Am. J. Hum. Genet. 66:1616–1630, 2000

Power of Linkage versus Association Analysis of Quantitative Traits, by Use of Variance-Components Models, for Sibship Data

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Optimal design of quantitative-trait loci (QTL) mapping studies requires a precise understanding of the power of QTL linkage versus QTL association analysis, under a range of different conditions. In this article, we investigate the power of QTL linkage and association analyses for simple random sibship samples, under the variance-components model proposed by Fulker et al. After a brief description of an extension of this variance-components model, we show that the powers of both linkage and association analyses are crucially dependent on the proportion of phenotypic variance attributable to the QTL. The main difference between the two tests is that, whereas the power of association is directly related to the QTL heritability, the power of linkage is related more closely to the square of the QTL heritability. We also describe both how the power of linkage is attenuated by incomplete linkage and incomplete marker information and how the power of association is attenuated by incomplete linkage disequilibrium.

Introduction

The incorporation of genetic-marker information into variance-components models represents an integration between molecular and biometric genetics that promises to isolate quantitative-trait loci (QTL) and to elucidate their phenotypic actions (Schork 1993; Amos 1994; Kruglyak and Lander 1995; Eaves et al. 1996; Fulker and Cherny 1996; Almasy and Blangero 1998). We have recently proposed a method of combined QTL linkage and association analysis through the simultaneous modeling of the means and covariances of sibling pairs (Fulker et al. 1999). The linkage test is based on differences in covariances according to the identity-by-descent (IBD) status, at the candidate locus, of sibling pairs. The association test is based on differences in means, given the genotypes at the candidate locus. The model for the means is partitioned into between- and within-pairs (i.e., inter- and intrasibship) components; an association test based on the within-pairs component has the same desirable property as the transmission/disequilibrium test (Spielman et al. 1993)—of being robust to population stratification.

Although the proposed method can separately or simultaneously model both linkage and association, the properties of these two phenomena are very different. Linkage extends over substantial genetic distances and is therefore suited for long-range mapping. Association, on the other hand, relies on either the presence of linkage disequilibrium between the marker and trait loci or on the marker locus being the trait locus itself and is therefore likely to be useful only for short-range mapping. The shorter range of association is, however, compensated by its potentially far greater power, for the detection of alleles with minor or modest phenotypic effects (Risch and Merikangas 1996). These complementary properties of linkage and association are important in gene-mapping studies of complex disorders and quantitative traits, in which the effect sizes of individual contributory loci are unknown but likely to be modest.

Fulker et al. (1999) performed some simulation studies of the power of the linkage and association tests, under a range of conditions. The pattern of results suggested the existence of simple relationships between the average values of the test statistics and genetic parameters such as the proportion of variance accounted for by the QTL and the degree of linkage disequilibrium between the QTL and the candidate locus. In the present article, we proceed to derive analytical formulas for the noncentrality parameters for the linkage and association tests. In addition to allowing power calculations to be performed without the need for simulations, these formulas also provide useful insight into the various factors that determine the power of linkage and association analysis.

Received February 12, 1999; accepted for publication January 2, 2000; electronically published April 12, 2000.

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0002-9297/2000/6605-0017$02.00

QTL Linkage and Association Analysis under a Variance-Components Model

Fulker et al. (1999) presented a variance-components model for sib pairs, incorporating additive effects at the QTL. Here, we extend this model to larger sibships and to incorporate dominance. The candidate locus is assumed to be diallelic with genotypes A_1A_1, A_1A_2, and A_2A_2. For an individual, the variable A encodes the additive effect of the candidate locus genotype and is assigned the values 1, 0, and -1 for the genotypes A_1A_1, A_1A_2, and A_2A_2, respectively. Likewise, the variable D represents the dominance deviation of the candidate locus genotype and is assigned the values 0, 1 and 0 for the genotypes A_1A_1, A_1A_2, and A_2A_2, respectively. For every sibling pair, the proportion of alleles IBD (π) and the probability of complete IBD sharing (z) at the candidate locus are estimated from marker-genotype data, by means of one of several available methods (Curtis and Sham 1994; Fulker et al. 1995; Kruglyak and Lander 1995; Almasy and Blangero 1998).

The variance-components model for a sibship of size s specifies that, conditional on the vectors of additive effects and dominance deviations of the candidate-locus genotypes $\mathbf{A} = (A_1,A_2,...,A_s)'$ and $\mathbf{D} = (D_1,D_2,...,D_s)'$, and the IBD sharing matrices $[\Pi]_{ij} = \hat{\pi}_{ij}$ and $[\mathbf{Z}]_{ij} = \hat{z}_{ij}$, the vector $\mathbf{y} = (y_1,y_2,...,y_s)'$ of quantitative-trait values of the siblings has a multivariate normal distribution, with mean vector and covariance matrix

$$[\boldsymbol{\mu}]_i = m + aA_i + dD_i$$

and

$$[\boldsymbol{\Sigma}]_{ij} = \begin{cases} \sigma_N^2 + \sigma_S^2 + \sigma_A^2 + \sigma_D^2 & \text{if } i = j \\ \sigma_S^2 + \hat{\pi}_{ij}\sigma_A^2 + \hat{z}_{ij}\sigma_D^2 & \text{if } i \neq j \end{cases},$$

where m is a constant, a and d represent, respectively, the magnitudes of the additive effects and dominance deviations at the candidate locus, σ_A^2 and σ_D^2 represent, respectively, the additive and dominance components of QTL variance that are not already accounted for by the effects of the genotypes at the candidate locus (i.e., $\mathbf{A}$ and $\mathbf{D}$), and σ_S^2 and σ_N^2 represent, respectively, the residual shared and nonshared variances.

This model makes no allowance for any correlation or interaction between the candidate gene and the polygenic background or the environment. Components of variance not involving the candidate locus are partitioned into σ_S^2 and σ_N^2. Under random mating, half the additive genetic variance will load on σ_S^2, the remaining half on σ_N^2; one-quarter of dominance and additive-additive epistatic variance will load on σ_S^2, the remaining three-quarters on σ_N^2; and other components of higher-order epistatic variance will likewise load differentially on σ_S^2 and σ_N^2 in accordance with biometrical genetic theory (Kempthorne 1957; Sham 1998). Common sibling environment loads entirely on σ_S^2, whereas nonshared environment loads entirely on σ_N^2.

As mentioned, Fulker et al. (1999) suggested partitioning the candidate-locus effects $\mathbf{A}$ and $\mathbf{D}$ into between-sibship and within-sibship components:

$$(\mathbf{A})_i = \left(\frac{\sum_{j=1}^{s} A_j}{s}\right) + \left(A_i - \frac{\sum_{j=1}^{s} A_j}{s}\right) = (\mathbf{A}_b)_i + (\mathbf{A}_w)_i$$

and

$$(\mathbf{D})_i = \left(\frac{\sum_{j=1}^{s} D_j}{s}\right) + \left(D_i - \frac{\sum_{j=1}^{s} D_j}{s}\right) = (\mathbf{D}_b)_i + (\mathbf{D}_w)_i \ .$$

For each sibling, the between-sibships component is the mean effect of the sibship, whereas the within-sibship component is the deviation of the sibling's effect from the sibship mean, for both additive effects and dominance. This partition modifies the mean vector to

$$\boldsymbol{\mu} = \mathbf{m} + a_b\mathbf{A}_b + a_w\mathbf{A}_w + d_b\mathbf{D}_b + d_w\mathbf{D}_w \ ,$$

where a_b and d_b are the magnitudes of the between-sibships components, and a_w and d_w are the magnitudes of the within-sibship components, of the additive effects and dominance deviations at the candidate locus, respectively. This modified model is identical to the original model when $a_b = a_w = a$ and $d_b = d_w = d$, which is the case when there is no population stratification or other causes of "spurious associations."

