Optimal Allele-Sharing Statistics for Genetic Mapping using Affected Relatives

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Abstract

The choice of allele-sharing statistic can have a great impact on the power of robust affected relative methods. Similarly, when allele-sharing statistics from several pedigrees are combined, the weight applied to each pedigree’s statistic can affect power. Here we describe the direct connection between the affected relative methods and traditional parametric linkage analysis, and we use this connection to give explicit formulae for the optimal sharing statistics and weights, applicable to all pedigree types. One surprising consequence is that under any single gene model, the value of the optimal allele-sharing statistic does not depend on whether observed sharing is between more closely or more distantly related affected relatives. This result also holds for any multigene model with loci unlinked, additivity between loci, and all loci having small effect. For specific classes of two-allele models, we give the most powerful statistics and optimal weights for arbitrary pedigrees. When the effect size is small, these also extend to multigene models with additivity between loci. We propose a useful new statistic, $S_{robust}$, which performs well for dominant and additive models with varying phenocopy rates and varying predisposing allele frequency. We find that the statistic $S_{-\#alleles}$, performs well for recessive models with varying phenocopy rates and varying predisposing allele frequency. We also find that for models with large deviation from null sharing, the correspondence between allele-sharing statistics and the models for which they are optimal may also depend on which method is used to test for linkage.

Key words: complex traits, robust linkage analysis, relative pairs, affected pedigree member, discordant sib pairs
Introduction

Genetic mapping of a trait by linkage analysis involves finding regions of the genome with a tendency to be shared identical by descent (IBD) by close relatives affected with the trait and not shared between affected and unaffected relatives. Full parametric linkage analysis entails specification of a model for inheritance of the trait, with the location of the gene then estimated by the method of maximum likelihood. For a single-gene two-allele model, the full parametric model would include the frequency, \( a \), of the trait-causing allele, as well as penetrances \( f_0, f_1, f_2 \), for noncarriers, heterozygote carriers, and homozygote carriers, respectively. More complicated models might include 1) a single gene model with \( h \) alleles with frequencies \( a_1, \ldots, a_h \), respectively, and penetrance \( f_{ij} \) for an individual whose genotype consists of the \( i \)th and \( j \)th alleles or 2) multigene versions of the above models, in which loci are unlinked and effects are additive across loci. In cases when the parameters of the model are not known, they are sometimes impossible to estimate, and the maximum likelihood analysis has been found to be very sensitive to model misspecification [Clerget-Darpoux et al. 1986]. Allele-sharing methods have been proposed as a way to avoid these difficulties. This class of methods includes the sib pair method, originated by Penrose [1935] and developed by many others [e.g., Day and Simons (1976); Green and Woodrow (1977); Fishman et al. (1978); Suarez (1978); Hodge (1984); Lange (1986); Fimmers et al. (1989)], the affected pedigree member method (APM) of Weeks and Lange [1988] which uses identity by state (IBS) information, work on affected relative pairs by Risch [1990b], and general affected relative methods that use IBD information [Whittemore and Halpern (1994); Kruglyak et al.
(1996); Whittemore (1996); Kong and Cox (1997)]. These methods are clearly not model-
free, but they are believed to be more robust than full parametric likelihood analysis in those
cases when the model is not known.

We now describe the framework for these allele-sharing methods. For any genome loca-
tion \( x \) and any pedigree with \( n \) members and \( l \) founders, \( l < n \), following Thompson [1974],
we number the founders’ alleles 1 through \( 2 \times l \), and we define the gene-identity state \( g \) at
each location \( x \) in the genome by \( g(x) = (p_1, m_1, p_2, m_2, \ldots, p_n, m_n) \) where \( p_i \) represents the
founder allele inherited by individual \( i \) from his or her father and \( m_i \) that from his or her
mother. We consider two gene-identity states to be equivalent if one can be obtained from
the other by simply permuting the allele labels. The resulting equivalence classes of gene-
identity states are called IBD configurations and denoted by \( c \). We consider an allele-sharing
statistic \( S(c, \Phi) \) to be a function of the allele configuration \( c \) and the phenotype information
\( \Phi \) in the pedigree (more generally, \( S \) might depend on \( g \) rather than \( c \)).

Allele-sharing methods generally consider sharing among affecteds only, and with the
exception of a brief discussion of discordant sib pairs, we limit this study to statistics \( S \)
depending on affecteds only. Note that in principle, \( S \) may use information on sharing with
unaffecteds as well. For instance, full parametric linkage analysis may be seen as the case
where \( S \) is chosen to be the likelihood ratio [Kruglyak et al. 1996], which of course depends
on the genotype information on both affecteds and unaffecteds. The three rationales for
considering affecteds only are, first, that this effectively eliminates one penetrance param-
ter from the model, leading to greater robustness when the model is unknown. (When only
affecteds are considered, the two-allele model can be parametrized by the frequency \( a \) of the predisposing allele and the relative risks \( f_2/f_0 \) and \( f_1/f_0 \). Second, affecteds contribute most of the information to the study, and elimination of unaffecteds from consideration does not usually cause a severe loss of power. Third, for many complex diseases or traits, some individuals classified as unaffected may simply not yet have developed the disease or trait. For instance Alzheimer’s disease, many cancers, and many phenotypes related to heart disease tend to have a late age of onset. Thus, in some cases, the designation of an individual as “unaffected” may be much more uncertain than the designation of an individual as “affected.” Note that although \( S \) depends only on affecteds, genotype information on unaffecteds may be used for inferring IBD information on affecteds.

We concentrate on allele-sharing methods based on IBD rather than IBS sharing, as the former are more powerful [Kruglyak et al. (1996); Sobel and Lange (1996)]. In practice, of course, full IBD information is not available, but instead, the conditional distribution of the allele configuration \( c(x) \) at any given location \( x \), conditional on the marker data, may be computed. For instance, the software package GENEHUNTER of Kruglyak et al. [1996] can compute, for small to moderate-size pedigrees, the conditional distribution of what they call the inheritance vector, which is equivalent to the allele configuration, at a location \( x \), given the multipoint marker information for all pedigree members. In that case, instead of considering \( S(c(x), \Phi) \), one could consider, e.g., its null expectation conditional on the multipoint marker information, \( \bar{S}(x, \Phi) = \sum_{w \in C} S(w, \Phi) P_O[c(x) = w|\text{data}] \), where \( P_O[c(x) = w|\text{data}] \) is calculated under the null hypothesis of no gene for the trait linked to that location.
Under the null hypothesis of no gene for the trait linked to location $x$, the distribution of an allele-sharing statistic $S$ is in principle known. The hope is that $S$ will show significant deviation from its null distribution when there is a gene at that location affecting the trait. Proposed tests for detecting this deviation are described below. Not surprisingly, the power to detect linkage using any particular statistic $S$ can vary greatly depending on the underlying genetic model for the trait. For instance, Figures 1a and b depict the power to detect dominant alternatives with various phenocopy rates and penetrances using 30 trios consisting of affected sib pairs each with affected parent, while Figures 1e and f show the power to detect recessive alternatives under the same conditions. Four different allele-sharing statistics are compared (definitions given in Definitions of Allele-Sharing Statistics below). Note that those that perform best in the dominant case perform worst in the recessive case and vice versa, although the statistics perform similarly in the dominant and additive cases, as shown by a comparison of Figures 1a - d. In this paper, we investigate the relationship between allele-sharing statistics and two-allele models, with extension to special cases of multiple unlinked genes.

*Prior work on choice of sharing statistic*

For the special case of sib pairs, there are several relevant studies. Schaid and Nick [1990], Knapp [1991], and Schaid and Nick [1991] derived an expression for the optimal sib pairs allele-sharing statistic in terms of the probabilities of sharing 0, 1, or 2 alleles under an alternative model. Knapp et al. [1994] pointed out that for affected sib pairs, using the first method for testing linkage described below in Methods for Testing Linkage, $S$
equal to the number of shared alleles (equivalent to $S_{\text{pairs}}$ defined below) is optimal for the recessive model with full penetrance and no phenocopies, $f_2 = 1, f_1 = f_0 = 0$. However, they did not discuss the fact that it is optimal for many other models as well, nor that it is no longer optimal for the recessive case if there are phenocopies, as shown in Feingold and Siegmunch [1997]. These results are verified as special cases of our results below, and we give a more exhaustive list of situations in which $S_{\text{pairs}}$ is optimal. Feingold and Siegmund [1997] includes an investigation of the power of sharing statistics for sib pairs with an emphasis on recessive and partially recessive models. For this, they use a Gaussian approximation, which is equivalent to assuming small effect size, and assume multiple unlinked genes acting additively between, but not necessarily within, loci.

