Affected Sib Pair Identity by State Analyses

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Four methods using identity by state (IBS) data from affected sib pairs are compared for their ability to detect linkage between a diallelic marker and disease. A joint null hypothesis of no linkage and no linkage disequilibrium between the marker and disease must be considered. Two tests have undesirable properties in the case of linkage disequilibrium. Which of the other two tests has more power is dependent on the presence or not of linkage disequilibrium. The procedure of choice when possible is to type parents of affected sib pairs: the null hypothesis of no linkage can then be tested using identity by descent (IBD) values from informative parents, and the null hypothesis of no marker association with disease (linkage equilibrium) can be tested independently using the marker allele frequencies in the affected sib pairs.   © 1994 Wiley-Liss, Inc.

INTRODUCTION

Initial studies to detect the presence of a disease predisposing gene in a genetic region will often involve marker systems which are not highly polymorphic. The affected sib pair method, which has been used extensively to demonstrate linkage for a number of diseases associated with the human leukocyte antigen (HLA) system [see, for example, Cudworth and Woodrow, 1975; deVries et al., 1976; Stewart et al., 1981; Hors and Dausset, 1983; Payami et al., 1985, 1986; Rigby et al., 1991], is also applicable to systems other than HLA. In the affected sib pair method, linkage of a disease with a marker system is established by demonstration within families of nonrandom segregation of parental alleles to affected children. For markers which are not highly polymorphic, either only the segregation from informative parents can be considered, or else the deviations from random expectations in affected sib pairs, or other relatives, of identity by state (IBS), rather than identity by descent (IBD),

values can be considered [Lange, 1986a,b; Weeks and Lange, 1988; Bailey-Wilson et al., 1989; Cantor, 1989; Fimmers et al., 1989; Goldstein et al., 1989; Maestri et al., 1989; Motro et al., 1989; Sandkuyl, 1989; Van Eerdewegh et al., 1989; Bishop and Williamson, 1990; Risch, 1990].

In comparison to lod score analysis and association studies, which are two other standard approaches used in mapping disease genes to a particular genetic region, the affected sib pair method has some appealing features. It is nonparametric: mode of inheritance of the disease does not need to be specified as it does for lod score analysis. Further, linkage disequilibrium between the marker and disease genes, i.e., a marker association with disease, is not necessary for establishing linkage using the affected sib pair method.

Our aim in this paper is to consider the statistical power to detect linkage between a diallelic marker and disease of four different approaches using affected sib pairs. These tests, the marker genotype combinations test, the IBS values test, the mean IBS value test, and the mean IBD value test, only use information on IBS values in affected sib pairs, and do not take account of parental marker information.

THE MODEL AND MARKER GENOTYPE COMBINATIONS

We consider a single locus, two allele disease model, and allow for an intermediate mode of inheritance. Thus, if D is the disease predisposing allele, the probabilities of DD, Dd, and dd individuals being affected with the disease (the penetrance values) are x, λx, and 0 (respectively), where $0 < x \leq 1$ and $0 \leq \lambda \leq 1$. The mode of inheritance of the disease is recessive when $\lambda = 0$, additive when $\lambda = 1/2$ and dominant when $\lambda = 1$.

Let A be a marker locus with two codominant alleles A_1 and A_2 (thus the three marker genotypes A_1A_1, A_1A_2, and A_2A_2 can be distinguished), and denote by θ ($0 \leq \theta \leq 1/2$) the recombination fraction between the marker and disease loci. Let p_D ($0 < p_D < 1$) denote the frequency of the disease predisposing allele in the general population. Using the notation of Thomson and Bodmer [1977a,b], and Thomson [1983], the frequency of haplotype A_1D is given by kp_D, and the frequency of A_1d by $c(1 - p_D)$, where $k = P(A_1 \mid D)$ and $c = P(A_1 \mid d)$. Clearly, $kp_D + c(1 - p_D) = P(A_1)$, the frequency of the marker allele A_1 in the general population, and in the absence of linkage disequilibrium between the marker and disease loci $k = c = P(A_1)$.

