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Further Evidence for the Increased Power of LOD Scores Compared with Nonparametric Methods

Martina Durner,[1] Veronica J. Vieland,[3] and David A. Greenberg[1,2]

Departments of [1]Psychiatry and [2]Biomathematics, Mount Sinai Medical Center, New York; and [3]Department of Preventive Medicine & Environmental Health, Division of Biostatistics, and Department of Psychiatry, University of Iowa College of Medicine, Iowa City

Summary

In genetic analysis of diseases in which the underlying model is unknown, "model free" methods—such as affected sib pair (ASP) tests—are often preferred over LOD-score methods, although LOD-score methods under the correct or even approximately correct model are more powerful than ASP tests. However, there might be circumstances in which nonparametric methods will outperform LOD-score methods. Recently, Dizier et al. reported that, in some complex two-locus (2L) models, LOD-score methods with segregation analysis–derived parameters had less power to detect linkage than ASP tests. We investigated whether these particular models, in fact, represent a situation that ASP tests are more powerful than LOD scores. We simulated data according to the parameters specified by Dizier et al. and analyzed the data by using a (*a*) single locus (SL) LOD-score analysis performed twice, under a simple dominant and a recessive mode of inheritance (MOI), (*b*) ASP methods, and (*c*) nonparametric linkage (NPL) analysis. We show that SL analysis performed twice and corrected for the type I–error increase due to multiple testing yields almost as much linkage information as does an analysis under the correct 2L model and is more powerful than either the ASP method or the NPL method. We demonstrate that, even for complex genetic models, the most important condition for linkage analysis is that the assumed MOI at the disease locus being tested is approximately correct, not that the inheritance of the disease per se is correctly specified. In the analysis by Dizier et al., segregation analysis led to estimates of dominance parameters that were grossly misspecified for the locus tested in those models in which ASP tests appeared to be more powerful than LOD-score analyses.

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Address for correspondence and reprints: Dr. Martina Durner, Department of Psychiatry, Mount Sinai Medical Center, Box 1229, One Gustave Levy Place, New York, NY 10029. E-mail: martina@shallot.salad.mssm.edu

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Introduction

In genetic analysis of common complex diseases, in which the underlying genetic model is unknown, many researchers prefer the use of affected sib pair (ASP) tests over LOD-score methods. This is the case despite the evidence that LOD scores calculated under the correct or even approximately correct model have a greater power to detect linkage than ASP tests (Goldin and Weeks 1993; Greenberg et al. 1996). The ASP tests and other "model-free" methods, although having less power to detect linkage, are perceived as having an advantage over LOD-score methods, because they do not assume an MOI, an assumption that is necessary in LOD-score analysis. However, it has been shown that LOD scores calculated with genetic parameters that are only approximated (i.e., "maximized maximum lod scores" ["Mod score" {Clerget-Darpoux et al. 1986}, "MMLS" {Greenberg 1990}, or "MODs" {Hodge and Elston 1994}]) are almost as powerful as LOD scores calculated under the correct model. This has been shown for a variety of complex genetic models, including epistatic (Greenberg and Hodge 1989; Vieland et al. 1992, 1993; Goldin 1994), heterogeneity (Durner and Greenberg 1992), and additive and intermediate models (Greenberg et al. 1998). One might expect, therefore, that MODs or MMLS are also more powerful than ASP tests. The question remains, however, whether there are any circumstances under which ASP will demonstrate more power than LOD-score methods?

Work by Dizier et al. (1996) has approached this question. They compared the power of one particular ASP test to the power of LOD scores when the genetic model is misspecified. They considered nuclear-family data and a variety of two-locus (2L) models, for which segregation analysis with the program POINTER (Lalouel and Yee 1980) gave evidence for a single major-gene (MG) effect. They then calculated exact expected maximum LOD scores (ELODs), using the MG model with the parameter estimates taken from the segregation analysis, as well as the correct 2L generating models. Finally, they compared the power of the MG LOD scores versus the power of an ASP test.

In 11 of 14 generating models that they used, the MG ELODs were extremely close to the ELODs calculated under the correct 2L model. As expected, in those 11 of 14 cases, the LOD-score method had higher power than the ASP test, despite the misspecification of the underlying model.

In the remaining three cases, however, the misspecified, POINTER-derived parameters led to a remarkable reduction of the ELOD, compared with that of the correct 2L ELOD. The corresponding loss of power was sufficiently great that the ASP test yielded higher power than the LOD-score test based on the misspecified MG model for these three cases. Thus, it might appear that Dizier et al. (1996) have shown that there do indeed exist complex genetic models for which an ASP test has higher power than a LOD test using a misspecified genetic model. In fact, the Dizier et al. (1996) article has already been cited as having established this result (Kidd 1997).