Kruglyak et al. [1996] performed simulations comparing the power of two statistics, $S_{\text{pairs}}$ and $S_{\text{alt}}$, defined below, for a scheme where the particular pedigree was randomly determined and allowed to vary across realizations, and the method used to test linkage was the first method described below. Their results indicated that $S_{\text{alt}}$ performed much better than $S_{\text{pairs}}$ in the dominant case and for the two complex models they consider, and that the two statistics performed equally well in the recessive case.

As to the choice of the weighting factors $\gamma_i$, Kruglyak et al. [1996] suggest equal weights (but note that they are first dividing each pedigree’s statistic by its null standard deviation). Sobel and Lange [1996] suggest summing the statistics they consider, without normalizing by the standard deviation. In the case of $S_{\text{pairs}}$, they suggest using weight $\sqrt{2/[n(n-1)]}$, where $n$ is the number of affecteds in the pedigree, to downweight large pedigrees. In both
studies, the authors imply that these choices are *ad hoc*.

Teng and Seigmund [1997] consider both choice of sharing statistic and of weights. For relative pairs, they restrict consideration to the case of additivity within and between loci, with large-sample asymptotics, i.e. small effect size, assumed to hold. They consider a few special cases of multiple affected relatives and make the additional assumption of a two-allele model at each locus in those cases. A statistic that they find to work well can be generalized to the statistic $S_{everyone}$ considered here. We note that while this statistic may work well for the large-sample asymptotics with the particular small pedigrees considered in Teng and Siegmund [1997], if one instead uses smaller samples with larger pedigrees, $S_{everyone}$ is very sensitive to genotyping errors and loses most of its power in the presence of phenocopies or with segregation of multiple copies of the predisposing allele within a pedigree. While Teng and Siegmund [1997] consider each special case of pedigree type separately, we are instead able to describe general optimal statistics with explicit algorithms for computing them in any pedigree.

**Methods for Testing Linkage**

1. $Z^{tot}$ [Kruglyak et al. 1996] Given a sharing statistic $S$, a pedigree, and a genome location $x$, consider the normalized version of $S$, $Z(c(x), \Phi) = \frac{S(c(x), \Phi) - \mu_o}{\sigma_o}$, where $\mu_o$ is the expected value of $S$ and $\sigma_o$ the standard deviation of $S$ under the null hypothesis of no gene for the trait linked to that location. In the case of incomplete IBD data on location $x$,
let \( \bar{Z}(x, \Phi) = \frac{\delta(x, \Phi) - \mu_0}{\sigma_0} \). (With complete IBD data on \( x \), \( \bar{Z}(x, \Phi) = Z(c(x), \Phi) \).) Note that \( \sigma_0 \) is the null standard deviation of \( Z \), which will tend to be larger than the null standard deviation of \( \bar{Z} \). Thus, inference based on \( \bar{Z} \) can be overly conservative [Kong and Cox 1997]. Consider \( p \) pedigrees, with \( \bar{Z} \) for the \( \text{ith} \) pedigree denoted by \( \bar{Z}_i \). To combine the \( \bar{Z}_i \)'s for different pedigrees into an overall \( \bar{Z}^{\text{tot}} \), choose appropriate weight \( \gamma_i \) for the \( \text{ith} \) pedigree, with \( \sum_{i=1}^{p} \gamma_i^2 = 1 \), and let \( \bar{Z}^{\text{tot}} = \sum_{i=1}^{p} \gamma_i \bar{Z}_i \). Kruglyak et al. [1996] propose using equal weights for all pedigrees, \( \gamma_i = 1/\sqrt{p} \) for all \( i \), and they suggest comparing \( \bar{Z}^{\text{tot}} \) to a standard normal distribution or computing an exact p-value for \( \bar{Z}^{\text{tot}} \) in order to test linkage. Both methods are implemented in their GENEHUNTER package.

2. \textbf{LR}^{\text{lin}} \textit{Whittemore [1996] showed that in the complete data case, the test statistic } \( Z^{\text{tot}} = \sum_{i=1}^{p} \gamma_i Z_i \text{ is the efficient score statistic corresponding to the likelihood} \)

\[
(*) \quad L_A^{\text{lin}}(c(x), \Phi) = \prod_{i=1}^{p} [L_O(c_i(x), \Phi_i)(1 + \delta \gamma_i Z_i)] = \\
L_O(c(x), \Phi) \times \prod_{i=1}^{p} (1 + \delta \gamma_i Z_i).
\]

Here \( L_A \) denotes the likelihood under an alternative model involving a gene at the given location contributing to the trait. The superscript \textit{lin}, for “linear”, denotes the particular class of alternative models given by \((*)\), \( L_O \) denotes the likelihood under the null hypothesis that no predisposing gene is linked to the given location, \( c_i(x) \) is the allele-sharing configuration for the affecteds in the \( \text{ith} \) pedigree, \( c(x) \) is the configuration for all the pedigrees together, and \( \Phi_i \) and \( \Phi \) are the affection status information for the \( \text{ith} \) pedigree and all
pedigrees combined, respectively. This model is not biologically-based, but is a convenient mathematical representation of the deviation from null sharing. The parameter $\delta$ measures the magnitude of deviation of the alternative likelihood from the null likelihood in the direction specified by the $\gamma_iZ_i$'s, and $\delta$ must be estimated. Among other things, $Z^\text{tot}$ being the efficient score statistic corresponding to the given likelihood implies that the test based on $Z^\text{tot}$ is asymptotically equivalent to the test based on the maximized log-likelihood ratio for the given likelihood (let $\log(LR^{\text{lin}})$ denote this maximized log-likelihood ratio). Furthermore, the framework of maximum likelihood estimation provides for computation of lod scores and creation of confidence intervals for the true gene location.

3. $LR^{\text{exp}}$ Kong and Cox [1997] have suggested a different likelihood,

\[
(**) \quad L_A^{\text{exp}}(c(x), \Phi) = \Pi_{i=1}^{p} [L_O(c_i(x), \Phi_i) e^{\delta \gamma_i Z_i} / E_O(e^{\delta \gamma_i Z_i})] =
\]

\[
L_O(c(x), \Phi) \times \exp(\sum_{i=1}^{p} \delta \gamma_i Z_i) / E_O[\exp(\sum_{i=1}^{p} \delta \gamma_i Z_i)]
\]

(where $E_O$ denotes expected value under the null hypothesis), which also has $Z^{\text{tod}}$ as efficient score statistic, and is another mathematically convenient representation of the deviation from null sharing. The likelihood $L_A^{\text{exp}}$, where $\exp$ is for “exponential”, has an advantage over the likelihood $L_A^{\text{lin}}$ in that for the latter, $\delta$ is restricted to the range $(-1/(\gamma Z)_{\text{max}}, -1/(\gamma Z)_{\text{min}})$, where $(\gamma Z)_{\text{max}}$ and $(\gamma Z)_{\text{min}}$ are the largest and smallest possible values, respectively, of $\gamma_iZ_i$, $i = 1, ..., p$. Thus, for models with large deviation from null sharing, power may be lost using $\log(LR^{\text{lin}})$ when the sharing statistic $S$ used is not close to the optimal and hence the pa-
rameter $\delta$ maximizes on the boundary. There are no such restrictions on $\delta$ in $L_A^{exp}$. We note that in the case of complete data, the statistic $\log(\hat{LR}^{exp})$ (the maximized log-likelihood ratio under likelihood $L_A^{exp}$) is just a monotone transformation of $Z^{tot}$, so the two methods give identical tests for linkage if exact p-values are used. This is not the case, however, for the linear model, nor for either model with incomplete data, nor if approximate p-values are used.

**Guiding principles for the optimal choice of $S$ and the $\gamma_i$’s**

By drawing a connection between the test statistics described above and the likelihood ratio for the affecteds under a parametric model, we can derive completely general, exact formulae for the optimal $S$ and $\gamma_i$’s. For the test based on $\log(\hat{LR}^{lin})$, the $S$ and $\gamma_i$’s given below are asymptotically most powerful against the alternative, while for the tests based on $\log(\hat{LR}^{exp})$ and $Z^{tot}$, the $S$ and $\gamma_i$’s given below are most powerful for any sample size.

