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Dolan, C.V.; Boomsma, D.I.

published in
Behavior Genetics
1998

DOI (link to publisher)
10.1023/A:1021423214032

document version
Publisher's PDF, also known as Version of record

Behavior Genetics, Vol. 28, No. 3, 1998

Optimal Selection of Sib Pairs from Random Samples for Linkage Analysis of a QTL Using the EDAC Test

Conor V. Dolan[1] and Dorret I. Boomsma[1]

Received 27 May 1997—Final 20 Feb. 1998

Percentages of extremely concordant and extremely discordant sib pairs are calculated that maximize the power to detect a quantitative trait locus (QTL) under a variety of circumstances using the EDAC test. We assume a large fixed number of randomly sampled sib pairs, such as one would hope to find in the large twin registries, and limited resources to genotype a certain number of selected sib pairs. Our aim is to investigate whether optimal selection can be achieved when prior knowledge concerning the QTL gene action, QTL allele frequency, QTL effect size, and background (residual) sib correlation is limited or absent. To this end we calculate the best selection percentages for a large number of models, which differ in QTL gene action allele frequency, background correlation, and QTL effect size. By averaging these percentages over gene action, over allele frequency, over gene action, and over allele frequencies, we arrive at general recommendations concerning selection percentages. The soundness of these recommendations is subsequently in a number of test cases.

KEY WORDS: Quantitative trait locus (QTL); sib pairs; linkage analysis; random samples; sib pair selection; EDAC test.

INTRODUCTION

The importance of selective sampling to increase power in linkage analyses of a quantitative trait locus (QTL) using on sib pair data has been demonstrated both in Monte Carlo studies (Carey and Williamson, 1991; Eaves and Meyer, 1994; Cardon and Fulker, 1994) and analytically (Risch and Zhang, 1995, 1996; Gu *et al.*, 1996). Carey and Williamson (1991) and Cardon and Fulker (1994) considered selective sampling on the basis of proband ascertainment, where one sibling is defined as the proband and is selected from an extreme of the phenotypic distribution. The cotwin trait scores vary over the full range of the distribution. Eaves and Meyer (1994) considered a variety of selection strategies, including selection of high and low concordant and discordant sib pairs. Risch and Zhang (1995) presented an analytic method to derive the required number of selected sib pairs to achieve a specific level of statistical power given the alpha level, background correlation, QTL allele frequency, QTL gene action, and effect size. Their power calculations are based of the null hypothesis that the mean proportion of alleles shared identically by descent equals .5 (i.e., the expected value given the absence of linkage). The results are presented for selection of discordant sib pairs from the extreme deciles of the phenotypic distribution. Methods to correct the required number for polymorphic information content of flanking markers and recombination are provided in Risch and Zhang (1996). While Risch and Zhang (1995, 1996) concentrate on extremely discordant sib pairs, Gu *et al.* (1996) consider the gains in power

[1] Department of Psychology, Vrije Universiteit, De Boelelaan 1111, 1081 HV Amsterdam, The Netherlands. Fax: 31-20-4448832. E-mail: op_dolan@macmail.psy.uva.nl and dorret@psy.uva.nl.

0001-8244/98/0500-0197$15.00/0

that are achieved by combining extremely high-and low-scoring concordant sibs with extremely discordant sibs. They present results relating to selection from random samples and to selection on the basis of extreme probands. Gu *et al.* (1996) show that the inclusion of high- and low-scoring concordant siblings may increase the power appreciably.

Although these studies have demonstrated the efficiency of selective sampling in QTL detection using sib pair data, the problem remains that it is difficult to arrive at general recommendations concerning selection in the absence of specific knowledge concerning allele frequency and gene action. Generally a "mixed" selection strategy is advocated involving the selection of both extremely scoring concordant and extremely scoring discordant sib pairs (Gu *et al.*, 1996; Carey and Williamson, 1994, p. 793; Cardon and Fulker, 1994, p. 831; Eaves and Meyer, 1994, p. 445).

The aim of the present paper is to investigate whether more precise recommendations be derived. These recommendation are formulated in terms of selection percentages. We base our investigation on power calculations using the EDAC (extreme discordant and concordant) test statistic presented by Gu *et al.* (1996). We consider selection of extreme concordant and discordant sib pairs from a large random sample of phenotyped sib pairs, as available, for instance, in the large twin registries. The soundness of our derived recommendations is evaluated by calculating the optimal power and the power realized by following our recommendations in a number of test cases.

