

Affected Kin-Pair IBD Methods: Genetic Models

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Cases of interest using affected sib-pair methods to distinguish between recessive and additive (dominant) modes of inheritance of a disease-predisposing gene involve goodness-of-fit tests with a small expected number in the "share-zero parental haplotypes" category, as well as an unknown parameter, the frequency of the disease-predisposing allele. Our simulations demonstrate that the real significance level of the chi-square test using the three-haplotype-sharing IBD values (share 2, 1, and 0 parental haplotypes) is close to the assumed (.05) level in these cases, so that the haplotype-sharing classes do not have to be lumped, which would leave no degrees of freedom for a statistical test. The validity of the chi-square approximation in cases of small expected frequencies has previously been described, but the situations that have been considered do not cover the very small values in the share-zero category that are often expected in the affected sib-pair analysis, nor do they involve estimation of an unknown parameter. Although including IBD values from affected kin pairs other than sibs can be a very powerful tool in demonstrating linkage of a marker and disease, these pairs do not add power, in fact they reduce the power, of the chi-square tests of goodness-of-fit of modes of inheritance.

Key words: identity by descent, mode of inheritance, disease parameter estimates

INTRODUCTION

Non-parametric affected sib methods using identity-by-descent (IBD) values have been used to demonstrate linkage for a number of diseases associated with the human leukocyte antigen (HLA) system. Examples include insulin-dependent diabetes mellitus (IDDM) [see, for example, Cudworth and Woodrow, 1975; Payami et al., 1985], leprosy [de Vries et al., 1976], rheumatoid arthritis [de Vries et al., 1985; Payami et al., 1986],

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multiple sclerosis [Stewart et al., 1980], and Hodgkin's disease (using various affected kin relationships) [Berberich et al., 1983; Hors and Dausset, 1983]. Linkage of a disease with a marker system is established by demonstration within families of non-random segregation of parental alleles to affected children (unaffected children and other affected kin pairs can also be considered in the analysis) [see, for example, Haseman and Elston, 1972; de Vries et al., 1976, 1985; Day and Simons, 1976; Thomson and Bodmer, 1977a,b; Green and Woodrow, 1977; Suarez, 1978; Thomson, 1981; Berberich et al., 1983; Majumder and Pal, 1987; Cantor and Rotter, 1987]. Risch [1990] gives a detailed analysis of the power to detect linkage using pairs of affected relatives and affected-unaffected pairs.

An advantage of the affected kin-pair method is that since it uses haplotypes as markers to trace the inheritance of disease susceptibility genes within families, difficulties associated with population stratification effects in the analysis of disease association are eliminated. Further, when only affected sibs or other kin are used in the analysis the problem of incomplete penetrance of the disease is avoided. These affected-kin methods do not require linkage disequilibrium for the detection of disease-predisposing genes, in contrast to association studies. Deviations from random segregation of haplotype-sharing values in affected sibs can theoretically be detected over a range of recombination distances between the marker and disease-predisposing loci [Suarez et al., 1978; Payami et al., 1984; Risch, 1990].

The use of haplotype-sharing IBD data has been extended by theoretical studies to distinguish between possible modes of inheritance of the "disease" genes once linkage has been established [see, for example, Day and Simons, 1976; Thomson and Bodmer, 1977a,b; Suarez, 1978; Suarez et al., 1978; Spielman et al., 1980; Louis et al., 1983; Ewens and Clarke, 1984; Motro and Thomson, 1985; Payami et al., 1985; Thomson, 1986, 1988]. The expected IBD values under a single-predisposing-allele model, for given frequencies of the disease-predisposing allele, have been determined, and allow for tests of specific modes of inheritance [Motro and Thomson, 1985]. These can sometimes be very useful in determining modes of inheritance of a disease-predisposing gene, especially for determining which models can be rejected. For example, accumulated data from 538 families with affected sib pairs with IDDM show they share 2, 1, and 0 parental HLA haplotypes in proportions 53.6%, 39.1%, and 7.3% and differ significantly from dominant expectations [Payami et al., 1985]. (Excess sharing of two HLA haplotypes over one haplotype is a distinguishing feature of recessive vs. dominant inheritance.) The affected sib-pair data fit recessive expectations very closely, even though we know there is genetic heterogeneity in IDDM predisposition [see, e.g., Thomson et al., 1988]. Evidence of the heterogeneity is indicated, but not proven statistically, if one looks at the affected sib-trio haplotype-sharing distribution [Payami et al., 1985; Louis et al., 1987].