An affected sib pair can belong to one of six possible genotype combinations at the marker locus, namely both affected sibs can be A_1A_1, both A_1A_2, or both A_2A_2, or one sib can be A_1A_1 and the other A_1A_2, one A_1A_2 and the other A_2A_2, or one A_1A_1 and the other A_2A_2. Let $\pi_1, \pi_2, \ldots, \pi_6$ denote the corresponding probabilities for these six marker genotype combinations.

Under the usual assumptions with affected sib methods of no selective disadvantage of affected individuals, random mating of parents and Mendelian segregation at the disease locus, the values of π (for any mode of disease inheritance) can be explicitly expressed. These probabilities, which are functions of λ, p_D, $P(A_1)$, k, and θ, are generally quite complicated, and will not be given here. The probabilities for any general set of parameter values can be obtained using the ordered notation method of Thomson [1994] for affected sib pairs, i.e., multiplex sibs (MS) pedigrees. The probabilities for a recessive model with $\theta = 0$ are given in Motro et al. [1989].

If the marker and the disease are unlinked ($\theta = 1/2$), and there is no linkage disequilibrium between the marker and disease loci, i.e., $k = c = P(A_1)$, the probabilities of the six marker genotype combinations can readily be obtained, and are, for any model of disease,

$$\pi_1 = \text{Pr(both are } A_1A_1) = P(A_1)^2[1 + P(A_1)]^2/4 \tag{1a}$$

$$\pi_2 = \text{Pr(both are } A_1A_2) = P(A_1)P(A_2)[1 + P(A_1)P(A_2)] \tag{1b}$$

$$\pi_3 = \text{Pr(both are } A_2A_2) = P(A_2)^2[1 + P(A_2)]^2/4 \tag{1c}$$

$$\pi_4 = \text{Pr}(A_1A_1 \text{ and } A_1A_2) = P(A_1)^2 P(A_2)[1 + P(A_1)] \tag{1d}$$

$$\pi_5 = \text{Pr}(A_1A_2 \text{ and } A_2A_2) = P(A_1)P(A_2)^2[1 + P(A_2)] \tag{1e}$$

$$\pi_6 = \text{Pr}(A_1A_1 \text{ and } A_2A_2) = P(A_1)^2 P(A_2)^2/2 \tag{1f}$$

where $P(A_2) = 1 - P(A_1)$.

One can also consider the distribution of identity by state (IBS) values for an affected sib pair, that is, the distribution of the number of marker alleles which are common (whether or not through identity by descent) to both sibs [Lange, 1986a,b]. Thus, the IBS values for an affected sib pair can be either 2, 1, or 0, with probabilities $A = \pi_1 + \pi_2 + \pi_3$, $B = \pi_4 + \pi_5$, and $C = \pi_6$ (respectively). Figure 1 illustrates the IBS probabilities for the full range of values of p_D, the disease allele frequency ($0 < p_D < 1$) (in a two-dimensional space) for the three modes of disease inheritance
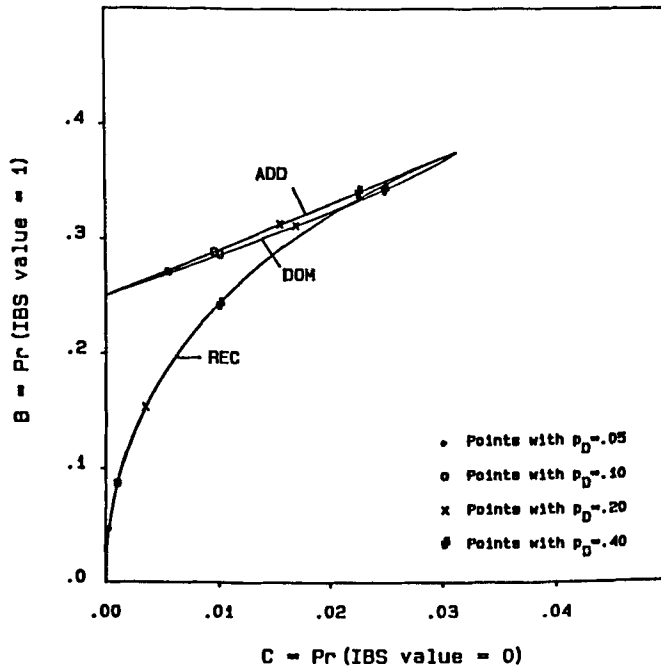

Fig. 1. The affected sib pair IBS distribution values of sharing 1 (B) and sharing 0 (C) marker alleles, for recessive, dominant and additive models for $0 < p_D < 1$, with $k = c = 0.5 = P(A_1)$.