A consequence of the work of Whittemore [1996] is that for a test based on $\log(\hat{LR}^{lin})$, the asymptotically optimal $S$ is $S = L_A(c(x), \Phi)/L_O(c(x), \Phi) - 1$, where $L_A(c(x), \Phi)$ is the likelihood under the true alternative sharing distribution, as opposed to the mathematically convenient alternative likelihoods $L_A^{lin}$ and $L_A^{exp}$. $S$ is optimal in the sense that for a given pedigree, the choice of parameter $\delta = \sqrt{\sum_{j=1}^{p} \sigma_{0j}^2}$ in likelihood $L_A^{lin}$ corresponds to the true alternative likelihood $L_A$. In that case, the likelihood ratio in the allele-sharing framework would equal the true likelihood ratio for the affecteds in the full parametric framework, giving greatest power to detect the alternative. Since the parameter $\delta$ is estimated, the equivalence of the allele-sharing and parametric likelihoods, with $S$ chosen as above, is asymptotic. (Note
that \( S = b(L_A/L_O - 1) + d \) would serve just as well, where \( b \) and \( d \) are any constants). To combine pedigrees in this situation, we find that the asymptotically optimal weights are 

\[
\gamma_i = \sigma_{oi} \sqrt{\sum_{j=1}^{p} \sigma_{o,j}^2}
\]

where \( \sigma_{oi} \) is the standard deviation of \( S = L_A/L_O - 1 \) in pedigree \( i \) under the null hypothesis. These are asymptotically optimal weights in the sense that when \( S \) and the \( \gamma_i \)'s are so chosen, then the case \( \delta = \sqrt{\sum_{j=1}^{p} \sigma_{o,j}^2} \) in likelihood \( L^{iin}_A \) corresponds to the true alternative likelihood \( L_A \). Thus, the likelihood ratio in the allele-sharing framework, with multiple pedigrees combined in this way, would equal the true likelihood ratio for the affecteds in the full parametric framework.

For \( \log(L^\text{exp}_R) \) and for the efficient score statistic \( Z^{tot} \), the optimal choice of \( S \) is instead \( S = \log(L_A/L_O) \) (here again, \( b \log(L_A/L_O) + d \) would serve just as well), while the corresponding choices of \( \gamma_i \)'s are the same as above, except that the null standard deviations are now for the new choice of \( S = \log(L_A/L_O) \). In the case of complete data, these are non-asymptotic results. Although the non-asymptotic optimality of these \( S \) and \( \gamma_i \)'s is not surprising for \( Z^{tot} \), it is somewhat surprising that such a non-asymptotic result would hold in the case of \( \log(L^\text{exp}_R) \), since the parameter \( \delta \) is estimated. In fact, when \( S \) and the \( \gamma_i \)'s are so chosen, \( \log(L^\text{exp}_R) \) is a monotone transformation of the true likelihood ratio for any sample size, even though the parameter \( \delta \) is estimated by maximizing the likelihood. In the case of incomplete data, the result for \( \log(L^\text{exp}_R) \) would be asymptotic, as above for the case of \( \log(L^\text{lin}_R) \). Note that when the optimal \( S \) is used and pedigrees are combined, the optimal weight \( \gamma_i = \sigma_{oi} \sqrt{\sum_{j=1}^{p} \sigma_{o,j}^2} \) is equivalent to combining pedigrees on the unnormalized \( S \) scale, rather than on the normalized \( Z \) scale as was done in Kruglyak et al. 1996, i.e. \( Z^{tot} \) should be a normalized version of \( \sum_i S_i \) rather than a normalized version of \( \sum_i Z_i \) as in
Kruglyak et al. 1996.

Although the $\log(LR^{\text{lin}})$ has a different optimal choice of $S$ from the other two test statistics, these two optimal choices of $S$, $L_A/L_O - 1$ and $\log(L_A/L_O)$, are approximately equal for alternative models with small deviation from null sharing. However, for alternative models with large deviation from null sharing, these statistics may be quite different.

To choose the $\gamma_i$'s when the $S$ used is not the optimal $S$, we note that $E_A(Z_{\text{tot}})$ is maximized when $\gamma_i$ is taken equal to $E_A(Z_i)/\sqrt{\sum_{j=1}^{p} E_A(Z_j)}$. This coincides with the choice of $\gamma_i$ given above when the optimal $S$ is used. For alternative models with small deviation from null sharing, when the $S$ used is not the optimal $S$, the same choice of $\gamma_i \propto E_A(Z_i)$ also approximately maximizes $E_A(\log(LR^{\text{lin}}))$ and $E_A(\log(LR^{\text{esp}}))$.

The principles given above, which connect allele-sharing statistics with parametric likelihoods, can be applied to any specific disease model to determine the optimal $S$. The resulting $S$ will be applicable to every pedigree type, not just special cases. Similarly, the principles can be applied in reverse to determine for which disease models a particular $S$ is optimal. As described in Methods for Testing Linkage, Whittemore [1996] and Kong and Cox [1997] have shown the equivalence of the allele-sharing methods to likelihood-based methods using a sharing statistic and a model misfit parameter. Combining this with our results on optimal statistics, we can view allele sharing methods as equivalent to picking a particular parametric disease gene model and then introducing a parameter $\delta$ to absorb model misfit. A method will perform well when the model chosen is close to the true model,
but may perform very poorly if it is far from the true model, as illustrated in Figure 1.

Exchangeability of Relatives in optimal $S$

All of the sharing statistics discussed below treat relatives exchangeably. By this we mean that if the genotypes of some affected individuals were permuted among them, with the two alleles of each individual’s genotype treated as a unit, never separated, then, assuming that a biologically possible IBD configuration resulted, the values of the allele-sharing statistics would not be changed. For instance, consider the case of an affected sib pair with an affected first cousin, with the possible IBD configurations shown in Table I, where the allele labels are arbitrary. In configuration $c_2$, one sib shares an allele with the cousin, and in $c_3$, the sibs share one allele. Intuitively, one might think that since sharing of one allele between a sib and cousin is more unusual than sharing of one allele between the sibs, the former should receive more weight in an evaluation of linkage under many genetic models of interest, e.g. when the risk to relatives of a proband is high, and perhaps less weight when this risk is low. However, all of the allele-sharing statistics $S$ considered here depend only on the collection of genotypes and not on which relative has which genotype, i.e. not on whether the observed sharing is between close or distant relatives (although calculation of the null mean and variance, $\mu_0$ and $\sigma_0^2$, does use the relationship information). One might think that it would be very important to take into account the closeness of the relatives who share among the affecteds, and one might see the failure to do this as a flaw in the proposed allele-sharing statistics $S$. Surprisingly, we can show that under rather general conditions, relatives actually should be treated in this exchangeable way. This result follows from the
fact that the optimal $S$ is some function of the likelihood ratio, here either $L_A/L_O - 1$ or 
$\log(L_A/L_O)$ (see Appendix A for proof).

Note that the exchangeability result does not contradict the results of Risch [1990b] and
Feingold et al. [1993] that affected first-cousin pairs are more powerful for detecting linkage
than affected sib pairs (assuming a single-gene model with full IBD information and at least
a moderately large relative risk to offspring of affecteds). Here, the configuration $c_2$ contains
more information than just sharing between first cousins. It also contains an affected sib
pair that shares no alleles at the given location. Thus, it is weaker evidence for linkage than
the observation of sharing between affected first cousins.

Conditions under which the optimal $S$ should treat relatives exchangeably include models
in which a single gene affecting the trait has $h$ alleles with frequencies $a_1$, ..., $a_h$ and
penetrance $f_{ij}$ for an individual with genotype $(i,j)$, and also multigene models where the
genes are unlinked and multiallelic, with additivity between but not necessarily within loci,
and with small effect size. The result does not depend on the values of $h$, the $a_i$’s, the $f_{ij}$’s,
nor on the type of pedigree. For all of the models in this class, $P_A(\Phi|c(x)) = P_A(\Phi|c'(x))$
where $c'(x)$ is obtained from $c(x)$ by any permutation of the genotypes of the individuals,
with the two alleles of each genotype treated as a unit, never separated. The models un-
der which the result would not hold would be those under which $P_A(\Phi|c(x)) \neq P_A(\Phi|c'(x))$.
Multigene models outside the class described above, and environmental effects on penetrance
that could be expected to be more similar for close relatives than for more distant relatives
could cause such dependence. In the case of an affected sib pair with affected first cousin,
these complications could cause the optimal sharing statistic to give more weight either to
\( c_3 \) (sib-sib sharing) or to \( c_2 \) (sib-cousin sharing), depending on the specific model.