It is noteworthy, however, that these 3 models have in common one important feature that distinguishes them from the other 11; these 3 were the only models for which the MOI at the linked locus was recessive, whereas the segregation analysis yielded parameter estimates corresponding to a predominantly dominant MOI. Thus these were the only three models, considered by Dizier et al. (1996), for which the MOI (dominant vs. recessive) was misspecified *at the linked locus*.

Earlier work has clearly shown that misspecification of the MOI at the linked locus can lead to a substantial deflation of the power to detect linkage when LOD scores are used in simple Mendelian models (Greenberg 1990), in epistatic models (Greenberg and Hodge 1989; Vieland et al. 1992), and in heterogeneity models (Durner and Greenberg 1992), even to the point of falsely excluding linkage at the true recombination fraction (θ) (Vieland et al. 1993).

To a large extent, the Dizier et al. (1996) results for these complex models are further confirmation of previous observations. First, the power to detect linkage in a 2L model analyzed as though it were single-locus (SL) model is very close to the power when the true model is assumed, if the correct MOI is specified at the linked locus (Greenberg and Hodge 1989; Vieland et al. 1992, 1993). Dizier et al. (1996) have demonstrated this for models that are more complex than those that previously had been examined. Second, Dizier et al. (1996) also confirmed that, when the model *at the linked locus* is misspecified, the LOD score drops considerably. Third, they clearly point out the danger in using segregation analysis–derived parameters in a linkage analysis. Since segregation analysis looks for the overall pattern of inheritance of the trait, it can mislead with regard to the inheritance at the particular disease locus that is linked to the marker (Dizier et al. 1993).

There is one finding by Dizier et al. (1996) that appears to contradict previous literature. As noted above, in three of the models that they tested, ASP tests had more power to detect linkage than the LOD-score method using the segregation analysis-derived parameters. They concluded that there are circumstances in which ASP tests have more power than LOD scores.

We have hypothesized that the LOD-score method *appeared* to be less powerful than an ASP approach in the three above-mentioned cases because of the misleading nature of the segregation analysis-derived parameters. We observed that, whereas the segregation analysis suggested an essentially dominant MOI for the trait, the actual inheritance at the locus linked to the marker was, in fact, recessive. We believe that, in these cases, had the analyses of these data sets been performed twice—once under a simple dominant model and once under a recessive SL model—the evidence for linkage from LOD-score methods would also have been higher than from ASP tests. We were also curious to know how the nonparametric linkage (NPL) statistic (Kruglyak et al. 1996) would fare when presented with these complex models, compared with ASP and LOD-score methods.

In the present article, we used the framework put forward by Dizier et al. (1996). Using Monte-Carlo simulation, we generated nuclear families under the same generating parameters given by Dizier et al. (1996). We analyzed these data with the following linkage-analysis methods and compared the ELODs and the power to detect linkage of these different methods: (1) SL LOD-score methods performed twice—once under a dominant MOI and once under a recessive MOI (Greenberg and Hodge 1989)—and corrected for multiple testing (Hodge et al. 1997); (2) LOD-score methods with the segregation-derived parameters from Dizier et al. (1996); (3) the same ASP test used by Dizier et al. (1996); and (4) NPL analysis (Kruglyak et al. 1996), which is implemented in the computer program GENEHUNTER.

We show that, in all the situations tested, the power of LOD-score analysis performed twice (i.e., under a simple dominant and a recessive SL model) exceeded the power of the ASP test, even when we made conservative adjustment in the significance threshold to compensate for the fact that we conducted two LOD tests. Although, in these models, NPL analysis had greater power than ASP tests, LOD-score methods under misspecified SL models outperformed NPL analysis; and we observed instances in which NPL analysis would have missed linkage whereas LOD-score analysis, even after correction for multiple testing, gave strong evidence in favor of linkage. We conclude that, for those cases in which Dizier et al. (1996) reported that the ASP test had higher power than an MG LOD score, a simple pair of dominant and recessive SL LOD scores is more powerful than the ASP test.

Methods

Generating Methods

Nuclear families were simulated under models B2, E2, and F2, as specified by Dizier et al. (1996) (table 1). All three models are 2L models with one gene dominant and with the other gene recessive. Model B2 is a 2L epistasis model, whereas model E2 is a 2L heterogeneity model; model F2 represents a more complex model. The explicit penetrance vectors for the three models are shown in table 1.

