

Simple, Robust Linkage Tests for Affected Sibs

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Summary

Parametric-linkage analysis applied to large pedigrees with many affected individuals has helped in the identification of highly penetrant genes; but, for diseases lacking a clear Mendelian inheritance pattern or caused by several genes of low to moderate penetrance, a more robust strategy is nonparametric analysis applied to small sets of affected relatives, such as affected sib pairs. Here we show that the robustness of affected-sib-pair tests is related to the shape of the constraint set for the sibs' identity-by-descent (IBD) probabilities. We also derive a set of constraints for the IBD probabilities of affected sib triples and use common features of the shapes of the two constraint sets to introduce new nonparametric tests (called "minmax" tests) that are more robust than those in current use. Asymptotic-power computations support the robustness of the proposed minmax tests.

Introduction

Classical linkage analysis assumes a parametric model for the effects of genotypes at a single locus, on risk of a trait (Ott 1991). This method has helped in the identification of highly penetrant genes for human diseases, such as Huntington disease and Alzheimer disease, whose etiologies follow simple Mendelian patterns; but it has been less successful in detecting the genetic basis of more-complex diseases, such as schizophrenia and diabetes (Risch 1990a). These disorders may involve multiple genes, each with low penetrance. Because the classical approach is sensitive to misspecification of the mode of inheritance at a particular locus, which usually

is unknown, its power is apt to be poor for complex, multigenic diseases.

This problem has led to the use of nonparametric methods, which require fewer model assumptions. These include both the likelihood-ratio (or maximum-LOD-score) test described by Risch (1990b) and modified, by Faraway (1993) and Holmans (1993), for affected sib pairs and the means (or affected-sib-pair) test (Penrose 1953). In contrast to the sensitivity of the classical method, these tests perform reasonably well under a broad range of assumptions (Kruglyak et al. 1996; Teng and Siegmund 1997). Here we examine the power and robustness of various nonparametric tests for linkage based on affected sibships. We follow Schaid and Nick (1990) in presenting affected-sib-pair tests as weighted sums of observed frequencies of pairs sharing zero, one, or two alleles identical by descent (IBD). We show that the constraints of Faraway (1993) and Holmans (1993) provide a simple geometric interpretation of the weights, one that shows graphically when a test is optimal. The geometric interpretation motivates a new test, called the "minmax test," that is more robust than the nonparametric tests currently used. Finally, we derive, for the IBD configuration probabilities of sib triples, a set of constraints analogous to those derived, by Faraway (1993) and Holmans (1993), for sib pairs. We use these constraints to provide a geometric interpretation of test optimality and to derive robust minmax tests for affected sib triples.

Affected Sib Pairs

To simplify the discussion, we restrict attention to a single marker for which the IBD status of siblings is unambiguously determined. Suppose that we have typed marker alleles for a total of n sib pairs, all of which are affected with a given trait. We wish to determine whether the marker is near a gene that predisposes to the trait. Let n_i denote the number of sib pairs that inherit i marker alleles IBD, $i = 0, 1, 2$, with $n_0 + n_1 + n_2 = n$. Also, let z_i denote the probability that two sibs inherit i marker alleles IBD, $i = 0, 1, 2$, with $z = (z_0, z_1, z_2)$, and let $\hat{z} = (\hat{z}_0, \hat{z}_1, \hat{z}_2) = \frac{1}{n}(n_0, n_1, n_2)$ represent the relative frequencies observed for the n sib pairs. We want to test the null hypothesis $z = (\frac{1}{4}, \frac{1}{2}, \frac{1}{4}) \equiv p$, using a test that performs well regardless of the true value of z .

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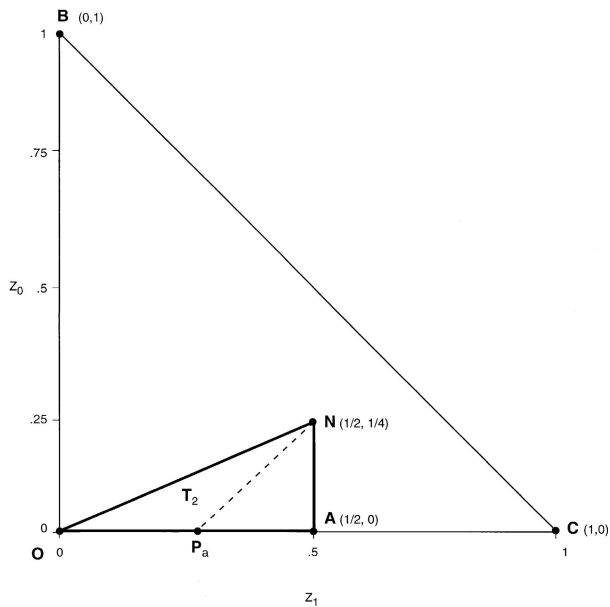


Figure 1 Unit simplex with vertices O , B , and C in the z_1, z_0 plane containing all points (\hat{z}_1, \hat{z}_0) , where \hat{z}_i is the observed proportion of sib pairs who inherit i alleles IBD, $i = 0, 1$. Also shown is the triangle T_2 with vertices N, O , and A containing all true IBD probabilities (z_1, z_0) (Holmans 1993).

Considerable research has focused on the relative power of three tests. The first is the *likelihood ratio test* (also called the “maximum-lod-score test”), described by Risch (1990b). It is based on the ratio

$$\frac{L(\hat{z})}{L(p)}, \quad (1)$$

where $L(z) \propto z_0^{n_0} z_1^{n_1} z_2^{n_2}$ denotes the multinomial likelihood of the observed IBD sharing frequencies when the true probabilities are given by z . Faraway (1993) and Holmans (1993) showed that the power of this test can be increased by evaluating the numerator not at the point \hat{z} but, rather, at a different point \tilde{z} . The coordinates of \tilde{z} are constrained to lie within the triangle of values consistent with the underlying genetics of IBD sharing by the sibs (triangle T_2 with vertices N, O , and A in fig. 1). Specifically, \tilde{z} corresponds to that point within the triangle T_2 for which $L(z)$ is maximized. This *constrained likelihood ratio* (CLR) test is based on the ratio $L(\tilde{z})/L(p)$.

The second test, the *means test* (also called the “mean-pairs” test, or the “affected-sib-pair” test), compares the mean number $2\hat{z}_2 + \hat{z}_1$ of alleles shared IBD by the sib pairs with its null expectation $2(\frac{1}{4}) + \frac{1}{2} = 1$. The third test, the *proportions test* (also called the “pairs” test, or the “two-alleles” test), compares the proportion \hat{z}_2 of sib pairs sharing both alleles IBD with its null expecta-

tion, $\frac{1}{4}$. These two tests have been studied by several investigators, including Suarez et al. (1978), Suarez and Van Eerdewegh (1984), Blackwelder and Elston (1985), Schaid and Nick (1990), and Tierney and McKnight (1993). Both tests are special cases of tests obtained by taking the difference between a weighted sum $w_0\hat{z}_0 + w_1\hat{z}_1 + w_2\hat{z}_2$ of the observed IBD sharing frequencies and its null expectation and then dividing this difference by its standard error (Schaid and Nick 1990). Under the null hypothesis of no linkage, the test statistic has a standard Gaussian distribution asymptotically, as $n \rightarrow \infty$. Because the square of a standard Gaussian variate is a χ^2 variate on 1 df, we shall call such tests “1df tests.”

The test statistic for a 1df test is invariant under linear transformations of the weights w_i . Therefore, the weights can be standardized arbitrarily so that $w_0 = 0$ and $w_2 = 1$. The test is then completely determined by the weight w_1 assigned to \hat{z}_1 . Thus the statistics for the means test and the proportions test are special cases of statistics of the form

$$X = \frac{\hat{z}_2 + w_1\hat{z}_1 - E_0(\hat{z}_2 + w_1\hat{z}_1)}{\sqrt{V_0(\hat{z}_2 + w_1\hat{z}_1)}} \\ = \frac{\sqrt{n} \left[\hat{z}_2 - \frac{1}{4} + w_1 \left(\hat{z}_1 - \frac{1}{2} \right) \right]}{\frac{1}{4}\sqrt{3 - 4w_1 + 4w_1^2}}. \quad (2)$$

Here $E_0[\circ]$ and $V_0(\circ)$ denote null expectation and variance, respectively. In particular, $w_1 = \frac{1}{2}$ for the means test, and $w_1 = 0$ for the proportions test.