PROCEDURE

We suppose that we have at our disposal phenotypic data from a large random sample comprising N sib pairs. From this random sample, we wish to select the most informative subsample of M sib pairs for genotyping. Using the methods presented by Risch and Zhang (1995) and Gu *et al.* (1996), it is possible to determine the combination of extremely discordant (ED) and extremely concordant high (ECH)- and low (ECL)-scoring sib pairs that maximizes the power to reject the null hypothesis of no linkage using the EDAC test (Gu *et al.*, 1996).

We adopt the model employed by Risch and Zhang (1995) and Gu *et al.* (1996): we assume that the phenotypic individual differences are attributable in part to a biallelic QTL. Conditioned on the genotype of the sibs at the QTL, the bivariate phenotypic distribution of the sibs is bivariate normal with zero means and a possibly nonzero correlation. This correlation, which we refer to as the background correlations and denote ρ, is due to factors other than, and unrelated to, the QTL. These factor are polygenetic influences and (or) shared environmental influences.

We partition the marginal phenotypic distributions of the sibs identically into a fixed number of bins, not necessarily of equal size. We assume that these marginal distributions are identical. Each bin is denoted b_i ($i = 1, \ldots$). The probability of the phenotypic score of a randomly chosen member of a sib pair falling into a given bin is indicative of the bin size. Based on the notation in Risch and Zhang (1995), we denote the outcome of one sib's phenotypic score falling in the ith bin and the other sib's phenotypic score falling in the jth bin as $O(b_i, b_j)$.

Information that is central to the EDAC test is the expected distribution of the number of alleles that are identical by descent (IBD) at the QTL within a selected sample of sib pairs [see Blackwelder and Elston (1985) for a discussion of related tests]. Risch and Zhang (1995) derive the following formula to compute the expected IBD distribution in a sample of siblings selected from bins b_i and b_j:

$$\text{prob}\,[\text{IBD} = n \mid O(b_i, b_j)] = D_n/D \qquad (1)$$

where $n = 0, 1, 2$ and $D = D_0 + D_1 + D_2$. The symbol D_n denotes

$$D_n = \text{prob}\,[\text{IBD} = n] \sum_{k=1}^{9} \text{prob}\,[G_k \mid \text{IBD} = n]\ \text{prob}\,[O(b_i, b_j) \mid G_k]$$

where prob [IBD = n] is the unconditional probability of IBD = n; prob [G_k | IBD = n] is the probability of G_k, given IBD = n; and G_k represents the kth genotype combination of the siblings. There are nine ordered combinations: *AA–AA, AA–Aa, AA–aa, Aa–AA, Aa–Aa, Aa–aa, aa–AA, aa–Aa*, and *aa–aa*. Finally, prob[$O(b_i, b_j) \mid G_k$] represents the probability of outcome $O(b_i, b_j)$ given genotype combination G_k. The probabilities of IBD = 0, IBD = 1, and IBD = 2 are 1/4, 1/2, and 1/4, respectively. The probability of G_k given IBD = n are tabulated by Risch and Zhang (1995, Table 1; Has-

eman and Elston, 1972, Table 1). The probability of $O(b_i, b_j)$, conditional on G_k, is obtained by integrating the bivariate normal distribution (see Risch and Zhang, 1995, Eq. 3).

Below we require the probability associated with the outcome $O(b_i, b_j)$. This equals

$$\text{prob}\,[O\,(b_i, b_j)] = \sum_{n=0}^{9} \text{prob}\,[O\,(b_i, b_j) \mid G_k]\ \text{prob}\,[\mathrm{G}_k] \quad (2)$$

where

$$\text{prob}\,[G_k] = \sum_{n=0}^{2} \text{prob}\,[G_k \mid \text{IBD} = n]\ \text{prob}\,[\text{IBD} = n]$$

For a given choice of N, the total number of phenotyped sib pairs, and M, the number of sib pairs to be genotyped, we want to find the top p_{ch} percentage of ECH pairs, the bottom p_{cl} of ECL pairs, and the ED pairs from the top p_{dh} and bottom p_{dl} percentage that maximize the power of the EDAC test. We consider only symmetric selection in the choice of concordant sib pairs. This means we employ an identical cutoff point for the marginal distributions of the sibs. If both members of a sib pair have scores exceeding this identical cutoff point, they are labeled ECH. The single percentage p_{cl} (p_{ch}) determines the number of ECL (ECH) sib pairs. In identifying ED sib pairs, we allow for asymmetric selection, hence we have two percentages, p_{dh} and p_{dl}. So whereas the phenotypic cutoff points are identical for concordant siblings, this is not necessarily the case for discordant sib pairs.

Note that we are expressing our recommendations in terms of the selection percentages, not the actual number of sib pairs to select. Given the optimal choice of the four percentages, the actual number of ECL, ECH, and ED sib pairs to select can be determined from N, the total number of available sib pairs, and the probability of $O(b_i, b_j)$ [Eq. (2)].