Nuclear families were generated with exactly two affected sibs, as used by Dizier et al. (1996). However, in our simulation, sibship sizes were not fixed but were determined according to a well-specified distribution (Cavalli-Sforza and Bodmer 1971). The special selection requirement of two affected sibs shifted average sibship size to 4.6 sibs per family. Fully informative markers linked to each disease locus were generated according to the method of Dizier et al. (1996). θ between the marker and the disease locus was .05. For each model, 10,000 families were generated and were grouped into data sets of 100 families each. Because this was a Monte Carlo–type simulation, we were able to calculate means and SDs across the LOD scores and thus to observe the variation in the results that was due to chance. Linkage to each of the disease loci was determined separately.

Analysis Methods

1. LOD scores were calculated for all data under the following *analysis* models: (*a*) an SL dominant model with 50% penetrance (designated "SL_{dom}"), (*b*) an SL recessive model with 50% penetrance (designated "SL_{rec}"), (*c*) an SL model with parameters derived from the POINTER segregation analysis from Dizier et al. (1996) (see table 1) (designated "MG," since segregation analysis provided evidence for a major-gene effect), and (*d*) an exact 2L linkage analysis that used the generating-model parameters.

We calculated the population prevalence of the 2L trait from the generating parameters for each model. This population prevalence (table 1), in turn, was used to derive the gene frequencies for an assumed SL trait for SL_{dom} and SL_{rec}, by means of the following formulas: $q = \sqrt{k/f}$ (for the recessive gene frequency) and $q = 1 - \sqrt{(1 - k/f)}$ (for the dominant gene frequency), where k is the population prevalence and f is the penetrance. For the SL calculations, LIPED (Ott 1974) was used to calculate the LOD scores. TMLINK (Lathrop and Ott 1990) was used to calculate the LOD scores for the 2L analysis.

2. The distribution of allele sharing in ASPs was determined, and a goodness-of-fit test was used to compare the observed identical-by-descent (IBD) distribution to that expected under independent segregation of disease and of marker (i.e., .25, .5, and .2).

3. NPL analysis was performed with GENEHUNTER (Kruglyak et al. 1996), and the scoring function was set so that all individuals were examined simultaneously. For each generating model, the families were analyzed in 1,000 groups of 100 families/data set, which was the data-set size used by Dizier et al. (1996). We calculated the average LOD score (i.e., ELOD) and SD from the 1,000 data sets.

We also calculated the *power* of the aforementioned analysis methods. The power is presented as the proportion of data sets exceeding a given value of the test statistic. For comparison of the power of these different parametric and nonparametric methods, we were faced with the problem that each test follows or approximates a different distribution, which made the comparison and representation in one graph difficult. LOD scores can be approximated as a χ^2 with 1 df. The NPL scores approximately follow a standard normal distribution (Kruglyak et al. 1996). ASP scores, however, are

Table 1

Generating Parameters and Parameters Estimated by POINTER Segregation Analysis (Dizier et al. 1996)

Model	Penetrance Matrix	Generating Gene Frequencies	Marginal Penetrances	Population Prevalence	MG Parameters Estimated by POINTER
B2	$F = \begin{matrix} .5 & .5 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{matrix}$	$q_1 = .5$, $q_2 = .1$	$V_1 = (.095, 0, 0)$, $V_2 = (.125, .125. 0)$	.024	$q = .033$, $V = (.999, .30, .004)$
E2	$F = \begin{matrix} .5 & .5 & .5 \\ .5 & .5 & 0 \\ .5 & .5 & 0 \end{matrix}$	$q_1 = .2$, $q_2 = .01$	$V_1 = (.5, .01, .01)$, $V_2 = (.5, .5, .02)$	.030	$q = .037$, $V = (.999, .495, .003)$
F2	$F = \begin{matrix} .5 & .5 & 0 \\ .1 & 0 & 0 \\ .1 & 0 & 0 \end{matrix}$	$q_1 = .5$, $q_2 = .05$	$V_1 = (.05, 0, 0)$, $V_2 = (.2, .125, 0)$	.012	$q = .015$, $V = (.934, .329, .003)$