Consider now the following family of models for the true IBD sharing probabilities z , in which z is a function $z(\lambda)$ of a scalar parameter λ :

$$F_a = \left[z: z = \lambda(0, a, 1 - a) + (1 - \lambda) \left(\frac{1}{4}, \frac{1}{2}, \frac{1}{4} \right); \right. \\ \left. 0 \leq \lambda \leq 1 \right]. \quad (3)$$

Here a is a fixed constant, and the parameter λ varies from 0 to 1. The value $\lambda = 0$ corresponds to the null hypothesis $z = p$. We shall give a geometric interpretation of the F_a family of models in the next section. It is well known that the proportion z_1 of sib pairs sharing one allele IBD satisfies $0 \leq z_1 \leq \frac{1}{2}$ (Risch 1990b). This constraint, when used in family of models (3) with $\lambda = 1$, implies that $0 \leq a \leq \frac{1}{2}$. The following proposition, which is discussed in a more general context by Whittemore (1996), relates the test statistic X of equation (2) to the F_a family of models.

PROPOSITION 1. The statistic X of equation (2) is the

efficient score statistic for the likelihood function (1) and the F_a family of models (3) if and only if

$$w_1 = \frac{\frac{1}{2}a}{1-a} \text{ and } 0 \leq a \leq \frac{1}{2}. \quad (4)$$

In this case,

$$X = X_a = \frac{\sqrt{n}[4(a-1)\hat{z}_0 + (6a-4)\hat{z}_1 + 3-4a]}{\sqrt{3-8a+6a^2}}. \quad (5)$$

Conversely, the efficient score statistic for each F_a family of models (3) with $0 \leq a \leq \frac{1}{2}$ is a statistic of the form given in equation (2). A proof of the proposition can be found in Appendix A.

We shall call the family of 1df tests (2) with w_1 given by formula (4) “admissible” 1df tests. The means test and the proportions test are the two extremes in this family, corresponding to $w_1 = a = \frac{1}{2}$ and $w_1 = a = 0$, respectively.

The efficient score test is locally most powerful (in the sense discussed by Cox and Hinkley [1974, p. 113]; hereafter called “optimal”) when its family of models correctly specifies the mechanism generating the data. Proposition 1 states that 1df tests are efficient score statistics; therefore, they are optimal when a is correctly specified. In particular, the means test and the proportions test are optimal for the $F_{1/2}$ and F_0 families of models, respectively. But $F_{1/2}$ is the family of additive genetic models (i.e., those with no dominance variance component), whereas F_0 is the family of models with no additive variance component (Crow and Kimura 1970). Thus, the means test is optimal under genetic additivity, whereas the proportions test is optimal when the additive variance component is small in comparison with the dominance component, a situation that describes a rare recessive allele. Hence, if an additive model or such a recessive model is known to hold, the choice of optimal test is clear.

In practice, however, the correct model is seldom known. This lack of knowledge suggests use of the more general CLR test described by Risch (1990b), Faraway (1993), and Holmans (1993). However, this test is complicated, and it does not generalize easily to more than two sibs or to other types of relatives. Moreover, its distribution involves 2 df, and so it may be less powerful than a 1df test. A geometric representation of the problem will help to clarify the issues and will suggest simple robust tests that perform as well as or better than the CLR test.

Geometric Considerations

Since the three probabilities z_0 , z_1 , and z_2 sum to 1, any two of them determine the third, so only two need

be specified. We shall work with z_1 and z_0 . Figure 1 shows the unit simplex in the (z_1, z_0) plane, with vertices O , B , and C , within which the observed proportions (\hat{z}_1, \hat{z}_0) must lie, and the smaller triangle T_2 , with vertices O , N , and A , containing the true IBD probabilities (z_1, z_0) (Faraway 1993; Holmans 1993). The point N corresponds to the null hypothesis $(z_1, z_0) = (\frac{1}{2}, \frac{1}{4})$. The point $(\tilde{z}_1, \tilde{z}_0)$ used in the CLR test is that point, within T_2 , that maximizes likelihood (1); in fact, $(\tilde{z}_1, \tilde{z}_0)$ is the point, in T_2 , that is closest to (\hat{z}_1, \hat{z}_0) in a certain metric (Holmans 1993; also see Appendix B).

A family, F_a , of models of the form given in formula (3) specifies that $(z_1, z_0) = [a\lambda + \frac{1}{2}(1-\lambda), \frac{1}{4}(1-\lambda)]$ lies on the ray NP_a , where $P_a = (a, 0)$ is a point on the line segment OA . In particular, the family $F_{1/2}$ of additive models consists of points on the ray NA , and the F_0 family of models with no additive variance component consists of points on the ray NO . (Because the F_0 family of models describes rare recessive genes, we shall call it a “family of recessive models.”) As a consequence of proposition 1, a 1df test based on X_a is optimal when the true point lies on the ray NP_a . For example, the means test is optimal when the true point lies on NA , and the proportions test is optimal when the true point lies on NO .

A test that is optimal on a given ray should perform well when the true point is near the ray. For this reason, the shape of T_2 is noteworthy. Because N is a vertex of T_2 , the two edges meeting at N form an acute angle. For complex multigenic traits with small effects at any single locus, the true IBD probabilities at such a locus represent a point (z_1, z_0) that is close to N and, therefore, close to any ray emanating from N . Therefore, a 1df test, which is optimal for true points on a particular ray, can be expected to perform well in comparison with the more general CLR test. When the true point is far from N , the relative power of different tests is less important, since a large proportion of affected sib pairs will share one or two alleles IBD and most tests will do well.

Because the means test and the proportions test correspond to extreme rays NA and NO on the boundary of T_2 , each forfeits power when the other’s family of models governs the data. It thus seems plausible that a more robust 1df test would be optimal on a ray NP , where P is a point approximately midway between A and O on the line segment OA . In the next section we use asymptotic-power computations to show that this is indeed the case, and we also find the best choice of P .

Asymptotic Power

We shall evaluate the asymptotic power of the 1df tests and of the CLR test under a range of possibilities for the true IBD probabilities. We also shall determine the most robust 1df test—that is, the test with minimal asymptotic-power loss due to model misspecification. Fi-

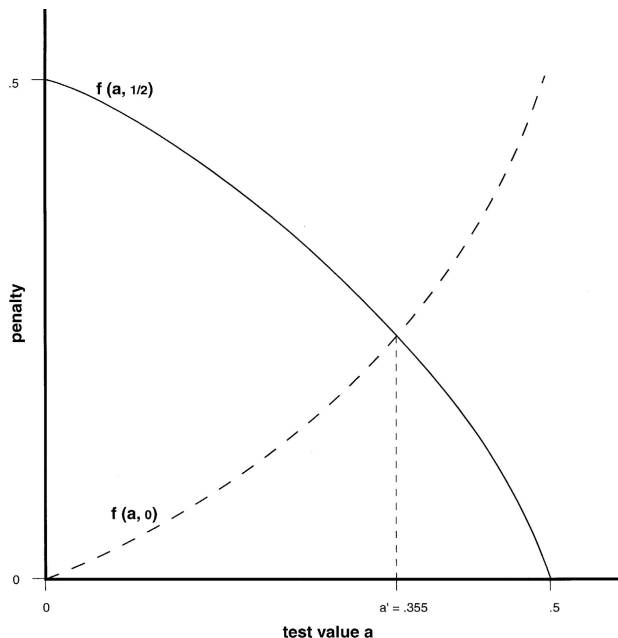


Figure 2 Curves showing penalties $f(a, a_*)$ associated with a test based on a when the true value is a_* , for $a_* = \frac{1}{2}$ (additive model) and $a_* = 0$ (recessive model). The point $a' = .355$, where the curves intersect, gives the minmax test.

nally, we shall compare the power of this most robust 1df test with that of the means test and with that of the CLR test.