In a typical allele-sharing analysis in which genome locations are tested individually, without attempting to look for interactions between loci, we argue that, among other considerations, a gene is detectable to the extent that it shows some similarity to a single gene model in at least some proportion of the families. Thus, the implication of the above result is that, in those cases when the allele-sharing method is likely to have power to detect a gene, treating relatives exchangeably is the right approach, to a first approximation, even for complex traits. Note that this result depends on an IBD analysis (incomplete data allowed) with linkage tested at every point, as in, e.g. the GENEHUNTER package [Kruglyak et al. 1996].

Definitions of Allele-Sharing Statistics

Before presenting results on optimal allele-sharing statistics, we introduce the following statistics, which can be applied to individual pedigrees with arbitrary numbers of affecteds. Table I gives sample calculations for the first seven statistics on the list for the the case of an affected sib pair with affected first cousin. (For that pedigree type, two of the statistics, \( S_{g-prs} \) and \( S_{\#geno} \) are equivalent.)

1. \( S_{pairs} \) [Weeks and Lange (1988); Fimmers et al. (1989); Whittemore and Halpern (1994); Kruglyak et al. (1996); Sobel and Lange (1996); Teng and Siegmund (1997)], counts,
for each pair of affected relatives, the number of alleles they share, and then sums that over all pairs of affected relatives. For a pair of relatives with respective IBD genotypes \((i, j)\) and \((k, l)\), the number of alleles they share is calculated as \(\delta(i, k) + \delta(i, l) + \delta(j, k) + \delta(j, l)\), where \(\delta(x, y) = 1\) if \(x = y\), 0 otherwise.

2. \(S_{all}\) [Whittemore and Halpern (1994); Kruglyak et al. (1996); Teng and Siegmund (1997)] Consider a vector of length \(m\), where \(m\) is the number of affecteds, whose \(i\)th component is one of the two alleles of the \(i\)th person at the given location. There are \(2^m\) such possible vectors \(\omega\). For each \(\omega\), let \(h(\omega) = \prod_{j=1}^{\text{#alleles}} g_j^!,\) where \(g_j\) is the number of times allele \(j\) occurs in \(\omega\), i.e. \(h(\omega)\) is the number of permutations that preserve \(\omega\). Define \(S_{all} = 1/2^m \times \sum_{\omega \in \Omega} h(\omega)\). The value assigned to a configuration by \(S_{all}\) increases with the number of people sharing the same allele. Whittemore and Halpern [1994] proposed this statistic to weight more heavily group sharing of a single allele over pairwise sharing of different alleles by different affected pairs.

3. \(S_{-\text{alleles}}\) (negative of Statistic A in Sobel and Lange [1996]) equals \(-1\) times the number of distinct-by-descent alleles appearing among the affecteds. Sobel and Lange [1996] suggest that this statistic would be useful for recessive traits.

4. \(S_{everyone}\) If all affecteds in the pedigree have a common ancestor in the pedigree, let \(S_{everyone}(c) = \) the number of alleles shared by all affecteds. If not all affecteds have a common ancestor, but it is possible to choose two pedigree members such that all affecteds are descendants of at least one of them, then let \(S_{everyone}(c) = \) the number of ways to choose two alleles from among those in \(c\) so that all affecteds have at least one of them, and so on. In general, if it is not possible to choose \(i\) pedigree members such that all affecteds are descendants of at least one of them, but it is possible to choose \(i + 1\) such, then let
$S_{everyone}(c) = \text{the number of ways to choose } i + 1 \text{ alleles from among those in } c \text{ so that all affecteds have at least one of them. In certain special cases, Teng and Siegmund [1997] have proposed statistics that are equivalent to } S_{everyone}, \text{ but they have not proposed a general definition, such as the one given here, that would be applicable to all types of pedigrees of affected relatives.}

5. $S_{-\#\text{geno}}$ counts -1 for each distinct genotype appearing in the observed IBD configuration of affecteds in a pedigree.

6. $S_{g-pra}$ counts the number of pairs of affecteds in a pedigree who have the same genotype.

7. $S_{\text{fewest}}$ equals one if the observed IBD configuration of affecteds in a pedigree contains the fewest possible distinct-by-descent alleles for that pedigree type, and it equals zero otherwise.

8. $S_{\#\text{triples}}$ equals the number of ways to choose three alleles $i, j, k$ from the set of those appearing among the affecteds in a pedigree so that $(i, j), (i, k), \text{ and } (j, k)$ each appear as genotypes of at least one affected.

9. $S_{\#\text{aff} \ HBD}$ (for inbred pedigrees) is the number of affected individuals who are homozygous by descent (HBD) at the given locus. Let $S_{-\#\text{aff} \ HBD} = -S_{\#\text{aff} \ HBD}$.

10. $S_{-\#\text{mal HBD}}$ (for inbred pedigrees) equals $-1$ times the number of distinct-by-descent alleles that occur at least once in HBD form among the affecteds in a pedigree.

11. $S_{\text{rob dom}} = \sum_{i \in A} (c(i) - 1)$, where $A$ is the set of all alleles observed for the particular locus among the affecteds in the pedigree, and $c(i)$ is equal to the number of affecteds in the pedigree with at least one copy of allele $i$. 
Optimal $S$’s for All Pedigree Types

The principles given above for choice of $S$ and $\gamma_i$, giving the direct connection with the parametric likelihood, are completely general and could be applied to any specific case. What is somewhat remarkable is that for many cases of interest, the resulting $S$ can be given in a very simple form that is applicable to all pedigree types. Following are some examples. Proofs are given in Appendix B. We assume for convenience that the penetrances satisfy $f_0 \leq f_1 \leq f_2$.

Rare dominant with phenocopies:
If a dominant model is assumed with predisposing allele frequency $a \to 0$ (i.e. each allele is introduced no more than once into a pedigree), and with phenocopy rate $f_0$ satisfying $f_1 > f_0 > 0$, then let $r = f_1 / f_0$ be the relative risk of having the trait with and without the predisposing allele. Then the optimal allele-sharing statistic for any pedigree in this case is

$$S = \sum_{i \in A} (r^{c_1(i)} - 1),$$

where $A$ is the set of all alleles observed for the particular locus among the affecteds in the pedigree, and $c_1(i)$ is equal to the number of affecteds in the pedigree with at least one copy of allele $i$. In practice, we find that the power to detect linkage is not very sensitive to the choice of $r$. We somewhat arbitrarily choose $r = 7$, and call the resulting statistic $S_{rob \, dom}$ for “robust dominant.” Figures 1a-d show that $S_{rob \, dom}$ performs well for a variety of additive and dominant models with varying predisposing allele frequency and phenocopy rate.
Allele with small effect, single or multigene:

If the phenocopy rate is close to the penetrance of the homozygote carrier in the two-allele model, i.e. if \( f_0 \to f_2 \), then for all outbred pedigrees, the optimal sharing statistic is given by

\[
\alpha S_{\text{pairs}} + (1 - \alpha) S_{\text{prs}},
\]

where \( \alpha = (a\tilde{m} + m\tilde{a})^2/(m^2\tilde{a} + \tilde{m}^2a) \), \( m = (f_1 - f_0)/(f_2 - f_0) \), \( \tilde{a} = 1 - a \), and \( 0 < a < 1 \). This still holds if there are assumed to be multiple unlinked genes, all with small effect (i.e. \( f_0 \to f_2 \) at each locus), with additivity between loci, while the individual locus follows a two-allele model. This sharing statistic is optimal for tests based on any of \( \log(LR^{\text{lin}}) \), \( \log(LR^{\text{exp}}) \), and \( Z_{\text{tot}} \). In the dominant case, this becomes \( \tilde{a}S_{\text{pairs}} + aS_{\text{prs}} \), in the recessive case \( aS_{\text{pairs}} + \tilde{a}S_{\text{prs}} \), and in the additive case, simply \( S_{\text{pairs}} \). If the number of pairs sharing a genotype cannot vary among the different possible configurations of the outbred pedigree, e.g. for an affected first cousin pair, where the number of shared genotypes is always 0, then when \( f_0 \to f_2 \), the optimal statistic is \( S_{\text{pairs}} \). For inbred pedigrees, when \( f_0 \to f_2 \), the optimal statistic is \( S_{\text{#aff } HBD} \) when \( m < 1/2 \), \( S_{-\text{#aff } HBD} \) when \( m > 1/2 \), and \( S_{\text{pairs}} \) when \( m = 1/2 \) (additive).

