and heritability of the trait = 0.10 and 0.50, respectively. *Figure 5* shows that the QTL location was not clearly indicated with a low heritability and a low number of marker alleles. Increasing the number of marker alleles to ten improved the estimate of the QTL location. With the heritability of 0.50 (*figure 6*), the estimates of the QTL position were significantly improved. LR also increased with increasing marker polymorphism, especially when the number of marker alleles increased from two to four.

4.3. Number of alleles at QTL

The effect of the number of QTL alleles on the estimates of the QTL position and the corresponding confidence intervals for different heritabilities of the

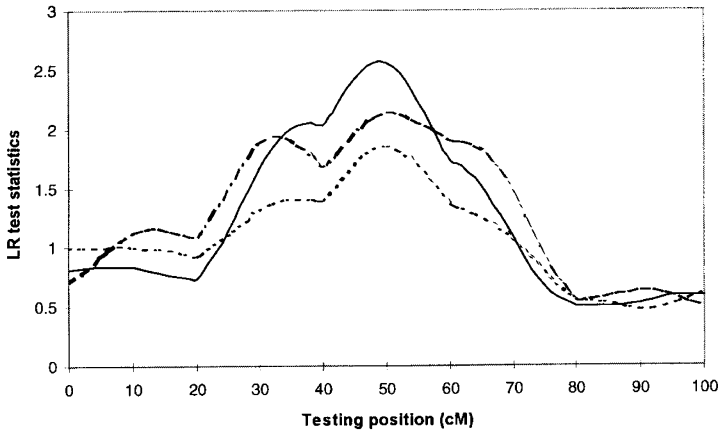

Figure 5. Comparison of LR profiles for different numbers of marker alleles, for heritability = 0.10, QTL effect = 100 % and number of families = 50, averaged over 100 replicates. Ten alleles (——), four alleles (– – –), two alleles (- - - - -).

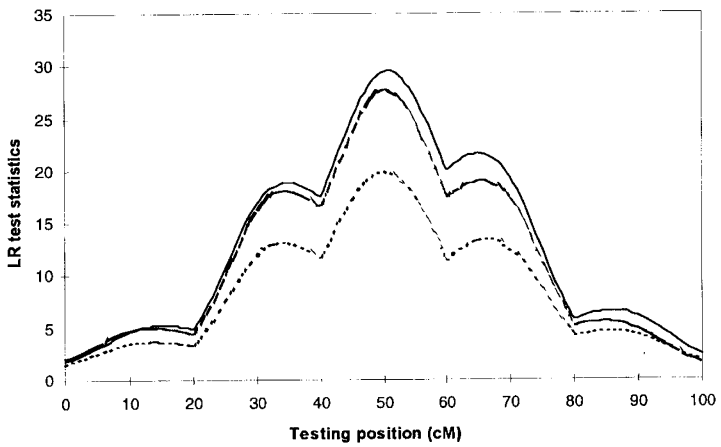

Figure 6. Comparison of LR profiles for different numbers of marker alleles, for heritability = 0.50, QTL effect = 100 % and number of families = 50, averaged over 100 replicates. Ten alleles (——), four alleles (– – –), two alleles (- - - - -).

trait and sample sizes, assuming the complete genetic variance as due to the QTL, are shown in *table VII*. For all parameter combinations, regardless of any parameter, the estimates for the QTL position were close to the simulated value of 50 cM. Empirical confidence intervals depended on the heritability of the trait and sample size. The confidence interval was considerably decreased by increasing heritability of the trait from 0.10 to 0.50. Increasing sample size from 50 to 100 families also had a certain positive influence on the accuracy of estimation. The number of alleles at the QTL does not seem to have any systematic influence on the estimated QTL position, nor on the confidence interval.

Table VII. Effect of the number of QTL alleles on the estimates and the confidence interval for the QTL position, averaged over 100 replicates.

