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The Quantitative LOD Score: Test Statistic and Sample Size for Exclusion and Linkage of Quantitative Traits in Human Sibships

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Summary

We present a test statistic, the quantitative LOD (QLOD) score, for the testing of both linkage and exclusion of quantitative-trait loci in randomly selected human sibships. As with the traditional LOD score, the boundary values of 3, for linkage, and −2, for exclusion, can be used for the QLOD score. We investigated the sample sizes required for inferring exclusion and linkage, for various combinations of linked genetic variance, total heritability, recombination distance, and sibship size, using fixed-size sampling. The sample sizes required for both linkage and exclusion were not qualitatively different and depended on the percentage of variance being linked or excluded and on the total genetic variance. Information regarding linkage and exclusion in sibships larger than size 2 increased as approximately all possible pairs $n(n-1)/2$ up to sibships of size 6. Increasing the recombination (θ) distance between the marker and the trait loci reduced empirically the power for both linkage and exclusion, as a function of $\sim(1-2\theta)^4$.

Introduction

During the past 20 years, many genes that underlie human disease have been localized by genetic linkage analysis and, subsequently, have been cloned (Collins 1995). However, few linkages have been firmly established for quantitative traits in humans, and no previously unknown genes have yet been positionally cloned as a result of such analyses. Several methods have been developed for detection of linkage to quantitative traits in humans (Haseman and Elston 1972; Hill 1975; Smith 1975; Goldgar 1990; Amos 1994; Kruglyak and Lander 1995; Risch and Zhang 1995; Amos et al. 1996). However, methods for exclusion of the involvement of a gene or a chromosomal region in a quantitative trait are underdeveloped.

Exclusion analysis by use of the LOD-score method (Ott 1991) has long been established for qualitative traits. By identification of regions of the genome where disease-causing genes are not likely to be located, such analyses facilitate the identification of regions where disease-causing genes are likely to be located, by a process of elimination. Exclusion analysis has been used successfully to help localize genes underlying diseases such as Marfan syndrome (Blanton et al. 1990) and is especially important in studies of a list of candidate genes.

The traditional LOD-score critical values of 3 and −2 are independent of the likelihoods used to determine the LOD score (Morton 1955; Govindarajulu 1975). In this article, we evaluate a test statistic, the quantitative LOD score, which can use the likelihood, from the variance-component method of quantitative-trait linkage analysis (Goldgar 1990; Amos 1994), in a sequential test-statistic framework similar to that of the traditional LOD score (Morton 1955). We then explore the properties of the QLOD score for quantitative-trait linkage analysis, with emphasis on exclusion analysis.

The Genetic Model

The quantitative-trait value of the ith individual is assumed to result from the effect of a single gene, a_i, for which segregation with a marker is being monitored; pg_i denotes residual polygenic effects, and e_i denotes random environmental effects. Therefore, $X_i = \mu + a_i + pg_i + e_i$, where μ is a fixed effect and where pg_i and e_i are random effects with mean 0 and variances σ^2_{pg} and σ^2_e, respectively. We assume that a_i is a fixed but unobservable effect. However, a_i can be modeled by consideration of the effect that it has on the similarities among related individuals. A description of the genetic model for a two-allele system can be found in the article by Amos (1994). When a, pg, and e are assumed to be independent and

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to act additively, the total variance of the trait is $\sigma_t^2 = \sigma_a^2 + \sigma_{pg}^2 + \sigma_e^2$, with the total genetic variance being $\sigma_g^2 = \sigma_a^2 + \sigma_{pg}^2$.