The purpose of our present analysis is twofold: 1) to determine the quality of the chi-square approximation for testing mode of inheritance using the affected sib-pair haplotype-sharing IBD distribution, given that expected numbers in the "share zero" category are often very small, and 2) to calculate the IBD distribution for other affected kin pairs for given intermediate modes of inheritance (which includes recessive and dominant) and then determine if available affected kin pairs should be included or not with affected sib pairs in goodness-of-fit chi-square tests for mode of inheritance.

ASSUMPTIONS OF THE MODELS

We consider a single-locus, two-allele disease model, with 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 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 $\lambda = 1$.

We assume a highly polymorphic marker locus, closely linked to the disease locus, so that recombination during a single generation is assumed negligible and taken as zero. Additionally, the usual assumptions with affected-sib methods of no selective disadvantage of affected individuals, a single panmictic population with Hardy-Weinberg proportions, and Mendelian segregation at the disease locus are made [e.g., see Louis et al., 1987].

AFFECTED SIB PAIRS: ESTIMATING THE DISEASE ALLELE FREQUENCY AND TESTING FOR THE MODE OF INHERITANCE OF THE DISEASE

The number of shared parental haplotypes identical-by-descent (IBD) within a pair of affected sibs can be either 2, 1, or 0. Under random segregation, the expected probabilities of these classes are 1/4, 1/2, and 1/4, and deviations from these expected values would be taken to imply genetic linkage of a disease gene with the marker system. The corresponding probabilities for the general disease model, where dd individuals are also assumed to be disease susceptible (that is, where sporadic cases of the disease are possible), were obtained by Suarez [1978]. From these, the distribution of the IBD values for the intermediate model is

$$X = \text{Pr (share 2/both affected)} = \frac{(1 - 2\lambda^2)p + 2\lambda^2}{(1 - 2\lambda)^2p^3 + 2(1 - 4\lambda^2)p^2 + (1 + 4\lambda)p + 4\lambda^2} \quad (1a)$$

$$Y = \text{Pr (share 1/both affected)} = \frac{2(1 - 2\lambda)p^2 + 2\lambda(2 - \lambda)p + 2\lambda^2}{(1 - 2\lambda)^2p^3 + 2(1 - 4\lambda^2)p^2 + (1 + 4\lambda)p + 4\lambda^2} \quad (1b)$$

$$Z = \text{Pr (share 0/both affected)} = \frac{(1 - 2\lambda)^2p^3 + 4\lambda(1 - 2\lambda)p^2 + 4\lambda^2p}{(1 - 2\lambda)^2p^3 + 2(1 - 4\lambda^2)p^2 + (1 + 4\lambda)p + 4\lambda^2} \quad (1c)$$

where p is the frequency of the disease-predisposing allele D. Figure 1 illustrates this distribution (in a two-dimensional space) for the three modes of inheritance (recessive, additive, and dominant) and demonstrates that the additive and the dominant models are practically indistinguishable from each other.

Special Case I: Recessive Disease

For a recessive mode of disease inheritance ($\lambda = 0$), the distribution of the IBD values is

$$X = 1/(1 + p)^2 \quad (2a)$$

$$Y = 2p/(1 + p)^2 \quad (2b)$$

$$Z = p^2/(1 + p)^2. \quad (2c)$$

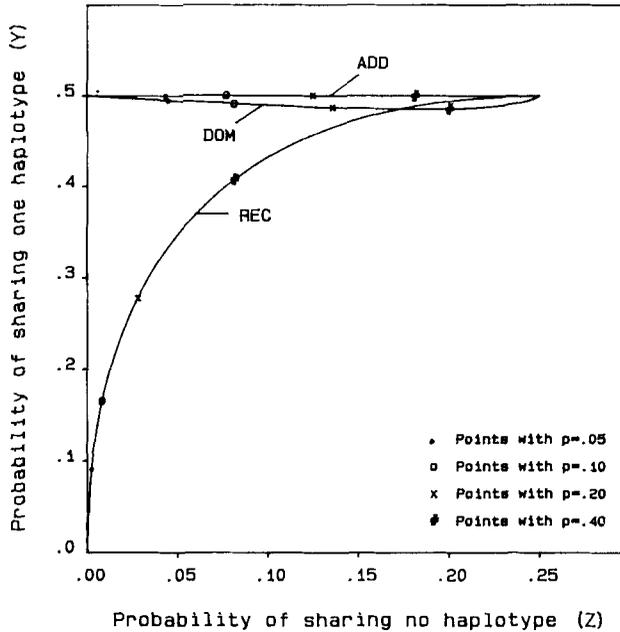


Fig. 1. The affected sib-pair IBD haplotype-sharing probabilities for recessive, additive, and dominant models.