Rare gene with no phenocopies:

In the dominant case with \( f_0 \to 0 \) and \( a \to 0 \), i.e. a rare dominant with no phenocopies, the optimal sharing statistic for tests based on \( \log(LR^{\text{lin}}) \) is \( S_{\text{everyone}} \). In outbred pedigrees in which it is possible for all affected to share an allele IBD, this result holds also for any
\(m > 0\) (i.e. any non-recessive model). The corresponding optimal statistic in the recessive case is \(S_{\text{fewest}}\).

Table II gives optimal allele-sharing statistics \(S\) in a number of other special cases. These results hold for arbitrary pedigrees. For outbred pedigrees in which it is not possible for a pair of affecteds to share an IBD genotype, the statistics statistics \(S_{\#g^{\#0}}\) and \(S_{g-prs}\) will each be the same for all possible \(c\), and thus, are not useful as sharing statistics. As noted in the second column of sharing statistics in Table II, \(S_{\text{pairs}} - S_{\text{all triples}}\) and \(S_{\text{pairs}}\) should be substituted for \(S_{\#g^{\#0}}\) and \(S_{g-prs}\), respectively, in such cases. With the exceptions of \(S_{\text{everyone}}\) and \(S_{\text{fewest}}\), the statistics given are optimal for tests based on \(Z^{\text{tot}}\), \(\log(\hat{L}R^{\text{lim}})\) or \(\log(\hat{L}R^{\text{exp}})\). For models under which the deviation from null sharing is great, the optimal sharing statistics for tests based on \(Z^{\text{tot}}\) and \(\log(\hat{L}R^{\text{exp}})\) will be different from those for \(\log(\hat{L}R^{\text{lim}})\). Under such models, the same allele-sharing statistic can give substantially different power when used with \(\log(\hat{L}R^{\text{lim}})\) as opposed to \(Z^{\text{tot}}\) or \(\log(\hat{L}R^{\text{exp}})\), as shown in Figure 2. The cases for which \(S_{\text{everyone}}\) and \(S_{\text{fewest}}\) are listed as optimal are models for which the deviation from null sharing is great. In those cases \(S_{\text{everyone}}\) and \(S_{\text{fewest}}\) are optimal for the test based on \(\log(\hat{L}R^{\text{lim}})\), whereas \(\log(S_{\text{fewest}}/\mu_o(S_{\text{fewest}}))\) and \(\log(S_{\text{everyone}}/\mu_o(S_{\text{everyone}}))\) are optimal for tests based on \(Z^{\text{tot}}\) or \(\log(\hat{L}R^{\text{exp}})\). Note that in these two cases, \(\log(S/\mu_o(S))\) takes on the value \(-\infty\) with positive probability under the null hypothesis, corresponding to the fact that some allele-sharing configurations possible under the null hypothesis are impossible when \(a \to 0\) and \(f_0 \to 0\). The statistics \(S_{\text{fewest}}\) and \(S_{\text{everyone}}\) would obviously not be very robust to genotyping errors or other slight deviations from the model.
When choosing the weight $\gamma_i$ to assign to the normalized optimal sharing statistic $Z_i$ from the $i$th pedigree using a model given above or in Table II, it is important to make the distinction between pedigrees that have the same optimal $S$ for that model and those that do not. For instance, under model 2 in Table II, an inbred and an outbred pedigree do not have the same optimal $S$, while under model 6 they do. When the optimal statistic $S$ is used and the same statistic is optimal for all pedigrees to be combined, then except for $S_{\text{everyone}}$ and $S_{\text{fewest}}$, the optimal weight $\gamma_i$ for the normalized statistic $Z_i$ from the $i$th pedigree is $\gamma_i = \sigma_{oi}(S)$. This is so because in these cases, for the given $S$, both $L_A(c_i)/L_O(c_i) - 1$ and $\log(L_A/L_O)$ are proportional to $S - \mu_{oi}(S)$, with the constant of proportionality not depending on $i$. When $S_{\text{everyone}}$ or $S_{\text{fewest}}$ is optimal and is used, taking $\gamma_i$ equal to $\sigma_{oi}(S)/\mu_{oi}(S)$ is optimal for tests based on $\log(\hat{L}R^{\text{lin}})$, because $L_A(c_i)/L_O(c_i) = S/\mu_{oi}(S)$ in these cases. (For tests based on $\log(\hat{L}R^{\text{exp}})$ and on $Z^{\text{tot}}$ in this case, sharing statistic $\log(S/\mu_{o}(S))$, where $S = S_{\text{everyone}}$ or $S_{\text{fewest}}$ respectively, is optimal. Here, $\mu_{oi}(\log(S/\mu_{o}(S))) = \infty$, so the statistic would not be normalized, nor would it be weighted when combined with other pedigrees. As noted before, this last statistic is entirely non-robust to deviations from the model.)

When the optimal statistic $S$ is used for each pedigree and different pedigrees have different optimal $S$’s, then care must be taken when combining the statistics from these pedigrees. For instance, inbred and outbred pedigrees have different optimal sharing statistics under models 2, 3, 4, 7, and 8 of Table II, and outbred pedigrees that can have variation in $S_{g-prs}$ and $S_{-\#geno}$ and those that cannot have different optimal sharing statistics under models 2, 4, and 7. In model 2, for example, $\log(L_A/L_O)$ and $L_A/L_O - 1$ are both equal to $(S_{-\#geno} - \mu_o(S_{-\#geno}))(1 - \alpha)^2 + o(1 - \alpha)^2$ for outbred pedigrees for which $S_{-\#geno}$ can take
on different values. They are both equal to $(S_{\text{pairs}} - S_{\text{at} \text{ triples}} - \mu_o(S_{\text{pairs}} - S_{\text{at} \text{ triples}}))(1 - a)^3 + o(1 - a)^3$ for outbred pedigrees for which $S_{-\#\text{no}}$ cannot vary, and they are both equal to $(S_{-\#\text{at HBD}} - \mu_o(S_{-\#\text{at HBD}}))(1 - a) + o(1 - a)$ for inbred pedigrees, where $\mu_o(S)$ is the expected value of $S$ under the null hypothesis for a particular pedigree (this information on the likelihood ratio is given in Appendix B for all models discussed). Thus, in this case, outbred pedigrees have negligible value relative to inbred pedigrees, and outbred pedigrees for which $S_{-\#\text{no}}$ cannot vary have negligible value relative to those for which it can. This is true for all models described here for which the optimal statistics are different for these two pedigree types. This is also the result if, e.g., a collection of inbred and outbred pedigrees is regarded as a single (inbred) pedigree and the optimal statistics are applied: the outbred part of the pedigree does not contribute to the sharing statistic under models 2, 3, 4, 7, and 8.

Note that the optimal weight assigned to a pedigree type can vary greatly with the model. Figure 3 gives the optimal weight for an affected sib quartet relative to an affected sib pair, assuming that the optimal $S$ is used, under dominant and recessive models with varying allele frequency and relative risk $f_2/f_0 = 10$. In addition, for some models in which the predisposing allele frequency is high, an affected sib pair may actually receive greater weight than an affected sib trio or quartet, because the latter cases are more likely to involve multiple copies of the predisposing allele segregating in the family. (Of course, this depends on the assumption that the affection status of any additional siblings is unknown, so that the overall size of the sibship from which each affected sib pair, trio, or quartet is drawn is not a consideration.)

Example 1: Concordant and Discordant Sib Pairs
For sib pairs, $S_{\text{everyone}} = S_{\text{pairs}} = S_{\#\text{alleles}} = S_{\text{all}}$ and $S_{\text{prs}} = S_{\#\text{geno}} = S_{\text{fewest}}$. The former assign value $i$ to pairs who share $i$ alleles and the latter assign value 1 to pairs who share two alleles and 0 to those who do not. Consider any single-gene two-allele model parametrized by $m, r$, and $a$, where $m = (f_1 - f_0)/(f_2 - f_0)$, $m = 0$ corresponding to recessiveness, $m = 1$ corresponding to dominance, and $m = 1/2$ corresponding to additivity, $r = f_2/f_0$ is the relative risk of a homozygote carrier to a homozygote non-carrier, and $a$ is allele frequency. Then for the test statistic $\log(\hat{L}^\text{in})$, the optimal sharing statistic $S$ in the case of affected sib pairs is given by

$$S_{\text{optimal}} = \alpha S_{\text{pairs}} + (1 - \alpha)S_{\text{fewest}},$$

where $\alpha$ is as given above under **Allele with small effect**. Note that it does not depend on $r$. This statistic is also approximately optimal for tests based on $\log(\hat{L}^\text{exp})$ and $Z^{\text{tot}}$ when the deviation from null sharing is small. This same statistic is optimal in any outbred pedigree for models in which the relative risk $r$ approaches 1. For discordant sib pairs, the optimal statistic is just the negative of the optimal statistic for concordant sib pairs.