Let us assume that the marker locus and the trait locus are linked, with a recombination fraction of θ, but that they are in linkage equilibrium with one another, in the population. Under this model, the covariance between relatives has been given by Amos (1994). For two siblings, the covariance is $[\frac{1}{2} + (1-2\theta)^2(\pi_{mij} - \frac{1}{2})]\sigma_a^2 + \sigma_{pg}^2$, where π_{mij} is the proportion-of-alleles identity-by-descent at marker locus *m*, between relatives *i* and *j*. We will assume that the quantitative-trait values are normally distributed in the population and that the distribution of the trait in the families follows an approximately multivariate normal distribution (Lange 1978), with the likelihood for a sample of R ($r = 1,\ldots,R$) families, of

$$\ln(L) = c - \frac{1}{2}\sum_{r=1}^{R}\left[\ln|\Sigma_r| - (\boldsymbol{X}_r - \mu_r)'\Sigma_r^{-1}(\boldsymbol{X}_r - \mu_r)\right] ,$$

where $\boldsymbol{X}_r$ represents the vector of observed phenotypic values of the trait, for individuals in the rth family, μ_r is the mean vector for the quantitative trait in the same family, and Σ_r is the variance-covariance matrix among family members.

The QLOD Score

The LOD score is the $\log_{10}$ of the ratio of the likelihood of the alternative hypothesis, given the data, to the likelihood of the null hypothesis, given the same data. Under a sequential testing approach, if the LOD score is greater than a defined boundary value, *A*, then the alternative hypothesis (linkage) is accepted. If the LOD score is less than some other boundary value, *B*, then the null hypothesis (exclusion) is accepted. If the LOD score lies between *B* and *A*, then there are insufficient data to accept either hypothesis (Wald 1947), and additional data must be collected.

Here, we have chosen to adopt the traditional critical values of 3 and −2 (Morton 1955), for use with the QLOD score. These values approximately correspond to a type I error rate of .0001 (Lander and Kruglyak 1995) and a type II error rate that is considerably <.01 (Morton 1955; Chotai 1984), independent of the likelihood used. Bayesian arguments also have been offered in support of these critical values (Morton 1955; Govindarjulu 1975).

Although our approach in implementing the QLOD score was motivated by sequential testing approaches, sequential methods have actually been implemented rarely, if ever, in studies of humans (Chotai 1984). Therefore, we present sample-size results by following a fixed–sample-size design but, in the Discussion, contrast these results with the slightly small average sample sizes for sequential tests, at a few parameter values.

Simulation Methods

A computer program (Amos 1994) was used to simulate the nuclear-family data. Parental data were used only as a framework for simulation of the offsprings' markers and traits and are not analyzed; as a result, all the results that we present are restricted to sibships. Parental genotypes at a trait locus, with allele frequencies *p* and *q*, were assigned on the basis of their expected frequencies, by use of a uniform (0,1) random-number generator. A completely informative multiallelic marker locus was linked to the trait locus, at various values of θ. The polygenic values for the parents were obtained by sampling from a normal distribution with mean 0 and variance σ_{pg}^2. For each child, the polygenic contribution was obtained from the average of the polygenic values of the parents plus a deviate drawn from a normal distribution with mean 0 and variance $\sigma_{pg}^2/2$. Finally, the phenotype was assigned from the trait-locus value, the polygenic value, and a deviate from a normal distribution with mean 0 and variance σ_e^2.

For each family, the likelihoods for the observed data were calculated under the null and alternative hypotheses, by use of data from the children only. For all cases, the total phenotypic variance $\sigma_t^2 = 100$; thus, all values of σ_a^2, σ_{pg}^2, and σ_g^2 can be interpreted as percentages of the total phenotypic variance. In each case, we assumed that parameter values were known, and the hypotheses used to evaluate sample sizes were constructed as follows: for the alternative hypothesis, $\sigma_a^2 = x$, $\sigma_{pg}^2 = y$, and $\sigma_e^2 = 100 - (x + y)$; and, for the null hypothesis, $\sigma_a^2 = 0$, $\sigma_{pg}^2 = x + y$, and $\sigma_e^2 = 100 - (x + y)$. For each study simulated under the alternative model (with a linked genetic effect), the tested alternative hypothesis used the simulation parameters, whereas, for the null hypothesis, the polygenic variance was assumed to be the sum of the simulated linked and polygenic variances. For each study simulated under the null model (with no linked genetic effects), the tested null hypothesis used the simulation parameters. For the alternative hypothesis tested under the null model, the simulated polygenic variance was partitioned into linked and unlinked components. All estimates for linkage were derived from 5,000,000 nuclear families, and all estimates for exclusion were derived from 500,000 nuclear families. We used a larger number of families for the linkage model in order to ensure more-precise sample-size estimates, since general interest often focuses on linkage more than on exclusion. The results from these simulations were used to determine the mean QLOD score per family and the variance among families, for each set of parameters.