Table 2

Results of LOD-Score Analysis Assuming Different Analysis Models

Generating Model and Linked Gene	ELOD ± SD (θ ± SD)			
		SL		
	2L	Dominant[a]	Recessive[a]	MG[b]
B2:				
Recessive	7.1 ± 2.3 (.05 ± .04)	2.7 ± 1.5 (.21 ± .05)	6.7 ± 2.2 (.18 ± .05)	3.6 ± 1.7 (.14 ± .06)
Dominant	6.6 ± 2.2 (.05 ± .04)	6.1 ± 2.3 (.12 ± .05)	2.8 ± 1.5 (.24 ± .05)	6.4 ± 2.2 (.08 ± .04)
E2:				
Recessive	9.1 ± 2.3 (.03 ± .03)	3.7 ± 1.8 (.18 ± .05)	8.9 ± 3.0 (.14 ± .05)	4.0 ± 1.9 (.17 ± .05)
Dominant	2.1 ± 1.3 (.03 ± .05)	2.1 ± 1.3 (.23 ± .06)	0.5 ± 0.6 (.36 ± .08)	2.1 ± 1.3 (.22 ± .07)
F2:				
Recessive	6.1 ± 2.1 (.06 ± .04)	2.4 ± 1.3 (.22 ± .05)	5.7 ± 2.0 (.20 ± .03)	3.1 ± 1.5 (.16 ± .06)
Dominant	8.8 ± 2.4 (.05 ± .02)	8.2 ± 2.5 (.10 ± .03)	3.6 ± 1.7 (.22 ± .04)	8.7 ± 2.4 (.06 ± .02)

[a] Penetrance = .5.
[b] Model with parameters estimated by POINTER.

distributed as a χ^2 with 2 df. To facilitate comparison, we chose to plot power versus significance values associated with each test statistic. To put all the test statistics on the same scale, we plotted power versus −log10(significance level), instead of the significance level. For example, a LOD score of 3, an NPL score of 3.72, and an ASP score of 17 all correspond to a $P = .0001$; −log10 of $P = .0001$ is 4. A LOD score of 4 corresponds to approximately $P = 10^{-5}$ and $-\log(10^{-5}) = 5$, etc.

A LOD score maximized only with respect to θ follows approximately a one-sided χ^2 with 1 df. By testing with two dominance models (i.e., dominant and recessive), we have increased the type I error. Hodge et al. (1997) have shown that maximizing over dominance models at most doubles the significance levels. Thus, LOD scores maximized over θ and two dominance models can be approximated by a *two-sided* χ^2 test with 1 df. Hodge et al. (1997) have derived this result only for SL models. However, since an SL analysis well approximates more-complex models (Greenberg and Hodge 1989; Vieland et al. 1992, 1993; Goldin 1994) and linkage is tested for one locus at a time, one can conclude that this correction also applies for SL analysis when the MOI is a 2L model. In our power calculation, we therefore have adjusted the significance levels of the LOD scores, obtained by assuming a simple dominant or recessive MOI accordingly. The significance levels of the LOD scores under the correct genetic parameters, as well as those of the LOD scores for the POINTER-derived estimates, have been calculated from a one-sided χ^2 test with 1 df. The significance levels of the NPL statistic were calculated from the exact distribution as implemented in GENEHUNTER.

Results

2L LOD Scores versus SL LOD Scores

It is important to recall that we are focusing here on the three models reported by Dizier et al. (1996), in which the evidence for linkage with LOD scores was less than the evidence under the ASP method.

As has been noted above, an SL analysis provides a very close approximation of the correct LOD-score (i.e., the LOD score calculated under a 2L model with the correct [generating] genetic parameters) when the MOI *at the linked locus* is assumed in the SL analysis. We show in table 2 that this SL approximation can be also found in the models investigated here. When we examined linkage to the *recessive* locus, the ELODs for a *simple recessive* inheritance are almost as high as the 2L ELODs; and, vice versa, the ELODs for the *dominant* locus are very similar under the 2L parameters and under the approximated *dominant* SL parameters. For example, when linkage to the recessive locus in model B2 was investigated, the ELOD for the correct 2L model (calculated under the parameters of the generating model) was 6.4, whereas the SL_{rec} ELOD for simple recessive inheritance was 5.8.

Misspecification of the Dominance Model at the Linked Locus

When the dominance model in the SL analysis for the linked locus was misspecified, the SL ELOD was substantially reduced compared with the 2L ELOD, in all the examined models (table 2). For the example given above, in which linkage to the *recessive* locus was examined, the SL *dominant* ELOD was 1.7, compared with a 2L ELOD of 6.4.

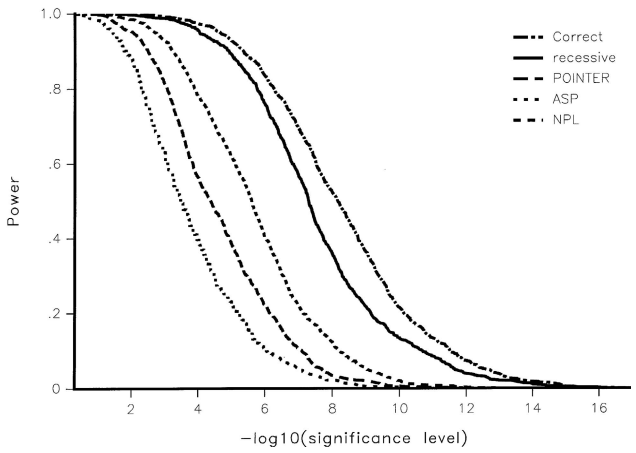

Figure 1 Power curves for SL analysis, corrected for multiple testing (recessive), 2L analysis (Correct), LOD-score analysis with POINTER-derived parameters (POINTER), ASP analysis (ASP), and NPL analysis (NPL)—for generating model B2, with linked gene recessive.