As mentioned, the EDAC test focuses on departures from the expected value of the proportion of alleles shared IBD by the sibs in the selected sample. The expected value of the IBD distribution equals .5 under the null hypothesis. Under the alternative hypothesis, the proportion of IBD = 0 sibs is >.25 in sib pairs selected for extreme discordance and <.25 in sib pairs selected for extreme concordance. The expected values of the IBD distributions are <.5 and >.5, respectively. The EDAC test is based on the difference between the expected proportion in the concordant and the discordant pairs. The expected values are calculated using Eq. (1). The expected value is zero under the null hypothesis and greater than zero under the alternative hypothesis. Using the method described by Gu *et al.* (1996), one can calculate the power for any choice of the four percentages, given the specified allele frequency, gene action, heritability, and alpha level.

Near-optimal values of the selection percentages are obtained in the following manner. We partition the marginal phenotypic distributions identically into 29 bins of the following sizes: 3.33% (6×), 2.5% (8×), 20% (1×), 2.5% (8×), and 3.33% (6×). Using a FORTRAN program,[2] we seek out the selection percentages p_{ch}, p_{cl}, p_{dl}, and p_{dh} that maximize the power of the EDAC test given a total random sample of N sib pairs from which no more than M pairs are selected. The selection percentages are found by means of an exhaustive search: each possible accumulation of the top 14 and the bottom 14 bins (14^4 in total) is evaluated. A given choice of the four percentages is viewed as optimal, if it maximizes power, subject to the restriction that the number of selected sib pairs does not exceed M. The partitioning of the phenotypic distribution (into 29 bins) is relatively coarse, so that in some cases the number of sib pairs selected given the selection percentages may deviate from the maximum of M. Furthermore, the selection percentages may be suboptimal, because of the chosen bin sizes and the maximum bin size of .40. For instance, each percentage may equal 3.33%, 6.66, etc., to the maximum of 40%, but percentages cannot assume intermediate values such as 5%, or 21%, or values exceeding the maximum of 40%. Bearing these limitations in mind, we refer to near optimal selection (percentages) simply as optimal selection (percentages) to ease presentation.

Increasing allele frequency was set to equal .2, .3, .4, .5, .6, .7, or .8. The background correlation attributable to polygenetic and shared environmental influences, ρ, equaled .05, .10, .15, .20, or .25.

[2] Our FORTRAN program includes the FORTRAN routine MULNOR (Schervish, 1984) to integrate the bivariate normal distribution. The source code of MULNOR and its auxiliary routines were downloaded from the website http://lib.stat.cmu.edu/apstat/.

If shared environmental influences are absent, twice ρ would equal the heritability due to genetic factors other than the QTL. The percentage of phenotypic variance attributable to the QTL equaled .05, .10, .15, and .20. Finally, additive, recessive and dominant gene action was specified. Optimal values of the percentages p_{cl}, p_{ch}, p_{dl}, and p_{dh} were found for the 420 cases to which these 4 factors gave rise (7 × 5 × 4 × 3). By considering both recessive and dominant gene action and allowing the allele frequency to range from .2 to .8, we introduce some redundancy into our results. For instance, results obtained for dominant gene action and a frequency of .3 are essentially same as those obtained for recessive gene action and a frequency of .7.

The mean optimal percentages are reported in the situation of no prior knowledge, of prior knowledge relating to gene action, and of knowledge relating to allele frequency. Mean optimal percentages are obtained by simply averaging over frequency, over gene action, or over both gene action and frequency. Having obtained recommendations in terms of these mean percentages, we investigate how well the recommendations fair in a small number of cases.

The obtained mean values of the percentages depend on the choice of N and M. To obtain an indication of how the percentages vary with N and M, we carried out the procedure mentioned for an N of 5,000, 10,000, and 15,000 and an M of 500 and 250. In all we have 420 cases within 6 conditions, i.e., a total of 2520 analyses.

RESULTS

Table I contains the overall means and standard deviations of the four percentages, p_{ch}, p_{cl}, p_{dh}, and p_{dl}. These values are obtained by averaging over both QTL gene action, QTL gene frequency, background correlation ρ, and QTL effect size. Depending on the values of N, the percentage of ED sib pairs to select exceeds the percentage of ECL and ECH sib pairs by a factor 1.9 to a factor 2.6. The mean values of the EC percentages range from about 4 to 11% and the ED percentages range from 11 to 21%. The standard deviations are quite large. In the case of p_{ch} and p_{cl} percentages, the standard deviation lies between 4.5 and 1.5%; in the case of the p_{dh} and p_{dl} percentages, the standard deviations equal about 10. As we are considering overall means, these large standard deviations are not surprising. So on the basis of the results in Table I, we would recommend, in the case of N = 5000 and M = 500, selecting the concordant sib pairs whose members both have phenotypic scores in the top 11% (ECH sib pairs) or the bottom 11% (ECL sib pairs) of the phenotypic distribution. We would recommend selection of discordant sib pairs, whose members have phenotypic scores in the top 21% and the bottom 21% of the phenotypic distribution.