The asymptotic power of a 1df test statistic X_a is determined by its noncentrality parameter. The latter is the expected value of X_a , which is given in equation (5), with (\hat{z}_1, \hat{z}_0) replaced by the true point (z_1, z_0) :

$$\frac{\sqrt{n}[3 - 4a + 4(a - 1)z_0 + (6a - 4)z_1]}{\sqrt{3 - 8a + 6a^2}} \quad (6)$$

But it is clear from figure 1 that the true point (z_1, z_0) must lie on a ray NP_{a_*} for some a_* , with $0 \leq a_* \leq 1/2$. So, on the basis of family of models (3), we can write

$$(z_1, z_0) = \left[\lambda a_* + (1 - \lambda) \frac{1}{2}, (1 - \lambda) \frac{1}{4} \right] \quad (7)$$

for some λ with $0 \leq \lambda \leq 1$. Substitution of the right side of equation (7) for (z_1, z_0) into expression (6) gives the noncentrality parameter $\sqrt{n}\xi(a, a_*)$ for X_a as

$$\sqrt{n}\xi(a, a_*) \equiv \sqrt{n}\lambda \frac{k(a, a_*)}{\sqrt{k(a, a)}}, \quad (8)$$

where $k(a, a_*) = 3 - 4(a + a_*) + 6aa_*$. The optimal test

statistic when the true point is on the ray NP_{a_*} is X_{a_*} , with noncentrality parameter

$$\sqrt{n}\xi(a_*, a_*) = \sqrt{n}\lambda \sqrt{k(a_*, a_*)}. \quad (9)$$

Two 1df tests with noncentrality parameters $\sqrt{n}\xi$ and $\sqrt{n'}\xi'$ have equal asymptotic power when their noncentrality parameters are equal. Then their sample sizes are related by $n' = n(\xi/\xi')^2$. For example, if X_{a_*} is the asymptotically optimal test based on n sib pairs, then, on the basis of expression (8) and expression (9), the number of sib pairs needed to obtain the same asymptotic power from a suboptimal test based on X_a , $a \neq a_*$, is

$$n' = n \left[\frac{\xi(a_*, a_*)}{\xi(a, a_*)} \right]^2 = n \frac{k(a, a)k(a_*, a_*)}{k^2(a, a_*)}. \quad (10)$$

The quantity

$$\frac{n' - n}{n} = \left[\frac{\xi(a_*, a_*)}{\xi(a, a_*)} \right]^2 - 1 \equiv f(a, a_*)$$

is the penalty (in terms of increased sample size) associated with the use of the suboptimal test X_a instead of the optimal one, X_{a_*} . For any fixed test value a , $f(a, a_*)$ is a convex function of a_* (i.e., the second derivative of f with respect to a_* is nonnegative). This convexity implies that the maximum penalty for a occurs at an endpoint $a_* = 0$ or $a_* = \frac{1}{2}$; that is, the maximum penalty $\max_{0 \leq a_* \leq \frac{1}{2}} f(a, a_*)$ for any admissible 1df test X_a occurs when the true point lies on the ray NP_{a_*} , where $a_* = 0$ or $a_* = \frac{1}{2}$. The two curves in figure 2 show penalties for tests based on X_a when $a_* = 0$ and $a_* = \frac{1}{2}$. The curves cross at $a' = (3 - \sqrt{6})/(4 - \sqrt{6}) = 0.355$. For $a \leq .355$ the maximum penalty is $f(a, \frac{1}{2})$, whereas for $a \geq .355$ the maximum penalty is $f(a, 0)$.

We seek a test whose maximum penalty is smaller than that of any other admissible 1df test, and such a test is the minmax test. The value a' determining the minmax test is defined by

$$\max_{0 \leq a_* \leq \frac{1}{2}} f(a', a_*) = \min_{0 \leq a \leq \frac{1}{2}} [\max_{0 \leq a_* \leq \frac{1}{2}} f(a, a_*)].$$

It is evident from figure 2 that the intersection point $a' = .355$ of the two curves has the smallest maximum penalty; that is, the poorest performance of the minmax statistic $X_{.355}$ is better than the poorest performance of all other 1df test statistics. On the basis of expressions (4), the minmax test assigns the weight $w_1 = .275$ to affected sib pairs sharing one allele IBD. This weight differs slightly from the midpoint, .25, of the weights $w_1 = .5$, used by the means test, and $w_1 = 0$, used by the proportions test; it is slightly closer to that of the

means test. Feingold and Siegmund (1997) proposed using the midpoint, $w_1 = .25$.

Table 1 shows, for a range of rays NP_{a_*} containing the true point (z_1, z_0) and for the means, proportions, and minmax tests, the sample sizes n' needed to achieve the same asymptotic power as is seen with the optimal test, on the basis of $n = 100$ sib pairs. The sample sizes n' are obtained from formula (10) and thus depend only on the values a and a_* . Table 1 shows that the means test incurs a 50% penalty when the data are generated by a recessive model, and, conversely, that the proportions test incurs a 50% penalty when the data are generated by an additive model; in contrast, the most severe penalty incurred by the minmax test is 10%, regardless of the true IBD probabilities.

We next compare the asymptotic power of the minmax test with that of the CLR test. The asymptotic distribution of the CLR statistic is a mixture of χ^2 distributions having 0, 1, and 2 df (a χ_0^2 distribution is one that puts all probability mass at the origin). The χ_1^2 and χ_2^2 distributions are central under the null hypothesis of no linkage and are noncentral under the alternative hypothesis of linkage. Appendix B describes the noncentrality parameters and weights used in the mixture, under the null and alternate hypotheses. Because the weights are integrals of the standard Gaussian density function, evaluating them for specific power calculations (such as those described below) requires numerical integration.

Table 2 shows the asymptotic power of the means, minmax, and CLR tests, with type 1 error probability $\alpha = .001$, for a range of true points (z_1, z_0) , at distance of either $\frac{1}{6}$ or $\frac{1}{8}$ from the null point. The calculations needed to determine the asymptotic power of the CLR test are outlined in Appendix B. The critical value of 10.592 for the CLR test was obtained by Holmans (1993). As expected, the means test is the most powerful of the three tests when (z_1, z_0) follows an additive model (table 2, row 6). However, the minmax test outperforms the means test in all other circumstances, and it outperforms the CLR test in all circumstances. Thus there are no asymptotic power gains from using the more complex CLR test rather than the simpler minmax test.

Affected Sib Triples

We now show that similar geometric considerations apply to tests based on n affected sib triples, although there are complications. IBD sharing among three sibs occurs in one of the four configurations shown in table 3 (Sribney and Swift 1992; Feingold et al. 1993). Table 3 also shows their Mendelian probabilities p_i , $i = 0, \dots, 3$. Let z_i denote the true IBD probability for a trio of affected sibs, $i = 0, \dots, 3$. Since these sum to 1, we need specify only three of them, say z_0, z_1 and z_2 . Figure

3 shows the three-dimensional unit simplex with vertices O, B, E , and G that contains the observed proportions $(\hat{z}_0, \hat{z}_1, \hat{z}_2)$. Figure 3 also shows a polyhedron T_3 with vertices N, A, B, C, D, E , and H that contains the true IBD probabilities (z_0, z_1, z_2) at the trait locus. Appendix C contains a proof of this result. The proof is based on the following assumptions: (1) there are two alleles at the disease locus, which are in Hardy-Weinberg equilibrium in the general population; (2) the penetrance for heterozygotes is intermediate between the two homozygote penetrances; (3) the sibs are noninbred; and (4) the probability of recombination between trait and marker loci is negligible. These assumptions, although weak, may limit the applicability of the constraint set T_3 .

Note that, as was true for T_2 , the null point N is a vertex of T_3 , and the faces of T_3 meeting at N form a small solid angle. Thus the geometric considerations suggesting robustness for 1df tests apply here also. As shown in Appendix C, an additive model specifies that (z_0, z_1, z_2) lies on the line NA , whereas a recessive model for a rare trait without phenocopies specifies that (z_0, z_1, z_2) lies near the line segment BA . A dominant model for a rare trait specifies that (z_0, z_1, z_2) lies near the line NA .

The analogue of the likelihood function (1) for affected sib triples is

$$L(z) \propto \prod_{i=0}^3 z_i^{mz_i}. \quad (11)$$

The unconstrained likelihood ratio (ULR) test is based on $L(\hat{z})/L(p)$, where $p = (\frac{3}{8}, \frac{1}{16}, \frac{3}{8}, \frac{3}{16})$. Restriction of the first three components (z_0, z_1, z_2) of the true point z to T_3 leads to a CLR test analogous to that proposed, by Holmans (1993), for sib pairs. The null distribution of this CLR test is a mixture of χ^2 distributions having 0, 1, 2, and 3 df. Although the asymptotic power of this test can be expected to exceed that of the ULR test, the previous considerations suggest that neither test will outperform a robust 1df test.