N	h^2	Number of QTL alleles					
		2		5		9	
		cM_A	CI	cM_A	CI	cM_A	CI
50	0.10	48.7	10.0	47.4	10.7	46.9	10.8
	0.50	50.0	2.9	48.9	2.2	50.2	3.1
100	0.10	49.0	9.1	52.3	7.9	49.9	8.7
	0.50	50.4	1.6	49.9	0.9	50.0	1.0

N, sample size (number of families); h^2, heritability of the trait; cM_A, estimated QTL location (cM); CI, empirical 95 % confidence interval, defined as $2t_{\alpha/2,99}\times$ between-replicates standard error. The genetic variance is completely due to the QTL.

Table VIII shows estimates for h_g^2, h_a^2 and h_t^2 for different numbers of QTL alleles, different heritabilities of the trait and different sample sizes. As in the previous analyses, a severe downward bias in the estimates for h_g^2 and a corresponding upward bias in the estimates for h_a^2 were encountered with a heritability of the trait = 0.50. Obviously, this bias was not caused by the number of alleles at the QTL, because it was found in all parameter combinations in which the simulated true heritability of the trait was 0.50.

Table VIII. Effect of the number of QTL alleles on estimated values for QTL, polygenic and total heritability, averaged over 100 replicates.

N	h^2	Number of QTL alleles								
		2			5			9		
		h_g^2	h_a^2	h_t^2	h_g^2	h_a^2	h_t^2	h_g^2	h_a^2	h_t^2
50	0.10	0.08	0.02	0.10	0.09	0.02	0.11	0.09	0.02	0.11
	0.50	0.29	0.20	0.49	0.29	0.20	0.49	0.29	0.19	0.49
100	0.10	0.08	0.02	0.10	0.08	0.02	0.10	0.08	0.02	0.11
	0.50	0.28	0.21	0.50	0.28	0.23	0.51	0.28	0.22	0.50

N, sample size (number of families); h^2, heritability of the trait; h_g^2 , estimated QTL heritability; h_a^2, estimated polygenic heritability; h_t^2, estimated total heritability. The genetic variance is completely due to the QTL.

Power of QTL detection for different numbers of QTL alleles, different heritabilities of the trait and different sample sizes is given in *table IX*. The power was 100 % with the heritability of the trait = 0.50, regardless of any other parameter. With the heritability of the trait = 0.10, the power ranged between 29 and 31 % and between 32 and 36 % for the sample size of 50 and 100 families, respectively. Power was not influenced by the number of QTL alleles.

Table IX. Effect of the number of QTL alleles on the power of QTL detection.

			Number of QTL alleles		
N	h^2	Thr.	2	5	9
50	0.10	5.47	31	29	29
	0.50	6.42	100	100	100
100	0.10	6.27	35	32	36
	0.50	6.53	100	100	100

N, sample size (number of families); h^2, heritability of the trait; Thr, empirical threshold value, obtained from data simulation under H_0 (no QTL) and defined as the 95th percentile of the empirical distribution of LR test statistics; P, power, defined as a percentage of replicates where the H_0 was rejected at a 5 % error rate. The genetic variance is completely due to the QTL.

5. DISCUSSION

In the first part of this study, we investigated the effects of the proportion of genetic variance due to QTL, heritability of the trait and sample size on the estimates of QTL parameters – QTL location and variance components, and power. The results of the simulation study showed significant effects of proportion of genetic variance due to QTL on the estimates for QTL location, heritabilites and power. A QTL with a small effect, which accounts for only 1 % of the total phenotypic variance, is very unlikely to be precisely located, especially when the sample comprises only 50 families. The location of the small QTL cannot be clearly indicated, as the estimates for QTL location are distributed along the chromosome, and the average estimate over the replicates takes almost a random value. On the contrary, a QTL with a large effect, accounting for 10 % of the total phenotypic variance, can be accurately located with only 50 families.

Estimation of QTL position yields better results with a larger proportion of genetic variance explained by QTL and a higher heritability of the trait. The empirical confidence interval for QTL location shows that accuracy decreased significantly when the proportion of genetic variance due to QTL decreased from 100 to 10 %, especially with high heritability of the trait. Sample size has little influence on the average estimates, but larger samples enable somewhat more accurate estimates. These results are consistent with those obtained by Xu and Atchley [22], who used the same approach to estimate QTL location and genetic parameters in full-sib families.