Table I. Overall Mean Percentages: Grand Means Calculated Over Gene Action, Allele Frequency, QTL Effect Size, and Background Correlation ρ

	$p_{cl} = p_{ch}$	$p_{dh} = p_{dl}$
N (M = 500)		
5,000		
Mean	11.0	21.0
SD	4.5	10.0
10,000		
Mean	7.6	17.0
SD	3.4	10.0
15,000		
Mean	6.2	15.0
SD	2.5	11.0
N (M = 250)		
5,000		
Mean	7.6	16.8
SD	3.4	10.0
10,000		
Mean	5.3	13.7
SD	2.1	10.0
15,000		
Mean	4.2	11.6
SD	1.5	8.6

Table II contains the mean percentages associated with each mode of gene action. Average percentages are calculated over QTL allele frequency, QTL effect size, and background correlation. The mean percentages for codominant action are quite similar to the overall mean percentages reported in Table I. In the case of recessive gene action, a greater percentage of ECH sib pairs than ECL sib pairs is selected (about a factor of 2). The percentage P_{dl} exceeds the percentage P_{dh} (a factor of 2.5 to 3). The percentages are reversed for dominant gene action. Table III contains the mean percentages associated with the increasing allele frequencies .2, .5, and .7. Here the averages percentages are calculated over QTL gene action, background correlation, and QTL effect size. The means associated with the allele frequency .5 are very close to

Table II. Mean Percentages for Each Mode of Gene Action, Averaging Over QTL Effect Size, Allele Frequency, and Background Correlation, ρ

	Model	p_{ch}	p_{cl}	p_{dh}	p_{dl}
M = 500					
N = 5,000	cod				
	Mean	13.0	13.0	20.0	20.0
	SD	2.5	2.5	7.0	7.0
	rec				
	Mean	13.5	8.2	12.5	30.0
	SD	3.6	4.9	6.3	10.0
	dom				
	Mean	8.2	13.5	30.0	12.5
	SD	4.9	3.6	10.0	6.0
N = 10,000	cod				
	Mean	8.1	8.1	15.4	15.4
	SD	2.9	2.9	6.9	6.9
	rec				
	Mean	9.5	5.3	9.2	26.0
	SD	2.7	3.0	5.0	10.6
	dom				
	Mean	5.3	9.5	26.0	9.2
	SD	3.0	2.7	10.6	5.0
N = 15,000	cod				
	Mean	6.4	6.5	13.6	13.3
	SD	2.2	2.2	7.3	7.3
	rec				
	Mean	7.6	4.7	7.4	24.0
	SD	2.1	2.2	5.1	11.0
	dom				
	Mean	4.7	7.6	24.0	7.4
	SD	2.2	2.1	11.0	5.1
M = 250					
N = 5,000	cod				
	Mean	8.1	8.1	15.5	15.5
	SD	2.9	2.9	6.9	6.9
	rec				
	Mean	9.5	5.3	9.2	25.6
	SD	2.7	3.0	5.0	10.0
	dom				
	Mean	5.3	9.5	25.6	9.2
	SD	3.0	2.7	10.0	5.0
N = 10,000	cod				
	Mean	5.3	5.5	12.0	12.0
	SD	2.1	2.0	6.6	6.7
	rec				
	Mean	6.4	4.1	6.6	22.0
	SD	1.8	1.7	4.6	10.8
	dom				
	Mean	4.1	6.4	22.0	6.6
	SD	1.7	1.8	10.8	4.6
N = 15,000	cod				
	Mean	4.2	4.4	11.0	11.0
	SD	1.5	1.6	7.6	7.6
	rec				
	Mean	4.8	3.6	5.7	17.8
	SD	1.7	1.0	4.7	8.2
	dom				
	Mean	3.6	4.8	17.8	5.7
	SD	1.0	1.7	8.2	4.7

the overall mean values. The mean percentages associated with the frequency .2 are similar to those associated with recessive gene action. The mean percentages associated with the frequency .7 resemble those associated with dominant gene action.

