DETECTION AND MAPPING QUANTITATIVE TRAIT LOCI IN SEGREGATING POPULATIONS: THEORY AND EXPERIMENTAL RESULTS

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SUMMARY

Genetic markers can be used to map loci affecting quantitative traits (QTL's). For most livestock species, the time and expense involved in producing crosses are prohibitive, and data from existing populations must be used. For species with large half-sib families, linkage between QTL's and genetic markers can be detected within the progeny of a sire heterozygous for a genetic marker if the sire is also heterozygous for a linked QTL. If several families are analyzed, the analysis must account for different linkage phases across families. Genetically linked markers increase the power of QTL localization; however, for samples of moderate size, the number of recombination events also limits precision of QTL mapping. Power per individual genotyped can be increased if sons of a sire heterozygous for the genetic marker are genotyped and the granddaughters are scored for the quantitative traits. If each son has at least 50 recorded daughters, the granddaughter design is more than twice as powerful as the daughter design for moderately heritable traits but still requires genotyping several hundred to several thousand individuals to achieve power of .5 to detect a QTL responsible for 1% of the phenotypic variance. Algorithms based on maximum likelihood (ML) are able to make optimum use of all data. Estimates for the QTL effect corrected for recombination between the QTL and the genetic marker and for the frequencies of the QTL alleles have been obtained from field and simulated data. The granddaughter design was applied to the Israeli Holstein population. A segregating QTL affecting milk and protein production was found linked to 1 of 10 DNA microsatellites analyzed. This result was confirmed by the daughter design with an independent sample of daughters of one grandsire.

INTRODUCTION

Sax (1923) first demonstrated with garden beans that genetic markers can be used to map individual QTL's. Until 1980, application of these techniques was limited by the scarcity of segregating markers in populations of interest. Recently new classes of highly polymorphic DNA-level genetic markers, including DNA microsatellites, have been developed and applied to QTL detection (Georges, 1993; Kashi et al., 1990; Ron et al., 1993; Soller, 1990).

This paper summarizes the experimental techniques that have been proposed or applied to detect QTL's in segregating populations, the sample sizes required for a given statistical power, the methods to optimize experimental design relative to cost, and the statistical methods for estimation of QTL parameters in various experimental designs. Experimental results from the Israeli dairy cattle population using DNA microsatellites as genetic markers are presented.

METHODS

Experimental designs for detection of QTL's in outcrossing populations

A segregating QTL is assumed to be linked genetically to a marker locus, and a particular individual is assumed to be heterozygous for both loci. The genotype of this individual can be denoted as M_1M_2 for the marker locus and A_1A_2 for the QTL. Half of this individual's progeny receives the allele M_1, and the other half receive M_2. If the allele A_1 is located on the same chromosome as M_1, then those progeny that receive M_1 receive A_1, whereas those individuals that receive M_2 receive A_2 (except for recombinants). The effect of the QTL can be detected by comparing the means of the two progeny groups receiving the alternative marker alleles from the

heterozygous parent. All other environmental and genetic effects should be randomly distributed among the two progeny groups. Various designs differ in the methods used to create the heterozygous parent and the crosses performed.

Most studies have used crosses between inbred lines to generate linkage disequilibrium between genetic markers and QTL's. For large farm animals, this method generally is not practical because of long generation intervals and cost of raising each individual. Thus, similar to human population genetics, existing populations must be analyzed. Experimental designs have generally been based on the analysis of many progeny of a single or a few heterozygous individuals (Neimann-Sorensen and Robertson, 1961; Soller and Genizi, 1978). This type of analysis is termed the daughter design (Weller et al., 1990) and has been used chiefly for dairy cattle because a single sire can have hundreds or thousands of progeny with records for a number of quantitative traits whereas each dam usually has only a few progeny.

Two main problems occur with this type of analysis. First, if either of the marker alleles of the heterozygous parent are common in the population, a large fraction of the progeny have the same heterozygous genotype as the parent. Because determining which allele was passed by the common parent is not possible, records of these progeny have generally been deleted even though methods have been described to include information from these heterozygotes in the analysis (Dentine and Cowan, 1990; Mackinnon and Weller, 1994). This problem has become much less serious because of the development of new classes of multiallelic genetic markers. For all species studied, DNA microsatellites have been both highly polymorphic and multiallelic. The mean frequency of heterozygous sires in a commercial dairy cattle population was 77%. The mean number of alleles per locus was 8.2, and the frequency of informative sons per locus ranged from 60 to 80% with a mean of 72% (Ron et al., 1993).