The log-likelihood function for a sample of N sibships, $\mathbf{y}_1, \mathbf{y}_2,\ldots,\mathbf{y}_N$, is then

$$\ln L = -\frac{1}{2}\sum_{i=1}^{N}[\ln|\boldsymbol{\Sigma}_i| + (\mathbf{y}_i - \boldsymbol{\mu}_i)'\boldsymbol{\Sigma}_i^{-1}(\mathbf{y}_i - \boldsymbol{\mu}_i)] \ .$$

Various likelihood-ratio statistics of the form $2(\ln L_1 - \ln L_0)$ can be constructed, where $\ln L_0$ is the maximum log-likelihood under a null hypothesis, obtained by imposing restrictions on certain parameters of interest, and $\ln L_1$ is the maximum log-likelihood under an alternative hypothesis, where these restrictions are removed. Here, we consider four tests, which share the same null hypothesis, which is obtained by restricting all the parameters σ_A^2, σ_D^2, a_w, d_w, a_b, and d_b to 0. A test of linkage is obtained by setting free σ_A^2 and σ_D^2; a test of overall association is obtained by setting free a_w, d_w, a_b, and d_b; a test of between-sibships association is obtained by freeing only a_b and d_b; and a test of

within-sibship association is obtained by freeing only a_w and d_w.

It is also possible to extend the mean vector to model candidate loci with multiple alleles. Two parameters, one for between-sibships and the other for within-sibship association components, can be specified for each allele, to model additive effects (except for the last allele, where the parameters are fixed at 0 to avoid linear dependencies). Similarly, two parameters can be specified for each heterozygous genotype—one for the between-sibships and the other for the within-sibship components of dominance deviations.

Power and Noncentrality Parameter of the Likelihood-Ratio Test

The four tests defined above are generalized likelihood-ratio tests that, in large samples and under standard conditions, have a central χ^2 distribution when the null hypothesis is true and that have a noncentral χ^2 when an alternative hypothesis is true (Kendall and Stuart 1979). Although we wish to investigate the power of these tests, power itself is not a convenient quantity, since it is dependent on the arbitrary choice of critical p value and is not linearly related to sample size. However, given a chosen critical p value, the power of a χ^2 test can be determined approximately from the noncentrality parameter (λ) and the df of the non-central χ^2 distribution. The noncentrality parameter is determined by the "true model" (incorporating the magnitudes of the hypothesized effects) and is directly proportional to sample size. Given the noncentrality parameter (and the df) of a test, one can refer to the appropriate noncentral χ^2-distribution function to obtain power estimates for any sample size at any chosen critical p value. Although these estimates of power are not exact (e.g., when the sample is small or if conditions are nonstandard), they will usually be sufficiently accurate for practical purposes. For these reasons, it is more convenient to derive analytic formulas for the noncentrality parameters than for the powers of the tests.

We adopt a two-step procedure for deriving the noncentrality parameter of a likelihood-ratio test under an assumed "true model." The first step is to obtain the asymptotic values of the maximum-likelihood estimates of the parameters under both the null and the alternative hypotheses. The second step is to take the expectations of the log-likelihoods under the null and alternative hypotheses, evaluated at their respective asymptotic parameter estimates. The noncentrality parameter is then given by twice the difference between these expected log-likelihoods.

In our derivations, we denote the true values of the variance components due to the QTL additive effects, QTL dominance deviations, residual shared effects, and residual nonshared effects as V_A, V_D, V_S, and V_N, respectively. These are to be distinguished from parameter estimates, which may be biased when the model is misspecified. For notational convenience, we assume that the quantitative trait has unit variance, so that V_A, V_D, V_S, and V_N represent both the variances and the proportions of variance.

The Noncentrality Parameter of the QTL Linkage Test

The linkage test proposed by Fulker et al. (1999) is twice the difference in log-likelihood between a model in which σ_A^2 is free and a model in which σ_A^2 is fixed at 0. If these two log-likelihoods are denoted as "ln L_1" and "ln L_0," respectively, then the test statistic $2(\ln L_1 - \ln L_0)$ is asymptotically a 50:50 mixture of 0 and χ_1^2, under the null hypothesis of no linkage. If we include σ_D^2, then the distribution of the test statistic under the null hypothesis will be a mixture of 0, χ_1^2, and χ_2^2.

Under the null hypothesis, the asymptotic parameter estimates are

$$[\boldsymbol{\mu}]_i = m$$

and

$$[\boldsymbol{\Sigma}_N]_{ij} = \begin{cases} V_N + V_S + V_A + V_D & \text{if } i = j \\ V_S + \frac{1}{2}V_A + \frac{1}{4}V_D & \text{if } i \neq j \end{cases},$$

whereas, under the alternative hypothesis of linkage, the asymptotic parameter estimates are

$$[\boldsymbol{\mu}]_i = m$$

$$[\boldsymbol{\Sigma}_L]_{ij} = \begin{cases} V_N + V_S + V_A + V_D & \text{if } i = j \\ V_S + \hat{\pi}_{ij}V_A + \hat{z}_{ij}V_D & \text{if } i \neq j \end{cases}.$$

The expectations of twice the log-likelihood under the null and alternative hypotheses, for a sibship of size s, are therefore

$$\begin{aligned} E(2\ln L_N) &= -E(\ln|\Sigma_N|) - E(\mathbf{y}-\mu)'\Sigma_N^{-1}(\mathbf{y}-\mu) \\ &= -\ln|\Sigma_N| - s \end{aligned}$$

and

$$\begin{aligned} E(2\ln L_L) &= -E(\ln|\Sigma_L|) - E(\mathbf{y}-\mu)'\Sigma_N^{-1}(\mathbf{y}-\mu) \\ &= -\sum_{i=1}^{M} p_i \ln|\Sigma_i| - s \ , \end{aligned}$$

where the summation is over all M possible marker-genotype configurations, with p_i and Σ_i being, respectively, the probability and the covariance matrix of the ith marker-genotype configuration.

In the simple case of sib pairs with complete linkage information, each pair can be unambiguously assigned a covariance matrix, depending on whether the proportion of alleles IBD is 0, $\frac{1}{2}$, or 1. These covariance matrices have diagonal elements 1 because the trait has been standardized to have unit variance, and they differ only in their off-diagonal elements (i.e., sib-pair correlations), which are $[\Sigma_{\pi=0}]_{12} = r_0 = V_S$, $[\Sigma_{\pi=0.5}]_{12} = r_1 = V_S + \frac{1}{2}V_A$, and $[\Sigma_{\pi=1}]_{12} = r_2 = V_S + V_A + V_D$. In a random sample of sib pairs, these covariance matrices are expected to occur in the proportions $\frac{1}{4}:\frac{1}{2}:\frac{1}{4}$, so that the expected twice log-likelihood evaluated under the alternative hypothesis is

$$\begin{aligned} E(2\ln L_L) &= -\frac{1}{4}\ln|\Sigma_{\pi=0}| \\ &\quad -\frac{1}{2}\ln|\Sigma_{\pi=0.5}| - \frac{1}{4}\ln|\Sigma_{\pi=1}| - s \\ &= -\frac{1}{4}\ln(1-r_0^2) - \frac{1}{2}\ln(1-r_1^2) \\ &\quad -\frac{1}{4}\ln(1-r_2^2) - s \ . \end{aligned}$$

Similarly, the expected twice log-likelihood evaluated under the null hypothesis is $E(2\ln L_N) = -\ln|\Sigma_N| - s$, where the off-diagonal elements in the covariance matrix are equal to the average sib-pair correlation—namely, $[\Sigma_N]_{12} = r_s = V_S + \frac{1}{2}V_A + \frac{1}{4}V_D$.

The noncentrality parameter, per sib pair, for linkage is therefore

$$\begin{aligned} \lambda_L &= E(2\ln L_L) - E(2\ln L_N) \\ &= -\frac{1}{4}\ln(1-r_2^2) - \frac{1}{2}\ln(1-r_1^2) \\ &\quad -\frac{1}{4}\ln(1-r_0^2) + \ln(1-r_s^2) \ . \end{aligned}$$

When the approximation $\ln(1-x) \approx -x - x^2/2$ is used, the noncentrality parameter, per sib pair, for the linkage test, is given by

$$\begin{aligned} \lambda_L \approx\ & \frac{1}{8}V_A^2 + \frac{3}{16}V_D^2 + \frac{1}{4}V_AV_D \\ & + \frac{7}{64}V_A^4 + \frac{63}{512}V_D^4 + \frac{45}{64}V_A^2V_D^2 \\ & + \frac{7}{16}V_A^3V_D + \frac{31}{64}V_AV_D^3 \\ & + V_S\left[\frac{3}{8}V_A^3 + \frac{15}{32}V_D^3 + \frac{9}{8}V_A^2V_D + \frac{21}{8}V_AV_D^2\right] \\ & + V_S^2\left[\frac{3}{8}V_A^2 + \frac{9}{16}V_D^2 + \frac{3}{4}V_AV_D\right] . \end{aligned}$$

This expression shows that the noncentrality parameter of the linkage test for sib pairs is to a first-order approximation proportional to the squares and products of the additive and dominance QTL components of variance. It also shows that the power to detect a given QTL effect increases with increasing proportion of residual shared variance, V_S.