Table IV contains the mean percentages associated with the background correlation ρ. Averages are calculated over frequency, mode of gene action, and QTL effect size. Only the mean percentages for the most extreme values (.05 and .25) are reported. For the values of M and N considered and the range of ρ, this correlation has a minor effect on the mean percentages. Table V, finally, contains the mean percentages calculated for the most extreme values of the percentage of variance accounted for by the QTL. For the range of values considered, and for the given N and M, we again find that the mean values of the percentages are hardly affected by the effect size of the QTL.

To show how the percentages vary, we plot the values of p_{cl}, p_{ch}, p_{dl}, and p_{dh} against the allele frequencies for each mode of gene action for the N = 5000 and M = 500 condition. The relationship between the percentages and the frequencies are approximated by means of second-order polynomials. The plots are shown in Fig. 1. As a measure of goodness of fit, we report the percentage of variance explained by the polynomial regression (R^2; rendered in the figure). From these values it is clear that the approximation of the relation between allele frequency and the selection percentages is quite good when gene action is known. In contrast, second-order polynomial regressions of the selection percentages on the background correlation and on the QTL effect size (not shown) explained no more than 8% (usually substantially less) of the variance in the percentages.

Test of Recommendations Based on the Mean Percentages

It is clear from the results in the tables that selection based on the overall mean percentages (Table I) will result in little loss of power when the QTL is codominant and (or) the allele frequency is about .5. In the present section, we present a more detailed account of loss of power incurred by sampling in the absence of specific knowledge concerning gene action or allele frequency. We consider a number of specific cases that are characterized by a given QTL effect size, QTL allele

Table III. Mean Percentages for Frequency Equaling .2, .5, and .7, Averaging Over Gene Action, QTL Effect Size, and Background Correlation (ρ)

	Freq.	p_{ch}	p_{cl}	p_{dh}	p_{dl}
M = 500					
N = 5,000	.2				
	Mean	13.0	7.7	10.0	32.0
	SD	4.2	3.8	4.8	7.5
	.5				
	Mean	12.0	12.0	20.8	20.8
	SD	4.5	4.5	10.0	10.0
	.7				
	Mean	10.0	13.0	27.0	14.0
	SD	4.8	1.8	10.0	5.4
N = 10,000	.2				
	Mean	10.0	4.1	7.4	28.0
	SD	2.3	1.5	3.2	9.3
	.5				
	Mean	8.0	8.0	15.8	16.2
	SD	3.5	3.5	9.0	9.0
	.7				
	Mean	6.3	9.3	22.0	11.0
	SD	3.2	2.3	11.0	5.1
N = 15,000	.2				
	Mean	8.0	3.9	5.7	27.0
	SD	1.6	1.3	2.3	10.0
	.5				
	Mean	6.3	6.3	14.6	13.9
	SD	2.6	2.6	9.2	9.2
	.7				
	Mean	5.1	7.5	21.0	8.6
	SD	2.2	1.8	11.8	5.1
M = 250					
N = 5,000	.2				
	Mean	9.9	4.1	7.4	28.0
	SD	2.3	1.5	3.2	9.3
	.5				
	Mean	8.0	8.0	16.0	16.0
	SD	3.5	3.5	8.8	8.8
	.7				
	Mean	6.3	9.3	22.0	11.0
	SD	3.2	2.3	11.0	5.1
N = 10,000	.2				
	Mean	6.7	3.4	5.3	23.7
	SD	1.7	0.4	2.0	9.3
	.5				
	Mean	5.2	5.6	13.5	13.1
	SD	2.1	2.1	10.0	10.0
	.7				
	Mean	4.6	6.1	18.8	7.7
	SD	1.9	1.8	10.0	4.2
N = 15,000	.2				
	Mean	4.9	3.3	3.8	20.0
	SD	1.7	0.0	1.4	6.0
	.5				
	Mean	4.2	4.5	11.0	11.0
	SD	1.5	1.6	8.7	8.7
	.7				
	Mean	4.0	4.4	15.1	7.6
	SD	1.4	1.6	8.5	5.6

Table IV. Mean Percentages for the Two Extreme Values of Background Correlation, ρ = .05 and ρ = .25, Averaging Over QTL Effect Size, Gene Action, and Allele Frequency