There are several other common parametrizations of the allele-sharing distribution for sib pairs. To see the connections between those and the two-allele model used here, see Appendix C.

**Example 2: Outbred Sib Trio**
In this case, $S_{g-p} = S_{\#\text{geno}} + S_{\text{fewest}}$, $S_{\text{pairs}} = 2S_{\text{everyone}}$, and $S_{\#\text{alleles}} = S_{\text{everyone}}$. For any two-allele model with $0 < a < 1$, the optimal sharing statistic for a test based on $\log(LR^{\text{trim}})$, approximately optimal for tests based on $\log(LR^{\text{exp}})$ and $Z^{\text{tot}}$ when deviation from null sharing is small, is given by

$$S_{\text{opt}} \propto a\bar{m}(\bar{m} - m)(1 - 2m\bar{p} - \rho m^2)S_{\text{fewest}} +$$

$$(a\bar{m} + \bar{a}m)[a(1 + \bar{p}(1 - 4m) - 2\rho m^2) + m(m\bar{p} + 2\bar{p})]S_{\text{everyone}} +$$

$$a\bar{a}(\bar{m} - m)(\bar{p}(\bar{m} - m) - \rho m^2)S_{\#\text{geno}},$$

where $\rho = 1 - r^{-1}$, i.e. it is a linear combination of three statistics, giving a two-parameter model.

**Example 3: Single Inbred Individual**

In this case, the two possible configurations are 1 1 and 1 2, and the possible sharing statistics are $S_{\#\text{aff \, HBD}}$ and $S_{\#\text{aff \, HBD}}$. When $0 < a < 1$ and $r > 1$, for any two-allele model, $S_{\#\text{aff \, HBD}}$ is optimal whenever $m < .5$. Then it is clear that $S_{\#\text{aff \, HBD}}$ must be optimal whenever $m > .5$, because if the trait follows a two-allele model with $m < .5$, then the dual trait, defined as the lack of the original trait, also follows a two-allele model with $m > .5$. Single inbred individuals convey no information for linkage when the model is ad-
itive ($m = .5$).

**Example 4: Lethal Embryonic**

For a rare ($a \to 0$) recessive that is always lethal, the dual trait is a common ($a \to 1$) dominant with no phenocopies. Thus, model 2 in Table II applies to the surviving family members.

**To What Models do $S_{pairs}$ and $S_{all}$ Correspond?**

For some small pedigrees such as sib pairs or sib trios, these two statistics, $S_{pairs}$ and $S_{all}$, coincide. For both affected sib pairs and affected sib trios, the two-allele models under which this statistic is optimal for $\log(\hat{L}R^{irr})$ are 1) any additive model or 2) any nonrecessive model ($m > 0$) with allele frequency $a \to 0$, or 3) any nondominant model ($m < 1$) with $a \to 1$. The two-allele models under which this statistic is optimal for $\log(\hat{L}R^{exp})$ and for $Z^{tot}$ using sib pairs are 1) $m < .5$ and $r = \tilde{m}^2/m^2$ (e.g. recessive model with no phenocopies) or 2) $m > .5$ and $r = [2(a\tilde{m} + \tilde{a}m)^2 - \tilde{m}^2]/[2(a\tilde{m} + \tilde{a}m)^2 - m^2]$ (e.g. dominant model with $r = 1 + 1/(2\tilde{a}^2)$, i.e. either low relative risk or allele frequency close to one or 3) $m = .5$ and $r \to 1$, i.e. additive with low relative risk. Note that this class of models, for which $S_{pairs} = S_{all}$ is optimal for sib pairs, using $\hat{L}R^{exp}$ and $Z^{tot}$, is just the class of models where the number of alleles shared by the sib pair is binomial. These results agree with the previous work of Knapp et al. [1994] who found that when testing with $Z^{tot}$, the optimal statistic for the single gene recessive model with no phenocopies is $S_{pairs}$. The results also
agree with Feingold and Siegmund [1997] who found, using a Gaussian approximation which is equivalent to assuming small effect size, that $S_{\text{pair}}$ is no longer optimal for detecting recessive alternatives in that case, although it works well for models that are far from recessive.

We now turn to general pedigrees. For outbred pedigrees and two-allele models, we have seen that $S_{\text{pair}}$ is the optimal statistic for use with $\hat{L}R^\text{lin}$, $\hat{L}R^\text{exp}$, or $Z^\text{tot}$ when the relative risk approaches 1 and at least one of the following holds: 1) the model is additive, 2) the predisposing allele frequency approaches 0 and the model is nonrecessive ($m \neq 0$), 3) the predisposing allele frequency approaches 1 and the model is nondominant ($m \neq 1$), or 4) it is not possible for anyone in the pedigree to share an IBD genotype. Thus, in practice, one might expect it to work well for non-recessive conditions in which the predisposing allele has small effect.

To discover if $S_{\text{all}}$ is optimal for any two-allele models in general pedigrees, we have performed adaptive searches of the two-allele-model parameter space for various pedigrees. $S_{\text{all}}$ does not appear to be exactly optimal for any two-allele model in general pedigrees. When $\hat{L}R^\text{lin}$ is used as a test statistic, the two-allele model for which the optimal sharing statistic (i.e. $LR - 1$) most closely matches $S_{\text{all}}$ is always an additive model with different predisposing allele frequencies and relative risks for different pedigrees, but empirically with allele frequency $a$ in the range of .03 to .15 and relative risk $f_2/f_0$ in the range of 5.7 to 8.1. However, when $\hat{L}R^\text{exp}$ or $Z^\text{tot}$ is used as a test statistic, the optimal sharing statistic ($\log(LR)$) is in general not as close to $S_{\text{all}}$ as $LR - 1$ can be, and the closest fits vary widely with the pedigree types.
Discussion

We have investigated the correspondence between allele-sharing statistics and the two-allele models for which they are optimal, with extension to multigene models with unlinked loci, additivity between loci, and small gene effects. From an understanding of this connection, the robust affected relative methods of Kruglyak et al. [1996], Whittemore [1996], and Kong and Cox [1997] can be seen as equivalent to picking a particular parametric disease gene model (or class of models) and introducing a parameter \( \delta \) to absorb model misfit. They are not fundamentally different from parametric linkage methods except in the particular parametric form in which the model misfit is specified. (In single-point parametric linkage methods, the recombination fraction parameter \( \theta \) was often, in effect, the model misfit parameter.) In practice, much of the robustness of the affected relative method is due to choices such as using affecteds only or using sib pairs, which reduce the dimension of the parameter space.

We find that for any single gene model, the optimal \( S \) treats relatives exchangeably. This result also extends to multigene models with unlinked loci, additivity between loci, and small gene effects. Thus, even when robust affected relative methods are applied to extended families, there is no need for the sharing statistic \( S \) to take into account whether it is the close or the more distant relatives in a family who exhibit sharing. We argue that in cases in which the robust affected relative methods discussed here are likely to have power to detect a gene, the exchangeability result should still provide a useful approximate rule of thumb,
even if the true model does not fall into the above classes.

We are able to find simple expressions for the optimal \( S \), applicable to any pedigree type, for a variety of two-allele and some multigene models. While previous theoretical work in this area depends on asymptotic scenarios and small effect sizes [e.g. Kong and Cox (1997), Teng and Siegmund (1997)], the theory given here applies to realistic sample sizes with large effects as well. We propose a new statistic, \( S_{\text{rob dom}} \), which is easy to compute and robust across a variety of models. Our power calculations for the case of affected sib pair with affected parent (Figure 1a-d) give the following order of performance, in decreasing order of power, against a variety of dominant and additive models: \( S_{\text{rob dom}}, S_{\text{all}}, S_{\text{pairs}}, S_{-\#\text{alleles}} \), while for recessive models (Figures 1e and f), this order is reversed. We have done similar calculations for a variety of outbred pedigree types, and have found first, that the orderings in terms of power given above for the four statistics hold more or less across the board, and second, that the differences in power among the statistics may be quite small or quite large, depending on the particular pedigree (results not shown). In the case of a large inbred pedigree, \( S_{\text{rob dom}} \) was found to be powerful against a wide variety of dominant, additive, and recessive alternative models, although \( S_{\text{pairs}} \) performed slightly better in the recessive case [Mark Abney, unpublished results]. In the case of the large inbred pedigree used, exact computation of \( S_{\text{all}} \) was impossible, so this statistic was not considered.