(recessive, additive, and dominant), for a case in which there is no linkage disequilibrium between the marker and the disease [that is, for a case in which $k = c = P(A_1)$], and $P(A_1) = 1/2$. The figure clearly demonstrates that the additive and the dominant models are practically indistinguishable from each other, a phenomenon already familiar from identity by descent (IBD) distributions for affected sib pairs [see Motro and Thomson, 1991]. Further, note that the range of values of C [Pr(IBS value = 0)] is very small, and in practice it is difficult to distinguish between recessive and dominant expectations, unless for the recessive model p_D is sufficiently small.

If the marker and the disease are unlinked ($\theta = 1/2$), and $k = c = P(A_1)$, the distribution of the IBS values is

$$A = \text{Pr(IBS value} = 2) = (1 - \alpha)^2 + \alpha^2/2 \tag{2a}$$

$$B = \text{Pr(IBS value} = 1) = 2\alpha(1 - \alpha) \tag{2b}$$

$$C = \text{Pr(IBS value} = 0) = \alpha^2/2, \tag{2c}$$

where $\alpha = P(A_1)P(A_2)$.

The expectation of the mean IBS value for a diallelic marker locus, when $\theta = 1/2$ and $k = c$, is

$$\mu = 2A + B = 1 + (1 - \alpha)^2. \tag{3}$$

TESTING FOR LINKAGE (USING ONLY AFFECTED SIBS)

In testing for linkage between a marker and a disease, using only data from affected sibs, we have considered four different approaches. An assumption common to all the approaches is that the marker allele frequencies in the general population are known [that is $P(A_1)$ is given]. Erroneous specification of $P(A_1)$ can lead to incorrect conclusions about the presence, or absence, of linkage. This has been documented by Babron et al. [1993] for the affected-pedigree-member method of linkage analysis of Weeks and Lange [1988].

A further problem with IBS affected sib pair methods is that we cannot test if the marker and disease are unlinked ($\theta = 1/2$), without also confounding the test with the assumption of linkage equilibrium. If there is linkage disequilibrium ($k \neq c$), the expectations for $\pi_1, \pi_2, \ldots, \pi_6$ [see Eqs. (1)] will differ, depending on mode of inheritance, even when $\theta = 1/2$. Any test of $\theta = 1/2$ which allowed for $k \neq c$ would thus be partially confounded with a test of mode of inheritance. Thus, in all the tests below the null hypothesis of marker and disease "unlinked" refers to the joint null hypothesis, $H_0 : \theta = 1/2$, and the alleles are in linkage equilibrium [$k = c = P(A_1)$]. Thus, evidence for "linkage" implies that $\theta \neq 1/2$, or $k \neq c$, or both.

The Marker Genotype Combinations (MGC) Test

The first approach, which we call the marker genotype combinations (MGC) test, is based on fitting the observed frequencies in each of the six marker genotype combinations ("both A_1A_1," "both A_1A_2," $\ldots$, "one A_1A_1 and one A_2A_2") to the frequencies expected under the assumption the marker and the disease are "unlinked"

[that is, to the frequencies obtained from Eqs. (1)]. The goodness of fit is measured by a chi-square statistic, which under the null hypothesis has approximately a chi-square distribution of 5 degrees of freedom.

The IBS Values Test

The second approach, the IBS values test, is based on fitting the observed frequencies in each of the three IBS categories (2, 1, or 0) to the frequencies expected for "unlinked" marker and disease loci [that is, to the frequencies obtained from Eqs. (2)]. Under the null hypothesis, the goodness of fit statistic has a chi-square distribution with 2 degrees of freedom.