	ρ	$p_{ch} = p_{cl}$	$p_{dh} = p_{dl}$
M = 500			
N = 5,000	.05		
	Mean	12.0	19.0
	SD	5.0	10.0
	.25		
	Mean	10.5	22.0
	SD	4.5	10.0
N = 10,000	.05		
	Mean	8.5	15.0
	SD	4.1	10.0
	.25		
	Mean	6.7	18.0
	SD	3.4	10.0
N = 15,000	.05		
	Mean	7.0	13.0
	SD	3.0	10.0
	.25		
	Mean	5.4	16.0
	SD	1.7	10.0
M = 250			
N = 5,000	.05		
	Mean	8.5	15.0
	SD	4.0	10.0
	.25		
	Mean	6.7	18.4
	SD	3.1	10.0
N = 10,000	.05		
	Mean	6.1	11.6
	SD	2.7	9.0
	.25		
	Mean	4.9	14.6
	SD	1.7	10.0
N = 15,000	.05		
	Mean	4.8	10.0
	SD	1.7	7.0
	.25		
	Mean	3.3	14.0
	SD	0.0	10.0

frequency, background correlation, and mode of QTL gene action. In each case we calculate the selection percentages and the associated power of the EDAC test given full knowledge of the underlying QTL and background correlation. We refer to this power as "full information" (f.i.) power. In addition, we calculate the power using the mean selection percentages presented in Tables I to III. We refer to this power as "realized" power. In a number of these cases we deviate slightly from the values of the mean percentages to ensure that the number of selected sib pairs does not differ too greatly from the given M.

Table V. Mean Percentages for the Two Extreme QTL Effect Sizes, 5 and 20% of the Phenotypic Variance, Averaging Over Gene Action, Allele Frequency, and Background Correlation

	Effect	$p_{ch} = p_{cl}$	$p_{dh} = p_{dl}$
$M = 500$			
$N = 5{,}000$	5%		
	Mean	12.0	20.0
	SD	3.8	9.3
	20%		
	Mean	10.8	21.0
	SD	5.0	11.0
$N = 10{,}000$	5%		
	Mean	8.2	16.0
	SD	3.0	9.5
	20%		
	Mean	7.2	17.4
	SD	3.5	11.0
$N = 15{,}000$	5%		
	Mean	6.5	14.0
	SD	2.4	9.8
	20%		
	Mean	6.	15.7
	SD	2.5	11.0
$M = 250$			
$N = 5{,}000$	5%		
	Mean	8.2	16.0
	SD	3.0	9.5
	20%		
	Mean	7.2	17.4
	SD	3.5	11.0
$N = 10{,}000$	5%		
	Mean	5.5	12.7
	SD	2.3	9.1
	20%		
	Mean	5.0	14.8
	SD	1.7	11.0
$N = 15{,}000$	5%		
	Mean	4.5	10.7
	SD	1.7	7.5
	20%		
	Mean	4.0	12.0
	SD	1.4	9.2

Table VI contains the results for the $N = 5000$ and $M = 500$ condition, in which the QTL accounts for 15% of the phenotypic variance and the background correlation equals .20. The "realized" power is calculated using the percentages calculated in the $N = 5000$ and $M = 500$ condition (see Table I). The most serious deviation between realized power and full information power is observed in the case of recessive gene action and a low increasing allele frequency (or, equivalently, dominant gene action and a high increasing allele frequency). When gene action is dominant (recessive) and increasing allele frequency is low (high), the loss of power incurred using the overall mean selection percentages (Table I) is not large. When QTL gene action is codominant, the realized power again is close to the full information power.

Table VII contains result for the $N = 10{,}000$ and $M = 250$ condition. The QTL accounts for 10% of the phenotypic variance and the background correlation equals .1. We assume that our knowledge is limited to mode of gene action, i.e. codominant or recessive gene action. The realized power in Table VII is based on the mean percentages presented in Table II. When gene action is known, realized power and f.i. power do not differ greatly. Table VIII, finally, contains results for the situation in which our knowledge is limited to the increasing allele frequency (i.e., .7). Realized power is based on the selection percentages presented in Table III. Given the known allele frequency, again we observed quite good agreement between f.i. power and realized power.

DISCUSSION

It is striking that the background correlation, ρ, and the effect size of the QTL have little bearing on the selection per se. The latter finding has important practical implications. Although recombination between a marker and the QTL reduces the effect size (Risch and Zhang, 1996) by rendering the IBD distribution in a selected sample closer to the null distribution, this will not greatly affect the optimal values of the selection percentages. Of course, the QTL effect size will affect the power to reject the null hypothesis.

With respect to our comparisons of realized power and f.i. power (Tables VI–VIII), we may conclude that sib pair selection based on overall mean percentages will result in a serious loss of power only when the gene action is recessive (dominant) and the allele frequency is low (high). This agrees with previous findings (e.g., Eaves and Meyer, 1994; Carey and Williamson, 1991). When either the allele frequency or the gene action is known, the f.i. power and realized power do not differ greatly.