In the more general case of a sibship of size s, the noncentrality parameter is still given by $\lambda_L = E(2\ln L_L) - E(2\ln L_N) = -E(\ln|\mathbf{\Sigma}_L|) + \ln|\mathbf{\Sigma}_N|$. Since the trait is standardized to have unit variance, both covariance matrices have diagonal elements equal to 1 and have off-diagonal elements equal to the correlations between pairs of siblings (which, under the alternative hypothesis, are conditional on the number of alleles IBD between the pairs). To derive an approximation for the determinant of such a covariance matrix, we note that the determinant of any matrix, say $\mathbf{A}$, can be written as $|\mathbf{A}| = \Sigma(-1)^N a_{1i_1}a_{2i_2}\ldots a_{si_s}$, where the sum is over all possible permutations $i_1, i_2, \ldots, i_s$ and where N is the total number of inversions, of adjacent pairs of indices, necessary to reduce the given permutation $i_1, i_2, \ldots, i_s$ to the standard order $1, 2, \ldots, s$. (An inversion is required whenever, in the given permutation, a larger index precedes a smaller one). Note that each product contains exactly one element from each row and each column. For the covariance matrix $\mathbf{\Sigma}$, each product contributing to its determinant will be composed of factors that are a mixture of diagonal elements (which are equal to 1) and off-diagonal elements (i.e., correlations). The largest of such products consists only of diagonal elements, and, because $N = 0$, this product is equal to 1. It is impossible to have a product containing only 1 off-diagonal element, and so the second-largest products will tend to be those containing $s - 2$ diagonal elements and 2 off-diagonal elements. Let the two missing diagonal elements in such a product be indexed by j and k; then the product is equal to the square of the correlation between sib j and sib k (i.e., r_{jk}^2). There are $s(s-1)/2$ such products, one for each possible sib pair. Each of

these will make a negative contribution to the determinant, because N is an odd number in all these cases. Thus we have the approximation $\ln|\mathbf{\Sigma}| \approx \ln(1 - \Sigma r_{jk}^2) \approx -\Sigma r_{jk}^2$, where the summation is taken over all possible (j, k) pairs, $j < k$. When this approximation is applied to the covariance matrix under the null hypothesis, we obtain $\ln|\mathbf{\Sigma}_N| \approx -\Sigma[E(r_{jk})]^2$. Under the alternative hypothesis, we obtain $E(\ln|\mathbf{\Sigma}_L|) \approx -\Sigma E(r_{jk}^2)$. Hence the noncentrality parameter is approximately

$$\begin{aligned}\lambda_L &\approx \sum \{E(r_{jk}^2) - [E(r_{jk})]^2\} \\ &= \frac{s(s-1)}{2}\mathrm{Var}(r_{jk}) \\ &= \frac{s(s-1)}{2}\mathrm{Var}(\hat{\pi}_{jk}V_A + \hat{z}_{jk}V_D + V_S) \\ &= \frac{s(s-1)}{2}[\mathrm{Var}(\hat{\pi}_{jk})V_A^2 + \mathrm{Var}(\hat{z}_{jk})V_D^2 \\ &\quad + 2\,\mathrm{Cov}(\hat{\pi}_{jk},\hat{z}_{jk})V_AV_D] \ .\end{aligned}$$

This shows that the noncentrality parameter for linkage is approximately proportional to the number of possible pairs in a sibship. It also suggests the use of $\mathrm{Var}(\hat{\pi})$ as a measure of the marker informativeness for linkage analysis. With complete marker information, $\mathrm{Var}(\hat{\pi})$, $\mathrm{Var}(\hat{z})$, and $\mathrm{Cov}(\hat{\pi},\hat{z})$ approach $\frac{1}{8}$, $\frac{3}{16}$, and $\frac{1}{8}$, respectively, so that the approximate expression of the noncentrality parameter simplifies to

$$\lambda_L \approx \frac{s(s-1)}{2}\left(\frac{1}{8}V_A^2 + \frac{3}{16}V_D^2 + \frac{1}{4}V_AV_D\right) \ .$$

It is possible to derive a more accurate approximation, by involving higher-order terms; however, the approximation is meant only as an aid for appreciating how power is affected by various factors and for obtaining very rough estimates of power. For precise numerical work we recommend exact evaluation of the logarithms of the determinants.

Power Attenuation Due to Incomplete Linkage

We now examine a situation in which linkage analysis is suboptimal and in which the extent of loss of information can be quantified. This situation occurs when analysis is performed at a candidate locus that is not the QTL itself but is linked to the QTL. The IBD distribution for a sib pair at the QTL, conditional on the IBD distribution at a candidate locus, is a function of the recombination fraction between the two loci, which is denoted as "θ." This conditional distribution was given by Haseman and Elston (1972), with $\theta^2 + (1-\theta)^2$ being denoted as "ψ" for convenience (table 1). The conditional sib-pair correlations in trait values, given the IBD status at the candidate locus, can be derived from this conditional distribution, as

$$\begin{aligned}c_0 &= \psi^2V_s + 2\psi(1-\psi)(V_S + V_A/2) \\ &\quad + (1-\psi)^2(V_S + V_A + V_D) \\ &= V_s + 2\theta(1-\theta)V_A + 4\theta^2(1-\theta)^2V_D \ , \\ c_1 &= \psi(1-\psi)V_s + [1 - 2\psi(1-\psi)](V_S + V_A/2) \\ &\quad + \psi(1-\psi)(V_S + V_A + V_D) \\ &= V_S + V_A/2 + 2\theta(1-\theta)[1 - 2\theta(1-\theta)]V_D \ , \\ c_2 &= (1-\psi)^2V_s + 2\psi(1-\psi)(V_S + V_A/2) \\ &\quad + \psi^2(V_S + V_A + V_D) \\ &= V_S + [1 - 2\theta(1-\theta)]V_A + [1 - 2\theta(1-\theta)]^2\,V_D \ .\end{aligned}$$

The noncentrality parameter, per sib pair, of the linkage test at recombination fraction θ from the QTL is then given by

$$\begin{aligned}\lambda_L = &-\frac{1}{4}\ln(1 - c_0^2) - \frac{1}{2}\ln(1 - c_1^2) \\ &-\frac{1}{4}\ln(1 - c_2^2) + \ln(1 - r_s^2) \ .\end{aligned}$$

For small values of V_A, V_D, and V_S, a first-order approximation of the noncentrality parameter is

$$\begin{aligned}\lambda_L \approx &\frac{(1-2\theta)^4\,V_A^2}{8} + \frac{(1-2\theta)^4[2 + (1-2\theta)^4]V_D^2}{16} \\ &+ \frac{(1-2\theta)^4\,V_AV_D}{4} \ .\end{aligned}$$

Table 1

Conditional IBD Distribution at QTL, Given IBD at Candidate Locus

	Conditional IBD Distribution at QTL, for π_Q =		
π_M	0	1/2	1
0	ψ^2	$2\psi(1-\psi)$	$(1-\psi)^2$
1/2	$\psi(1-\psi)$	$1 - 2\psi(1-\psi)$	$\psi(1-\psi)$
1	$(1-\psi)^2$	$2\psi(1-\psi)$	ψ^2

Note.—π_M = proportion of alleles IBD at candidate locus; and π_Q = proportion of alleles IBD at QTL; $\psi = \theta + (1-\theta)^2$.

Note that, if the QTL is additive, then the attenuation in the noncentrality parameter is by a factor of $(1 - 2\theta)^4$, which is the square of the correlation between the proportions of alleles IBD at two loci separated by recombination fraction θ.

