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, for diseases 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.

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 $z = (\frac{1}{4}, \frac{1}{2}, \frac{1}{4}) = \rho$, using a test that performs well regardless of the true value of $z$. 
Considering research has focused on the relative power of three tests. The first is the likelihood ratio test (also called the “maximum-likelihood test”), described by Risch (1990b). It is based on the ratio

$$L(\hat{\xi}) / L(p), \quad (1)$$

where $L(\xi) \propto z_{01}^{\hat{\xi}_0} z_{11}^{\hat{\xi}_1} z_{22}^{\hat{\xi}_2}$ denotes the multinomial likelihood of the observed IBD sharing frequencies when the true probabilities are given by $\xi$. Faraway (1993) and Holmans (1993) showed that the power of this test can be increased by evaluating the numerator at the point $\hat{\xi}$ but, rather, at a different point $\tilde{\xi}$. The coordinates of $\tilde{\xi}$ are constrained to lie within the triangle of values consistent with the underlying genetics of IBD sharing by the sibs (triangle $T_1$ with vertices $N, O$, and $A$ in fig. 1). Specifically, $\tilde{\xi}$ corresponds to that point within the triangle $T_1$ for which $L(\xi)$ is maximized. This constrained likelihood ratio (CLR) test is based on the ratio $L(\hat{\xi}) / L(p)$.

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

Here $E(\xi)$ and $V(\xi)$ 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 $\xi$, in which $\xi$ is a function $z(\lambda)$ of a scalar parameter $\lambda$:

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

Here $a$ is a fixed constant, and the parameter $\lambda$ 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 $\xi_1$ of sib pairs sharing one allele IBD satisfies $0 \leq \xi_1 \leq \frac{1}{2}$ (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 $F_1$ family of models (3) if and only if

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

(4)

In this case,

$$X = X_1 = \frac{\sqrt{n}[4(a - 1)\hat{z}_0 + (6a - 4)\hat{z}_3 + 3 - 4a]}{\sqrt{3 - 8a + 6a^2}} .$$

(5)

Conversely, the efficient score statistic for each $F_1$ 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 $z_2$. Figure 1 shows the unit simplex in the $(z_1, z_2)$ plane, with vertices $O$, $B$, and $C$, within which the observed proportions $(\hat{z}_1, \hat{z}_2)$ must lie, and the smaller triangle $T_2$, with vertices $O$, $N$, and $A$, containing the true IBD probabilities $(z_1, z_2)$ (Faraway 1993; Holmans 1993). The point $N$ corresponds to the null hypothesis $(z_1, z_2) = (\frac{1}{2}, \frac{1}{2})$. The point $(\hat{z}_1, \hat{z}_2)$ used in the CLR test is that point, within $T_2$, that is closest to $(\hat{z}_1, \hat{z}_2)$ in a certain metric (Holmans 1993; also see Appendix B).

A family $F_\alpha$, of models of the form given in formula (3) specifies that $(\hat{z}_1, \hat{z}_2) = [\alpha \lambda + \frac{1}{2}(1 - \lambda), \frac{1}{2}(1 - \lambda)]$ lies on the ray $NP_\alpha$, where $P_\alpha = (a, 0)$ 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 $X_1$ is optimal when the true point lies on the ray $NP_\alpha$. 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 $(\hat{z}_1, \hat{z}_2)$ 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-
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 $(z_1, z_0)$ replaced by the true point $(z_1, z_0)$:

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

But it is clear from figure 1 that the true point $(z_1, z_0)$ must lie on a ray $NP_{a_2}$ for some $a_2$, with $0 \leq a_2 \leq 1/2$. So, on the basis of family of models (3), we can write

$$f(a, a_*) = [\lambda a_* + (1 - \lambda) \left( {1 \over 2}(1 - \lambda) \right) \left( {1 \over 4} \right) \right]$$

for some $\lambda$ 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 $X_{a_2}$ as

$$\sqrt{n}\xi(a, a_*) = \sqrt{n}\lambda k(a, a_*) \over \sqrt{k(a, a_*)},$$

where $k(a, a_*) = 3 - 4a + 4a_* + 6aa_*$. The optimal test statistic when the true point is on the ray $NP_{a_2}$ is $X_{a_2}$, with noncentrality parameter