It is important to stress that all our results were presented for fixed values of N and M. We make no attempt to generalize the results obtained to other values of N and M. We see no real neces-

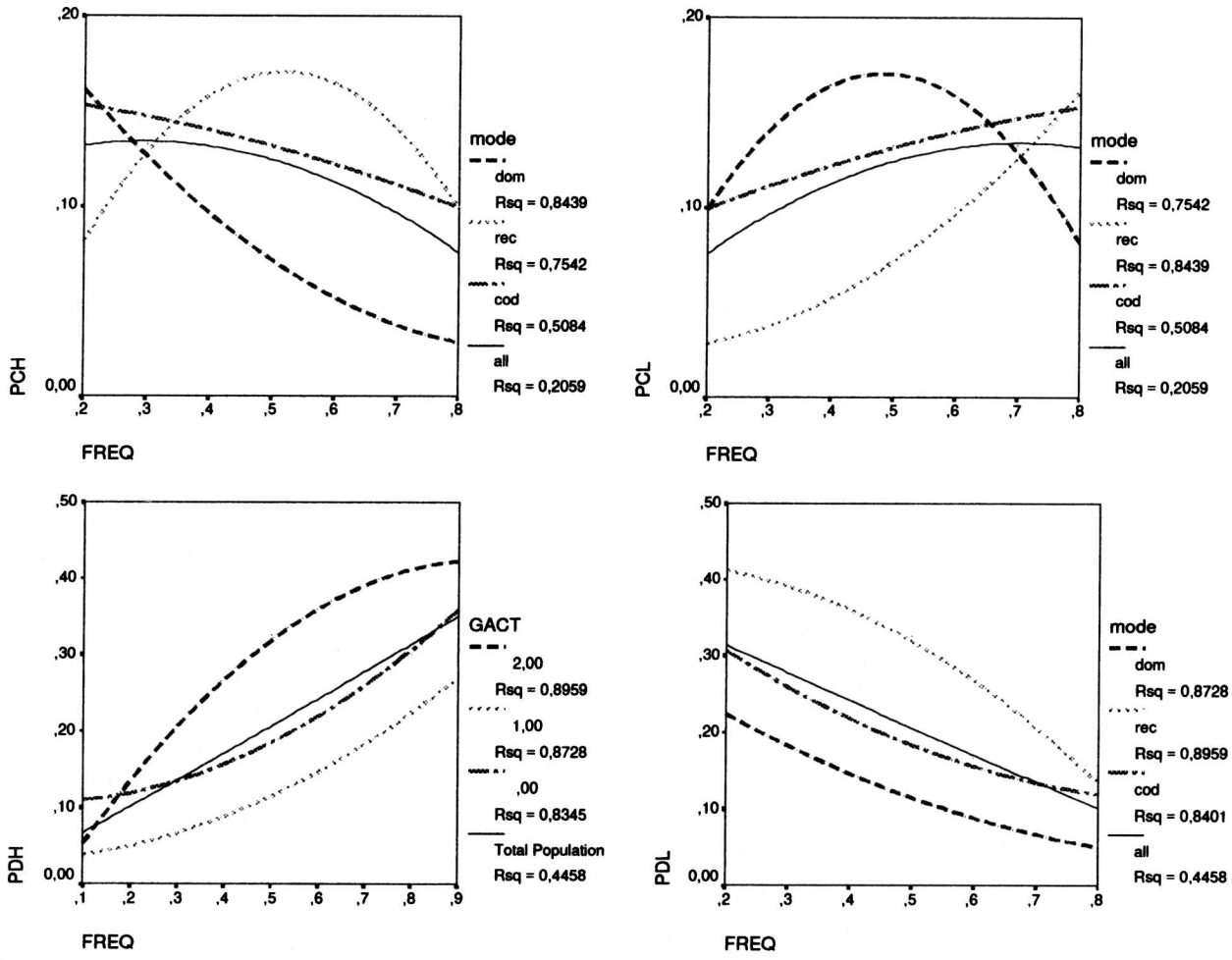

Fig. 1. Second-order polynomial regression of selection percentages on allele frequency for the three modes of gene action (N = 5000, N = 500).

sity to attempt such a generalization, because it is a relatively small effort to the calculate the optimal values of the percentages for specific values of N and M. On a 133-MHz PC, it takes about 7 h to carry out the calculations for each of the 6 sets of 420 cases.[3] This could be speeded up by ignoring genotype order, as Risch and Zhang (1995) do. This would reduce the number of G_k from 9 to 6. In addition, we have based or calculations on the full range of frequencies (.2–.8) and both types of nonadditive QTL gene action (recessive and dominance). As mentioned, this introduces a degree of redundancy, which can be avoided.