Table 1

Number of Independent Sib Pairs Required for 90% Power of Exclusion, for Various Linked and Total Genetic Variances, When $\sigma_t^2 = 100$

	No. of Sib Pairs, When σ_g^2 =								
σ_a^2	10	20	30	40	50	60	70	80	90
5	71,374	72,822	71,921	69,080	64,628	58,914	52,290	45,076	37,488
10	17,014	16,965	16,555	15,831	14,833	13,608	12,208	10,680	9,060
15		7,254	7,148	6,822	6,392	5,872	5,282	4,643	3,958
20		4,077	3,952	3,767	3,527	3,241	2,917	2,565	2,191
25			2,495	2,376	2,223	2,041	1,836	1,614	1,379
30			1,713	1,628	1,521	1,395	1,254	1,101	939
35				1,181	1,101	1,009	905	793	674
40				891	830	759	679	593	503
45					645	588	525	457	386
50					513	467	415	360	302
55						377	334	288	240
60						309	273	234	193
65							225	191	157
70							187	158	128
75								131	105
80								109	86
85									70
90									57

Our objective was to determine the probability that a single sample of R independent families will have a QLOD score <-2 or >3. We assumed that the sample mean and variance of the QLOD score obtained from the simulation studies described in the previous paragraph were the same as the population mean, μ, and variance, σ^2 (Wald 1947; Govindarajulu 1972). The mean and variance of the QLOD score for a single sample of R families are $R\mu$ and $R\sigma^2$, respectively. Let D be the boundary value of interest (either 3 or -2). The probability, indicated by the Z score, that a single sample of R families will have a QLOD score $>D$ can be obtained by use of the normal deviate, $Z = (R\mu - D)/\sqrt{R\sigma^2}$. This function can be solved for $\sqrt{R}$ as follows: $\sqrt{R} = (Z\sigma \pm \sqrt{Z^2\sigma^2 + 4\mu D})/2\mu$, from which the positive roots can be found. The formula is the same for linkage or exclusion.

Results

Exclusion

Tables 1 and 2 give the number of two-sibling and three-sibling families, respectively, required for establishing exclusion with 90% power. As expected, fewer families were needed for exclusion of the involvement of a trait accounting for a larger proportion of the genetic variance than for exclusion of a trait accounting for a smaller proportion. Increasing the number of children in the sibship increased the amount of information per member that the sibship contained. For values of the parameters investigated, there was an approximately threefold decrease in the number of three-sibling families (table 2), compared with the number of two-sibling families (table 1), required for exclusion.

Although it is desirable to find a highly polymorphic marker within or very near each candidate gene, this often is not possible. In addition, one may want to use exclusion analyses as part of a genomewide search for quantitative-trait loci. Therefore, we tested the ability of the QLOD score to determine, as a function of θ, that a particular region around a marker locus does not contain a gene with a given effect on the phenotype (i.e., given a specific linked genetic variance). A precipitous decrease in the information for exclusion, per family, as defined by an increase in the number of families required for establishing exclusion, was observed as a function of increasing θ (table 3).

Linkage

The QLOD-score test statistic can be used for both linkage and exclusion analyses. Table 4 shows the number of two-sibling sibships required, to infer linkage, for varying values of the linked and total genetic variances. Table 5 indicates the samples sizes required for linkage, as a function of θ values from .0 to .2.