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

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 $X_{a_2}$ 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 $X_{a_2}, a \neq a_2$, is

$$n' = n \left[ {\xi(a, a_*)} \over {\xi(a_2, a_*)} \right]^2 = n' \left[ {k(a, a_*)} \over {k(a_2, a_*)} \right].$$  

The quantity

$$n' = n \left[ {\xi(a, a_*)} \over {\xi(a_2, a_*)} \right]^2 - 1 = f(a, a_*)$$

is the penalty (in terms of increased sample size) associated with the use of the suboptimal test $X_{a_2}$ instead of the optimal one, $X_{a_1}$. 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 $a_* = 1/2$, that is, the maximum penalty $\max_{0 < a_* < 1} f(a, a_*)$ for any admissible 1df test $X_{a_2}$ occurs when the true point lies on the ray $NP_{a_2}$, where $a_2 = 0$ or $a_2 = 1/2$. The two curves in figure 2 show penalties for tests based on $X_{a_2}$ when $a_2 = 0$ and $a_* = 1/2$. The curves cross at $a' = (3 - \sqrt{6})(4 - \sqrt{6}) = 0.355$. For $a \leq .355$ the maximum penalty is $f(a, 1/2)$, 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

$$\max_{0 < a_* < 1} f(a', a_*) = \min_{0 < a_* < 1} \left[ \max_{0 < a_* < 1} f(a, a_*) \right].$$

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, \( \omega_3 = .25 \).

Table 1 shows, for a range of rays \( N_p \), containing the true point \((z_o,z_o,z_o)\) 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 \( a_\cdot \). 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 \( \chi^2 \) distributions having 0, 1, and 2 df (a \( \chi^2 \) distribution is one that puts all probability mass at the origin). The \( \chi^2 \) and \( \chi^3 \) 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 \((z_o,z_o,z_o)\), at distance of either \( \frac{1}{2} \) or \( \frac{1}{4} \) 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 \((z_o,z_o)\) 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 four configurations shown in table 3 (Sribney and Swift 1992; Feingold et al. 1993). Table 3 also shows their Mendelian probabilities \( p_\cdot \). Let \( z \) denote the true IBD probability for a trio of affected sibs, \( i = 0, \ldots, 3 \). 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 \( O, B, F \), and \( G \) that contains the observed proportions \((\hat{z}_0,\hat{z}_1,\hat{z}_2)\). Figure 3 also shows a polyhedron \( T_s \) with vertices \( N, A, B, C, D, E, \) and \( H \) that contains the true IBD probabilities \((z_o,z_1,z_2)\) 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 \( T_s \). Note that, as was true for \( T_s \), the null point \( N \) is a vertex of \( T_s \), and the faces of \( T_s \) 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 \((z_o,z_1,z_2)\) lies near the line \( NA \), whereas a recessive model for a rare trait without phenocopies specifies that \((z_o,z_2,z_2)\) lies near the line segment \( BA \). A dominant model for a rare trait specifies that \((z_o,z_1,z_2)\) lies near the line \( NA \).

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

\[
L(z) \propto \prod_{i=0}^{3} z_i^{w_i}.
\]

The unconstrained likelihood ratio (ULR) test is based on \( L(z)/L(\hat{p}) \), where \( p = (\frac{1}{4},\frac{1}{4},\frac{1}{4},\frac{1}{4}) \). Restriction of the first three components \((z_o,z_1,z_2)\) of the true point \( z \) to \( T_s \) 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 \( \chi^2 \) 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 \( w_0 = 0 \) 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 Whittmore 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