1df Tests

The 1df tests for sib triples are based on weighted sums $\sum_{i=0}^3 w_i \hat{z}_i$ of the observed frequencies of the IBD configurations in table 3. For example, the means test (Sribney and Swift 1992) gives each configuration a weight that is proportional to the mean number of alleles shared by each of the three possible pairs of the three sibs. This rule yields the weights $w_0, w_1, w_2, w_3 = 4, 6, 2, 2$. After being standardized arbitrarily so that $w_3 = 0$ and $w_1 = 1$, the weights are $\frac{1}{2}, 1, 0, 0$. This choice of weights also yields the repeats test of Green and Woodrow (1977) and the "all relatives" test proposed by Whittemore and Halpern (1994). A sib-triple ana-

Table 1

Sample Sizes Required for the Same Asymptotic Power as Is Shown by the Optimal 1df Test, Based on 100 Affected Sib Pairs

TRUE VALUE a_*	LOCATION OF (z_1, z_0)	OPTIMAL WEIGHT w_1^a	SAMPLE SIZE REQUIRED FOR		
			Means Test $(w_1 = .5)$	Proportions Test $(w_1 = 0)$	Minmax Test $(w_1 = .275)$
.000	Edge NO ^b	.000	150	100	110
.167	Interior	.100	132	101	104
.250	Interior	.167	122	103	102
.333	Interior	.250	113	108	100
.429	Interior	.375	103	122	102
.500	Edge NA ^c	.500	100	150	110

^a w_1 = weight for sib pairs sharing one allele IBD, when $w_0 = 0$ and $w_2 = 1$.

^b Recessive model.

^c Additive model.

logue of the proportions test for sib pairs is based on the proportion of triples in which all three sibs share both alleles IBD. This test assigns weights $w_0, w_1, w_2, w_3 = 0, 1, 0, 0$; we shall call this test the “proportions test.” After standardizing the weights in the form $w_0, 1, w_2, 0$, we can write the 1df test statistics in the form

$$X = J/\sqrt{K}, \tag{12}$$

where

$$J = \sqrt{n} \left[w_0 \left(\hat{z}_0 - \frac{3}{8} \right) + \hat{z}_1 - \frac{1}{16} + w_2 \left(\hat{z}_2 - \frac{3}{8} \right) \right]$$

and

$$K = \frac{15}{64}(w_0^2 + w_2^2) - \frac{9}{32}w_0w_2 - \frac{6}{128}(w_0 + w_2) + \frac{15}{256}.$$

To put these tests in a geometric context, we shall focus on the subset of T_3 consisting of all points lying

on some ray NP_{ab} , where (a, b) is an arbitrary point in the polygon $ABCDH$ in the z_1z_0 plane, shown in figure 3. Specifically, we shall consider the family of models,

$$F_{ab} = \left[z:z = \lambda(a, b, 0, 1 - a - b) + (1 - \lambda) \times \left(\frac{3}{8}, \frac{1}{16}, \frac{3}{8}, \frac{3}{16} \right); 0 \leq \lambda \leq 1 \right], \tag{13}$$

for $z = (z_0, z_1, z_2, z_3)$, where a and b satisfy the constraints

$$\begin{aligned} 0 &\leq a \leq \frac{3}{4}; \\ \frac{7}{40} &\leq b \leq 1; \\ a + b &\leq 1; \\ 6a + 8b &\geq 5. \end{aligned} \tag{14}$$

We have the following analogue of proposition 1.

Table 2

Asymptotic Power of Means, Minmax, and CLR Tests Using 100 Affected Sib Pairs

TRUE VALUE a_*	LOCATION OF (z_1, z_0)	OPTIMAL WEIGHT w_1	ASYMPTOTIC POWER WHEN DISTANCE OF (z_1, z_0) FROM NULL POINT = ^a					
			$\frac{1}{8}$			$\frac{1}{6}$		
			Means	Minmax	CLR	Means	Minmax	CLR
.000	Edge NO ^b	.000	.524	.722	.705	.868	.966	.959
.167	Interior	.100	.670	.810	.762	.947	.986	.974
.250	Interior	.167	.742	.844	.790	.971	.991	.981
.333	Interior	.250	.794	.855	.806	.983	.993	.984
.429	Interior	.375	.782	.791	.756	.981	.983	.977
.500	Edge NA ^c	.500	.670	.606	.578	.946	.918	.905

^a Data are for tests of size $\alpha = .001$ —i.e., critical values of 3.1 for means and minmax tests and of 10.592 for the CLR test.

^b Recessive model.

^c Additive model.

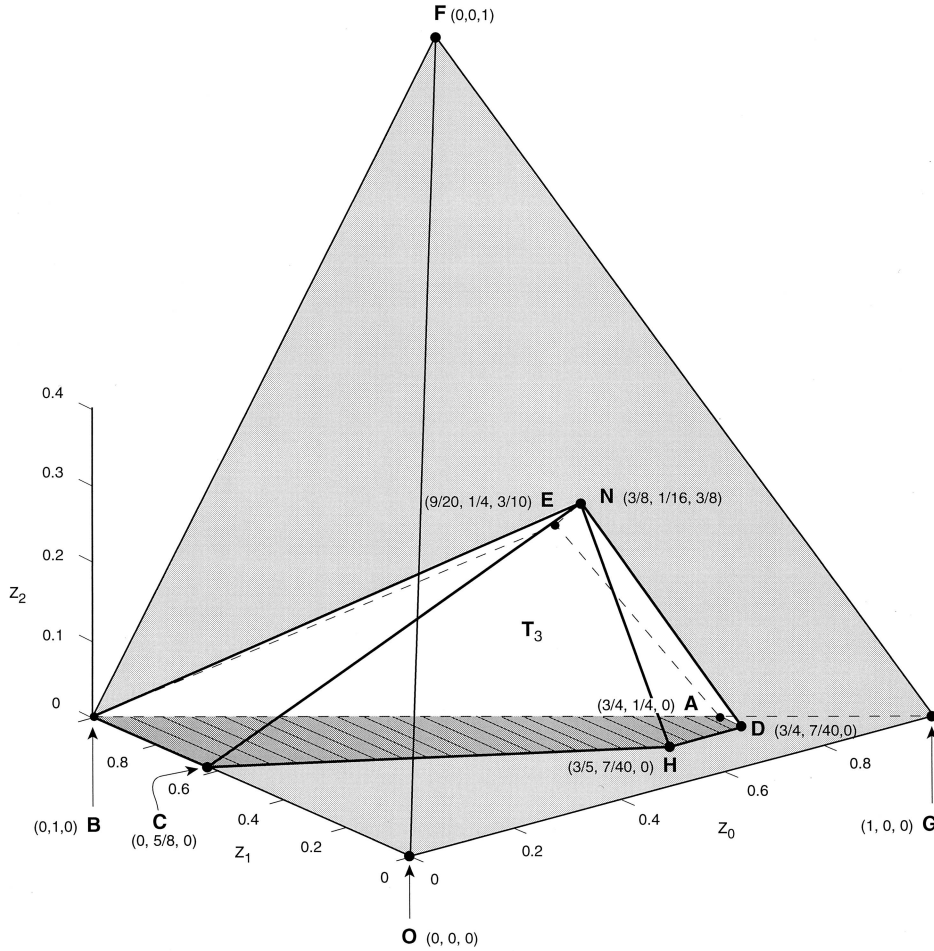


Figure 3 Unit simplex with vertices O, B, F, and G in three-dimensional z_0, z_1, z_2 space containing all points $(\hat{z}_0, \hat{z}_1, \hat{z}_2)$, where \hat{z}_i is the observed proportion of sib triples with IBD_i given in table 3, $i = 0, 1, 2$. Also shown is the polyhedron T_3 with vertices N, A, B, C, D, E, and H, containing all true IBD probabilities (z_0, z_1, z_2) , as shown in Appendix C.

PROPOSITION 2. The test statistic (12) is the efficient score statistic for the likelihood function (11) and the family of models (13) if and only if

$$w_0 = \frac{\frac{3}{2}a + b - 1}{a + 4b - 1} \text{ and } w_2 = \frac{a + b - 1}{a + 4b - 1}, \quad (15)$$

where (a, b) satisfies constraints (14).

The proof of this proposition is analogous to that of proposition 1 and therefore has been omitted.