MG Model versus Simple Dominant or Recessive Model

In those cases in which a LOD-score analysis using POINTER-derived parameters performed well (models B2 dominant, E2 dominant, and F2 dominant), the LOD scores were very similar to those derived from the simple SL analysis with a dominant MOI and 50% penetrance (table 2). However, when linkage to the recessively linked gene was investigated, the approach of using an SL analysis assuming a simple recessive MOI and 50% penetrance actually outperformed the analysis using the POINTER-derived parameters (table 2).

The ELODs in our analyses were, on average, slightly higher than the LOD scores reported by Dizier et al. (1996). We attribute this to the somewhat larger sibship size in our simulations. Also, as can be seen in table 2, there is broad variation in the LOD scores among the data sets of 100 families each. We cannot compare our results with those of Dizier et al. (1996), because the latter did not estimate such variation.

θ

The estimates of θ at the maximum LOD score, however, were quite inaccurate under a simple dominant or recessive SL analysis, as well as under the MG analysis with POINTER-estimated parameters (table 2). The θ values were .09–.21, when the true (i.e., generating) θ was .05.

Power to Detect Linkage

The results of our power simulations are presented in figure 1–6. Note that, for the ASP, NPL, 2L LOD-score analyses and for the LOD-score analysis using POINTER-derived parameters, we used one-sided tests. For the simple dominant or recessive analyses, we present the curve corresponding to the SL analysis (either simple dominant or recessive) that had more power, but, by applying a two-sided test (also see the Methods section), we correct for testing with two modes of inheritance.

The LOD-score analysis under the correct genetic parameters is considered the gold standard in linkage analysis, which is reflected in the fact that the highest power was found by assuming the true, or 2L, model in the linkage analysis. An SL analysis performed twice and corrected for the increase in type I error had almost as much power as a 2L analysis. In all the models tested, a simple dominant or recessive SL analysis was more powerful than either an ASP analysis or an NPL analysis. NPL analysis had more power than ASP tests, in all instances. When we looked at the power at a nominal significance level of .0001 (i.e., the number of data sets reaching or exceeding this level), we found that, for model B2, ASP tests were approximately half as powerful as an SL analysis, for detection of linkage to either the dominant or the recessive gene. The loss of power was most pronounced at the dominant locus in model E2. Here, ASP tests had ~13%—and NPL analysis had ~36%—of the power of an SL analysis performed twice and corrected for multiple testing. The power of detection of evidence for linkage to the dominant locus was,

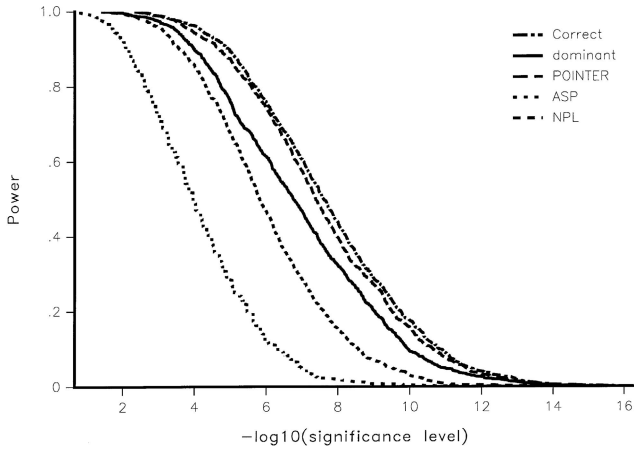

Figure 2 Power curves for SL analysis, corrected for multiple testing (dominant), 2L analysis (Correct), LOD-score analysis with POINTER-derived parameters (POINTER), ASP analysis (ASP), and NPL analysis (NPL)—for generating model B2, with linked gene dominant.