<table>
<thead>
<tr>
<th>TRUE VALUE (a_0)</th>
<th>LOCATION OF ((z_1, z_0))</th>
<th>OPTIMAL WEIGHT (w_1^*)</th>
<th>MEANS TEST ((w_1 = .5))</th>
<th>PROPORTIONS TEST ((w_1 = 0))</th>
<th>MINMAX TEST ((w_1 = .275))</th>
</tr>
</thead>
<tbody>
<tr>
<td>.000</td>
<td>Edge NO(^b)</td>
<td>.000</td>
<td>150</td>
<td>100</td>
<td>110</td>
</tr>
<tr>
<td>.167</td>
<td>Interior</td>
<td>.100</td>
<td>132</td>
<td>101</td>
<td>104</td>
</tr>
<tr>
<td>.250</td>
<td>Interior</td>
<td>.167</td>
<td>122</td>
<td>103</td>
<td>102</td>
</tr>
<tr>
<td>.333</td>
<td>Interior</td>
<td>.250</td>
<td>113</td>
<td>108</td>
<td>100</td>
</tr>
<tr>
<td>.429</td>
<td>Interior</td>
<td>.375</td>
<td>103</td>
<td>122</td>
<td>102</td>
</tr>
<tr>
<td>.500</td>
<td>Edge NA(^c)</td>
<td>.500</td>
<td>100</td>
<td>150</td>
<td>110</td>
</tr>
</tbody>
</table>

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

\(^b\) Recessive model.

\(^c\) Additive model.

Table 2
Asymptotic Power of Means, Minmax, and CLR Tests Using 100 Affected Sib Pairs

<table>
<thead>
<tr>
<th>TRUE VALUE (a_0)</th>
<th>LOCATION OF ((z_1, z_0))</th>
<th>OPTIMAL WEIGHT (w_1^*)</th>
<th>(1/\sqrt{\lambda}) MEANS</th>
<th>(1/\sqrt{\lambda}) MINMAX</th>
<th>CLR</th>
</tr>
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<tbody>
<tr>
<td>.000</td>
<td>Edge NO(^b)</td>
<td>.000</td>
<td>.524</td>
<td>.722</td>
<td>.705</td>
</tr>
<tr>
<td>.167</td>
<td>Interior</td>
<td>.100</td>
<td>.670</td>
<td>.810</td>
<td>.762</td>
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<td>.250</td>
<td>Interior</td>
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<td>.742</td>
<td>.844</td>
<td>.790</td>
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<tr>
<td>.333</td>
<td>Interior</td>
<td>.250</td>
<td>.794</td>
<td>.855</td>
<td>.806</td>
</tr>
<tr>
<td>.429</td>
<td>Interior</td>
<td>.375</td>
<td>.782</td>
<td>.791</td>
<td>.756</td>
</tr>
<tr>
<td>.500</td>
<td>Edge NA(^c)</td>
<td>.500</td>
<td>.670</td>
<td>.606</td>
<td>.578</td>
</tr>
</tbody>
</table>

\(^a\) 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.
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

\[ w_0 = \frac{3a + b - 1}{a + 4b - 1} \quad \text{and} \quad w_2 = \frac{a + b - 1}{a + 4b - 1} , \]

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

\[ X = X_{ab} = J/K , \]

where

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

\[ + \left( \hat{z}_1 - \frac{1}{16} \right) + (a + b - 1) \left( \hat{z}_2 - \frac{3}{8} \right) \]

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 \( X_{abc} \) 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 \( X_{an} \) 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 \( (\hat{z}_a, \hat{z}_b) \) replaced by the true point \((z_a, z_b)\). We assume that the true point lies on the ray \( NP_{ab} \) given by one of the \( F_{ab} \) family of models (13), say \( F_{ab}^{*} \). Then, by substituting family of models (13) for \((\hat{z}_a, \hat{z}_b)\) in equation (16), we can write the noncentrality parameter for \( X_{ab} \) as

\[
\sqrt{n}(a,b,a_*,b_*) = \sqrt{n} k(a,b,a_*,b) \left( \frac{1}{k(a,b,a_*,b)} \right),
\]

where

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

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

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

where

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

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 \((a,b) = (.332, .307)\). (This value was determined by evaluating the penalty associated with all pairs of points \( [a,b] \) and \([a_*,b_*] \) in the polygon \( ABCDHN \) 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 equations (15), the weights for this test are \( w_0 = .138 \) and \( w_1 = -.212 \).