If in a random sample of n independent sib pairs, n_2 of these pairs share 2 haplotypes, n_1 share 1, and n_0 share 0 ($n_2 + n_1 + n_0 = n$), the maximum likelihood estimate (MLE) of p is [Motro and Thomson, 1985]

$$\hat{p} = \frac{2n_0 + n_1}{2n_2 + n_1}, \tag{3a}$$

provided that $n_2 \geq n_0$. (If $n_2 < n_0$, then $\hat{p} = 1$.) An approximation for the variance of the MLE is

$$\text{Var}(\hat{p}) \approx p(1 + p)^2/2n \tag{3b}$$

(which is, in fact, an upper bound for the asymptotic variance of \hat{p}).

In order to test if the disease is recessive, a chi-square test for goodness-of-fit can be constructed, where the expected frequencies in each of the three IBD categories are estimated by using the MLE of p . An assumed recessive model would then be rejected whenever the chi-square statistic exceeds the appropriate percentile of the chi-square distribution with one degree of freedom.

For practical sample sizes, however, the expected number in the "share zero" category can be quite small. (If $n = 100$ and $p = .1$, for example, the expected number can be less than one, and if $p = .05$ it can be less than one-fourth.) If the "share zero" category is combined with another category because of these small expected numbers, we are left with no degrees of freedom for a statistical test for mode of inheritance compatible with a recessive model.

To determine if this problem can be circumvented, we have investigated the quality of the chi-square approximation when the three haplotype-sharing classes are left distinct, i.e., the “share zero” class is not lumped even when expected values are very small. In this regard we estimated the real significance level of the test for different values of the disease allele frequency (p) with two different sample sizes ($n = 100$ and $n = 200$). This was done by simulating samples of affected sib pairs under an assumed recessive model and calculating the proportion of samples that led to a false rejection at the (supposed) .05 significance level (i.e., the proportion of samples that generated a chi-square value larger than 3.841). The results, based on 10,000 samples for each combination of p and n , are very satisfactory. The average significance level was .0442, with only a single case (out of 11) having a significance level slightly exceeding .06 (see Fig. 2, points labelled +). The asymptotic variance of \hat{p} and the estimated variance of \hat{p} (from the simulations) are both quite small, and are quite close to each other (also for the additive case considered below).

Figure 2 also demonstrates the power of the test (points labelled x)—more specifically, its ability to reject an assumed recessive model when the real mode of inheritance of the disease is additive. It turns out that for small values of p (which are not unrealistic for an additive disease), the power can be quite high. (For example, if $p = .02$ for an additive model, the estimates for the power are .8891 if $n = 100$ and .9974 if $n = 200$.) For larger values of p , however, larger samples are needed in order to have an adequate probability of rejecting a false null hypothesis.

Special Case II: Additive Disease

The distribution of the IBD values in the additive case ($\lambda = 1/2$) is

$$X = (1 + p)/[2(1 + 3p)] \tag{4a}$$

$$Y = 1/2 \tag{4b}$$

$$Z = p/(1 + 3p). \tag{4c}$$

Here, the MLE of p is [Motro and Thomson, 1985]

$$\hat{p} = \frac{n_0}{2n_2 - n_0} \tag{5a}$$

provided that $n_2 \geq n_0$. (If $n_2 < n_0$, then $\hat{p} = 1$). An approximation for the variance of \hat{p} is

$$\text{Var}(\hat{p}) \approx p(1 + p)(1 + 3p)^2/n. \tag{5b}$$

Testing the null hypothesis of an additive mode of disease inheritance vs. an alternative recessive model can be done in a similar way as in the recessive case. Figure 3 presents both the significance level (points +) and the power (points x) of the relevant chi-square test (again, without lumping of categories) for different values of the disease allele frequency (p) and sample size $n = 50$. The estimates are based on 10,000 simulated samples for each case, with a supposed significance level of .05. The aver-