In figure 1 we depict the mean QLOD score, for a sibship of a given size (x-axis), divided by the mean QLOD score for a sibship of size 2, for $\sigma_a^2 = \sigma_g^2 = 5\%$, 25%, or 50% of the total phenotypic variance. Also graphed in figure 1 are several functions for the increase in information, as a function of sibship size (n): for all possible pairs, $[n(n-1)]/2$, suggested by Blackwelder and Elston (1985); $[2n - 3 + (\frac{1}{2})^{n-1}]/1.5$, suggested by Hodge (1984); and $n-1$, suggested by Suarez and

Table 2

Number of Independent Sib Trios Required for 90% Power of Exclusion, for Various Linked and Total Genetic Variances, When $\sigma_t^2 = 100$

	No. of Sib Trios, When σ_g^2 =								
σ_a^2	10	20	30	40	50	60	70	80	90
5	23,670	23,147	22,964	22,243	21,049	19,434	17,448	15,143	12,543
10	5,615	5,569	5,396	5,121	4,758	4,352	3,885	3,382	2,850
15		2,459	2,364	2,229	2,065	1,877	1,671	1,454	1,230
20		1,383	1,324	1,244	1,149	1,042	926	805	681
25			847	794	731	661	586	509	430
30			588	550	505	455	403	349	294
35				402	370	332	293	252	212
40				307	280	252	221	190	159
45					220	196	172	147	122
50					176	157	137	116	95
55						128	111	94	75
60						105	90	75	62
65							75	63	50
70							63	52	41
75								43	22
80								36	27
85									22
90									18

Hodge (1979). When the number of siblings in a sibship was <6, the amount of information obtained for linkage was within 95% of the expected information suggested by all possible pairs. However, for sibships of size $\leqslant 6$, the information was considerably less than that suggested by all possible pairs. We also noted that the larger the linked genetic effect, the smaller the increase in information, with increasing sibship size. For example, 10-sibling families provided 42 times as much information as 2-sibling families, for a 5% linked genetic effect, but only 32 times as much information for a 50% linked genetic effect.

Discussion

Sequential testing approaches have several advantages over other methods of quantitative-trait linkage analysis. An important advantage is the method's ability to exclude a gene's or a region's involvement in a percentage of the interindividual variation in a quantitative trait. This is especially important in candidate-gene linkage analysis, in which a priori knowledge suggests that certain genes are involved in quantitative variation and that linkage analysis is the primary method of prioritizing them or of rejecting some from further analysis.

In addition, the ability to pool data from several studies is likely to be very important, because most quantitative-trait loci will have small effects (Paterson 1995). Thus, the results of many studies probably will have to be combined, to locate many of the genes affecting a quantitative trait (Li and Rao 1996). For this to be carried out, however, a standardized format for communication of the results for quantitative-trait linkage studies is required. Therefore, a convention for the reporting of human quantitative-trait linkage statistics that permits combining information across studies must be developed. The traditional method used in two-point LOD-score analysis is to provide a table of LOD scores as a function of θ. We suggest a table reporting the QLOD score for every 5% of the total phenotypic variance, up to the estimated total genetic variance, for candidate genes.

The literature on the methods and properties of genetic exclusion analysis of quantitative traits is sparse, despite considerable literature on the methods and properties of linkage analysis. Therefore, this discussion will focus mostly on those results pertaining to exclusion analysis.

Table 3

Number of Independent Sib Pairs Required for 90% Power of Exclusion, When All the Genetic Variance Is Linked, at Various θs, and When $\sigma_t^2 = 100$

	No. of Sib Pairs, at θ =						
σ_a^2	.0	.05	.1	.15	.2	.25	.3
10	17,014	26,227	42,668	74,461	142,937	315,060	867,897
20	4,077	6,281	10,191	17,692	33,637	72,822	193,100
30	1,713	2,647	4,299	7,452	14,106	30,251	78,588
40	891	1,387	2,262	3,927	7,423	15,831	40,581
50	513	809	1,329	2,318	4,385	9,324	23,679
60	309	497	828	1,456	2,764	5,872	14,817
70	187	311	530	945	1,805	3,843	9,655
80	109	193	341	628	1,200	2,565	7,340
90	57	114	214	404	796	1,717	4,302