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 fivfold 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 \( l_1 \) (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 \( l_2 \), when the true point lies on a plane determined by both the null point \( N \) and another line segment \( l_2 \). 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 \( \hat{z}_i \) represent the observed proportion of sib pairs having IBD configuration \( i \), \( i = 0, 1, 2 \), and let \( \hat{z}_i^0 \) denote the observed proportion of sib triples having IBD configuration \( i \). For tests based on pairs and have chosen weights \( w_i \), \( i = 0, 1, 2, 3 \), 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

<table>
<thead>
<tr>
<th>TRUE VALUE $a_1,b_1$</th>
<th>LOCATION OF $(\xi_0,\xi_1,\xi_2)$</th>
<th>OPTIMAL WEIGHTS $w_0,w_2$</th>
<th>MEANS Test $(w_0 = .5, w_2 = 0)$</th>
<th>PROPORTIONS Test $(w_0 = 0, w_2 = 0)$</th>
<th>MINMAX Test $(w_0 = .139, w_2 = -.207)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>.75,.25</td>
<td>Edge NA</td>
<td>.5,.0</td>
<td>100</td>
<td>250</td>
<td>126</td>
</tr>
<tr>
<td>0</td>
<td>Edge NB</td>
<td>0,.0</td>
<td>250</td>
<td>100</td>
<td>137</td>
</tr>
<tr>
<td>.75,.175</td>
<td>Edge ND</td>
<td>.67,.17</td>
<td>106</td>
<td>472</td>
<td>146</td>
</tr>
<tr>
<td>0,.625</td>
<td>Edge NC</td>
<td>-25,-25</td>
<td>400</td>
<td>111</td>
<td>147</td>
</tr>
<tr>
<td>.6,.175</td>
<td>Edge NH</td>
<td>.25,.75</td>
<td>133</td>
<td>333</td>
<td>123</td>
</tr>
<tr>
<td>.375,.375</td>
<td>Interior of $T_1$</td>
<td>-.07,.29</td>
<td>188</td>
<td>118</td>
<td>109</td>
</tr>
<tr>
<td>.3,.6</td>
<td>Interior of $T_1$</td>
<td>.03,.06</td>
<td>190</td>
<td>102</td>
<td>117</td>
</tr>
</tbody>
</table>

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

*Additive model.

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

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 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 mis-specification
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 T3. Although
it seems plausible that the marker IBD probabilities for
sib triples also must lie within T3, we have not been able
to extend Holman’s arguments in order to prove it.

The assumptions used to derive the constraint sets T2
and T3 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 T3 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 T3 can be extended
to arbitrarily many alleles, all in Hardy-Weinberg equi-
librium. 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 max-
imum, \( X = \max(X_0, X_3) \), of the means and proportions
statistics. They developed critical values for X and ex-
amined 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 propor-
tions 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.

Acknowledgments

This research was supported by National Institutes of Health
grant CA47448. The authors are grateful to Aparna Gupta
and Walter Murray for computational assistance and to Joseph

Appendix A

Proof of Proposition 1

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

\[
l'(0)/\sqrt{\text{E}[l'(0)^2]} \quad (A1)
\]

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

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

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

\[
l(\lambda) = \text{constant} + n\hat{z}_0 \log(1 - \lambda).
\]

\[
+n\hat{z}_1 \log \left( \lambda a + (1 - \lambda) \frac{1}{2} \right)
\]

\[
+n\hat{z}_2 \log \left( \lambda (1 - a) + (1 - \lambda) \frac{1}{4} \right). \quad (A3)
\]

Differentiating this expression with respect to \( \lambda \) and evalu-
ating 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 \( \text{E}_a[-l'(0)] = n[3 - 8a +
6a^2] \). 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 \( z = \ldots \)
(z₀, z₁) represent a point in the unit simplex and let $p = (p₀, p₁) = (1, 1)$ be the null point. Let $I$ be the $2 \times 2$ Fisher information matrix of the likelihood function (1), evaluated at $z = p$:

$$I = \begin{bmatrix} p₀(1 - p₀) - p₀p₁ \\ -p₀p₁ \\ p₁(1 - p₁) \end{bmatrix}^{-1} = \begin{bmatrix} 8 & 4 \\ 4 & 6 \end{bmatrix}.$$

Following Self and Liang, we introduce the transformation $y = h(z) = (z - p)\Lambda$, where $\Lambda$ is the $2 \times 2$ 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 $X^2$ variate with 2 df. In symbols, $X_{ULR} \sim \chi^2(0)$, where $\chi^2(\delta^2)$ denotes the $X^2$ distribution with $\delta$ df and noncentrality parameter $\delta^2$.