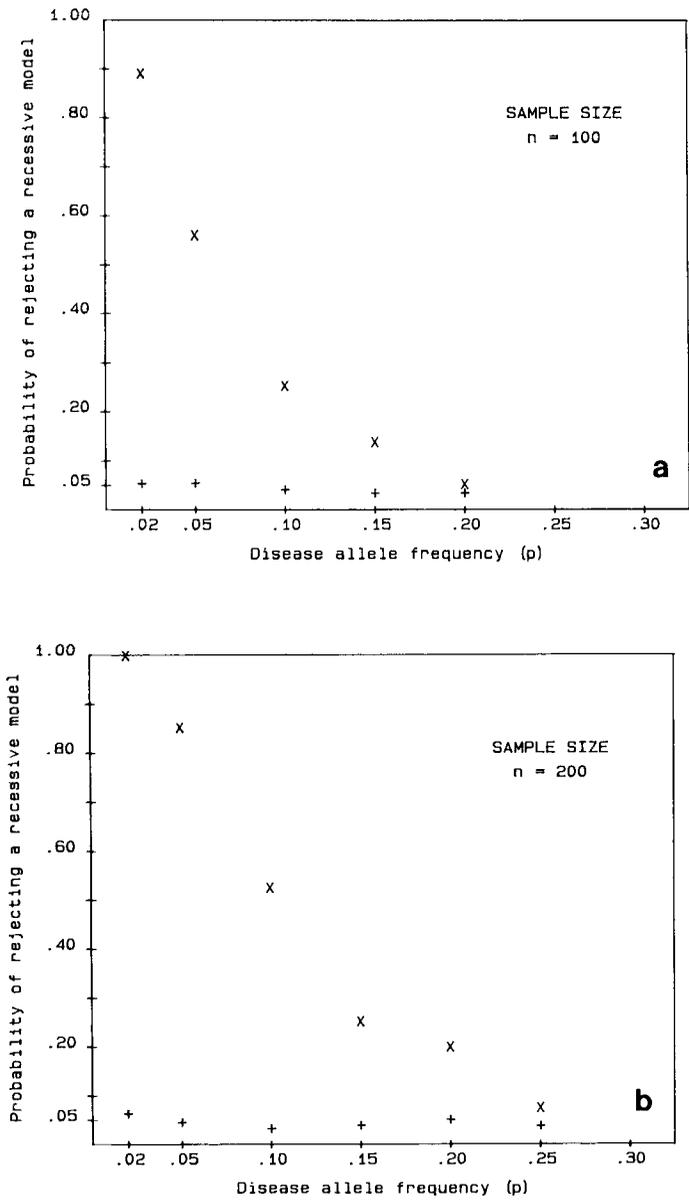


Fig. 2. The chi-square test for goodness-of-fit to the recessive model, without lumping of haplotype-sharing categories. Estimates of the significance level (+) of the test are indicated. The probability of rejecting an assumed recessive model, when the true mode of disease inheritance is additive (x), is also given. Each of these results is based on 10,000 simulated samples of size $n = 100$ (a) or $n = 200$ (b).

age significance level in the simulations was .0489, and never exceeded .06. The results clearly indicate that even with samples of size 50, we can expect good accuracy of the significance level and large power for rejecting a false additive assumption.

The results for the recessive and additive models indicate that despite small expected

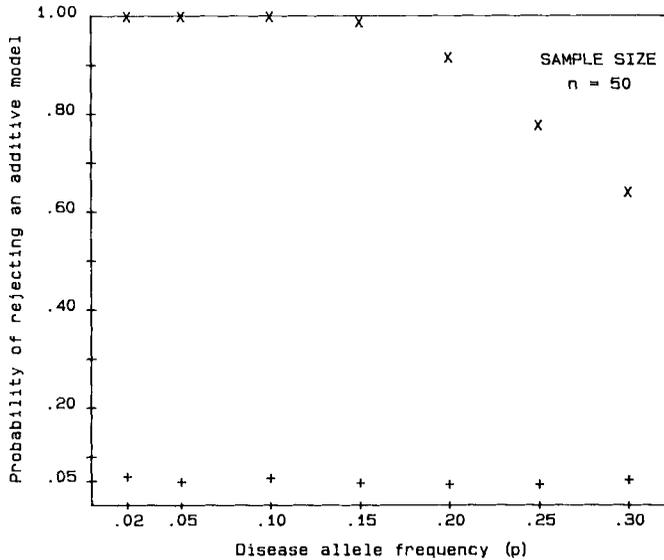


Fig. 3. The chi-square test for goodness-of-fit to the additive model, without lumping of haplotype-sharing categories. Estimates of the significance level (+) and the probability of rejecting an assumed additive model, when the true mode of disease inheritance is recessive (x), are each based on 10,000 simulated samples of size $n = 50$.

numbers in the “share zero” category, classes do not have to be lumped, which would leave no degrees of freedom for a statistical test. The real significance level of the chi-square test using the three haplotype-sharing values is always close to the assumed (.05) level.