Table 4

Number of Independent Sib Pairs Required for 90% Power of Linkage, for Various Linked and Total Genetic Variances, When $\sigma_t^2 = 100$

	No. of Sib Pairs, When σ_g^2 =								
σ_a^2	5	10	15	20	30	40	50	60	70
5	86,850	75,710	73,993	72,430	69,194	65,567	61,495	57,040	52,292
10		21,515	19,830	19,422	18,559	17,556	16,407	15,132	13,767
15			9,425	9,350	8,433	7,969	7,435	6,841	6,203
20				5,205	5,059	4,819	4,214	3,870	3,501
30					2,190	2,010	1,868	1,709	1,540
40						1,148	1,043	951	852
50							665	596	530
60								405	355
70									249

Comparison of the results presented in table 1, for exclusion analysis, and those presented in table 4, for linkage analysis, indicates that the sample size required for inferring exclusion and that required for linkage are not vastly different. For example, 17,014 two-sibling families were required for the exclusion of a 10% linked effect, compared with 21,515 two-sibling families required for establishing linkage with 90% power. Therefore, analyses that exclude the presence of a linked locus having a specified effect should be possible, on the basis of those studies that have been designed to be informative for genetic linkage analysis.

The sample sizes presented in tables 1–5 are for fixed-sample designs. By using equation (57) in chapter 3 of the work by Wald (1947), we can obtain the average sample number necessary for establishing linkage and exclusion, for a sequential test. A sequential test with a false-negative rate of 1% requires 10,793 two-sibling families, but, for fixed sampling, the sample size necessary for establishing linkage (QLOD = 3, $\beta \approx .01$) with 50% power is 10,976 two-sibling families. To establish exclusion by use of a sequential test with a false-positive rate of 0.1%, the average sample size required is 7,500 two-sibling families, whereas, for a fixed-sample design with 50% power, the sample size necessary for establishing exclusion (QLOD = -2, $\alpha \approx .001$) is 7,519 two-sibling families.

We observed that the sample size required for exclusion analysis was influenced by the magnitude of the polygenic component of the variance of the trait. The sample size required for exclusion decreased when the polygenic component of the variance increased, as was noted by Schork (1993). The exact reason for this relationship is not known; however, some speculation is possible. As the total polygenic component increases, the individual-specific environmental variance component, σ_e^2, decreases. This has the effect of reducing the random genetic variance (i.e., the “noise”) among siblings, which, in turn, improves the ability to make inferences about the linked genetic effect (i.e., the “signal” or the lack of one).

For tables 3 and 5, we investigated the impact that increasing the distance between the marker and trait loci had on the power for exclusion or linkage, respectively. For $\theta < .1$, multiplication of the sample size required at $\theta = .0$ by $1/(1-2\theta)^4$ provided an estimate of the sample size that was within 95% of the observed sample size. Similar results were seen for both linkage and exclusion. Thus, 2.5- and 5-cM maps have ~81% and ~66%, respectively, of the power at $\theta = .0$. Therefore, as part of a genomewide scan, gaps >10 cM between markers need to be narrowed by typing the intervening marker loci so that the power of the exclusion (or linkage) analysis remains acceptable.

Several ways of estimating the relative amount of information in sibships of differing sizes have been proposed, depending on the hypothesis being investigated. In figure 1, the results of these proposed methods were compared with the observed relative linkage information per sibships of various sizes, compared with sibships of size 2. When the linked genetic variance and the sibship size were small, the QLOD score behaved approximately

Table 5

Number of Independent Sib Pairs Required for 90% Power of Linkage, When All the Genetic Variance Is Linked, at Various θs, and When $\sigma_t^2 = 100$