When the null hypothesis is false, the asymptotic distribution of $X_{ULR}$ is that of $\chi^2(n\|y\|^2)$, where $\|y\|$ is the Euclidean norm of $y$. To describe the asymptotic distribution of the CLR statistic $X_{CLR}$, let $T_3$ denote the image of $T_2$ under the transformation $h(.)$. Let $\hat{y}$ be the point in $T_3$ that is closest to $\hat{y}$—that is, for which $\|\hat{y} - \hat{y}\|$ is minimized. The point $\hat{y}$ depends on the location of $\hat{y}$. If $\hat{y} \in T_2$, then $\hat{y} = \hat{y}$. The complement of $T_3$ consists of three subsets: the sets $U_i$ and $V_i$ of points $\hat{y}$ for which $\hat{y}$ lies on the line segment connecting the origin $b(N)$ to the points $y_i = h(A)$ and $y_O = h(O)$, respectively, and the set $V_i$ of points $\hat{y}$ for which $\hat{y}$ is the origin. Under the null hypothesis, the asymptotic distribution of $X_{CLR}$ is a mixture of central $X^2$ distributions: $X_{CLR} \sim P\chi^2_0 + (P_{U₁} + P_{U₂})\chi^2_1(0) + P_{V₁}\chi^2_2(0)$. Here $\chi^2_0 \equiv 0$ and $P_i$ is the probability that $\hat{y} \in V_i$, etc.

Here the $P_i$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

$$P_{U₁} = (2\pi)^{-1} \int_0^{\sigma} \int_0^{\pi} \frac{\delta \sin \phi}{\sin \rho} d\phi d\rho - \int_0^{\sigma} \int_0^{\pi} \frac{\delta \cos \phi}{\cos \rho} d\phi d\rho;$$

$$P_{U₂} = (2\pi)^{-1} \int_0^{\sigma} \int_0^{\pi} \frac{\delta \sin (\theta - \phi)}{\sin (\rho - \theta)} d\phi d\rho;$$

$$P_{V₁} = 1 - (2\pi)^{-1} \int_0^{\sigma} \int_0^{\pi} \frac{\delta \sin (\theta - \phi)}{\sin (\rho - \theta)} d\phi d\rho + \int_0^{\sigma} \int_0^{\pi} \frac{\delta \sin (\phi)}{\sin \rho} d\phi d\rho.$$

The latter appear to be in error, since they fail to satisfy the requirement

$$\lim_{\delta \to \infty} P_{U₁} = \lim_{\delta \to \infty} P_{U₂} = 0$$

and

$$\lim_{\delta \to \infty} P_{V₁} = 1.$$

### Appendix C

#### Constraints on IBD Probabilities for Affected Sib Triples

Let $E$ be the event that all three sibs are affected, and let IBD 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 $P(IBD) = p$. From Bayes’s rule, the IBD configuration probabilities of three affected sibs are
\[ z_i = P(\text{IBD}_i | E) = \frac{p_i P(E | \text{IBD}_i)}{P(E)} = p_i (1 + \eta_i) \quad \text{(C1)} \]

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

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. \( z_0 + \frac{4}{5} z_1 + z_2 \geq \frac{5}{6} \).