THE DISTRIBUTION OF IBD VALUES BETWEEN AFFECTED KIN PAIRS

An important question pertaining to the affected pairs method is: How, if at all, can pairs of affected kin (other than full-sibs) be included in the analysis? To answer this question, we must first obtain the distribution of the number of IBD haplotypes shared between affected kin, under a given mode of inheritance [also, see Bishop and Williamson, 1990, for recessive and dominant models].

For affected kin other than full-sibs, the number of IBD haplotypes is either one or zero. We start by obtaining the conditional probability of both kin being affected, given they share one IBD haplotype. This common haplotype is linked either to D or to d. In the former case, for each of the kin to be affected it is necessary and sufficient that the other allele at the disease locus be either D (thus the individual is a homozygote DD) and the individual will be affected (the probability of this event is px) or that the other allele is d (thus the individual is a heterozygote Dd) and the individual will be affected (the probability of this is $\lambda(1-p)x$). Hence, if the common haplotype is D, the probability of both kin being affected is $[p + \lambda(1-p)]^2x^2$. If the common haplotype is d, each individual is affected if, and only if, the other allele at the disease locus is D (thus the individual is a heterozygote Dd) and the individual contracts the disease (the probability for which is λpx). Hence, if the common haplotype is d, the probability of both kin being affected is $(\lambda p)^2x^2$. From that,

$$\Pr(\text{both affected/share 1}) = p[p + \lambda(1-p)]^2x^2 + (1-p)(\lambda p)^2x^2 = Apx^2, \quad (6a)$$

where $A = [p + \lambda(1-p)]^2 + \lambda^2p(1-p)$.

We then obtain the conditional probability of both kin being affected, given they share no common haplotype. Since for any random individual the probability of being affected is the probability of either being DD and contracting the disease (that is, p^2x) or of being Dd and contracting the disease (that is $2\lambda p(1-p)x$), it follows that for affected kin

$$\Pr(\text{both affected/share 0}) = [p^2x + 2\lambda p(1-p)x]^2 = Bpx^2, \quad (6b)$$

where $B = [p + 2\lambda(1-p)]^2$.

The probability that both kin share one haplotype is $2r$, where r is Wright's coefficient of relationship ($r = 1/4$ for half-sibs and for uncle [aunt]-nephew [niece], $r = 1/8$ for first cousins, etc.). Thus, by Bayes's rule, the distribution of the IBD values for affected kin pairs is

$$U = \Pr(\text{share 1/both affected}) = \frac{2rA}{2rA + (1-2r)B} \quad (7a)$$

$$V = \Pr(\text{share 0/both affected}) = \frac{(1-2r)B}{2rA + (1-2r)B}. \quad (7b)$$

An important feature of this distribution is that for any intermediate mode of inheritance, including recessive, additive, and dominant, the probability of sharing a common haplotype (U) tends to one as the disease allele frequency (p) tends to zero, and this is true for any r -degree kin (other than full-sibs). Figure 4 illustrates this feature for the special case $r = 1/4$ (i.e., half-sib pairs or uncle [aunt]-nephew [niece] pairs). [The dominant and recessive cases are given in Fig. 1 of Bishop and Williamson, 1990.] Recall that for full-sibs, $(X, Y, Z) \rightarrow (1/2, 1/2, 0)$ as $p \rightarrow 0$ for any mode of inheritance other than recessive, while $(X, Y, Z) \rightarrow (1, 0, 0)$ for the recessive model (see equations 1a-c and Fig. 1). This distinctive attribute of the full-sib case is what gives power to test for the mode of inheritance using affected sib pairs. The lack of this attribute in the affected-kin case suggests that one cannot expect great discriminatory power when using affected-kin pairs.