The Mean IBS Value Test

The third approach, the mean IBS value test, tests if the mean IBS value of the sample is equal to μ [given in Eq. (3)]. Thus if n_2, n_1, and n_0 are the observed numbers of sib pairs (in a sample of size n) that share 2, 1, and 0 marker alleles IBS (respectively), the null hypothesis of marker and disease "unlinked" will be rejected whenever

$$t_{IBS} = \frac{[(2n_2 + n_1)/n - \mu][n(n - 1)]^{1/2}}{[4n_2 + n_1 - (2n_2 + n_1)^2/n]^{1/2}} \tag{4}$$

is larger than the appropriate value of the t distribution with $n - 1$ degrees of freedom.

The Mean IBD Value Test

The fourth approach, the mean IBD value test, is based on transforming the six marker genotype combinations into mean identity by descent (IBD) values expected under the null hypothesis of marker and disease loci "unlinked" [see Haseman and Elston, 1972]. The mean IBD values for the six marker genotype combinations $(\tau_1, \tau_2, \ldots, \tau_6)$ are given in Table I. Under the assumption of the marker and the disease loci "unlinked," the expectation of the mean IBD value is 1. The test is done by calculating the sample mean of the transformed data and checking whether or not it is larger than 1 (using a t test). More specifically, if in a sample of n affected sib pairs, the observed numbers at the six marker genotype combinations are $n_1, n_2, \ldots, n_6$, the

TABLE I. Mean IBD Values for the Six Marker Genotype Combinations*

Marker genotype combinations	Mean IBD value
Both are A_1A_1	$\tau_1 = 2/[1 + P(A_1)]$
Both are A_1A_2	$\tau_2 = 3/2[1 + P(A_1)P(A_2)]$
Both are A_2A_2	$\tau_3 = 2/[1 + P(A_2)]$
A_1A_1 and A_1A_2	$\tau_4 = 1/[1 + P(A_1)]$
A_1A_2 and A_2A_2	$\tau_5 = 1/[1 + P(A_2)]$
A_1A_1 and A_2A_2	$\tau_6 = 0$

*From Haseman and Elston [1972].

null hypothesis of marker and disease loci "unlinked" will be rejected whenever

$$t_{IBD} = \frac{\sum \tau_k n_k/n - 1}{\left(\left[\sum \tau_k^2 n_k/n - \left(\sum \tau_k n_k/n\right)^2\right]/(n-1)\right)^{1/2}} \tag{5}$$

is larger than the appropriate value of the t distribution with $n - 1$ degrees of freedom.

Power Calculations

The power of these four tests was computed by simulating samples of affected sib pairs. Two different sets of samples were considered, one set under the assumption of a recessive mode of disease inheritance, and the other under the assumption of an additive mode of inheritance. For each set, samples of two different sizes ($n = 50$ and $n = 100$) were created for different combinations of θ (the recombination fraction), p_D (the disease allele frequency), and $P(A_1)$ (the marker allele frequency). Each combination was then considered twice, once assuming linkage equilibrium ($k = c$), and once assuming linkage disequilibrium ($k \neq c$). (Altogether we considered 210 different combinations.)

For each of these combinations, 1000 random samples were drawn, and for each sample the four relevant statistics (the chi-square of the MGC test, the chi-square of the IBS values test, the t statistic of the mean IBS test, and the t statistic for the mean IBD test) were calculated. Estimates for the power of each test were obtained by the proportion of samples that led to the rejection of the null hypothesis of the marker and the disease "unlinked" (at the 0.05 significance level).

RESULTS

The simulation results can be summarized as follows:

1. Both mean tests, the mean IBS value test (test 3) and the mean IBD value test (test 4) displayed very similar probabilities of rejecting the null hypothesis if the marker and disease are in linkage equilibrium ($k = c$) (graphs not shown, but examples given in Tables IIa and IIb). However, when the marker and disease are in linkage disequilibrium ($k \neq c$), the mean IBS value test (test 3) may show very little power to detect linkage, and in some cases the t statistic of equation 4 has a negative expectation, even when $\theta = 0$ (see Table IIc). Thus the use of the mean IBS test (test 3) is not recommended.