We shall call 1df tests satisfying equations (15) “admissible” 1df tests and shall denote them as “ X_{ab} .” Substituting equations (15) into test statistic (12) gives

$$X = X_{ab} = J/K, \quad (16)$$

where

$$J = \sqrt{n} \left[\left(\frac{3}{2}a + b - 1 \right) \left(\hat{z}_0 - \frac{3}{8} \right) + \left(\hat{z}_1 - \frac{1}{16} \right) + (a + b - 1) \left(\hat{z}_2 - \frac{3}{8} \right) \right]$$

and

$$K = \frac{\sqrt{3}}{4} (a + 4b - 1) \sqrt{\frac{3}{2}a^2 + 4b^2 - 2(a + b) + 2ab}.$$

From equations (15) the means test with $w_0 = \frac{1}{2}$, $w_1 = 1$, and $w_2 = w_3 = 0$ has test statistic X_{ab} , where $(a, b) = (.75, .25)$, which corresponds to point A in figure 3. Similarly, the proportions test, with $w_0 = w_2 = 0$, has test statistic X_{ab} , where $(a, b) = (0, 1)$, which corresponds to point B in figure 3.

Asymptotic Power

The test based on X_{ab} is optimal when the true point lies on the ray NP_{ab} . Therefore, the means test $X_{.75,.25}$ is optimal for true points on the edge NA of T_3 . Since points on this edge correspond to genetic additivity, the means test is optimal for data generated by an additive model. Moreover, the proportions test X_{01} is approximately optimal for data generated by a recessive model without phenocopies (Appendix C).

Comparison of asymptotic power among the 1df test statistics, via their noncentrality parameters, is analogous to that for affected sib pairs. The noncentrality parameter for a test statistic X_{ab} is its expected value, which is given by equation (16), with $(\hat{z}_0, \hat{z}_1, \hat{z}_2)$ replaced by the true point (z_0, z_1, z_2) . We assume that the true point lies on the ray NP_{ab} given by one of the F_{ab} family of models (13), say $F_{a,b,*}$. Then, by substituting family of models (13) for $(\hat{z}_0, \hat{z}_1, \hat{z}_2)$ in equation (16), we can write the noncentrality parameter for X_{ab} as

$$\sqrt{n}\xi(a,b,a_*,b_*) \equiv \sqrt{n}\lambda \frac{k(a,b,a_*,b_*)}{\sqrt{k(a,b,a,b)}}$$

where

$$k(a,b,a_*,b_*) = \frac{3}{2}aa_* + 4bb_* + ab_* + a_*b - (a + b + a_* + b_*) + \frac{13}{16} .$$

The same arguments as have been used for affected sib pairs indicate that the penalty, in increased sample size, associated with the use of a suboptimal test determined by X_{ab} , with $(a,b) \neq (a_*,b_*)$, is

$$f(a,b,a_*,b_*) = \left[\frac{\xi(a_*,b_*,a_*,b_*)}{\xi(a,b,a_*,b_*)} \right]^2 - 1 , \tag{17}$$

where

$$\left[\frac{\xi(a_*,b_*,a_*,b_*)}{\xi(a,b,a_*,b_*)} \right]^2 = \frac{k(a,b,a,b)k(a_*,b_*,a_*,b_*)}{k^2(a,b,a_*,b_*)} .$$

We shall evaluate the performance of a test whose maximum penalty is a minimum when the true point lies in the polyhedron with vertices $N, A, B, C, D,$ and H . This minmax test is based on X_{ab} , where $(a,b) = (.532,.307)$. (This value was determined by evaluating the penalty associated with all pairs of points $[a,b]$ and $[a_*,b_*]$ in the polygon $ABCDH$ that lie on a square grid of mesh size 0.01 and choosing the point $[a,b]$ whose maximum penalty was smallest.) On the basis of equa-

Table 3

IBD Configurations for Three Siblings, A-C

<i>i</i>	NO. OF ALLELES SHARED BY			MENDELIAN PROBABILITY	WEIGHTS USED IN 1df TESTS	
	AB	AC	BC		Means	Proportions
0	2	1	1	$\frac{3}{8}$	$\frac{1}{2}$	0
1	2	2	2	$\frac{1}{16}$	1	1
2	1	0	1	$\frac{3}{8}$	0	0
3	2	0	0	$\frac{3}{16}$	0	0

tions (15), the weights for this test are $w_0 = .138$ and $w_2 = -.212$.

Table 4 shows sample sizes required by the means test, the proportions test, and this minmax test, to achieve the same asymptotic power as that seen for the optimal 1df test based on 100 sib triples, for various true points in T_3 . Unlike the situation for sib pairs, the increased sample sizes required by the means test and the proportions test can be large, with four- to fivefold increases required in some circumstances. In contrast, the minmax test never requires more than a 50% sample-size increase over that of the optimal test.

Although we do not explore them here, other tests, having 2 df, may also perform well. A 2df test is one that is optimal when the true point lies on a plane (rather than on a line) that intersects T_3 and that passes through the null point N . Such a plane would intersect the polygon with vertices $A, B, C, D,$ and H in a line segment l (rather than at a point $[a,b]$). The principles described above could be used to calculate the penalty for a suboptimal 2df test based on such a line segment l_* when the true point lies on a plane determined by both the null point N and another line segment l^* . One could then consider the maximum penalty associated with any test and determine a minmax test, in much the same way as has been done here. Comparison of power for 1df and 2df minmax tests is an area in need of further research.

Combining Affected Sib Pairs and Affected Sib Triples

Many linkage studies using affected sibships involve both affected sib pairs and affected sib triples. This raises the question of how to combine pairs and triples into a single 1df test statistic. To describe the problem, let $\hat{z}_i^{(2)}$ represent the observed proportion of sib pairs having IBD configuration $i, i = 0,1,2,$ and let $\hat{z}_i^{(3)}, i = 0,1,2,3$ be defined analogously for sib triples. Suppose that we have chosen weights $w_i^{(2)}, i = 0,1,2,$ for tests based on pairs and have chosen weights $w_i^{(3)}, i = 0,1,2,3,$ for tests based on triples. How does one choose a value c so that the combined statistic

Table 4

Sample Sizes Required for the Same Asymptotic Power as Is Shown by the Optimal 1df Test, Based on 100 Affected Sib Triples

TRUE VALUE a_*, b_*	LOCATION OF (z_0, z_1, z_2)	OPTIMAL WEIGHTS w_0, w_2	SAMPLE SIZE REQUIRED FOR		
			Means Test $(w_0 = .5, w_2 = 0)$	Proportions Test $(w_0 = 0, w_2 = 0)$	Minmax Test $(w_0 = .139, w_2 = -.207)$
.75, .25	Edge NA ^a	.5, 0	100	250	126
0, 1	Edge NB	0, 0	250	100	137
.75, .175	Edge ND	.67, -.17	106	472	146
0, .625	Edge NC	-.25, -.25	400	111	147
.6, .175	Edge NH	.25, -.75	133	333	123
.375, .375	Interior of T_3	-.07, -.29	188	118	109
.3, .6	Interior of T_3	.03, -.06	190	102	117

w_0 and w_2 are the weights for the IBD configurations 0 and 2, respectively, in table 3, when $w_1 = 1$ and $w_3 = 0$.

^a Additive model.

$$X = \frac{\left\{ \sum_{i=0}^2 w_i^{(2)} \hat{z}_i^{(2)} + c \sum_{i=0}^3 w_i^{(3)} \hat{z}_i^{(3)} - E \left[\sum_{i=0}^2 w_i^{(2)} \hat{z}_i^{(2)} + c \sum_{i=0}^3 w_i^{(3)} \hat{z}_i^{(3)} \right] \right\}}{\sqrt{V \left[\sum_{i=0}^2 w_i^{(2)} \hat{z}_i^{(2)} + c \sum_{i=0}^3 w_i^{(3)} \hat{z}_i^{(3)} \right]}}$$

has good power? The parameter c determines the weight attached to the data from a sib triple, relative to that from a sib pair. Feingold et al. (1993) show that the asymptotically optimal choice for c is the ratio of noncentrality parameters of the test based on triples to that of the test based on pairs. Teng and Siegmund (1997) find noncentrality parameters for pairs and triples when the means test is used and the true model is additive.

We calculated the optimal value c for analyses based on the two minmax tests described here, for a range of scenarios determined by (1) the true model (dominant, additive, or recessive), (2) the disease probability in the general population (range 5%–35%), (3) the disease probability in those with one affected sib, relative to that of the general population (range 1.5%–3%), and (4) the disease probability in those with two affected sibs, relative to that of the general population (range 1.5%–7%). We found that, for each of these scenarios, the optimal value c was somewhere in the range 1.5–3, implying that sib triples should receive 1.5–3 times the weight given to sib pairs. In additional calculations, we also found that, under a recessive model, c can be quite large when the trait allele frequency is rare and the phenocopy rate is low.