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. \( \eta_0 + \eta_2 \leq 0 \); 4. \( \eta_0 \geq \eta_2 \); 5. \( \eta_1 + 5\eta_2 \leq 0 \);  \text{(C3)}
6. \( 5\eta_1 + 9\eta_2 \geq 0 \); 7. \( 9\eta_0 + 2\eta_1 + 9\eta_2 \geq 0 \).  \text{(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,

\[ 0 \leq q_2 \leq \frac{1}{2} \leq q_1 \leq 1 \quad \text{(C5)} \]

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 \( \varphi_i \) denote the penetrance for genotype \( A_iA_i \), we have

\[ P(E | \text{IBD}_0) = \sum_{i=0}^{3} \sum_{j=1}^{3} q_i q_j \varphi_i \varphi_j \varphi_{ij} ; \quad \text{P(E | IBD}_1) = \sum_{i=1}^{3} \sum_{j=1}^{3} q_i q_j \varphi_i^3 ; \quad \text{P(E | IBD}_2) = \sum_{i=1}^{3} \sum_{j=1}^{3} \sum_{k=1}^{3} q_i q_j q_k \varphi_i \varphi_j \varphi_{ik} ; \quad \text{P(E | IBD}_3) = \sum_{i=1}^{3} \sum_{j=1}^{3} \sum_{k=1}^{3} q_i q_j q_k \varphi_i \varphi_j \varphi_{ik} \varphi_{ij} \varphi_{ijk} \quad \text{(C6)} \]

We now write the penetrances \( \varphi_i \) as

\[ \varphi_{11} = f_0 ; \quad \varphi_{12} = \varphi_{21} = f_0 + f + d ; \quad \varphi_{22} = f_0 + 2f \quad \text{(C7)} \]

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

\[ 0 \leq f \quad \text{and} \quad -1 \leq -f \leq d \leq f \leq 1 \quad \text{(C8)} \]

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,

\[ \eta_0 = (\alpha + \beta + \gamma) q_1 q_2 / P(E) ; \quad \eta_1 = 3(\alpha + 3\beta + 3\gamma + 2\delta) q_1 q_2 / P(E) ; \quad \eta_2 = - (\alpha + 3\beta + \gamma + \delta) q_1 q_2 / P(E) ; \quad \eta_3 = (\alpha + \beta - 3\gamma) q_1 q_2 / P(E) \quad \text{(C9)} \]

Here

\[ \alpha = r^2 f_0 + \left( \frac{1}{2} + q_2 \right) f^3 + \left( \frac{3}{2} - 4q_2^2 \right) f^2 d + \left( \frac{1}{2} - q_2 \right) (3 - 4q_2^2) f d^2 + \frac{1}{2} (1 - 2q_2)^2 d^3 \quad \text{(C10)} \]

\[ \beta = q_1 q_2 d^2 (f_0 + 2q_2 f + \frac{1}{2} d) \quad \text{(C11)} \]
\[ \gamma = -q_1 q_2 d f r ; \quad (C12) \]

\[ \delta = 2 q_1 q_2 (1 - 2 q_2) f d^2 ; \quad (C13) \]

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

1. \( 2 \beta + \delta = 0 \);
2. \( 2 \alpha + 4 \beta + 2 \gamma + \delta = 0 \);
3. \( 4 \alpha + 12 \beta + 2 \gamma + 3 \delta = 0 \);
4. \( 2 \alpha + 6 \beta + 12 \gamma + 7 \delta = 0 \);
5. \( 2 \alpha + 6 \gamma + \delta = 0 \).

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 \( \alpha \) of equation (C10)) and in \( \beta \) of equation (C11) is nonnegative. For \( d < 0 \),

\[ \alpha \geq \frac{1}{2} r^2 (f + d) \geq 0 \quad (C14) \]

and

\[ \beta \geq 2 q_1 q_2 f d^2 + \frac{1}{2} q_1 q_2 d^3 \geq \frac{1}{2} q_1 q_2 d^3 . \quad (C15) \]

**Constraint 3.** To verify this constraint, we note that

\[ 2 \beta + \delta = 2 q_1 q_2 d^2 (f_0 + f + \frac{1}{2} d) \geq \text{nonnegative by inequality (C8)}. \]

**Constraint 4.** When \( d \geq 0 \), the lemma implies that

\[ 2 \alpha + 4 \beta + 2 \gamma + \delta \geq 2 \left( \frac{1}{2} f^3 \right) + 4 \cdot 0 + 2 \gamma + \delta = f^2 (f - 2 q_1 q_2 d) . \]

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

\[ 2 \alpha + 4 \beta + 2 \gamma + \delta \geq 2 \cdot 0 + 4 \left( \frac{1}{2} q_1 q_2 d^3 \right) + 2 \gamma + \delta = 2 q_1 q_2 (f^2 - d^2) (-d) . \]