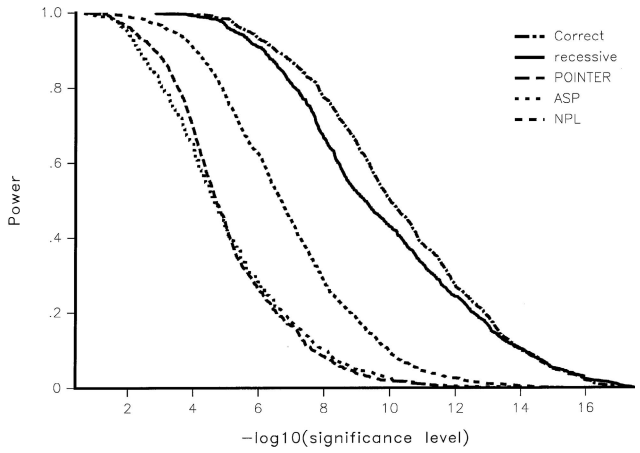

Figure 3 Power curves for SL analysis, corrected for multiple testing (recessive), 2L analysis (Correct), LOD-score analysis with POINTER-derived parameters (POINTER), ASP analysis (ASP), and NPL analysis (NPL)—for generating model E2, with linked gene recessive.

in general, low for this model, even when the correct parameters were assumed in the 2L analysis. Model E2 is basically a dominant-recessive 2L heterogeneity model. The amount of heterogeneity in each data set was determined by the gene frequencies of the different loci. Because of the low gene frequency of the dominant gene relative to the recessive gene, each data set contained more families with the recessive form than with the dominant form. On average, only one-third of the families had the dominant gene, whereas two-thirds of them had the recessive gene (the ascertainment scheme was not taken into account). This facilitated detection of linkage to the recessive locus. The overall information for linkage to the dominant locus, in contrast, was very low.

When linkage to the dominant loci was investigated, the LOD-score analysis with POINTER-derived parameters performed extremely well, compared with the 2L analysis. However, when linkage to the recessive loci was tested, MG LOD-score analysis and the ASP test had very little power. In model B2 the power of an MG analysis was slightly better than that of an ASP test, in model E2 the power was about equal, and in model F2 the power of the ASP test even exceeded the power of an SL analysis with POINTER-derived parameters.

Discussion

Unraveling the genetics of common complex diseases has proved to be more difficult than anticipated. With few success stories, much controversy has risen on which analysis method to use. The main issue at this point, however, is not so much the findings of spurious results but under what conditions the analysis methods fail to detect an existing linkage.

As noted above, several studies have now shown, for a broad range of complex generating models, that, if one analyzes data from a multilocus model assuming an SL, then one loses little ability to detect linkage (Greenberg and Hodge 1989; Vieland et al. 1992, 1993; Greenberg et al. 1998). The Dizier et al. (1996) work also has shown that simply applying the results of a segregation analysis to linkage data can lead to a major reduction in the power to detect linkage. However, the conclusion by Dizier et al. (1996) that there are circumstances in which ASP tests have more power to detect linkage than LOD-score analysis (Dizier et al. 1996, p. 1338) is misleading, in that it depends on the acceptance of the results of the segregation analysis, which already had been called into question by a previous study (Dizier et al. 1993). It is unfortunate that this misconception has led some to conclude that "individual loci in epistatic systems can be missed by standard linkage analysis" (Kidd 1997, p. 105).

We have shown here that, for the models tested by Dizier et al. (1996), an SL LOD-score analysis performed twice—once under a simple recessive model and once under a simple dominant model—has substantially greater power than nonparametric methods (both ASP tests and NPL tests), even after the type I–error inflation due to multiple testing is taken into account.

The crucial point here is not whether, in some situations, ASP tests have more power to detect linkage than LOD-score methods (and it still remains to be determined whether there are indeed such situations) but that Dizier et al. (1996) have used segregation analysis to

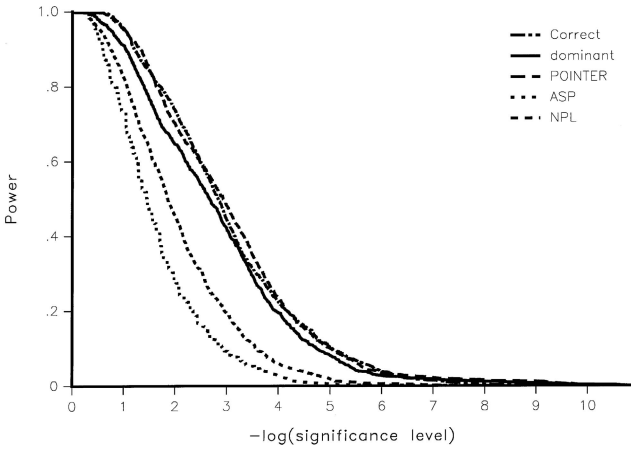

Figure 4 Power curves for SL analysis, corrected for multiple testing (dominant), 2L analysis (Correct), LOD-score analysis with POINTER-derived parameters (POINTER), ASP analysis (ASP), and NPL analysis (NPL)—for generating model E2, with linked gene dominant.