2. In no case was the IBS values test the most powerful (graphs not shown, examples given in Tables IIa–IIc). When there is linkage disequilibrium ($k \neq c$), the IBS values test (test 2) may show very little power to detect linkage, as with the mean IBS value test (test 3) (see Table IIc). Moreover, for skewed distributions of the marker allele frequencies, the IBS values test may display an unexpected, as well as undesired tendency, of being less powerful under stronger linkage between the marker and the disease. Thus, the use of the IBS values test (test 2) is not recommended.

3. The power of the MGC test (test 1) and of the mean IBD test (test 4) is greater the more the marker and the disease are in linkage disequilibrium (see Fig. 2). The power of these tests also increases as the recombination fraction (θ) between the marker and the disease loci decreases. However, satisfactory results can sometimes

TABLE II. Recessive Model Expectations and the Four Tests*

(a) $P(A_1) = 0.1, k = 0.1, p_D = 0.1$

The MGC Test (1)

	A_1A_1 and A_1A_1	A_1A_2 and A_1A_2	A_2A_2 and A_2A_2	A_1A_1 and A_1A_2	A_1A_2 and A_2A_2	A_1A_1 and A_2A_2
Recessive	0.84	16.39	79.53	0.30	2.92	0.01
"Unlinked"	0.30	9.81	73.10	0.99	15.39	0.41

$\chi_5^2 = 16.91, P < 0.025$

The IBS Values Test (2)

	Share 2	Share 1	Share 0	
Recessive	96.77	3.22	0.01	
"Unlinked"	83.21	16.38	0.41	$\chi_2^2 = 13.16, P < 0.01$

The Mean IBS Values Test (3)

	Mean	
Recessive	1.968	
"Unlinked"	1.828	$t = 7.80, P < 0.001$

The Mean IBD Value Test (4)

	Mean	
Recessive	1.096	
"Unlinked"	1.000	$t = 5.67, P < 0.001$

(b) $P(A_1) = 0.1, k = 0.1, p_D = 0.3$

The MGC Test (1)

	A_1A_1 and A_1A_1	A_1A_2 and A_1A_2	A_2A_2 and A_2A_2	A_1A_1 and A_1A_2	A_1A_2 and A_2A_2	A_1A_1 and A_2A_2
Recessive	0.63	14.02	77.30	0.66	7.30	0.09
"Unlinked"	0.30	9.81	73.10	0.99	15.39	0.41

$\chi_5^2 = 7.01$, n.s.

The IBS Values Test (2)

	Share 2	Share 1	Share 0	
Recessive	91.95	7.96	0.09	
"Unlinked"	83.21	16.38	0.41	$\chi_2^2 = 5.49$, n.s.

The Mean IBS Values Test (3)

	Mean	
Recessive	1.919	
"Unlinked"	1.828	$t = 3.26, P < 0.001$

The Mean IBD Value Test (4)

	Mean	
Recessive	1.062	
"Unlinked"	1.000	$t = 3.13, P < 0.001$

TABLE II. Recessive Model Expectations and the Four Tests* (*continued*)

(c) $P(A_1) = 0.1, k = 0.3, p_D = 0.3$

The MGC Test (1)

	A_1A_1 and A_1A_1	A_1A_2 and A_1A_2	A_2A_2 and A_2A_2	A_1A_1 and A_1A_2	A_1A_2 and A_2A_2	A_1A_1 and A_2A_2
Recessive	6.33	33.25	42.45	4.88	12.63	0.47
"Unlinked"	0.30	9.81	73.10	0.99	15.39	0.41

$\chi_5^2 = 204.59, P < 0.001$

The IBS Values Test (2)

	Share 2	Share 1	Share 0	
Recessive	82.02	17.51	0.47	
"Unlinked"	83.21	16.38	0.41	$\chi_2^2 = 0.10$, n.s.

The Mean IBS Value Test (3)

	Mean	
Recessive	1.816	
"Unlinked"	1.828	$t = -0.31$, n.s.