The estimates of variance components, herein given as heritabilities (h_t^2, h_g^2 and h_a^2) highly depend on the heritability of the trait and the proportion of genetic variance explained by the QTL. Although the estimates of the total genetic variance (expressed as h_t^2) are very close to the true parameter values in all parameter combinations, the proper partition of the QTL and polygenic component can be achieved only when the QTL explains approximately 10–15 % of the genetic variance. The variance of a smaller QTL tends to be overestimated. The variance of a larger QTL is always underestimated, with

a larger bias accompanying a larger QTL. However, an underestimated QTL variance is always accompanied by an overestimated polygenic variance, so that the sum of $h_g^2 + h_a^2$ is conserved at a value very close to a simulated true value of total heritability, indicating a successful partitioning of genetic and residual variance.

Confounding between h_g^2 and h_a^2 has been observed by Gessler and Xu [9], who explained this phenomenon by differences in the models used for data simulation and estimation. They simulated data using a monogenic model, and, because the simulated h_a^2 was zero, a partitioning into h_a^2 and h_g^2 under the conserved sum $h_g^2 + h_a^2$ tended to reduce h_g^2, and thus the estimates for h_g^2 were biased downwards. In another study, Xu and Gessler [23] found an overestimation of the QTL component under a model including a non-zero polygenic component. Their finding is, therefore, opposite of what we found in our study. Nevertheless, confounding between variance components has been considered to be a general difficulty of the sib-pair approach [1, 4, 9]. Recently, Xu [21] proposed a method to correct the bias in the estimates of the QTL variance using a quadratic approximation of the LR test statistic. This problem, however, requires further research.

The power of QTL detection, in general, depends mostly on the heritability of the trait and the proportion of genetic variance explained by QTL. A small QTL in a small sample is very difficult to detect with certainty. A large QTL can, however, be detected with a high power, even in a small sample. Increasing the number of families does not significantly improve the power when the QTL is small. Generally, it can be concluded that a QTL that explains at least 30 % of the phenotypic variance can be detected with 100 % power in any experimental design. To reach a satisfactory power of 70–80 % in a sufficiently large sample, a QTL must account for at least 15 % of the phenotypic variance.

The second part of this study focused on the influence of marker polymorphism on QTL parameter estimates and power, assuming low and high heritabilities of the trait ($h^2 = 0.10$ and $h^2 = 0.50$), and using small and large samples (50 and 100 families with 25 half-sibs each).

The results showed that the mean estimates of the QTL location were not affected by any of the parameters in the study (heritability of the trait, sample size and number of alleles at each of six marker loci). However, the accuracy of estimation, given as a 95 % empirical confidence interval, was markedly influenced by the heritability of the trait and the number of families, and also partially by the number of marker alleles.

Several previous studies found that the accuracy of QTL location is mostly influenced by the size of the QTL effect and sample size. Other parameters, such as marker map resolution, have little effect [6]. The results from our study also showed positive effects of larger samples on the confidence interval in all parameter combinations.

Furthermore, the accuracy of estimates for QTL location improves with an increased number of marker loci. For markers with four, six or ten equally frequent alleles and low heritability of the trait ($h^2 = 0.10$), 50 half-sib families give the same accuracy as for markers with two alleles and double the number of families. An increased accuracy of the estimates for the QTL location with polyallelic markers was also reported by Knott and Haley [17]. This indicates that the sample size can be reduced by half without a loss of accuracy if highly

polymorphic markers are used in the analysis. The reduction of the number of animals to be genotyped would significantly reduce the costs of QTL analysis, one of the major limitations in mapping and utilizing QTL [5].

In general, estimated values for heritabilities are similar to those from the first part of the study. Only for biallelic markers, the value of h_t^2 is biased upwards, which indicates that biallelic markers do not provide enough information to infer π_q properly. For markers with $\geq$ four alleles, the estimated heritabilities h_g^2, h_a^2 and h_t^2 are close to the simulated values in all parameter combinations when the heritability of the trait = 0.10. With the heritability of the trait = 0.50, h_g^2 and h_a^2 are strongly confounded, and the sum of $h_g^2 + h_a^2$ is relatively conserved, for all parameter combinations.