The second problem is that the specific parent analyzed may be homozygous for the QTL even if a QTL is segregating in the population. To overcome this problem, most studies have been based on analysis of several families. In that case, the linkage relationships may be different for different sires, and the following linear model should be used for analysis (Soller and Genizi, 1978):

$$y_{ijk} = s_i + g_{ij} + e_{ijk} \quad [1]$$

where y_{ijk} is the trait record for progeny k of sire i that inherited paternal allele j, s_i is the effect of sire i, g_{ij} is the effect of paternal marker allele j nested within sire i, and e_{ijk} is the random residual associated with each record. Although this analysis solves the problem of differing linkage relationships, a different effect is estimated for each marker allele within each sire family. If, in fact, only two QTL alleles are segregating, then g_{ij} should assume only one of two values. However, because of sampling error, the estimates for g_{ij} cover a broad range and may have an approximately normal distribution.

Significance can also be tested by computing the mean within-parent deviation between the two progeny groups with opposing marker alleles and dividing these differences by their standard errors. The sum of squares of these deviations have a χ^2 distribution with degrees of freedom equal to the number of parents (Neimann-Sorensen and Robertson, 1961). Power was estimated for both analysis of variance (ANOVA) (Soller and Genizi, 1978) and χ^2 (Weller et al., 1990).

Methods also have been developed to detect segregating QTL's using a large number of full-sib families even though the number of individuals per family may be small to moderate (Haseman and Elston, 1972; Goldgar, 1990). An analysis of this type is appropriate for humans, for which data often are available for a large number of small families, and for certain farm animals, such as sheep, goats, and pigs, for which many moderately sized full-sib families can be analyzed.

Fernando and Grossman (1989) developed a method based on the mixed model equations to estimate marker-linked QTL effects in any population structure. Each individual with unknown ancestors is assumed to have two random QTL alleles sampled from a normal distribution.

Accounting of QTL effects is through the animal model relationship matrix. However, this method assumes that the variance due to the QTL and the recombination frequency between the QTL and the genetic marker are known, and requires solving a system of equations of rank greater than three times the number of individuals scored in the analysis. Van Arendonk et al. (1993) used restricted maximum likelihood to estimate the recombination rate, the variance due to the QTL, and the remaining polygenic variance but found that the parameters were confounded. The method of Fernando and Grossman (1989) was extended by Goddard (1992) to handle multiple markers and QTL's and crosses between inbred lines.

Estimation of statistical power to detect QTL

Statistical power to detect segregating QTL's depends on the sample size, the magnitude of the type I error allowed, the effect of the segregating QTL in comparison to the genetic and environmental variances, the recombination distance between the QTL and the genetic marker, the specific experimental design employed, and the method of statistical analysis.

The magnitude of the QTL effect that can be detected is a function of the residual variance of the model. However, because residual variance is only known inductively, QTL effects are given in units of phenotypic standard deviation (SDU's). A statistical power of .9 to detect a tightly marker-linked QTL that accounts for 1% of phenotypic variance in the F_2 design with a type I error of .05 is obtained with a sample size of about 1000 individuals (Soller et al., 1976). The substitution effect for a QTL of this magnitude is .141 SDU. Thus, the mean difference between alternative homozygotes is .282 SDU (or about 400 kg of milk production for Israeli -Holstein dairy cattle). For the daughter design, power of .7 with a type I error of .01 is obtained for a QTL with a substitution effect of .2 SDU if 400 daughters of each of 10 sires are analyzed for a trait with a heritability of .2, which entails genotyping 4000 individuals.

Statistical methods that use more information and make more assumptions (provided these assumptions are correct) should be more powerful than methods that use less information and make fewer assumptions. Thus, ML, which uses all information available should be more powerful than ANOVA, which uses only means and variances. Simulation results to this effect were obtained (Simpson, 1989) but later retracted (Simpson, 1992).

The effects of the magnitude of the QTL and the proportion of recombination between the marker and the QTL on sample size to achieve a given power are quadratic; i.e., for an effect of half the magnitude, the number of individuals scored must be increased fourfold to achieve the same power. In either the F_2 or backcross (BC) designs, the magnitude of the effect measured decreases proportionally to $1-2r$ compared with complete linkage, where r is the recombination proportion between the QTL and the genetic marker. Thus, to achieve power equal to the case of complete linkage, the experiment size must be increased by a factor of $1/(1-2r)^2$ (Soller et al., 1976).