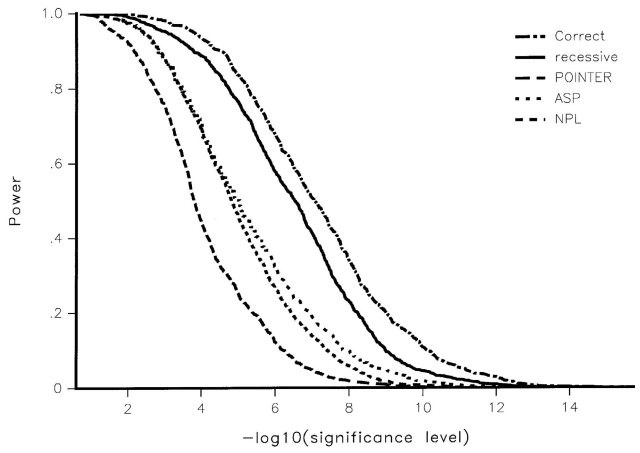

Figure 5 Power curves for SL analysis, corrected for multiple testing (recessive), 2L analysis (Correct), LOD-score analysis with POINTER-derived parameters (POINTER), ASP analysis (ASP), and NPL analysis (NPL)—for generating model F2, with linked gene recessive.

derive the genetic parameters for the LOD-score analysis. In the genetic models reported by Dizier et al. (1996), the disorder was caused by two loci—one dominant and one recessive. Segregation analysis supported a predominantly dominant major-gene effect for each model. Thus, the use of these estimated parameters in linkage analysis grossly misspecified the underlying genetic model for the linked recessive gene, in three cases. The resulting loss in power was sufficient to make the LOD-score test less powerful than the ASP test. We also note that these three cases, in which the MOI of the linked gene is roughly recessive, are the "best case" for an ASP test. When the MOI is dominant, then not only will the power of a LOD-score analysis assuming a recessive inheritance be reduced but so will the power of an ASP test.

Since segregation analysis looks at the overall pattern of inheritance of the trait, it cannot determine the pattern of inheritance related to any one locus in a multilocus system. Since linkage analysis only examines the chromosomes in a linear fashion—that is, one region at a time—the use of segregation analysis can lead to false specification of the dominance at a particular locus. This failure of segregation analysis had been observed earlier by Dizier et al. (1993). In that study, they had investigated simulated 2L data, using segregation analysis. Segregation analysis with POINTER led to the conclusion that there was a major-gene effect with or without a polygenic component. Sometimes, however, the estimate of the dominance parameter was different from the generating dominance parameter for one of the two loci, a result that we have shown can lead to the failure to detect linkage when such an estimate is used in linkage analysis.

We also want to stress an additional point: For linkage analysis, families are often collected only *because* they have multiple affected members; and the basic assumptions of standard ascertainment-correction approaches are often violated. Thus, the results of a segregation analysis may also be unreliable because of ascertainment bias, for which it may be almost impossible to correct (Greenberg 1986). These observations suggest that the usefulness of a combined segregation/linkage analysis approach is open to question.

It has been shown that LOD scores are relatively robust to the misspecification of certain parameters, such as penetrance and gene frequency (Clerget-Darpoux et al. 1986; Vieland et al. 1992, 1993). Misspecification of the apparent penetrance will affect the estimate of θ but will not have a profound effect on the LOD score (Greenberg 1990). The LOD score, however, is sensitive to the dominance model (Greenberg and Hodge 1989; Greenberg 1990; Hodge and Elston 1994); for example, evidence for linkage to a recessive gene can be missed, if the data are analyzed only under a dominant model, and vice versa.

In complex models, in which the trait expression may be influenced by several different loci, at each locus either one or both alleles contribute to the trait expression, thus conferring either dominant or recessive inheritance *at the specific locus*. Several simulation studies with complex genetic models have shown that, when linkage to one of these loci is examined, it is not necessary to correctly specify the genetic model for the trait *per se*, (i.e., to specify all the loci involved). The crucial issue in the analysis is the dominance model of that specific locus. The action of other gene(s) can be subsumed under re-