Our maximum bin size of 40% will have introduced some bias into the mean percentages reported in the tables. To assess the seriousness of this problem, we count the number of cases in which (1) this bound was hit, (2) the number of selected sib pairs was 10% below the maximum (i.e., $M < 225$ and $M < 450$), and (3) the power was less than .80 (α was set to equal .01). In the N = 5000, M = 250 condition, the N = 5000, M = 500 condition, the N = 10,000, M = 500 condition, and the N = 15,000, M = 500 condition, this was found to be so in 4, 8, 1, and 2% of the

[3] The FORTRAN program used to carry out the analyses reorted in the paper is available upon request. It calculates "optimal" selection percentages for a given choice of allele frequency, QTL gene action, background correlation, QTL effect size, N (total number of sibs), and M (maximum number of sibs to be genotyped). The results presented in this paper were obtained by repeated analyses which were driven by MSDOS batch files.

Table VI. Full Information Power and Realized Power Where QTL Effect = 15%, $\rho = .20$, $N = 5000$, $M = 500$, and $\alpha = .01$[a]

Freq.	Full information power	N0	N1	N2	NTOT	Realized power	N0	N1	N2	NTOT
					Mode: codominant					
.2	.75	46	218	231	495	.69	107	255	117	480
.3	.72	93	237	158	488	.69	109	254	115	478
.4	.71	94	237	156	487	.69	110	253	113	477
.5	.71	154	179	154	488	.69	112	253	112	477
					Mode: recessive					
.2	.96	13	76	60	149[b]	.62	90	316	112	518
.3	.90	13	252	161	426	.69	91	306	111	509
.4	.84	13	247	228	489	.68	93	299	107	499
.5	.77	45	225	226	496	.66	94	294	104	493
					Mode: dominant					
.2	.72	46	207	227	479	.65	97	206	103	487
.3	.70	152	183	152	487	.65	100	287	99	486
.4	.72	224	210	46	480	.65	102	290	97	488
.5	.77	226	225	45	496	.66	104	294	94	493

[a] Realized power is calculated using the selection percentages in Table I. $N0$, $N1$, and $N2$ are the number of ECL, ED, and ECH sib pairs selected, respectively. NTOT is the total number of selected sib pairs.

[b] This is a case in which the maximum bin size 40% was hit. Clearly this is not a problem here because the power is .96 given the selected 148 sib pairs. See the Discussion.

Table VII. Full Information Power and Realized Power When the QTL Gene Action Is Known: QTL Effect = 10%, $\rho = .10$, $N = 10{,}000$, $M = 250$, and $\alpha = .01$[a]

Freq.	Full information power	N0	N1	N2	NTOT	Realized power	N0	N1	N2	NTOT
					Mode: codominant (known)					
.2	.39	19	140	76	236	.32	40	154	46	240
.3	.34	20	141	74	234	.31	41	154	44	239
.4	.31	70	106	73	249	.30	42	154	43	239
.5	.30	71	79	71	222	.30	42	154	42	238
					Mode: recession (known)					
.2	.91	18	137	88	243	.85	25	166	74	263
.3	.70	18	148	80	247	.62	25	162	67	254
.4	.50	18	148	76	242	.45	26	160	63	248
.5	.38	19	145	74	237	.36	26	159	61	246

[a] Realized power is calculated using the selection percentages in Table II. $N0$, $N1$, and $N2$ are the number of ECL, ED, and ECH sib pairs selected, respectively. NTOT is the total number of selected sib pairs.

cases, respectively. In view of these findings, we are confident that the bias is slight. All cases that met the inclusion criteria involved either recessive gene action and a low allele frequency or dominant gene action and a high allele frequency.

Our power calculations are based on the EDAC test, which, as mentioned, focuses on the IBD distribution in selected samples. Several recent paper have been devoted to the incorporation of information relating to the IBD distribution in genetic covariance structure modeling (Fulker and Cherny, 1996; Eaves *et al.*, 1996). The resulting approach to QTL analysis is more flexible in that multivariate phenotypes can be accommodated

Table VIII. Full Information Power and Realized Power When the QTL Allele Frequency Is Known (.7): QTL Effect = 10%, ρ = .20, N = 15,000, M = 500, and α = .01[a]

Model	Full information power	$N0$	$N1$	$N2$	NTOT	Realized power	$N0$	$N1$	$N2$	NTOT
cod	.63	144	218	137	499	.62	155	198	84	471
rec	.56	138	186	138	462	.54	149	238	85	471
dom	.90	150	222	40	411	.83	161	248	79	488

[a] Realized power calculated using the percentages presented in Table III. $N0$, $N1$, and $N2$ are the number of ECL, ED, and ECH sib pairs selected, respectively. NTOT is the total number of selected sib pairs.

quite easily and provides a more powerful test of the presence of a QTL (Boomsma, 1996; Boomsma and Dolan, 1998). We are currently investigating how well our derived optimal selection percentages fair in this type of genetic covariance structure analysis.

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Edited by Stacey Cherny