These results suggest use of \( S_{\text{rob dom}} \) in practice, especially for non-recessive models. In many cases, the power of \( S_{\text{all}} \) will be nearly equivalent to \( S_{\text{rob dom}} \), but \( S_{\text{all}} \) is more difficult to calculate. In the recessive case, \( S_{\text{rob dom}} \) and \( S_{\text{all}} \) may or may not perform well, depending
on the pedigree type. There is no one statistic that performs well over all disease models in general, but $S_{pairs}$ is perhaps the compromise choice. As seen in Figure 1, it maintains a similar level of performance over many disease models, although that level may be very low for some pedigree types. Another advantage of $S_{pairs}$ is that its distribution is much less skewed than those of $S_{rob\; dom}$ and $S_{all}$, so the normal approximation is much more accurate for calculating p-values. In outbred pedigrees, $S_{-\#alleles}$ is also a good choice in the recessive case only.

Kruglyak et al. [1996] performed a simulation study comparing $S_{pairs}$ and $S_{all}$. For their particular simulation scheme, with the pedigree randomly determined and allowed to vary across realizations, they found that $S_{all}$ performed much better than $S_{pairs}$ in the dominant case and for the two complex models they consider, and that the two statistics performed equally well in the recessive case. Our findings are not necessarily inconsistent with theirs, but we would caution that the statistic $S_{all}$, and likewise $S_{rob\; dom}$, has a very skewed distribution and thus great care must be taken not to overrate its power if approximations are used. The calculations shown here result from consideration of every possible outcome, with no simulation or approximation involved.

The power calculations shown here are single-locus calculations, rather than taking into account testing on a whole region of the genome as in Feingold et al. [1993], Feingold and Siegmund [1997] and Teng and Siegmund [1997]. This simplification allows us to consider non-asymptotic as well as asymptotic models, with a unified approach that is applicable to all pedigree types, without requiring separate analysis of many special cases of relationship.
Simulation studies have indicated that the relative performance of the statistics changes little when one takes into account testing across a region of the genome [Mark Abney, unpublished results].

For models with nonnegligible deviation from null sharing, the choice of $Z^{\text{tot}}$ or $\log(\hat{L}R^{\text{exp}})$ on the one hand or $\log(\hat{L}R^{\text{lin}})$ on the other, as the basis for a test of linkage, can also affect which statistics are optimal against which alternative models. Similarly, we find that the optimal choice of weights $\gamma_i$ can be heavily influenced by the model. We find that when the optimal sharing statistic $S$ is used, pedigrees are appropriately combined by adding the values of $S$, rather than the normalized values $Z$ as in Kruglyak et al. [1996]. In other words, $\gamma_i$ should be taken to be proportional to the null standard deviation of $S$ in the $i$th pedigree. When a non-optimal $S$ is used, the optimal weight $\gamma_i$ depends on the model and is approximately proportional to $E_A(Z_i)$.

In the special case of weights for relative pairs, Teng and Siegmund's [1997] approach is equivalent to using weights proportional to $E_A(Z)$. This coincides with our suggestion above for the case of non-optimal $S$. Since the alternative model is unknown, they suggest using a crude estimate of $\lambda_O$, the relative risk to an offspring of an affected, to calculate the weights. They find that a choice of $\hat{\lambda}_O = 4$ works well in a variety of scenarios. For pedigrees with more than two affecteds, Teng and Siegmund [1997] consider selected examples and find ways to convert them, on a case-by-case basis, to effective numbers of different kinds of relative pairs. Their empirical results on optimal weightings in specific examples are consistent with our recommendation that for the optimal $S$, pedigrees should be combined on the $S$ scale,
before dividing by the null standard deviations.

Finally, for the statistic $S_{pairs}$, we have described the two-allele models for which it is optimal. $S_{all}$ does not appear to be optimal for any two-allele model in general, but the closest fits occurred among additive models.

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Appendix A: Derivation of Exchangeability Result

Let $c$ denote the sharing configuration among the affecteds in the pedigree at a particular location $x$ in the genome; $\Phi$ the affection status, where the unaffecteds are coded as “unknown”, e.g. for an affected sib pair with an additional unaffected sib, $\Phi$ would denote the event that the two sibs are affected; $L_O(\cdot)$ the likelihood under the null hypothesis that a gene at location $x$ has no effect on the trait; $L_A(\cdot)$ the likelihood under the true alternative model, assumed to involve a single gene at location $x$. Note that

$$L_A(c, \Phi)/L_O(c, \Phi) = P_A(c)P_A(\Phi|c)/[P_O(c)P_O(\Phi|c)],$$

and using the fact that $P_A(c) = P_O(c)$ and $P_A(\Phi) = P_O(\Phi) = P_O(\Phi|c)$, we get $L_A(c, \Phi)/L_O(c, \Phi) = P_A(\Phi|c)/P_A(\Phi)$, where

$$P_A(\Phi) = \sum_c P_O(c)P_A(\Phi|c) = E_O(P_A(\Phi|c)|\Phi).$$

Consider two pedigrees that are identical in terms of structure and affected members, but differ only in their IBD sharing. Further, assume that the configuration of IBD sharing among affecteds in one pedigree can be obtained from the configuration of IBD sharing among affecteds in the other pedigree by permutation of individuals’ IBD genotypes, where the two alleles of an individual’s genotype are treated as a unit, never separated. Let $c_1$ be the IBD configuration in pedigree 1 and $c_2$ be the IBD configuration in pedigree 2. Then in each case, for the optimal $S$, we have $S(c_i) = f(L_A(c_i, \Phi)/L_O(c_i, \Phi)) = f(P_A(\Phi|c)/P_A(\Phi))$, where $f(x) = x - 1$ or $\log(x)$. $P_A(\Phi)$ is clearly the same for both pedigrees. The assumption of conditional independence of phenotypes given genotypes and the fact that the IBD genotypes in one pedigree can be obtained from the other by permuting individuals imply that $P_A(\Phi|c)$ is the same for both pedigrees as well. Thus, the sharing score assigned to the
two different \(c\)'s by the most powerful sharing function \(S\) must be the same, i.e. affected relatives within a pedigree should be treated as exchangeable.

The extension to multiple unlinked genes with additivity between loci and small effect at each locus, i.e. \(f_0 \to f_2\) at each locus, follows from a Taylor expansion of the likelihood ratio around \(\rho = 1 - f_0/f_2\) for each locus. Details are available from the author.

**Appendix B: Derivation of Optimal Sharing Statistics Against Particular Alternatives**

Applying the connection between optimal allele-sharing statistics and parametric likelihoods laid out in the **Guiding principles** section, it remains to calculate a general expression for the likelihood ratio under each model. Let \(k\) denote the number of affected individuals in the pedigree; \(a\) the frequency of the predisposing allele; \(f_i\) the probability of being affected given \(i\) copies of the predisposing allele, \(i = 0, 1, 2; \#al(c)\) the number of distinct-by-descent alleles occurring in configuration \(c\). Using the fact that \(L_A(c, \Phi)/L_O(c, \Phi) = P_A(\Phi|c)/P_A(\Phi)\), where

\[
P_A(\Phi) = \sum_c P_O(c)P_A(\Phi|c) = E_O(P_A(\Phi|c)|\Phi),
\]

we get the following cases by simple Taylor expansion of the likelihood:

1. **Rare dominant with phenocopies** (i.e. \(a \downarrow 0, 0 < f_0 < f_1 = f_2 \leq 1\)): Then, letting \(S = \sum_{i\in A}(r^{c_i}) - 1\), we get \(L_A(c, \Phi)/L_O(c, \Phi) = 1 + a[S - E_O(S)] + o(a)\).