For a QTL bracketed by two markers, the effect measured is not reduced by recombination (except for double crossovers). However, in a simple linear model analysis, recombinant individuals are deleted. The proportion of recombinants is $(1-r_1)^2$ for the F_2 design and $1-r_1$ for the BC design, where r_1 is the recombination frequency between the markers. Power with a marker bracket, therefore, is reduced by this factor relative to complete linkage. The advantage of a marker bracket over a single marker is greatest when $r_1 = 2r$, where r is the recombination proportion between the QTL and the closer marker. In this case, power with a marker bracket is increased by $1-r_1$ for the BC design and is equal to a single-marker analysis for the F_2 design (Weller, 1992). For QTL's of moderate effect, an ML analysis with genetically linked markers increases the accuracy of QTL mapping over the range of .5 to .1 M. If less than 1000 individuals are genotyped, further saturation of the genetic map does not increase mapping precision for QTL's with substitution effect of less than .5 SDU (Darvasi et al., 1993).

Optimization of experimental designs

Three main techniques have been proposed to maximize statistical power to detect segregating QTL's as a function of the number of individuals genotyped: replicate progeny, selective genotyping, and sample pooling. Power per sample genotyped can be increased by application of techniques based on increasing the number of generations and the number of individuals scored for the quantitative traits (Soller, 1990, 1991; Weller, 1992). For crosses between inbred lines, multiple progeny can be produced from each F_2 or BC individual genotyped, and these progeny can be scored for the quantitative traits. This method reduces the residual variance by a factor equal to the number of progeny scored for each individual genotyped. If the other sources of variance are small, statistical power is increased by a factor of $\sqrt{n}$. Because only the residual variance is decreased, the advantage decreases as a function of heritability. Furthermore, many more individuals must be produced and measured.

In outbreeding populations, marker genotype can be determined for a sample of progeny of a heterozygous parent, and the quantitative traits can be scored on the grandprogeny (i.e., the progeny of the marker-genotyped offspring of the heterozygous parent). This design is termed a granddaughter design (as opposed to the daughter design) (Weller et al., 1990). A segregating marker-linked QTL can be detected by analysis with the following linear model:

$$y_{ijkl} = gs_i + g_{ij} + so_{ijk} + e_{ijkl} \qquad [2]$$

where y_{ijkl} is the trait record for granddaughter l of son k that inherited marker allele j from grandsire i, gs_i is the effect of grandsire i, g_{ij} is the effect of marker allele j inherited from grandsire i, so_{ijk} is the effect of son k that inherited marker allele j from grandsire i, and e_{ijkl} is the random residual. As with model [1], a significant g_{ij} effect is indicative of a linked QTL. Alternatively, genetic evaluations of the sons or daughter yield deviations (DYD's), which are readily available, have been analyzed (Andersson-Eklund and Rendel, 1993; Hoeschele and VanRaden, 1993) with a single observation for each son. However, the variance among the sons' genetic evaluations or DYD's is a function of the number of granddaughters, which is different for each son.

Increasing the number of granddaughters reduces the residual variation but not the between-son genetic variation. With a heritability of .2 and a type I error of .01, power is .74 to detect a QTL with a substitution effect of .2 SDU if genetic markers are analyzed for 100 sons of each of 10 grandsires with 50 quantitative trait-recorded granddaughters per son (Weller et al., 1990). Thus, greater power is obtained with the granddaughter design compared with the daughter design even though only one-fourth as many individuals are genotyped (4000 daughters vs. 1000 sons). With a heritability of .5, the advantage of the granddaughter design decreases, but power equal to the daughter design still is obtained with only half as many genotypings. The granddaughter design can be applied only if the population structure is suitable (several grandsires each with many progeny-tested sons) and only if DNA can be obtained from both the grandsires and sons. If DNA is not available for the grandsires, their genotypes can be deduced by genotyping a sample of their progeny. Georges (1993) analyzed the U.S. Holstein population using DNA microsatellites and found evidence of five segregating QTL's for milk production traits.

Lebowitz et al. (1987) noted that most QTL information can be derived from individuals with extreme phenotypic values for the quantitative trait. Thus, if the sample of individuals recorded for the quantitative trait is large, power per individual genotyped can be increased by selectively genotyping those individuals with the highest and lowest phenotypes. With selective genotyping, obtaining the same statistical power as for a random sample is possible by genotyping only one third as many individuals. The disadvantages of this method are 1) a much larger sample of individuals must be scored for the quantitative trait and 2) a different sample must be genotyped for each trait if several quantitative traits are of interest. Thus, this technique is useful only if the number of traits of interest is low. Finally, estimates of the QTL effect are biased.