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

**Constraint 5.** For \( d \geq 0 \), the lemma implies that

\[ 4 \alpha + 12 \beta + 2 \gamma + 3 \delta \geq 4 \left( \frac{1}{2} f^3 \right) + 12 \cdot 0 + 2 \gamma + 3 \delta = 2 f^3 - 2 q_1 q_2 f^2 d + 4 q_1 q_2 (1 - 2 q_2) f d^2 \geq 2 f^3 (f - q_1 q_2 d) \geq 0 . \]

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

\[ 4 \alpha + 12 \beta + 2 \gamma + 3 \delta \geq 4 \cdot 0 + 12 \left( 2 q_1 q_2 f d^2 + \frac{1}{2} q_1 q_2 d^3 \right) + 2 \gamma + 3 \delta = q_1 q_2 d^2 (16 q_2 f + 4 f) + 2 q_1 q_2 (-d) (f^2 - 3 d^2) . \]

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

\[ 4 \alpha + 12 \beta + 2 \gamma + 3 \delta \geq 16 q_1 q_2 d^2 f + 6 q_1 q_2 d^2 (f + d) , \]

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

**Constraint 6.** For \( d \geq 0 \), the lemma implies that

\[ 2 \alpha + 6 \beta + 12 \gamma + 7 \delta \geq 2 \left[ \frac{1}{2} (1 + 2 q_2) f^3 + \frac{1}{2} (3 - 8 q_2^3) f^2 d \right] + 6 \cdot 0 + 12 \gamma + 7 \delta = f^2 [(1 + 2 q_2) f + (3 - 8 q_2^3) d - 12 d] + 2 q_1 q_2 (1 - 2 q_2) f d^2 \geq f^2 [(1 + 2 q_2) f + (3 - 8 q_2^3) d - 12 d] \geq f^2 [(1 + 2 q_2) d + (3 - 8 q_2^3) d - 12 d] = 2 f^2 d (1 - 2 q_2) (2 - q_2) \geq 0 . \]

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

\[
2\alpha + 6\beta + 12\gamma + 7\delta.
\]

\[
\geq 2 \cdot 0 + 6\left(\frac{1}{2}q_1q_2d^2\right) + 12\gamma + 7\delta
\]

\[
= 3q_1q_2(-d)(-d^2 + 4f^2) + 2q_1q_2(1 - 2q_2)fd^2.
\]

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

\[
2\alpha + 6\gamma + \delta
\]

\[
\geq (1 + 2q_1)f^3 + (1 - 2q_2)(3 - 4q_2^2)
\]

\[
x fd^2 - 6q_1q_2d^2 - 4q_1q_2(1 - 2q_2)fd^2
\]

\[
\geq (1 + 2q_1 - 6q_1q_2)f^3 + (1 - 2q_2)
\]

\[
x(3 - 4q_2^2 - 4q_1q_2)fd^2
\]

\[
= \left[6(q_2 - \frac{1}{3})^2 + \frac{6}{3}\right]f^3 + (1 - 2q_2)
\]

\[
x(3 - 4q_2)fd^2 \geq 0 .
\]

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

\[
2\alpha + 6\gamma + \delta \geq 6\gamma + \delta
\]

\[
= -2q_1q_2[3df^2 + 2(1 - 2q_2)fd^2]
\]

\[
\geq 2q_1q_2(1 + 4q_2)fd^2 \geq 0 .
\]

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), \((z_0, z_1, z_2) = \left\{1(1 + \alpha), \frac{1}{2}(1 + 3\alpha), \frac{1}{2}(1 - \alpha)\right\}\); 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

\[
z_0 = \frac{6q_2}{1 + 6q_2 + 9q_2^2} ;
\]

\[
z_1 = \frac{1}{1 + 6q_2 + 9q_2^2} ;
\]

\[
z_2 = \frac{6q_2^2}{1 + 6q_2 + 9q_2^2} ;
\]

\[
z_3 = \frac{3q_2^2}{1 + 6q_2 + 9q_2^2} .
\]

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.

### References


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