Power Attenuation Due to Incomplete Marker Information

Another situation in which attenuation of power can be quantified is that of incomplete marker informativeness, when parental genotype data are available. In this case, Haseman and Elston (1972) have shown that only seven different sets of IBD estimates can arise (table 2). Each configuration implies a covariance matrix (as specified by $\hat{z}$ and $\hat{\pi}$). Under random mating, the probabilities of these configurations are determined by marker-allele frequencies m_1, m_2,…,m_k, through the probability that a parent has a heterozygous genotype (H) and through half the probability that two parents have the same heterozygous genotype (C). $H = 1 - \Sigma_{i=1}^{k} m_i^2$ and $C = \Sigma_{i=1}^{k} \Sigma_{j=i+1}^{k} 2m_i^2 m_j^2$. If the sib-pair correlation and the probability of configuration i, as specified in table 2, are denoted as "r_i"and "P_i," respectively, then the noncentrality parameter of the likelihood-ratio statistic for linkage is $\lambda_L = -\Sigma_{i=1}^{7} P_i \ln(1 - r_i^2) + \ln(1 - r_s^2)$. By use of the first-order approximation $\ln(1 - x) \approx -x$, it can be shown that, for small values of V_A, V_D, and V_S, the noncentrality parameter per sib pair simplifies to

$$\lambda_L \approx \frac{(H - C)V_A^2}{8} + \frac{(H^2 + 2H - 2C)V_D^2}{16} + \frac{(H - C)V_A V_D}{4} .$$

The quantity $H - C$ is the "polymorphism information content" of the marker locus (Botstein et al. 1980). The noncentrality parameter for the linkage test is therefore attenuated by approximately the polymorphism information content of the marker.

The Power of the QTL Association Test

We consider three tests of association: (1) an overall test based on individual differences, (2) a test based on differences between sibships means, and (3) a test based on differences within sibship. The first test involves estimation of all the association parameters a_b, d_b, a_w, and d_w; the second test involves estimation of the between-sibships parameters a_b and d_b; and the third test involves estimation of the within-sibship parameters a_w and d_w. For all three tests, the null hypothesis is obtained by fixing all the parameters—a_b, d_b, a_w, and d_w—to 0. In a pure test for association, the parameters σ_A^2 and σ_D^2 are fixed to 0 under both the null and the alternative hypotheses.

Table 2

Possible Configurations of Sib-Pair IBD Estimates, When Parental Genotypes Are Available

Configuration	Parental Mating Type	$\hat{z}$	$\hat{\pi}$	Probability
1	Hom × Hom	1/4	1/2	$(1 - H)^2$
2	Hom × Het	0	1/4	$H(1 - H)$
3	Hom × Het	1/2	3/4	$H(1 - H)$
4	Het × Het	0	1/2	$H^2/2$
5	Het × Het	0	0	$(H^2 - C)/4$
6	Het × Het	1	1	$(H^2 - C)/4$
7	Het × Het	1/2	1/2	$C/2$

NOTE.— Hom = homozygous; Het = heterozygous; $\hat{z}$ = estimated probability of sharing two alleles IBD; $\hat{\pi}$ = estimated proportion of alleles IBD; H = probability of heterozygosity; and C = half the probability that two parents have the same heterozygous genotype. Probabilities were calculated under the assumption of random mating.

Under the null hypothesis of no association, all QTL effects, both between and within sibships, are omitted from the mean vector and are therefore included in the covariance matrix, so that the asymptotic parameter estimates for a sibship of size s are

$$[\boldsymbol{\mu}_0]_i = m$$

and

$$[\boldsymbol{\Sigma}_{BW}]_{ij} = \begin{cases} V_N + V_S + V_A + V_D & \text{if } i = j \\ V_S + \frac{1}{2}V_A + \frac{1}{4}V_D & \text{if } i \neq j \end{cases} .$$

Under the alternative hypothesis of both between-sibships and within-sibship associations, all QTL effects are modeled in the mean vector, so that the asymptotic parameter estimates for a sibship of size s are

$$[\boldsymbol{\mu}_{BW}]_i = m + a_b A_{bi} + a_w A_{wi} + d_b D_{bi} + d_w D_{wi}$$

and

$$[\boldsymbol{\Sigma}_0]_{ij} = \begin{cases} V_N + V_S & \text{if } i = j \\ V_S & \text{if } i \neq j \end{cases} .$$

Under the alternative hypothesis of between-sibships association, QTL effects on sibship means are modeled in the mean vector, while QTL effects on within-sibship differences are included in the covariance matrix. The asymptotic parameter estimates for a sibship of size s are

$$[\boldsymbol{\mu}_B]_i = m + a_b A_{bi} + d_b D_{bi}$$

and

$$[\boldsymbol{\Sigma}_W]_{ij} = \begin{cases} V_N + V_S + \dfrac{s-1}{2s} V_A + \dfrac{3s-3}{4s} V_D & \text{if } i = j \\ V_S + \dfrac{-1}{2s} V_A + \dfrac{-3}{4s} V_D & \text{if } i \neq j \end{cases} .$$

Finally, under the alternative hypothesis of within-sibship association, QTL effects on within-sibship differences are modeled in the mean vector, whereas QTL effects on sibship means are included in the covariance matrix. The asymptotic parameter estimates for a sibship of size s are

$$[\boldsymbol{\mu}_W]_i = m + a_w A_{wi} + d_w D_{wi}$$

and

$$[\boldsymbol{\Sigma}_B]_{ij} = \begin{cases} V_N + V_S + \dfrac{s+1}{2s} V_A + \dfrac{s+3}{4s} V_D & \text{if } i = j \\ V_S + \dfrac{s+1}{2s} V_A + \dfrac{s+3}{4s} V_D & \text{if } i \neq j \end{cases} .$$

Derivations of the asymptotic estimates of the covariance matrices are given in Appendix A. The expectations of twice the log-likelihood under these four hypotheses, for a sibship of size s, are therefore

$$\begin{aligned} E(2 \ln L_0) &= -\ln |\boldsymbol{\Sigma}_{BW}| - E(\mathbf{y} - \boldsymbol{\mu}_0)' \boldsymbol{\Sigma}_{BW}^{-1} (\mathbf{y} - \boldsymbol{\mu}_0) \\ &= -\ln |\boldsymbol{\Sigma}_{BW}| - s , \end{aligned}$$

$$\begin{aligned} E(2 \ln L_{BW}) &= -\ln |\boldsymbol{\Sigma}_0| - E(\mathbf{y} - \boldsymbol{\mu}_{BW})' \boldsymbol{\Sigma}_0^{-1} (\mathbf{y} - \boldsymbol{\mu}_{BW}) \\ &= -\ln |\boldsymbol{\Sigma}_0| - s , \end{aligned}$$

$$\begin{aligned} E(2 \ln L_B) &= -\ln |\boldsymbol{\Sigma}_W| - E(\mathbf{y} - \boldsymbol{\mu}_B)' \boldsymbol{\Sigma}_W^{-1} (\mathbf{y} - \boldsymbol{\mu}_B) \\ &= -\ln |\boldsymbol{\Sigma}_W| - s , \end{aligned}$$

$$\begin{aligned} E(2 \ln L_W) &= -\ln |\boldsymbol{\Sigma}_B| - E(\mathbf{y} - \boldsymbol{\mu}_W)' \boldsymbol{\Sigma}_B^{-1} (\mathbf{y} - \boldsymbol{\mu}_W) \\ &= -\ln |\boldsymbol{\Sigma}_B| - s . \end{aligned}$$

The noncentrality parameters of the overall, between-sibships, and within-sibship tests of association are therefore

$$\begin{aligned} \lambda_{BW} &= E(2 \ln L_{BW}) - E(2 \ln L_0) \\ &= -\ln |\boldsymbol{\Sigma}_0| + \ln |\boldsymbol{\Sigma}_{BW}| , \end{aligned}$$

$$\begin{aligned} \lambda_B &= E(2 \ln L_B) - E(2 \ln L_0) \\ &= -\ln |\boldsymbol{\Sigma}_W| + \ln |\boldsymbol{\Sigma}_{BW}| , \end{aligned}$$

and

$$\begin{aligned} \lambda_W &= E(2 \ln L_W) - E(2 \ln L_0) \\ &= -\ln |\boldsymbol{\Sigma}_B| + \ln |\boldsymbol{\Sigma}_{BW}| . \end{aligned}$$