Indeed, simulations (not shown) have confirmed that the goodness-of-fit test based on affected kin pairs other than full-sibs has very weak power. (In order to have some degrees of freedom, samples consisting of at least two different r -degree kin were considered.) Moreover, adding affected kin pairs to a sample of affected full-sib pairs actually *reduces* the power of the test. Hence we do not recommend using affected kin (other than full-sibs) in testing for the mode of inheritance.

Affected kin pairs, either exclusively or together with affected sib pairs, can be used, however, for estimating the disease allele frequency once the true mode of inheritance of the disease is known (a situation probably not very common in practice).

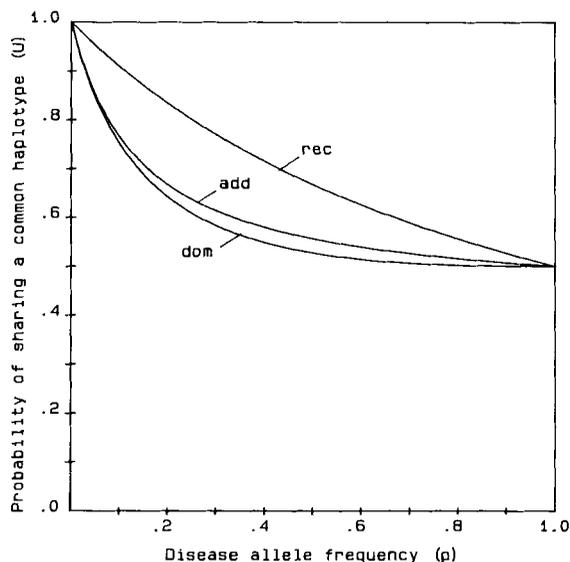


Fig. 4. The haplotype-sharing probabilities for affected half-sib (or uncle [aunt]-nephew [niece]) pairs.

DISCUSSION

The validity of the chi-square approximation in cases of small expected frequencies has been previously demonstrated. While many authors recommended that all expectations be at least five, Cochran [1954] pointed out that for goodness-of-fit tests of unimodal distributions (such as the normal or Poisson), where the expectations will be small only at one or both tails, one can group so that the minimum expectation at each tail is at least one. Yarnold [1970] proposed the following rule for guiding the use of the chi-square approximation: "If the number of classes s is three or more, and if r denotes the number of expectations less than five, then the minimum expectation may be as small as $5r/s$." While in some cases this rule allows even smaller expectations than Cochran has recommended, in the cases involving the affected sib-pair IBD distribution, Yarnold's rule would imply that the expected frequency in the "share zero" category should not be smaller than $5/3$. Moreover, Yarnold's results apply to cases of a single multinomial with no estimated parameters, which clearly is not the case with the affected sib-pair tests.

Roscoe and Byars [1971] demonstrated that for three classes, for example, the chi-square approximation is acceptable at the .05 significance level even in cases of very skewed distributions and small samples. Their smallest expected frequency, however, was at least 1.27. They also did not consider goodness-of-fit tests with unknown parameters.

Cochran [1954], Roscoe and Byars [1972], and recently Roff and Bentzen [1989] showed the robustness of the chi-square approximation for tests of independence in contingency tables with small expected frequencies.

The cases of interest to us with the affected sib-pair IBD distribution, i.e., where recessive and additive (dominant) models can be distinguished with a realistic sample size (Fig. 1), involve goodness-of-fit tests with small expected number in the "share

zero'' category, as well as an unknown parameter (p , the disease allele frequency). It is thus most reassuring that our simulations have demonstrated that the real significance level of the chi-square test using the three haplotype-sharing IBD values is close to the assumed (.05) level in these cases, so that the haplotype-sharing classes do not have to be lumped, which would leave no degrees of freedom for a statistical test.

Including IBD values from affected kin pairs other than sibs can be a very powerful tool in demonstrating linkage of a marker and disease [Berberich et al., 1983; Cantor and Rotter, 1987; Weeks and Lange, 1988; Risch, 1990; Bishop and Williamson, 1990]. Unfortunately, although the expected distribution of these IBD values for an intermediate model can be readily obtained, these do not add power to, and in fact they reduce the power of, the chi-square tests of goodness-of-fit of modes of inheritance. In general, with increasing recombination and the occurrence of sporadic cases of disease the power of the affected relatives methods decreases quite rapidly [Risch, 1990]; the situations we have considered here refer to the ideal case of a very highly polymorphic marker with close to zero recombination to the disease-predisposing locus.

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