Apart from the heritability of the trait and the number of families, another factor that influences power, especially when the heritability of the trait is low, is the heterozygosity of marker loci. With an increasing number of alleles at marker loci, one can expect a higher power of QTL detection [11, 17, 20]. The results of this study indicate that power increases approximately by 20 % when the number of marker alleles increases from two to four. This is consistent with the expectation that a linked QTL can be detected only if the parent is heterozygous for the marker locus. With biallelic markers, only 1/2 of the parents is expected to be heterozygous. On the other hand, with four marker alleles, the proportion of parents heterozygous for individual marker loci will be 0.75, which results in an increased proportion of informative sib-pairs. A further increase in marker heterozygosity (from four to six to ten alleles) does not result in a significant increase in power, because the proportion of heterozygous parents and informative half-sib pairs does not change drastically. Variations in power with four marker alleles found in our study can be regarded as random.

The third part of the study focused on the influence of the number of QTL alleles on estimates for QTL position, variance components and power. The results of the simulations proved the insensitivity of the random model approach against the number of alleles at the QTL. The estimates of the QTL position are very similar for biallelic and for multiallelic QTL. Also, the accuracy of the estimates is affected only by the heritability of the trait, the proportion of the genetic variance explained by QTL and sample size, but not by the number of QTL alleles.

Other authors who compared performance of the random model approach in analyses of biallelic and multiallelic QTL in full-sib families [22] and multigenerational pedigrees [12] reported comparable results. This underlines the main advantage of the random model approach over other parametric methods: its flexibility regarding the actual number of alleles at the QTL.

The estimates of the variance components, expressed as h_g^2, h_a^2 and h_t^2, are very similar to those from the previous analyses. With a higher heritability of the trait, h_g^2 is severely biased downwards, and h_a^2 is, accordingly, biased upwards. The same bias can be observed for QTL with two, five and nine alleles. This shows that the bias in estimates of the QTL variance is not caused by deviation of the distribution of QTL effects from normality, as in the case of a biallelic, and, partly, five-allelic QTL. Even with nine QTL alleles, when the assumption of the normal distribution of the QTL effect fully holds (with nine codominant alleles there are 45 different genotypes), the bias in the estimates of h_g^2 and h_a^2 is still present. The bias in estimates for variance components

is obviously due to a general frailty of a random model based on the sib-pair approach. Grignola et al. [12] who used a residual maximum likelihood method based on a multigenerational pedigree did not obtain biased estimates of QTL and polygenic variances.

Also, the power to detect a QTL shows little differences among designs with a QTL with two, five or nine alleles and depends only on the heritability of the trait, proportion of QTL variance and sample size.

6. CONCLUSIONS

In this study we showed that the interval mapping procedure based on the random model approach, initially designed for QTL mapping in human populations [22], can be applied to dairy cattle populations with large half-sib families. QTL with relatively large effects can be detected with high power and accurately located, especially if a larger number of families and polymorphic markers are used.

The random model based on a sib-pair approach requires marker data only on progeny and their parents, which can be seen as an advantage when marker data on older ancestors are not available. However, the method can be easily extended to make use of available data from general pedigrees. This would provide better estimates of πs because information from all relatives would be jointly used rather than just using data from a pair of individuals and their parents. The relationships among animals and inbreeding would be taken into account. Furthermore, in the case of missing parental genotypes, it would be possible to infer πs from the information available on other relatives.

Because of its robustness and simplicity, the random model approach is recommended for rapid screening of the whole genome, followed by a refined analysis applied to those chromosomal segments that show some signals of QTL presence, using more sophisticated methods. Also, more sophisticated methods should be used to estimate QTL variance, because the random model approach cannot partition QTL and polygenic variance properly. Furthermore, certain recently developed methods based on residual maximum likelihood [12] may be considered as a possible alternative to sib-pair based methods.

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