All the covariance matrices have equal diagonal elements and equal off-diagonal elements. It can be shown (see Appendix B) that the determinant of a matrix $\mathbf{A}$ having dimension s, diagonal elements a, and off-diagonal elements b is equal to $|\mathbf{A}| = (a - b)^{s-1}[a + (s - 1)b]$. Hence,

$$|\boldsymbol{\Sigma}_{BW}| = \left(V_N + \frac{1}{2} V_A + \frac{3}{4} V_D\right)^{s-1} \times \left(V_N + sV_S + \frac{s+1}{2} V_A + \frac{s+3}{4} V_D\right) ,$$

$$|\boldsymbol{\Sigma}_B| = V_N^{s-1} \left[V_N + sV_S + \frac{s+1}{2} V_A + \frac{s+3}{4} V_D\right] ,$$

$$|\boldsymbol{\Sigma}_W| = \left(V_N + \frac{1}{2} V_A + \frac{3}{4} V_D\right)^{s-1} (V_N + sV_S) ,$$

$$|\boldsymbol{\Sigma}_0| = V_N^{s-1} (V_N + sV_S) .$$

The noncentrality parameters of the overall, between-sibships, and within-sibship tests of association are therefore

$$\begin{aligned} \lambda_{BW} &= -\ln |\boldsymbol{\Sigma}_0| + \ln |\boldsymbol{\Sigma}_{BW}| \\ &= \ln \left(V_N + \frac{1}{2} V_A + \frac{3}{4} V_D\right)^{s-1} \\ &\quad + \ln \left(V_N + sV_S + \frac{s+1}{2} V_A + \frac{s+3}{4} V_D\right) \\ &\quad - \ln (V_N)^{s-1} - \ln (V_N + sV_S) , \end{aligned}$$

$$\begin{aligned} \lambda_B &= -\ln |\boldsymbol{\Sigma}_W| + \ln |\boldsymbol{\Sigma}_{BW}| \\ &= \ln \left(V_N + sV_S + \frac{s+1}{2} V_A + \frac{s+3}{4} V_D\right) \\ &\quad - \ln (V_N + sV_S) , \end{aligned}$$

$$\lambda_W = -\ln|\Sigma_B| + \ln|\Sigma_{BW}|$$
$$= \ln\left(V_N + \frac{1}{2}V_A + \frac{3}{4}V_D\right)^{s-1} - \ln(V_N)^{s-1} .$$

As expected, the noncentrality parameter of the overall test is equal to the sum of the noncentrality parameters of the between-sibships and within-sibship tests. For small values of V_S, V_A, and V_D, the expressions of the latter two noncentrality parameters can be approximated by

$$\lambda_B = \ln\left\{1 + \frac{[(s+1)/2]V_A + [(s+3)/4]V_D}{V_N + sV_S}\right\}$$
$$\approx \frac{[(s+1)/2]V_A + [(s+3)/4]V_D}{V_N + sV_S}$$

and

$$\lambda_W = (s-1)\ln\left[1 + \frac{(1/2)V_A + (3/4)V_D}{V_N}\right]$$
$$\approx (s-1)\left[\frac{(1/2)V_A + (3/4)V_D}{V_N}\right] .$$

In the case of sib pairs, these are simply

$$\lambda_B \approx \frac{(3/2)V_A + (5/4)V_D}{V_N + 2V_S}$$

and

$$\lambda_W \approx \frac{(1/2)V_A + (3/4)V_D}{V_N} .$$

These expressions show that, for sib pairs, the between-sibships test can be up to three times more informative than the within-sibship test. However, whereas the noncentrality parameter of the within-sibship test increases in proportion to $(s-1)$, the increase, with increasing sibship size, in the noncentrality parameter of the between-sibships test is more gradual. It should be noted also that the noncentrality parameters for the association tests are directly proportional to V_A and V_D and that a larger V_S (and hence a smaller V_N) will increase the power of the within-sibship test, for fixed values of V_A and V_D.

Power Attenuation Due to Incomplete Linkage Disequilibrium

The noncentrality parameters for the tests of association are directly related to the variance components due to the QTL. If association analysis is performed on a marker (or candidate) locus that is in partial linkage disequilibrium with the QTL, then the noncentrality parameters will be determined by the "apparent variance components" at the marker.

We adopt the notation of Falconer and Mackay (1996) and label the QTL alleles as "A_1" and "A_2" and label their population frequencies as "p" and "q." The effects of the three genotypes A_1A_1, A_1A_2, and A_2A_2 on the quantitative trait are arbitrarily assigned the values a, d, and $-a$, respectively. The additive and dominance variance components contributed by the QTL to the trait are then $V_A = 2pq[1 - d(p-q)]^2$ and $V_D = 4p^2q^2d^2$.

Suppose that a diallelic marker is tightly linked to the QTL. We denote the marker alleles as "M_1" and "M_2" and denote their frequencies as "m_1"and "m_2." The marker has no direct effect on the trait but is in linkage disequilibrium with the QTL; the magnitude of this linkage disequilibrium is measured by the quantity D, defined as the difference between the frequency of the haplotype A_1M_1 (denoted as "h_{11}") and the product of frequencies of alleles A_1 and M_1. The haplotype frequencies of the two loci are determined by D and the allele frequencies, as shown in table 3.

For convenience, haplotype frequencies are denoted as "h_{11}," "h_{12}," "h_{21}," and "h_{22}." There are 16 possible combinations of haplotypes in an individual, which can be reduced to 9 possible combinations of genotypes when the parental origin of a haplotype is unimportant; under random mating, the frequencies of these 9 possible combinations of genotypes are shown in table 4.

The "apparent effect" of a marker genotype (M_1M_1, M_1M_2, or M_2M_2) is an average of the effects of the three possible QTL genotypes (A_1A_1, A_1A_2, and A_2A_2), weighted by the conditional probabilities of the QTL

Table 3

Haplotype Frequencies at QTL (*A*) and Marker (*M*)

	Genotype Frequency at QTL and Marker, for		
	M_1	M_2	Total
A_1	$pm_1 + D$	$pm_2 - D$	p
A_2	$qm_1 - D$	$qm_1 + D$	d
Total	m_1	m_2	1

Note.—A_1 and A_2 = alleles at QTL; M_1 and M_2 = alleles at marker locus; p and q = allele frequencies at QTL; m_1 and m_2 = allele frequencies at marker locus; and D = linkage-disequilibrium parameter

Table 4

Genotype Frequencies at QTL (*A*) and Marker (*M*), Expressed in Terms of Haplotype Frequencies, under Random Mating h_{ij}: Frequency of Haplotype A_iM_j

	Genotype Frequency at QTL and Marker, for		
	M_1M_1	M_1M_2	M_2M_2
A_1A_1	h_{11}^2	$2h_{11}h_{12}$	h_{12}^2
A_1A_2	$2h_{11}h_{21}$	$2h_{11}h_{22} + 2h_{12}h_{21}$	$2h_{12}h_{22}$
A_2A_2	h_{21}^2	$2h_{21}h_{22}$	h_{22}^2

genotypes, given the marker genotype. Thus, the apparent effects of M_1M_1, M_1M_2, or M_2M_2, denoted, respectively, as "μ_{11}," "μ_{12}," and "μ_{22}," can be expressed, respectively, as

$$\mu_{11} = a\left(\frac{h_{11}^2}{m_1^2}\right) + d\left(\frac{2h_{11}h_{21}}{m_1^2}\right) - a\left(\frac{h_{21}^2}{m_1^2}\right) ,$$

$$\mu_{12} = a\left(\frac{2h_{11}h_{12}}{2m_1m_2}\right) + d\left(\frac{2h_{11}h_{22} + 2h_{12}h_{21}}{2m_1m_2}\right) - a\left(\frac{2h_{21}h_{22}}{2m_1m_2}\right) ,$$

and

$$\mu_{22} = a\left(\frac{h_{12}^2}{m_2^2}\right) + d\left(\frac{2h_{12}h_{22}}{m_2^2}\right) - a\left(\frac{h_{22}^2}{m_2^2}\right) .$$

The "apparent effect sizes" of the marker alleles can be expressed in terms of these effects, as follows: $d_M = \mu_{12} - [(\mu_{11} + \mu_{22})/2]$ and $a_M = [(\mu_{11} - \mu_{22})/2]$. Substituting the expressions for μ_{11}, μ_{12}, and μ_{22} into these formulas, we obtain $d_M = dD_M^2$ and $a_M = aD_M + d[(m_1 - m_2)D_M^2 - (p - q)D_M]$, where D_M is an abbreviation for the ratio $D/(m_1m_2)$. Note that, if the diallelic marker locus is the QTL itself, then $p = m_1$, $q = m_2$, and $D = m_1 - m_1^2 = m_1m_2$, so that the product m_1m_2 is simply the maximum possible value of D that can be attained by the marker. Consequently, the quantity D_M is the ratio between the actual magnitude of linkage disequilibrium and the maximum magnitude of linkage disequilibrium possible for the marker.