	No. of Sib Pairs, at θ =					
σ_a^2	.0	.01	.02	.05	.1	.2
5	86,850	92,702	99,689	122,416	198,497	585,690
10	21,515	23,091	25,027	31,753	51,420	154,848
15	9,425	10,133	11,013	14,140	22,916	69,703
20	5,205	5,601	6,096	7,878	12,789	39,179
25	2,190	3,505	3,819	4,958	8,064	24,858
30	1,148	2,361	2,574	3,356	5,470	16,962
35	665	1,682	1,837	2,404	3,930	12,258
40	405	1,240	1,355	1,779	2,919	9,163
45	249	721	790	1,047	1,733	5,520

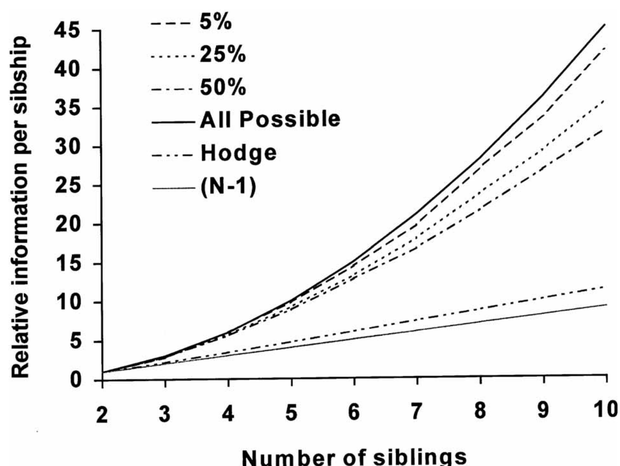

Figure 1 Graph of ratio of the mean QLOD score for a sibship of size n, given on the x-axis, divided by the mean QLOD score for a sibship of size 2. Relative information is given for linked loci accounting for 5%, 25%, and 50% of the total phenotypic variance, when all of the genetic variance is linked. Also shown are three ratios constructed from functions for the amount of information in sibships of various sizes: $n(n-1)/2$, for all possible pairs; $[2n-3+(\frac{1}{2})^{n-1}]/1.5$, a function identified by Hodge (1984); and $n-1$.

like that for all possible pairs, but, as the linked genetic variance and the sibship size increased, the increased information behaved less like that for all possible pairs. It should be mentioned, however, that variance-component–based methods, such as the QLOD score, analyze families as a unit and are not restricted to pairs of relatives.

In this study, the approach taken for quantitative-trait exclusion and linkage analysis assumes a virtually ideal model. A more realistic model would include less-than–fully informative markers, an error in the measurement of the quantitative trait, and joint estimation of the population mean and of the total genetic variance. All of these will lead to a decrease in the power of the test, for both exclusion and linkage. In addition, we assumed that only a single genetic locus acting additively affected the quantitative trait. Incorrect model specification might lead to a decrease in power for the linkage analysis but may not lead to an excess of false-positive findings. Results from Genetic Analysis Workshop 10 failed to find an excess of type I errors in variance-component procedures (Wijsman and Amos 1997), even though the data were generated with a complex genetic architecture and most variance-component procedures that were applied assumed a simple additive model. In general, exclusion analysis jointly excludes a region and a genetic model and, therefore, must be used cautiously.

Although most of the conditions were ideal for minimization of the sample size required for linkage and for exclusion, the sampling strategy may not have been ideal. We assumed random ascertainment of the sibships. A substantial increase in information per sibship had been noted for selected samples (Risch and Zhang 1995). However, nonrandom sampling may give biased estimates of the contribution of each quantitative-trait locus. To decide among sample strategies would require an additional comparison of costs of sample collection and genotyping, which is beyond the scope of these analyses.

In summary, we combined the likelihoods from the variance-component–based method of linkage analysis with the accepted principle of sequential analysis theory, to develop a method for genetic exclusion and linkage analysis of quantitative traits in humans. This method should help genomewide searches for quantitative-trait loci and prioritization of candidate genes for further analysis. We examined the performance of this test. The sample sizes required for inferring exclusion were presented and were not found to be very different from the sample sizes required for inferring linkage. Sequential approaches, such as the QLOD score, should be useful for the combination of information across studies, to facilitate mapping of quantitative-trait loci.

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