Discussion

We have provided a geometric interpretation for some of the nonparametric 1df tests commonly used in the analysis of affected sibships of sizes 2 and 3. This interpretation has prompted the investigation of new “minmax” tests, which perform well regardless of the true probabilities of IBD among the sibs. Asymptotic-power calculations suggest that the minmax tests are more robust against misspecification of these probabilities than are the 1df tests currently in use and that they perform as well as or better than the more complicated CLR test. Although we have used simulations (not shown) to verify the asymptotic-power comparisons given in table 2, we have not used them to examine the relative power of the minmax and CLR tests in small samples. This is an area in need of further work.

The results presented in table 1 show that, for affected sib pairs, all 1df tests are fairly robust; the penalties in increased sample size are never >50%, and the penalties for the most robust, minmax test are never >10%. However, the results presented in table 4 show that this is not the case for affected sib triples; the choice of test statistic, as well as its relation to the actual IBD probabilities, can have substantial impact on power; for example, the required sample size for the means test can be as much as four times that of the optimal test. In contrast, the increase in sample size required by the minmax test is never >50%. Of course, if there are a priori biological reasons supporting the hypothesis of genetic additivity, then the means test is preferable, since, when it is at least approximately appropriate, it is more powerful than the minmax tests.

Although, in principle, the aforementioned considerations could be extended to more-complex pedigrees, in practice such extension is difficult, because the computations become less tractable as the pedigrees increase in size and complexity. The observed drops in robustness

when one moves from sib pairs to sib triples suggests that, as the pedigree sizes increase, all nonparametric tests become considerably more sensitive to misspecification of the weights. Fortunately, much of the material used in linkage studies consists largely of sibships of small size.

The minmax tests described here can be used when the IBD configuration of some sibs cannot be determined unequivocally, when the marker locus does not coincide with the disease locus, and when data on multiple markers are available; for example, the multipoint linkage analyses implemented in the software GENEHUNTER (Kruglyak et al. 1996) are based on the additive weights of the means test but could be modified to accommodate the weights used by the minmax tests. Holmans (1993) showed that, when the marker locus does not coincide with the disease locus, the IBD probabilities at the marker locus still must lie in the triangle T_2 . Although it seems plausible that the marker IBD probabilities for sib triples also must lie within T_3 , we have not been able to extend Holman's arguments in order to prove it.

The assumptions used to derive the constraint sets T_2 and T_3 warrant comment. Both constraint sets assume that the sibs are not inbred. Both also assume that there are two alleles at the disease locus that are in Hardy-Weinberg equilibrium in the general population. The derivation of T_3 requires the additional assumption that the heterozygote penetrance be between that of the two homozygotes. This "sandwich" constraint may not be appropriate for traits whose etiologies involve multiple loci. In addition, the derivation of T_2 can be extended to arbitrarily many alleles, all in Hardy-Weinberg equilibrium. For sib triples, however, the introduction of more than two alleles would require similar sandwich constraints on the heterozygote penetrances.

Schaid and Nick (1990) also evaluated the asymptotic power of the means and proportions test applied to affected sib pairs, for various models for the true IBD probabilities. They proposed a test based on the maximum, $X = \max(X_o, X_{.s})$, of the means and proportions statistics. They developed critical values for X and examined the asymptotic power of this test. They showed that, for the models examined, the test based on X is more robust than either the means test or the proportions test. The results given in table 4, although limited, suggest that this robustness may extend to affected sib triples, because, when the means test does poorly, the proportions test does well, and vice versa.

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Appendix A

Proof of Proposition 1

For fixed a in the interval $[0, \frac{1}{2}]$, the F_a family of models (3) restricts the possible IBD probabilities z to those which depend on a single unknown scalar parameter λ . Accordingly, when the family F_a is assumed, we shall write $l(\lambda) = \log L[z(\lambda)]$, where $L(z)$ is given by the likelihood function (1). We show that, for fixed and known a with $0 \leq a \leq \frac{1}{2}$, the efficient score statistic

$$l'(0)/\sqrt{E_0[-l''(0)]} \quad (\text{A1})$$

for the F_a family of models is exactly X of equation (2), with w given by formulas (4). By substituting $\frac{1}{2}a/(1-a)$ for w in the right side of equation (2) and setting $\hat{z}_2 = 1 - \hat{z}_0 - \hat{z}_1$, we can rewrite equation (2) as

$$\begin{aligned} X &= X_a \\ &= \frac{\sqrt{n}[4(a-1)\hat{z}_0 + (6a-4)\hat{z}_1 + 3-4a]}{\sqrt{3-8a+6a^2}}. \end{aligned} \quad (\text{A2})$$

To compute the efficient score statistic, we substitute the family of models (3) into the log of the likelihood function (1), to obtain

$$\begin{aligned} l(\lambda) &= \text{constant} + n\hat{z}_0 \log(1-\lambda) \\ &\quad + n\hat{z}_1 \log \left[\lambda a + (1-\lambda) \frac{1}{2} \right] \\ &\quad + n\hat{z}_2 \log \left[\lambda(1-a) + (1-\lambda) \frac{1}{4} \right]. \end{aligned}$$

Differentiating this expression with respect to λ and evaluating it at $\lambda = 0$, we find that $l'(0) = n[4(a-1)\hat{z}_0 + (6a-4)\hat{z}_1 + 3-4a]$ and that $E_0[-l''(0)] = n[3-8a+6a^2]$. Substituting these expressions into formula (A1) gives equation (A2), as required.

Appendix B

Asymptotic Power of the CLR Test

The derivations follow those of Self and Liang (1987), as discussed by Holmans (1993). With notation that conflicts slightly with that of the main text, let $z =$

(z_0, z_1) represent a point in the unit simplex and let $p = (p_0, p_1) = (\frac{1}{4}, \frac{1}{2})$ be the null point. Let I be the 2×2 Fisher information matrix of the likelihood function (1), evaluated at $z = p$:

$$I = \begin{bmatrix} p_0(1-p_0) & -p_0p_1 \\ -p_0p_1 & p_1(1-p_1) \end{bmatrix}^{-1} = \begin{bmatrix} 8 & 4 \\ 4 & 6 \end{bmatrix}.$$

Following Self and Liang, we introduce the transformation $y = h(z) = (z - p)P\Lambda$, where Λ is the 2×2 diagonal matrix whose diagonal entries are the eigenvalues $7 + \sqrt{17}$ and $7 - \sqrt{17}$ of I and where P is the orthogonal matrix of eigenvectors of I :

$$P = \begin{pmatrix} .7882 & -.6154 \\ .6154 & .7882 \end{pmatrix}.$$

Let $\hat{y} = h(\hat{z})$, where \hat{z} is the observed value of z . When the null hypothesis is true, the asymptotic distribution of the ULR statistic $X_{ULR} = 2[l(\hat{y}) - l(p)]$ is that of a central χ^2 variate with 2 df. In symbols, $X_{ULR} \sim \chi^2_d(0)$, where $\chi^2_d(\delta^2)$ denotes the χ^2 distribution with d df and noncentrality parameter δ^2 .

When the null hypothesis is false, the asymptotic distribution of X_{ULR} is $\chi^2_2(n||y||^2)$, where $||y||$ is the Euclidean norm of y . To describe the asymptotic distribution of the CLR statistic X_{CLR} , let T'_2 denote the image of T_2 under the transformation $h(\cdot)$. Let \tilde{y} be the point in T'_2 that is closest to \hat{y} —that is, for which $||\hat{y} - \tilde{y}||$ is minimized. The point \tilde{y} depends on the location of \hat{y} . If $\hat{y} \in T'_2$, then $\tilde{y} = \hat{y}$. The complement of T'_2 consists of three subsets: the sets U_1 and U_2 of points \hat{y} for which \tilde{y} lies on the line segment connecting the origin $h(N)$ to the points $y_A = h(A)$ and $y_O = h(O)$, respectively, and the set V of points \hat{y} for which \tilde{y} is the origin. Under the null hypothesis, the asymptotic distribution of X_{CLR} is a mixture of central χ^2 distributions: $X_{CLR} \sim P_V\chi^2_0 + (P_{U_1} + P_{U_2})\chi^2_1(0) + P'_2\chi^2_2(0)$. Here $\chi^2_0 \equiv 0$ and P'_V is the probability that $\hat{y} \in V$, etc. By integrating the standard bivariate Gaussian density function over the regions in question, one obtains $P_{U_1} = P_{U_2} = \frac{1}{4}$ and $P'_2 = \frac{\theta}{2\pi}$, where θ is the angle between the vectors y_A and y_O :

$$\theta = \arccos\left(\frac{y_A y_O^T}{||y_A|| \cdot ||y_O||}\right) = \arccos\left(\frac{2}{\sqrt{6}}\right) = .1959\pi.$$