The number of genotypings can be reduced further by sample pooling (Plotsky et al., 1993). Instead of genotyping each individual separately, genetic material from several individuals with similar phenotypes for the quantitative trait can be combined prior to assay. In this case, a linked QTL is detected by band intensity when pools of individuals with high and low phenotypes are compared. For this method to be effective, determining the number of individuals of each genotype in a pool accurately from the band intensity must be possible, which may be a problem with dinucleotide microsatellites (Pacek et al., 1993). Sample pooling must be applied together with selective genotyping. Thus, similar to selective genotyping, this method is useful only if the number of quantitative traits of interest is relatively low. Because some degradation of information occurs when individuals are pooled, more individuals must be scored for the quantitative trait compared with selective genotyping without sample pooling.

ML estimation of QTL parameters

Algorithms based on ML are able to make optimum use of all data but require more computing resources than least squares analysis. For QTL's linked to a single marker, estimates of recombination frequency can only be derived by ML, and least squares estimates of QTL effects are biased. The BC design (under the assumptions of an underlying normal distribution and equal variances for the QTL genotypes) can be used to illustrate ML parameter estimation. The probability density function for a single individual with a quantitative trait value of X and genotype M_1M_1 is

$$f(X) = \frac{(1-r)e^{-(X-\mu_1)^2/2\sigma^2}}{\sqrt{2\pi\sigma^2}} + \frac{(r)e^{-(X-\mu_2)^2/2\sigma^2}}{\sqrt{2\pi\sigma^2}}$$

where σ is the standard deviation, μ_1 is the mean of individuals with QTL genotype A_1A_1, and μ_2 is the mean of individuals with QTL genotype A_1A_2. Individuals with marker genotype M_1M_2 have the same likelihood as for the QTL genotype except that the means are reversed. The complete likelihood (L) for a sample of individuals can be written as

$$L = \prod_{i}^{n_1} [f(X_i,M_1)] \prod_{j}^{n_2} [f(X_j,M_2)]$$

where Π represents the product of a series; $f(X_i,M_1)$ and $f(X_j,M_2)$ are the probability densities for observations i and j with genotypes M_1M_1 and M_1M_2, respectively; and n_1 and n_2 are the number of individuals with the two genotypes, respectively.

This L is a function of four parameters: μ_1, μ_2, σ, and r. The ML parameter estimates are those values that maximize L. A maximum for a function can be derived by differentiating with respect to these four parameters and simultaneously solving this system of four equations with the partial derivatives equal to 0. Generally, for ML, differentiating the log of the likelihood function is easier, but the resultant system of equations cannot be solved analytically even in this case.

Numerous methods have been applied to maximize likelihood functions (Bovenhuis and Weller, 1994; Darvasi et al., 1993; Jensen, 1989; Simpson, 1989; Weller, 1986). The expectation-maximization (EM) algorithm often is preferred because it is guaranteed to converge provided that a maximum exists within the parameter space (Dempster et al., 1977). Several studies (Lander and Botstein, 1989) have used partial EM for QTL detection by applying the EM algorithm to estimate QTL means and variances but not recombination frequency. Jansen (1992) developed a general technique to estimate all QTL parameters using the EM algorithm. The log likelihood function is decomposed into two terms so that parameters related to recombination frequency and parameters related to QTL means and variances can be estimated separately. This technique is amenable to analysis with standard statistical packages and can also be used to estimate fixed effects.

The confidence limits of the estimates or tests of significance for r against the null hypothesis were examined for complete linkage (r=0) (Weller, 1986, 1987) or random association (r=.5) (Simpson, 1989). Lander and Botstein (1989) scanned the likelihood function relative to r to determine a quasi-confidence interval for r. Simpson (1989) tested the ML estimate for r against the hypothesis of random association by a likelihood ratio test. Darvasi et al. (1993) and Jenson (1989) used the inverse of the matrix of second differentials to estimate prediction error variances and standard errors. Mackinnon and Weller (1994) used the expectation of the likelihood to construct single and multiple parameter confidence intervals.

Use of ML is more complicated in segregating populations for several reasons. First, linkage relationships are different in different families. Second, at least one additional parameter, the frequency of the QTL alleles, must be estimated. Finally, for analyses across families, accounting for common polygenic variation within families is necessary. Knott and Haley (1992) applied ML estimation to data simulated according to a full-sib family design, and assuming two linked flanking markers.