The Mean IBD Value Test (4)

	Mean	
Recessive	1.130	
"Unlinked"	1.000	$t = 3.96, P < 0.001$

*Some illustrative cases of the deviation between the frequencies expected under a recessive mode of disease inheritance with no recombination ($\theta = 0$), and the frequencies expected under the null hypothesis of marker and disease loci "unlinked" ($\theta = 1/2$ and $k = c$), as measured by the four test statistics, are given. [Note that in cases (a) and (b), the marker and disease are in linkage equilibrium.] Since the expected numbers under the null hypothesis for the MGC and IBS values tests are sometimes small, the P value was estimated by computer simulations.

be obtained even if the marker and the disease are in linkage equilibrium (that is, if $k = c$) and θ is quite large.

4. If there is no linkage disequilibrium between the marker and the disease (i.e., if $k = c$, resulting in the same marker allele frequencies among affected individuals as in the general population), the mean IBD test is more powerful than the MGC test (see Fig. 2). If, on the other hand, the linkage disequilibrium between the marker and the disease is large enough, the MGC test turns out to be more powerful than the mean IBD test.

Table II illustrates the different reaction of the four test statistics to changes in linkage disequilibrium and disease allele frequency. The frequencies expected to be observed under a recessive mode of disease inheritance with no recombination (i.e., $\theta = 0$) are compared to the frequencies expected under the null hypothesis that the marker and disease are "unlinked" (i.e., $\theta = 1/2$ and $k = c$). The test statistics are calculated assuming a sample of size $n = 100$, having sample frequencies which are equal to those expected under the relevant model.

The tests of choice for affected sib pair data to test for "linkage," if parental data are not available, are either the MGC test (test 1) or the mean IBD test (test 4).
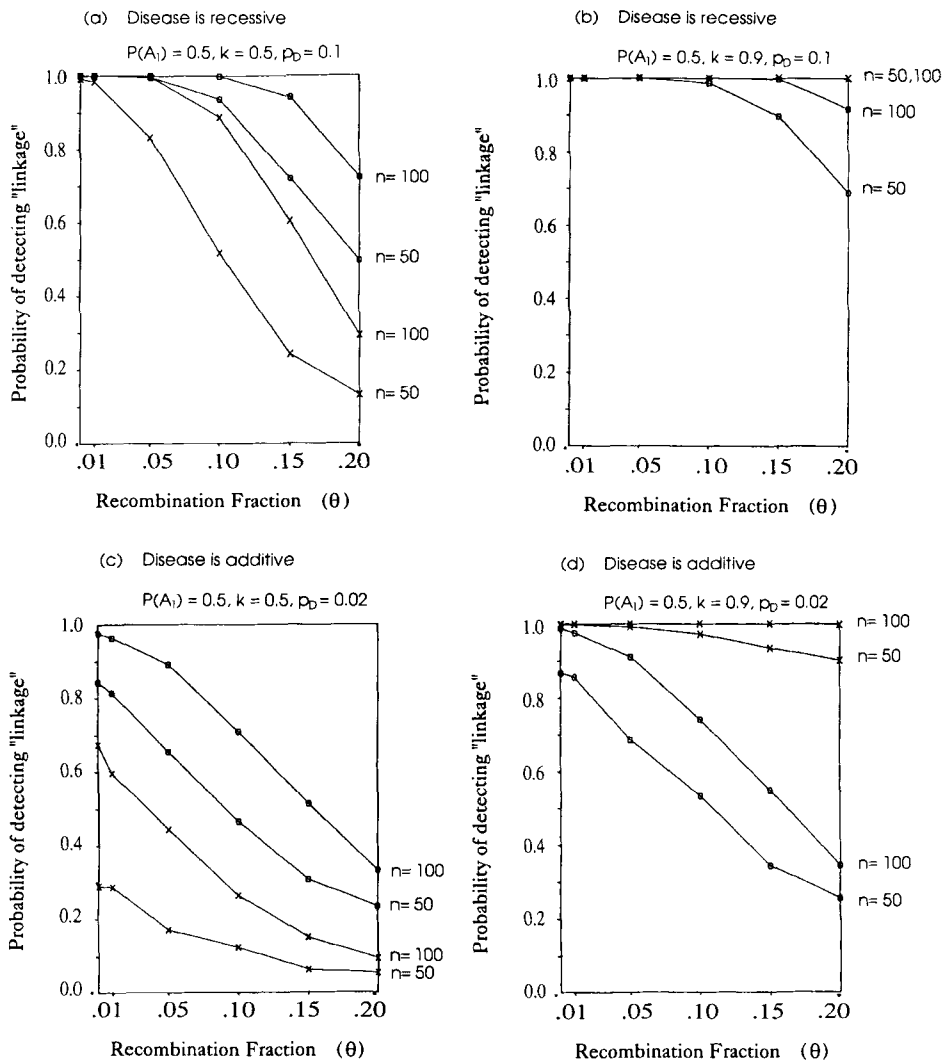
Fig. 2. Estimates of the power of the MGC test (×) and the mean IBD value test (○) for rejecting the null hypothesis of the marker and the disease being "unlinked" ($\theta = 1/2$ and $k = c$) for a recessive model with linkage equilibrium (**a**), and linkage disequilibrium (**b**), and an additive model with linkage equilibrium (**c**) and linkage disequilibrium (**d**). At each marker point, the estimate is based on 1,000 simulated samples of size $n = 50$ or 100 as indicated.