When the null hypothesis is false, the distribution of X_{CLR} is a mixture of noncentral χ^2 distributions:

$$X_{CLR} \sim P_V\chi^2_0 + P_{U_1}\chi^2_1[\delta^2 \cos^2(\theta - \phi)] + P_{U_2}\chi^2_1[\delta^2 \cos^2 \phi] + P'_2\chi^2_2(\delta^2).$$

Here the P 's are the probabilities that \hat{y} lies in the various regions when \hat{y} has a bivariate Gaussian density centered at the true point $y = (\delta \cos \phi, \delta \sin \phi)$. By integrating the bivariate Gaussian density centered at y and converting to polar coordinates, we obtain

$$P_{U_1} = (2\pi)^{-\frac{1}{2}} \left[\int_{\phi}^{\pi} f\left(\frac{\delta \sin \phi}{\sin \rho}\right) d\rho - \int_{\phi}^{\frac{\pi}{2}} f\left(\frac{\delta \cos \phi}{\cos \rho}\right) d\rho \right];$$

$$P_{U_2} = (2\pi)^{-\frac{1}{2}} \left\{ \int_{\theta}^{\pi+\phi} f\left[\frac{\delta \sin(\theta - \phi)}{\sin(\rho - \theta)}\right] d\rho - \int_{\theta+\frac{\pi}{2}}^{\phi+\pi} f\left[\frac{\delta \cos(\theta - \phi)}{\cos(\rho - \theta)}\right] d\rho \right\};$$

$$P'_2 = 1 - (2\pi)^{-\frac{1}{2}} \left\{ \int_{\theta}^{\pi+\phi} f\left[\frac{\delta \sin(\theta - \phi)}{\sin(\rho - \theta)}\right] d\rho + \int_0^{\phi} f\left[\frac{\delta \sin(\theta - \phi)}{\sin(\theta - \rho)}\right] d\rho + \int_{\phi}^{\pi} f\left(\frac{\delta \sin \phi}{\sin \rho}\right) d\rho \right\}.$$

Here $f(x) = (2\pi)^{-\frac{1}{2}} e^{-\frac{1}{2}x^2}$ is the standard univariate Gaussian density. These formulas differ from those obtained by Holmans (1993). The latter appear to be in error, since they fail to satisfy the requirement

$$\lim_{\delta \rightarrow \infty} P_{U_1} = \lim_{\delta \rightarrow \infty} P_{U_2} = 0$$

and

$$\lim_{\delta \rightarrow \infty} P'_2 = 1.$$

Appendix C

Constraints on IBD Probabilities for Affected Sib Triples

Let E be the event that all three sibs are affected, and let IBD_i be the event that the sibs have IBD configuration i , $i = 0, 1, 2, 3$, as shown in table 3. Table 3 also shows the Mendelian probabilities $P(IBD_i) = p_i$. From Bayes's rule, the IBD configuration probabilities of three affected sibs are

$$z_i = P(\text{IBD}_i|E) = \frac{p_i P(E|\text{IBD}_i)}{P(E)} = p_i(1 + \eta_i) \quad (C1)$$

where

$$\eta_i = \frac{P(E|\text{IBD}_i) - P(E)}{P(E)} \quad ; \quad P(E) = \sum_{i=0}^3 p_i P(E|\text{IBD}_i) \quad (C2)$$

We wish to show that any point (z_0, z_1, z_2) lies in the polyhedron T_3 shown in figure 3. This polyhedron is defined by the constraints

1. $z_2 \geq 0$;
2. $z_0 + z_1 + z_2 \leq 1$;
3. $z_0 + z_2 \leq \frac{3}{4}$
4. $z_0 \geq z_2$;
5. $2z_1 + 5z_2 \leq 2$;
6. $z_1 + \frac{3}{10}z_2 \geq \frac{7}{40}$
7. $z_0 + \frac{4}{3}z_1 + z_2 \geq \frac{5}{6}$.

Constraints 1 and 2 are obviously satisfied, since the z_i are probabilities. To verify the remaining five constraints, we use equation (C1) and the Mendelian probabilities p_i of table 3 to rewrite them as

$$3. \eta_0 + \eta_2 \leq 0; \quad 4. \eta_0 \geq \eta_2; \quad 5. \eta_1 + 5\eta_2 \leq 0 \quad ; \quad (C3)$$

$$6. 5\eta_1 + 9\eta_2 \geq 0; \quad 7. 9\eta_0 + 2\eta_1 + 9\eta_2 \geq 0 \quad . \quad (C4)$$

Verification of these constraints requires that we specify the probabilities $P(E|\text{IBD}_i)$ in equation (C2). To do so, we assume the existence of two alleles, A_1 and A_2 , at the trait locus. Let q_i denote the frequency of allele i , $i = 1, 2$, with $q_1 + q_2 = 1$ and, for concreteness,

$$0 \leq q_2 \leq \frac{1}{2} \leq q_1 \leq 1 \quad . \quad (C5)$$

We assume that the three genotypes A_1A_1 , A_1A_2 , and A_2A_2 occur in the population in the Hardy-Weinberg proportions: $P(A_1A_1) = q_1^2$; $P(A_1A_2) = 2q_1q_2$; and $P(A_2A_2) = q_2^2$. Then, referring to the IBD configurations in table 3 and letting φ_{ij} denote the penetrance for genotype A_iA_j , we have

$$P(E|\text{IBD}_0) = \sum_{i=1}^2 \sum_{j=1}^2 \sum_{k=1}^2 q_i q_j q_k \varphi_{ij}^2 \varphi_{ik} \quad ;$$

$$P(E|\text{IBD}_1) = \sum_{i=1}^2 \sum_{j=1}^2 q_i q_j \varphi_{ij}^3 \quad ;$$

$$P(E|\text{IBD}_2) = \sum_{i=1}^2 \sum_{j=1}^2 \sum_{k=1}^2 \sum_{l=1}^2 q_i q_j q_k q_l \varphi_{ij} \varphi_{ik} \varphi_{lk} \quad ;$$

$$P(E|\text{IBD}_3) = \sum_{i=1}^2 \sum_{j=1}^2 \sum_{k=1}^2 \sum_{l=1}^2 q_i q_j q_k q_l \varphi_{ij}^2 \varphi_{kl} \quad . \quad (C6)$$

We now write the penetrances φ_{ij} as

$$\begin{aligned} \varphi_{11} &= f \quad ; \\ \varphi_{12} &= \varphi_{21} = f_0 + f + d \quad ; \\ \varphi_{22} &= f_0 + 2f \quad . \end{aligned} \quad (C7)$$

We assume that the heterozygote penetrance φ_{12} is between the two homozygote penetrances φ_{11} and φ_{22} : $\varphi_{11} \leq \varphi_{12} \leq \varphi_{22}$. These inequalities, when used with equation (C7), imply that

$$0 \leq f \text{ and } -1 \leq -f \leq d \leq f \leq 1 \quad . \quad (C8)$$

The parameterization equation (C7) gives an additive model when $d = 0$, a dominant model when $d = f$, and a recessive model when $d = -f$. Substituting expressions (C7) for the penetrances in equations (C6) and then for those in equations (C2), we obtain, after straightforward but tedious calculations,

$$\begin{aligned} \eta_0 &= (\alpha + \beta + \gamma)q_1q_2/P(E) \quad ; \\ \eta_1 &= 3(\alpha + 3\beta + 3\gamma + 2\delta)q_1q_2/P(E) \quad ; \\ \eta_2 &= -(\alpha + 3\beta + \gamma + \delta)q_1q_2/P(E) \quad ; \\ \eta_3 &= (-\alpha + \beta - 3\gamma)q_1q_2/P(E) \quad . \end{aligned} \quad (C9)$$