The "apparent variance components" at the marker locus are therefore

$$V_{AM} = 2m_1m_2D_M^2[a - d(p - q)]^2$$

and

$$V_{DM} = 4m_1^2m_2^2d^2D_M^4 .$$

These expressions give rise to the following simple ratios of variance components: $V_{AM}/V_A = D^2/pqm_1m_2$ and $V_{DM}/V_D = (D^2/pqm_1m_2)^2$.

We denote the ratio $D^2/(pqm_1m_2)$ as "R^2." This quantity is the χ^2 statistic of the 2 × 2 table of population haplotype frequencies at the QTL and the marker locus (see table 3). Moreover, if each QTL and marker allele is assigned a numerical value, then R is the correlation between the QTL and the marker alleles. The quantity R^2 is a standard measure of association in 2 × 2 tables (Bishop et al. 1975) and of linkage disequilibrium between diallelic loci (Crow and Kimura 1970).

The derivation of the ratios of variances between a diallelic QTL and a multiallelic marker can be simplified by considering the additive and dominance components separately and by a suitable choice of scale and location parameters. Consider a marker locus containing the alleles M_1, M_2,…,M_k occurring at frequencies m_1, m_2,…,m_k. Denote the frequency of the haplotype A_iM_j as "h_{ij}."

For the additive component, we assign the arbitrary effects of 1 and 0 to alleles A_1 and A_2, respectively, giving a mean of p and a variance of pq. Allele M_j has apparent effect 1 with probability h_{1j}/m_j and has effect 0 with probability h_{2j}/m_j. The average apparent effect of allele M_j is therefore h_{1j}/m_j. The ratio of the apparent additive variance at the marker locus to the additive variance at the QTL is thus

$$\frac{V_{AM}}{V_A} = \frac{\sum_{j=1}^{k} m_j(h_{1j}/m_j - p)^2}{pq} = \sum_{j=1}^{k} \frac{(h_{1j} - m_jp)^2}{m_jpq} = \sum_{j=1}^{k} \left[\frac{(h_{1j} - m_jp)^2}{m_jp} + \frac{(h_{2j} - m_jq)^2}{m_jq}\right] .$$

This quantity is the χ^2 statistic of the 2 × k table of population haplotype frequencies. It is therefore a direct generalization of R^2 from 2 × 2 tables to 2 × k tables. This quantity, which we refer to as "Φ^2," has been used as a measure of the "kinship" between two loci (Morton and Wu 1988). The ratio of the apparent additive variance at the marker locus to the additive variance at a diallelic QTL is Φ^2.

To derive the ratio of apparent dominance variance at the marker locus to the dominance variance at the QTL, we assign the values of q, 0, and p to genotypes A_1A_1, A_1A_2, and A_2A_2, respectively, so that the QTL effects have mean pq, additive variance 0, and dominance variance p^2q^2. The apparent effect of marker genotype M_iM_j is then $(h_{1i}^2q + h_{2i}^2p)/m_i^2$ for $j = i$ and is $(2h_{1i}h_{1j}q + 2h_{2i}h_{2j}p)/2m_im_j$ for $j \neq i$. The ratio of the

apparent dominance variance at the marker locus to the dominance variance at the QTL is therefore

$$\frac{V_{DM}}{V_D} = \frac{\sum_{i=1}^{k} m_i^2\left(\frac{h_{1i}^2 q + h_{2i}^2 p}{m_i^2} - pq\right)^2 + \sum_{i=1}^{k}\sum_{j=i+1}^{k} 2m_i m_j\left(\frac{2h_{1i}h_{1j}q + 2h_{2i}h_{2j}p}{2m_i m_j} - pq\right)^2}{p^2q^2}$$

$$= \sum_{i=1}^{k} \frac{(h_{1i}^2 q + h_{2i}^2 p - m_i^2 pq)^2}{m_i^2 p^2 q^2} + \sum_{i=1}^{k}\sum_{j=i+1}^{k} \frac{2(h_{1i}h_{1j}q + h_{2i}h_{2j}p - m_i m_j pq)^2}{m_i m_j p^2 q^2}$$

$$= \sum_{i=1}^{k} \frac{(h_{1i} - m_i p)^4}{m_i^2 p^2 q^2} + \sum_{i=1}^{k}\sum_{j=i+1}^{k} \frac{(h_{1i} - m_i p)^2 (h_{1j} - m_j p)^2}{m_i m_j p^2 q^2}$$

$$= \left[\sum_{i=1}^{k} \frac{(h_{1i} - m_i p)^2}{m_i pq}\right]^2 .$$

Under the above-noted definition of Φ^2, this ratio is equal to $(\Phi^2)^2$. Hence the additive variance is attenuated by a factor of Φ^2, and the dominance variance is attenuated by a factor of Φ^4.

If the model does not include linkage ($\sigma_A^2 = \sigma_D^2 = 0$), then one-half of the nonattenuated part of the additive variance is shared between siblings, and one-quarter of the nonattenuated part of the dominance variance is shared between siblings. The apparent variance components at the marker locus are therefore

$$V_{AM} = \Phi^2 V_A ,$$

$$V_{DM} = \Phi^4 V_D ,$$

$$V_{SM} = V_S + \frac{(1 - \Phi^2)V_A}{2} + \frac{(1 - \Phi^4)V_D}{4} ,$$

$$V_{NM} = V_N + \frac{(1 - \Phi^2)V_A}{2} + \frac{3(1 - \Phi^4)V_D}{4} .$$

The noncentrality parameter for a sibship of size s, for the within-pairs test for association, is then approximately

$$\lambda_W \approx \frac{(s-1)\left[(1/2)V_{AM} + (3/4)V_{DM}\right]}{V_{NM}} .$$

When V_A and V_D are close to 0 and V_N is close to 1, the noncentrality parameter is approximately

$$\lambda_W \approx (s-1)\left(\frac{1}{2}\Phi^2 V_A + \frac{3}{4}\Phi^4 V_D\right) .$$

A similar approximation can be obtained for the noncentrality parameter of the between-sibships test of association.

Simulations

We checked the theoretically derived noncentrality parameters against the average χ^2-test statistics obtained by simulation studies reported in the article, by Fulker et al. (1999), that originally proposed the between-/within-sibship partition. The average χ^2 statistics obtained by simulation are given in tables 3 and 5 of the Fulker et al. (1999) article. Each average χ^2 statistic was calculated from 100 replicate samples of 1,000 sib pairs. The QTL was assumed to be additive with $V_A = .2$. The residual shared variance, V_S, was set at either 0 or .4. Linkage disequilibrium, as measured by D, was varied from .25 to .025. Since the QTL and the candidate locus were assumed to be diallelic with equal allele frequencies, D and R^2 are related by $R^2 = (4D)^2$.

The theoretical expectation of a χ^2-test statistic is equal to the sum of its noncentrality parameter and its df. All three tests considered (i.e., linkage, between-pairs association, and within-pair association) have 1 df (because Fulker et al. [1999] modeled only additive effects), but the test of linkage is one tailed. The theoretical expectations of the χ^2 statistics are therefore the noncentrality parameters plus half, for the linkage test, and the noncentrality parameter plus 1, for the association tests. The noncentrality parameters are calculated by use of exact formulas involving the logarithms of determinants, rather than by use of first-order approximations (because these latter are inaccurate for values of V_A, V_D, or V_S that are >.1). The observed and theoretical expectations are in fairly close agreement, for all situations examined (table 5).

Table 5

Average χ^2 Statistics Obtained from 100 Simulated Samples of 1,000 Sib Pairs, Compared with Theoretical Expectations

	Average χ^2 Statistic, for			
	$V_S = 0$		$V_S = .4$	
Analysis	Simulation	Theory	Simulation	Theory
Linkage	6.02	5.68	13.02	11.82
Association:				
Between pairs:				
$D = .25$	313.82	319.45	221.79	224.14
$D = .20$	190.28	192.82	136.99	137.97
$D = .10$	45.96	45.62	34.12	36.52
$D = .05$	12.87	11.97	9.95	9.03
$D = .025$	4.29	3.73	3.62	3.00
Within pairs:				
$D = .25$	115.46	118.78	201.42	224.14
$D = .20$	70.31	74.77	122.32	137.97
$D = .10$	17.43	18.95	29.30	36.52
$D = .05$	5.16	5.45	8.07	9.03
$D = .025$	2.18	2.11	2.95	3.00

Note.—$V_A = .2$; V_S = residual shared variance; and D = linkage-disequilibrium parameter. Both QTL and marker loci are diallelic, with equal allele frequencies.