Bovenhuis and Weller (1994) developed an ML algorithm to estimate both pleiotropic effects of the genetic marker and linked QTL effects and applied this algorithm to milk protein polymorphisms in the Dutch dairy cattle population. Both types of effects were found. Weller (1990) and Mackinnon and Weller (1994) used ML to estimate QTL parameters for the daughter design with the assumption that only two QTL alleles were present in the population. The likelihood for each family was computed based on each possible QTL genotype for the sire. Thus, a sire's genotype could be estimated by comparing the likelihoods obtained for his progeny based on the sire's possible genotypes and selecting the genotype with the highest likelihood. Using a recursive method, these researchers also were able to account for genetic differences among sires unrelated to the linked QTL but not for fixed environmental effects. Accurate estimates were derived for all five parameters and sire QTL genotypes with simulated data.

Hoeschele and VanRaden (1993, 1993a) derived Bayesian and ML parameter estimates for the granddaughter design (including grandsire effects) but analyzed the DYD for each son. They assumed that the residual variance was known and that data were preadjusted for all fixed effects. The method of Jansen (1992) was extended to estimate QTL parameters in daughter and granddaughter designs. This method also is able to estimate fixed effects such as herd-year-seasons and genetic effects not included in the segregating QTL. Accurate estimates of QTL effect, recombination proportion, allele frequencies, polygenic variance not explained by the linked QTL, and grandsire genotypes were obtained for a locus with a substitution effect of 1.0 SDU if 50 sons, each with 50 daughters, of 20 grandsires were genotyped. The method was not effective for QTL's with smaller substitution effects.

Multiple comparison problem

Most studies have analyzed several quantitative traits using several markers but performed a separate statistical analysis for each marker-trait combination. This method will result in a large number of invalid significant effects (Lander and Botstein, 1989). For example, if 5 markers are used to analyze 10 traits, there are 50 marker-trait combinations, and 2 to 3 combinations should be significant at the 5% level purely by chance.

A single multitrait analysis including information from all markers would be optimum but generally is not a viable option. Lander and Botstein (1989) suggested increasing the nominal significance level to the level required to obtain a significant result by chance among any of the individual marker-trait comparisons. This method will result in an increase in the type II error, and fewer true effects will be detected. Hoeschele and VanRaden (1993a) suggested a Bayesian analysis that takes account of prior information. The combined variance of the effects detected must then be less than the total genetic variance of the trait. However, a significant advantage for

a Bayesian analysis has not been demonstrated. Alternatively, significant results can be repeated with an independent sample. For the granddaughter design, Ron et al. (1994) suggested verification of significant within-family contrasts by analysis of an independent sample of the grandsire's daughters.

EXPERIMENTAL RESULTS

Ten DNA-microsatellites were used to detect QTL's affecting milk production traits in seven Israeli Holstein grandsire families. Semen was collected from the 7 grandsires and 91 of their progeny-tested sons. Mean reliability was 91%, and 45,072 granddaughter records were included in the analysis. The son evaluations were based on at least 64 granddaughter production records. For each microsatellite, the sons of the heterozygous sires were genotyped. Only those sons with a paternal allele origin that could be determined unequivocally were considered informative. At least 60% more grandsires were heterozygous and 40% fewer individuals were discarded because of unknown paternal allele origin as compared with diallelic markers. Using model [2], the effects of paternal allele for locus D21S4 on milk and protein yields were significant ($P<.025$). The substitution effects associated with the marker alleles for sire 783 were 283 kg for milk and 5.7 kg for protein. For both traits, progeny of sire 783 that inherited allele 18 had higher evaluations than progeny that inherited allele 21.

These results were verified by genotyping an independent sample of 151 daughters of sire 783. Mean reliability of the daughter evaluations was 52%. Differences in breeding values between the daughter groups were 117 kg for milk, 1.8 kg for fat, and 2.9 kg for protein. The one-tailed *t*-tests were significant ($P<.05$) for milk and protein yields but not for fat yield.

CONCLUSIONS

Seventy years after Sax's first experiment (1923), the only limiting factor to QTL detection in populations of interest is cost. Although many experiments have been reported in the literature, followup studies have been few. Thus, a large number of invalid results may have been reported. In many cases, the number of markers and traits has become so large that a separate analysis of each marker-trait combination is virtually meaningless unless significant results are repeated with independent samples. Methods must be developed for joint analysis of all data derived from a single experiment. Analysis of segregating populations presents challenges that have been met only partially by the methods described.

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