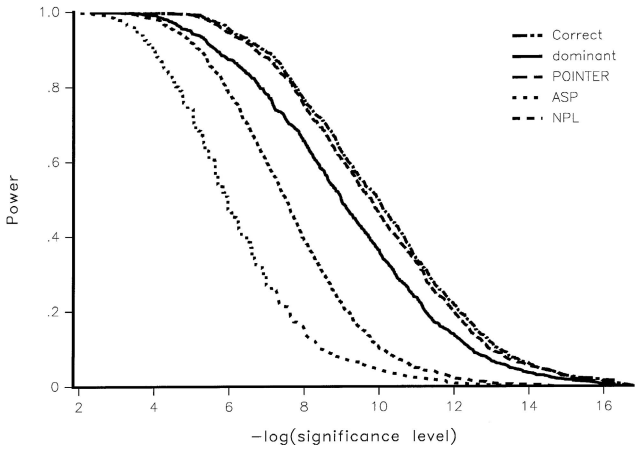

Figure 6 Power curves for SL analysis, corrected for multiple testing (dominant), 2L analysis (Correct), LOD-score analysis with POINTER-derived parameters (POINTER), ASP analysis (ASP), and NPL analysis (NPL)—for generating model B2, with linked gene dominant.

duced penetrance or phenocopies for analysis purposes, and information about linkage is almost as high as that which can be obtained from an analysis done with the correct genetic parameters. This has been shown for several epistatic and heterogeneity models (Greenberg and Hodge 1989; Durner et al. 1992; Vieland et al. 1992, 1993; Goldin 1994). Greenberg et al. (1998) also have demonstrated this for intermediate and additive models.

In general, the inheritance pattern of the specific gene under investigation in a multilocus disease cannot be known. Greenberg and Hodge (1989) and Vieland et al. (1992, 1993) have suggested that, in situations in which the "correct" dominance model is unknown, one performs an SL LOD-score analysis twice—once under a dominant model and once under a recessive model. The correction for multiple testing under these circumstances has been investigated by Hodge et al. (1997).

A simple SL LOD score calculated twice and "corrected" for the type I–error increase associated with the use of two tests had, in all instances considered by Dizier et al. (1996), more power to detect linkage than either the χ^2 ASP test or the NPL test, sometimes by a substantial amount. However, it might be asked whether this result hinges on the choice of these two particular model-free tests. We used the χ^2 test because this is the test used by Dizier et al. (1996) in their original analyses. Another choice would have been the test of the mean number of alleles shared IBD by ASPs (the "mean test"), which, in many circumstances, may be expected to have greater power than the χ^2 test (Blackwelder and Elston 1985). However, the mean test has statistical properties identical to those of a LOD-score analysis assuming recessive inheritance and full penetrance for data consisting of ASPs and their phenotypically unknown (or unaffected) parents (Knapp et al. 1994). Thus, this test would do as well as a simple recessive LOD-score for ASPs, when the true MOI at the linked locus is recessive, but would lose power, compared with a dominant LOD score, when applied to a dominant trait. The magnitude of this loss has been discussed by Hodge (1998). (Note also that, by allowing for reduced penetrance in our analyses, we were able to make efficient use of unaffected siblings, so that the power of the mean test would be expected to be lower than the power of our recessive SL LOD test). Other nonparametric-linkage tests also have been demonstrated to be more powerful than NPL or χ^2 ASP tests (Davis and Weeks 1997). However, our SL approximations have been so close to the correct 2L LOD scores that other methods are unlikely to be as powerful; but this is an area for further investigation.

For some of the models that we tested, the power of a simple SL approach has been underestimated because we did not make use of one of the major advantages of parametric linkage analysis—that is, the ability to account for heterogeneity. Heterogeneity is one of the most confounding factors in the detection of genes for common complex diseases. So far, there is no way to take heterogeneity into consideration when so-called model-free tests are used. It is also noteworthy that, in the heterogeneity model (model E2), the loss of power for the nonparametric methods compared with a simple SL analysis was the greatest. When linkage for the dominant locus was examined, the ASP test had 87% less power—and the NPL test had 64% less power—to detect linkage at a nominal significance level of $P = .0001$ than a simple dominant LOD-score analysis corrected for multiple testing. The low power for this model in general, even when the correct parameters are used in the analysis, also points to the need to find strategies to reduce heterogeneity—perhaps at a phenotypic level rather than on a statistical level—and suggests that the complexity of the underlying genetic model or the genetic analysis methods may be only secondary issues.

We conclude that segregation analysis can lead to false estimates of genetic parameters, estimates that, when used in linkage analysis, can miss the detection of linkage. If the genetic model is unknown, then the better way to proceed is to perform a linkage analysis twice—once under a simple dominant model and once under a simple recessive model—with an arbitrary penetrance such as .5. In the situations that we have tested, we have shown that an SL analysis provides higher power than the model-free tests, even after correction is mad for the use of two tests. Although these results confirm previous reports by Greenberg et al. (1998) and others (Greenberg and Hodge 1989; Vieland et al. 1992, 1993; Goldin and Weeks 1993; Goldin 1994), further work of course remains to be done, to establish whether there are indeed circumstances under which model-free methods may have higher power than the simple pair of LOD-score analyses that we have examined here.

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