In the assessment of the significance of the differences between the observed and theoretical expectations, it is useful to recall that the variance of a χ^2 random variable is equal to four times its noncentrality parameter plus twice its df (Kendall and Stuart 1979). These theoretical variances are in good agreement with the empirical variances of the χ^2 statistics of the simulated data. The standard error of the average of the χ^2 statistics of 100 replicates is one-tenth the square root of this theoretical sampling variance. The simulation-derived average χ^2 statistic should therefore be within plus or minus one-fifth of the square root of four times the theoretical noncentrality parameter. Inspection of table 5 shows that, only for the within-pairs association test in the presence of substantial residual sib-pair correlation, do the simulation-based χ^2 statistics appear to be significantly smaller than their theoretical predicted values. One possible explanation for these discrepancies is that, under these conditions, the within-pairs association parameter is somewhat underestimated even with a sample size of 1,000 sib pairs.

Sample-Size Considerations

Once the theoretical noncentrality parameter of a test has been obtained, it is easy to calculate the required sample size for any required level of significance and power. For linkage, the level of significance required is traditionally set at a LOD score of 3, which is equivalent to a χ^2 statistic of 13.8 and to a fixed-sample one-tailed significance level of .0001. This LOD-score criterion was initially proposed by Morton (1955) and can be justified, very roughly, as being the common logarithm, of the likelihood ratio (1,000), that is necessary to convert the odds from 50:1 against linkage to 20:1 in favor of linkage (see Ott 1991, p. 66). In order to adopt a similar argument for association, it is necessary to set a value for the prior odds for association, which will depend on the extent of linkage disequilibrium in the population. If we assume that linkage disequilibrium extends over a distance of 30 kb to either side of a QTL (see the Discussion section, below), then the prior odds for association would be 1:50,000, and a likelihood ratio of 1,000,000 would be required to produce a posterior odds of 20:1. This corresponds to a LOD score of 6, a χ^2 statistic of 27.6, and a fixed-sample significance level of ~.0000001.

If 13.8 and 27.6 are adopted as the critical χ^2 statistics for linkage and association, respectively, then the corresponding noncentrality parameters required for 80% power are 20.8 and 37.2, respectively. Under any given set of assumptions, the required number of sib pairs can be obtained by dividing the required noncentrality parameter (i.e., 20.8 for linkage and 37.2 for association) by the theoretical noncentrality parameter per sib pair.

Table 6 shows the required sample sizes for 80% power to detect linkage and association at the critical LOD scores of 3 for linkage and 6 for association, for a range of additive QTL variance (V_A), θ, and linkage disequilibrium (R^2). Dominance QTL variance (V_D) is assumed to be 0, and residual shared variance (V_S) is assumed to be 0.25. The required sample sizes indicate that detection of a QTL by linkage is only feasible when the proportion of phenotypic variance accounted for by the QTL is 10% or more. At this level of QTL variance, approximately 20,000 sib-pairs are required for linkage analysis. In contrast, association analysis can feasibly detect a QTL accounting for as little as 1% of the phenotypic variance, provided that the degree of linkage disequilibrium between QTL and marker is strong ($R^2 > .5$).

Discussion

We have derived intuitively appealing results concerning the power of QTL linkage and association analysis under a variance-components model for large samples of unselected sibships. These results are particularly simple when the effects at the QTL are small and additive. In this case, the expected noncentrality parameter, per sibship, for the detection of linkage is very approximately equal to the number of possible sib pairs in a sibship, times the product of the variance of $\hat{\pi}$ and the square of the QTL heritability. This simple result shows clearly how the power of linkage analysis declines rapidly with decreasing QTL heritability.

The same result also suggests the use of the variance of $\hat{\pi}$ as a measure of the degree of saturation of linkage information at a locus in a sample of sib pairs. The variance of $\hat{\pi}$ is determined by the positions as well as

Table 6

Sample Sizes (No. of Sib Pairs) Required for 80% Power to Detect Linkage and Association, at Critical LOD Scores of 3 for linkage and of 6 for Association, for a Range of V_A, Recombination Fraction θ, and Linkage Disequilibrium R^2

	Sample Size Required, for V_A =			
Analysis	.01	.05	.10	.15
Linkage:				
θ = .20	…	407,843	97,653	41,270
θ = .10	…	129,193	30,815	13,033
θ = .05	…	80,620	19,241	8,128
θ = .0	…	52,790	12,614	5,322
Within-pairs association:				
R^2 = .10	55,440	10,770	5,190	2,329
R^2 = .25	22,156	4,297	2,064	1,321
R^2 = .50	11,068	2,139	1,023	651
R^2 = 1.0	5,524	1,060	502	316

Note.—Dominance QTL variance (V_D) is assumed to be 0, and residual shared variance (V_S) is assumed to be .25.

by the polymorphism information contents of the marker loci; and it declines with increasing recombination fraction θ from a marker locus, according to the formula $(1 - 2\theta)^4$. This slow rate of decline means that only several hundred highly polymorphic markers are enough to almost saturate the entire genome with linkage information.

For an additive QTL, the noncentrality parameter, per sibship, for the robust within-pairs test of association is very approximately equal to the number of siblings minus one times half the QTL variance. The noncentrality parameter therefore decreases approximately linearly with decreasing QTL heritability. Since the noncentrality parameter is directly related to QTL heritability in the case of association but to the square of the QTL heritability in the case of linkage, it is clear that, with decreasing QTL heritability, association will become progressively more powerful than linkage.

Both the linkage and the within-sibship test of association have increasing power with increasing residual shared variance and correspondingly decreasing residual nonshared variance. Any study-design feature that may decrease the residual nonshared variance and increase the residual shared variance, such as the use of repeated or multivariate measures or the selection of DZ twins, will potentially have a beneficial effect on the statistical power of the tests.

The main disadvantage of using association for the detection of a QTL is that power declines rapidly with a decreasing degree of linkage disequilibrium between the QTL and the candidate locus. The noncentrality parameter is reduced by a factor equal to either R^2, in the case of a diallelic candidate locus, or Φ^2, in the case of a multiallelic candidate locus. The quantity R^2 is well known in the population-genetics literature, as a measure of linkage disequilibrium (Crow and Kimura 1970). It is related to the standard measure of linkage disequilibrium, D (the difference between the frequency of a haplotype and the product of the frequencies of its constituent alleles), by $R^2 = (D^2/pqm_1m_2)$, where p, q, m_1, and m_2 are the allele frequencies of the two loci. Although the quantities R^2 and D are closely related to each other, their theoretical properties in populations have been examined from different perspectives. In an infinite-population model, the magnitude of D is proportional to $(1 - \theta)^g$, where θ and g are, respectively, the recombination fraction between the loci and the number of generations since the mutational event responsible for the most recent polymorphism. In contrast, the quantity R^2 is usually examined in a finite-population model, in which the balance between genetic drift and recombination can be shown to lead to the approximate expectation $E(R^2) \approx (1 + 4N\theta)^{-1}$, where N is the size of the population (Hill and Robertson 1968; Ohta and Kimura 1969; Sved 1971). For a population of nonconstant size, the population size N can be replaced by an effective population size N_e. In reality, both models are likely to be approximations to the truth, since linkage disequilibrium is influenced by numerous factors, such as population size and structure, migration, and selection (for a discussion, see Weiss 1993); nevertheless, the reduction of R^2 with increasing recombination fraction is less rapid in a finite-population (i.e., drift) model than in an infinite-population model. This appears to be in better agreement with empirical data from human populations (Jorde et al. 1994), for which N_e has been estimated at ~10,000 (Nei and Graur 1984; Wills 1990; Harpending 1998; Halushka et al. 1999).

Under a finite-population model, the likely magnitude of θ necessary for preserving a certain proportion of the maximum attainable value of the noncentrality parameter (the case of complete linkage disequilibrium) is $\theta = (1/4N_e)[(1/R^2) - 1]$. Thus, in order to preserve 10% of the noncentrality parameter, θ should be <.000225 when $N_e = 10{,}000$. This translates to a physical distance of 22.5 kb, on the assumption that recombinations occur evenly over the genome. This may be the range over which QTL detection by linkage disequilibrium will usually be successful.