Which of these tests has the greater power is determined by the existence, or not, of linkage disequilibrium between the marker and the disease. It must be emphasized again that the null hypotheses is a compound test of no linkage ($\theta = 1/2$) and no association ($k = c$), and the greater power of the MGC test when there is linkage disequilibrium presumably reflects its greater ability to detect an association.

Obviously, the procedure of choice is to type both parents of affected sib pairs: the null hypothesis of no linkage ($\theta = 1/2$) can then be tested using IBD values from informative parents, and the null hypothesis no marker association with disease

($k = c$) can be tested independently using the marker allele frequencies in the affected sib pairs and the control group.

DISCUSSION

The recent advances in sequencing and restriction fragment length polymorphism (RFLP) mapping of the human genome make the study of complex human genetic diseases feasible, as well as study of those that are genetically more tractable. When the mode of inheritance of a disease is well established, lod score linkage analysis will most often be the method of choice for localizing disease predisposing genes. However, for diseases where the mode of inheritance is known, or suspected, to be genetically complex, other methods may be preferable, in particular the affected sib pair method. Additionally, affected sib pairs will generally be much more readily available for study than multigeneration pedigrees. Use of a number of restriction enzymes, oligonucleotide probes, and DNA sequencing should allow a high level of polymorphism to be detected in any genetic region, although the incredibly high level of polymorphism detected in the HLA region may not be attained. A number of authors have discussed affected sib pair and other relative methods to detect linkage when a marker is not 100% polymorphic [e.g., Lange 1986a,b; Weeks and Lange, 1988; Bishop and Williamson, 1990; Risch, 1990] and to determine mode of inheritance [Thomson, 1986].

Our aim in this study was to compare the power of four methods that use only identity by state (IBS) information in affected sib pairs for detecting linkage. It turns out that a joint null hypothesis of no linkage ($\theta = 1/2$), and linkage equilibrium of the marker and disease ($k = c$), must be considered, and we refer to this as the null hypothesis of marker and disease "unlinked." It is perhaps not surprising that the MGC test is the most powerful test of linkage in cases where there is linkage disequilibrium, since this test directly measures deviations from random segregation of the disease and marker loci and linkage disequilibrium. We had not anticipated that the IBS values test and the mean IBS value test would have undesirable statistical properties in the case of linkage disequilibrium. These results are not surprising though when one investigates particular cases.

It is important that the most powerful test for linkage be applied when possible, to avoid cases of false exclusion of linkage. Our results indicate the importance of first testing for a marker association with disease, and further of typing parents, so that a test of linkage that is not confounded with a test of association can be applied to the data.

ACKNOWLEDGMENTS

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