Here

$$\begin{aligned} \alpha &= r^2 f_0 + \left(\frac{1}{2} + q_2\right) f^3 + \left(\frac{3}{2} - 4q_2^2\right) f^2 d \\ &+ \left(\frac{1}{2} - q_2\right) (3 - 4q_2^2) f d^2 + \frac{1}{2} (1 - 2q_2)^2 d^3 \quad ; \end{aligned} \quad (C10)$$

$$\beta = q_1q_2d^2 \left(f_0 + 2q_2f + \frac{1}{2}d\right) \quad ; \quad (C11)$$

$$\gamma = -q_1q_2dfr ; \tag{C12}$$

$$\delta = 2q_1q_2(1 - 2q_2)fd^2 ; \tag{C13}$$

and $r = f + (1 - 2q_2)d$. Substituting the right sides of equations (C9) for the η 's in constraint (C3) and constraint (C4) allows us to rewrite them as

3. $2\beta + \delta \geq 0 ;$
4. $2\alpha + 4\beta + 2\gamma + \delta \geq 0 ;$
5. $4\alpha + 12\beta + 2\gamma + 3\delta \geq 0 ;$
6. $2\alpha + 6\beta + 12\gamma + 7\delta \geq 0 ;$
7. $2\alpha + 6\gamma + \delta \geq 0 .$

To verify them, we will need the following lemma, whose proof follows from inequality (C5) and inequality (C8). LEMMA. For $d \geq 0$, each of the summands in α of equation (C10)) and in β of equation (C11) is nonnegative. For $d < 0$,

$$\alpha \geq \frac{1}{2}r^2(f + d) \geq 0 \tag{C14}$$

and

$$\beta \geq 2q_1q_2^2fd^2 + \frac{1}{2}q_1q_2d^3 \geq \frac{1}{2}q_1q_2d^3 . \tag{C15}$$

CONSTRAINT 3. To verify this constraint, we note that $2\beta + \delta = 2q_1q_2d^2(f_0 + f + \frac{1}{2}d)$, which is nonnegative by inequality (C8).

CONSTRAINT 4. When $d \geq 0$, the lemma implies that

$$\begin{aligned} 2\alpha + 4\beta + 2\gamma + \delta &\geq 2\left(\frac{1}{2}f^3\right) + 4 \cdot 0 + 2\gamma + \delta \\ &= f^2(f - 2q_1q_2d) . \end{aligned}$$

But, by inequality (C5), the right side is at least as large as $f - \frac{1}{2}d$, which is nonnegative because $d \leq f$, by inequality (C8).

For $d < 0$, inequality (C14) and inequality (C15) imply that

$$\begin{aligned} 2\alpha + 4\beta + 2\gamma + \delta &\geq 2 \cdot 0 + 4\left(\frac{1}{2}q_1q_2d^3\right) + 2\gamma + \delta \\ &= 2q_1q_2(f^2 - d^2)(-d) . \end{aligned}$$

The last expression is nonnegative by inequalities (C8). This proves constraint 4.

CONSTRAINT 5. For $d \geq 0$, the lemma implies that

$$\begin{aligned} 4\alpha + 12\beta + 2\gamma + 3\delta &\geq 4\left(\frac{1}{2}f^3\right) + 12 \cdot 0 + 2\gamma + 3\delta \\ &= 2f^3 - 2q_1q_2f^2d + 4q_1q_2(1 - 2q_2)fd^2 \\ &\geq 2f^2(f - q_1q_2d) \geq 0 . \end{aligned}$$

The second inequality follows because, from inequality (C5), $q_2 \leq \frac{1}{2}$, and the third inequality follows because, from inequalities (C8), $d \leq f$.

For $d < 0$, inequality (C14) and inequality (C15) imply that

$$\begin{aligned} 4\alpha + 12\beta + 2\gamma + 3\delta &\geq 4 \cdot 0 + 12\left(2q_1q_2^2fd^2 + \frac{1}{2}q_1q_2d^3\right) + 2\gamma + 3\delta \\ &= q_1q_2d^2(16q_2f + 4f) + 2q_1q_2(-d)(f^2 - 3d^2) . \end{aligned}$$

From inequalities (C8), $f^2 \geq -df$. Using this relation in the second summand above gives

$$\begin{aligned} 4\alpha + 12\beta + 2\gamma + 3\delta &\geq 16q_1q_2^2d^2f + 6q_1q_2d^2(f + d) , \end{aligned}$$

which is nonnegative by inequalities (C8). This proves constraint 5.

CONSTRAINT 6. For $d \geq 0$, the lemma implies that

$$\begin{aligned} 2\alpha + 6\beta + 12\gamma + 7\delta &\geq 2\left[\frac{1}{2}(1 + 2q_2)f^3 + \frac{1}{2}(3 - 8q_2^2)f^2d\right] \\ &\quad + 6 \cdot 0 + 12\gamma + 7\delta \\ &= f^2[(1 + 2q_2)f + (3 - 8q_2^2)d - 12d] \\ &\quad + 2q_1q_2(1 - 2q_2)fd^2 \\ &\geq f^2[(1 + 2q_2)f + (3 - 8q_2^2)d - 12d] \\ &\geq f^2[(1 + 2q_2)d + (3 - 8q_2^2)d - 12d] \\ &= 2f^2d(1 - 2q_2)(2 - q_2) \geq 0 . \end{aligned}$$

The second and fourth inequalities follow because, by inequality (C5), $q_2 \leq \frac{1}{2}$, and the third inequality follows because, by inequalities (C8), $d \leq f$.

For $d < 0$, inequality (C14) and inequality (C15) imply that

$$\begin{aligned} & 2\alpha + 6\beta + 12\gamma + 7\delta \\ & \geq 2 \cdot 0 + 6\left(\frac{1}{2}q_1q_2d^3\right) + 12\gamma + 7\delta \\ & = 3q_1q_2(-d)(-d^2 + 4f^2) + 2q_1q_2(1 - 2q_2)fd^2. \end{aligned}$$

Each of the summands on the right side is nonnegative because, from inequalities (C8), $d^2 \leq f^2$ and because, from inequality (C5), $q_2 \leq \frac{1}{2}$.

CONSTRAINT 7. For $d \geq 0$, the lemma implies that

$$\begin{aligned} & 2\alpha + 6\gamma + \delta \\ & \geq (1 + 2q_2)f^3 + (1 - 2q_2)(3 - 4q_2^2) \\ & \quad \times fd^2 - 6q_1q_2df^2 - 4q_1q_2(1 - 2q_2)fd^2 \\ & \geq (1 + 2q_2 - 6q_1q_2)f^3 + (1 - 2q_2) \\ & \quad \times (3 - 4q_2^2 - 4q_1q_2)fd^2 \\ & = \left[6\left(q_2 - \frac{1}{3}\right)^2 + \frac{1}{3}\right]f^3 + (1 - 2q_2) \\ & \quad \times (3 - 4q_2)fd^2 \geq 0. \end{aligned}$$

The second inequality holds because $d \leq f$, from inequalities (C8), and the last one holds by inequality (C5).

For $d < 0$, inequality (C14) implies that

$$\begin{aligned} 2\alpha + 6\gamma + \delta & \geq 6\gamma + \delta \\ & = -2q_1q_2[3df^2 + 2(1 - 2q_2)fd^2] \\ & \geq 2q_1q_2(1 + 4q_2)fd^2 \geq 0. \end{aligned}$$

The second inequality holds because $f \geq -d$, by inequalities (C8). This completes the proof.

Notice that, from equations (C11), (C12), and (C13) an additive model ($d = 0$) gives $\beta = \gamma = \delta = 0$, and so, from equation (C1) and equations (C9), $(z_0, z_1, z_2) = [\frac{3}{8}(1 + \alpha), \frac{1}{16}(1 + 3\alpha), \frac{3}{8}(1 - \alpha)]$; that is, an additive model implies that the true point lies on the line segment NA in figure 3.

For a recessive model ($d = -f$), without phenocopies ($f_0 = 0$), equations (C1), (C10), (C11), (C12), and (C13) give

$$\begin{aligned} z_0 & = \frac{6q_2}{1 + 6q_2 + 9q_2^2}; \\ z_1 & = \frac{1}{1 + 6q_2 + 9q_2^2}; \\ z_2 & = \frac{6q_2^2}{1 + 6q_2 + 9q_2^2}; \\ z_3 & = \frac{3q_2^2}{1 + 6q_2 + 9q_2^2}. \end{aligned}$$

For $q_2 \ll 1$, these equations imply that $(z_0, z_1, z_2) \sim (\nu, 1 - \nu, 0)$, where $\nu = 6q_2/(1 + 6q_2)$; that is, under a recessive model for a rare trait without phenocopies, (z_0, z_1, z_2) lies near the line BA in figure 3.

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