For comparing the power of QTL linkage and that of association analyses, we assume that complete information is available for linkage (which, nowadays, because of the availability of numerous highly polymorphic markers for multipoint analysis, is almost realistic). For an additive QTL, the maximum attainable noncentrality parameter, per sib pair, for the linkage test is $\sim V_A^2/8$. Then, if we adopt the approximation that the noncentrality parameter for the within-pairs association test is $R^2V_A/2$, it is clear that the two tests will have approximately the same noncentrality parameter when $V_A^2/8 = R^2V_A/2$, which simplifies to $R^2 = V_A/4$. Thus, association will have a greater noncentrality parameter than will linkage, if we can get close enough to the QTL that $R^2 > V_A/4$. Since the expectation of R^2 is $\sim(1 + 4N_e\theta)^{-1}$, this translates to

$$\theta < \frac{1}{N_e}\left(\frac{1}{V_A} - \frac{1}{4}\right) \approx \frac{1}{N_eV_A} \ .$$

If we assume that $N_e = 10{,}000$, a QTL that accounts for 10% of the phenotypic variance will have a critical recombination fraction of .001 (i.e., ~100 kb), and a QTL that accounts for 1% of the phenotypic variance will have a critical recombination fraction of .01 (i.e., ~1Mb). Linkage analysis is an attractive strategy in the former scenario but would be infeasible in the latter. To detect QTLs that account for only 1% of the phenotypic variance, it may be necessary to perform a genome scan using not linkage but association. If association is usu-

ally detectable at <20 kb from a QTL, then a genome scan using association analysis may require 100,000 markers (for an alternative estimate, see Kruglyak 1999); however, further empirical data are required to resolve this important issue in the design of QTL association studies.

For both linkage and association, the noncentrality parameters are complicated by the inclusion of dominance. Whether the inclusion of a dominance component in the model will improve the power of QTL detection depends on whether the magnitude of V_D is sufficient to compensate for the extra df. It is notable, however, that the contribution of V_D to the noncentrality parameter of the association test decreases as a function of R^4 (rather than of R^2, as in the case of V_A). This suggests that the assumption of additivity may be reasonably adopted when one is searching for linkage disequilibrium and that dominance may be introduced only when the candidate is suspected to be the true QTL itself.

The considerations noted above apply to diallelic markers. It has been suggested that association analysis is more favorable with multiallelic markers (Ott and Rabinowitz 1997; Chapman et al. 1998); however, although the mean vector of the model can accommodate the effect of each allele of a multiallelic candidate locus by a separate parameter, such a procedure increases the df of the test and, therefore, may reduce power in some circumstances. It is therefore desirable that alternative test procedures be developed for association analysis with either highly polymorphic candidate loci or multilocus haplotypes.

Our finding that the noncentrality parameter for association is attenuated by a factor equal to Φ^2 suggests that this parameter may be an appealing measure of the degree of linkage disequilibrium between a QTL and a multiallelic locus. Although Φ^2 has been used, in previous studies, as an index of linkage disequilibrium (Morton and Wu 1988), further studies of its properties are urgently needed.

Although our results may seem somewhat disturbing, in showing that very large sample sizes are necessary for the detection of a QTL that accounts for a small proportion of the phenotypic variance, there are certain ways in which power may be improved. A two-step strategy of genome scanning may be adopted, with use of a critical level lower than the conventional criterion—a LOD score of 3—for an initial linkage-scan step, in order to identify promising genomic regions for further association analysis with very dense marker sets. The power of both linkage and association will be increased if residual nonshared variance can be reduced by more-accurate or repeated measurements of the trait. This naturally extends to the multivariate modeling of several traits that share a substantial proportion of their genetic bases (Eaves et al. 1996; Comuzzie et al. 1997; Martin et al. 1997; Vogler et al. 1997; Allison et al. 1998; Boomsma and Dolan 1998; Todorov et al. 1998). Efficiency may be gained by the selection of sibships whose trait values are such that they are likely to contribute the largest amounts to the noncentrality parameters of the tests (Eaves and Meyer 1994; Risch and Zhang 1995, 1996). However, the variance-components model described here is not directly applicable to either samples selected for extreme trait values or non-normal quantitative phenotypes (Dolan and Boomsma 1998; Allison et al. 1999), and further refinements in statistical methodology are required for these important scenarios.

Acknowledgments

This work was supported by Medical Research Council grant G9700821, Wellcome Trust grant 055379, and National Institutes of Health grants EY-12562, AA-07330, AA-10556, DA-11015, MH-43899, and MH-53668. We thank Sun-Wei Guo and an anonymous referee for valuable comments, and we thank Jing-Hua Zhao for technical assistance.

Appendix A

All elements of the covariance matrix for the between-sibships QTL effects are equal to

$$\begin{aligned}\mathrm{Var}\left(\sum_{i=1}^{s}\frac{g_i}{s}\right) &= \frac{1}{s^2}\left[\sum_{i=1}^{s}\mathrm{Var}\,(g_i)+\sum_{i=1}^{s}\sum_{j=i+1}^{s}2\,\mathrm{Cov}\,(g_i,g_j)\right]\\ &= \frac{1}{s^2}\left[s(V_A+V_D)+s(s-1)\left(\frac{V_A}{2}+\frac{V_D}{4}\right)\right]\\ &= \frac{s+1}{2s}V_A+\frac{s+3}{4s}V_D\ .\end{aligned}$$

In the covariance matrix for the within-sibship QTL effects, any kth diagonal element is given by

$$\begin{aligned}\mathrm{Var}\left(g_k-\sum_{i=1}^{s}\frac{g_i}{s}\right) &= \mathrm{Var}\,(g_k)+\mathrm{Var}\left(\sum_{i=1}^{s}\frac{g_i}{s}\right)\\ &\quad -2\,\mathrm{Cov}\left(g_k,\sum_{i=1}^{s}\frac{g_i}{s}\right)\\ &= (V_A+V_D)+\left(\frac{s+1}{2s}V_A+\frac{s+3}{4s}V_D\right)\\ &\quad -2\left[\frac{V_A+V_D}{s}+\frac{s-1}{s}\left(\frac{V_A}{2}+\frac{V_D}{4}\right)\right]\\ &= \frac{s-1}{2s}V_A+\frac{3s-3}{4s}V_D\ .\end{aligned}$$

Any off-diagonal element for the (kth,lth) pair is given by

$$\begin{aligned}
&\mathrm{Cov}\left[\left(g_k - \sum_{i=1}^{s}\frac{g_i}{s}\right),\left(g_l - \sum_{i=1}^{s}\frac{g_i}{s}\right)\right] \\
&= \mathrm{Cov}(g_k,g_l) + \mathrm{Var}\left(\sum_{i=1}^{s}\frac{g_i}{s}\right) \\
&\quad - \mathrm{Cov}\left(g_k, \sum_{i=1}^{s}\frac{g_i}{s}\right) - \mathrm{Cov}\left(g_l, \sum_{i=1}^{s}\frac{g_i}{s}\right) \\
&= \left(\frac{V_A}{2} + \frac{V_D}{4}\right) + \left(\frac{s+1}{2s}V_A + \frac{s+3}{4s}V_D\right) \\
&\quad -2\left[\frac{V_A + V_D}{s} + \frac{s-1}{s}\left(\frac{V_A}{2} + \frac{V_D}{4}\right)\right] \\
&= \frac{-1}{2s}V_A + \frac{-3}{4s}V_D \ .
\end{aligned}$$

Appendix B

Let $\mathbf{A}_s$ be an s-dimensional ($s \geqslant 2$) symmetric matrix with diagonal elements equal to a and with off-diagonal elements equal to b. Let $\mathbf{B}_s$ be identical to $\mathbf{A}_s$, except for the first diagonal element, which is b rather than a. The determinants of $\mathbf{A}_s$ and $\mathbf{B}_{s-1}$ can be shown (by subtraction of column 2 of the matrices from column 1 of the matrices) to be $|\mathbf{A}_s| = (a-b)(|\mathbf{A}_{s-1}| + |\mathbf{B}_{s-1}|)$ and $|\mathbf{B}_{s-1}| = (a-b)|\mathbf{B}_{s-2}|$. Application of these two formulas recursively then yields $|\mathbf{A}_s| = (a-b)^{s-1}[a + (s-1)b]$.

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