2. **Allele with small effect** (i.e. \(f_0 \uparrow f_2 \leq 1, 0 < a < 1\), **single or multigene with loci unlinked and additivity between loci**: If the pedigree is outbred, \(L_A(c, \Phi)/L_O(c, \Phi) = \)
1 + \bar{a} \rho^2 [(a\bar{m} + \tilde{a}m)^2 (S_{\text{pairs}}(c) - E_O(S_{\text{pairs}})) + a\bar{a} (\bar{m} - m)^2 (S_{g-prs}(c) - E_O(S_{g-prs}))] + o(\rho^2),\] where \bar{a} = 1 - a, \bar{m} = 1 - m, with \( S_{g-prs}(c) - E_O(S_{g-prs}) = 0 \) if it is not possible to have variation in the number of pairs of affecteds who share a genotype. If the pedigree is inbred and the model is not additive (m \neq .5), then \( L_A(c, \Phi)/L_O(c, \Phi) = 1 + \rho a \bar{a} (\bar{m} - m) S_{\#aff \ HBD} + o(\rho^2) \) If the pedigree is inbred and the model is additive, then \( L_A(c, \Phi)/L_O(c, \Phi) = 1 + \frac{1}{2} \rho^2 a \bar{a} [S_{\text{pairs}} - E_O(S_{\text{pairs}})] + o(\rho^2). \)

3. **Rare dominant, no phenocopies** (i.e. \( f_0 = 0 < f_1 = f_2 \leq 1, a \downarrow 0 \)): For \( 1 \leq i \leq \#al(c) \), let \( b_i(c) \) denote the number of ways to choose \( i \) distinct-by-descent alleles from among those in \( c \) so that all of the affecteds have at least one of the \( i \). (Note that when \( i = \#al(c), b_i(c)=1. \)) Let \( d(c) \) be the smallest \( i, 1 \leq i \leq \#al(c) \), such that \( b_i(c) > 0 \). Let \( d = \) the smallest possible value of \( d(c) \) for the particular type of affected relatives, e.g. if all affecteds have a common ancestor in the pedigree, \( d = 1 \). If there is not a single common ancestor, but everyone is descended from at least one of two ancestors in the pedigree, then \( d = 2 \), and so on. Let \( S_{\text{everyone}}(c) = b_d(c) \). Then \( \lim_{a \to 0} L_A(c, \Phi)/L_O(c, \Phi) = S_{\text{everyone}}(c)/E_O(S_{\text{everyone}}) \), where \( E_O(S_{\text{everyone}}) = \sum c' P_O(c') S_{\text{everyone}}(c') \). The same result is obtained for rare non-recessive with no phenocopies in outbred pedigrees in which it is possible for everyone to share an allele IBD.

4. **Dominant, no phenocopies, predisposing allele frequency approaches one** (i.e. \( f_0 = 0 < f_1 = f_2 \leq 1, a \uparrow 1 \)): If the pedigree is outbred and it is possible to have variation in the number of genotypes present, then

\[
L_A(c, \Phi)/L_O(c, \Phi) = 1 + [S_{-\#geno}(c) - E_O(S_{-\#geno})](1 - a)^2 + o(1 - a)^2. \]

If the pedigree is out-
bred and it is not possible to have variation in the number of genotypes present, e.g. if it is not possible for any pair of affecteds to have the same IBD genotype, then $L_A(c, \Phi)/L_O(c, \Phi) = 1 + [S_{\text{pairs}}(c) - S_{\text{\#al triples}} - E_O(S_{\text{pairs}}) + E_O(S_{\text{\#al triples}})](1 - a)^3 + o(1 - a)^3$. If the pedigree is inbred, then $L_A(c, \Phi)/L_O(c, \Phi) = 1 + [S_{\text{\#al HBD}}(c) - E_O(S_{\text{\#al HBD}})](1 - a) + o(1 - a)$.

5. **Rare dominant with small effect** ($f_0 \uparrow f_1 = f_2 \leq 1$, $a \downarrow 0$), **single or multigene with loci unlinked and additivity between loci**: Let $\rho = 1 - f_0/f_2$. If the pedigree is outbred, $L_A(c, \Phi)/L_O(c, \Phi) = 1 + a \rho^2[S_{\text{pairs}}(c) - E_O(S_{\text{pairs}})] + o(a^3) + o(a^2 \rho) + o(\rho^3)$. If the pedigree is inbred, $L_A(c, \Phi)/L_O(c, \Phi) = 1 - a \rho[S_{\text{\#aff HBD}}(c) - E_O(S_{\text{\#aff HBD}})] + o(a^2) + o(\rho^2)$.

6. **Dominant with small effect; predisposing allele frequency approaches one** ($f_0 \uparrow f_1 = f_2 \leq 1$, $a \uparrow 1$), **single or multigene with loci unlinked and additivity between loci**: Let $\rho = 1 - f_0/f_2$. If the pedigree is outbred and it is possible to have variation in the number of pairs of affecteds who share a genotype, then $L_A(c, \Phi)/L_O(c, \Phi) = 1 + (1 - a)^2 \rho^2[S_{\text{g-prs}}(c) - E_O(S_{\text{g-prs}})] + o(1 - a)^4 + o((1 - a)^2 \rho^2) + o(\rho^4)$. If the pedigree is outbred and it is not possible to have variation in the number of genotypes present, then $L_A(c, \Phi)/L_O(c, \Phi) = 1 + (1 - a)^3 \rho^2[S_{\text{pairs}}(c) - E_O(S_{\text{pairs}})] + o(1 - a)^5 + o((1 - a)^3 \rho^2) + o((1 - a)^2 \rho^3) + o(\rho^5)$. If the pedigree is inbred, then $L_A(c, \Phi)/L_O(c, \Phi) = 1 + [S_{\text{\#aff HBD}}(c) - E_O(S_{\text{\#aff HBD}})](1 - a) \rho + o(1 - a)^2 + o(\rho^2)$.

7. **Rare recessive, no phenocopies** ($0 = f_0 = f_1 < f_2 \leq 1$, $a \downarrow 0$): Then $\lim_{a \to 0} L_A(c, \Phi)/L_O(c, \Phi) = S_{\text{fewest}}/E_O(S_{\text{fewest}})$. 
8. Recessive, no phenocopies, predisposing allele frequency approaches one \(0 = f_0 = f_1 < f_2 \leq 1, a \uparrow 1\): Then \(L_A(c, \Phi)/L_0(c, \Phi) = 1 + (1 - a)[S_{\#aff}(c) - E_O(S_{\#aff})] + o(1 - a)^2\).

9. Rare recessive with small effect \(f_0 = f_1 \uparrow f_2 \leq 1, a \downarrow 0\), single or multigene with loci unlinked and additivity between loci: If the pedigree is outbred and it is possible to have variation in the number of pairs of affecteds who share a genotype, then \(L_A(c, \Phi)/L_O(c, \Phi) = 1 + a^2 \rho^2[S_{pairs}(c) - E_O(S_{pairs})] + o(a^4) + o(a^2 \rho^2) + o(\rho^4)\). If the pedigree is outbred and it is not possible to have variation in the number of pairs of affecteds who share a genotype, then \(L_A(c, \Phi)/L_O(c, \Phi) = 1 + a^3 \rho^2[S_{pairs}(c) - E_O(S_{pairs})] + o(a^5) + o(a^3 \rho^2) + o(a^2 \rho^3) + o(\rho^5)\). If the pedigree is inbred, \(L_A(c, \Phi)/L_O(c, \Phi) = 1 + a \rho[S_{\#aff HBD}(c) - E_O(S_{\#aff HBD})] + o(a^2) + o(\rho^2)\).

10. Recessive with small effect; predisposing allele frequency approaches one \(f_0 = f_1 \uparrow f_2 \leq 1, a \uparrow 1\), single or multigene with loci unlinked and additivity between loci:

If the pedigree is outbred, \(L_A(c, \Phi)/L_O(c, \Phi) = 1 + (1 - a) \rho^2[S_{pairs}(c) - E_O(S_{pairs})] + o(1 - a)^3 + o((1 - a)^2 \rho) + o(\rho^3)\). If the pedigree is inbred, \(L_A(c, \Phi)/L_O(c, \Phi) = 1 + (1 - a) \rho[S_{\#aff HBD}(c) - E_O(S_{\#aff HBD})] + o(1 - a)^2 + o(\rho^2)\).

Appendix C: Alternative Parametrizations of Sharing Distribution for Sib Pairs

Note that the sharing distribution for affected sib pairs involves only two indepen-
dently varying quantities, \( P(\text{share 2}|\text{both sibs affected}) \) and \( P(\text{share 1}|\text{both sibs affected}) \), with \( P(\text{share 0}|\text{both sibs affected}) = 1 - P(\text{share 2}|\text{both sibs affected}) - P(\text{share 1}|\text{both sibs affected}) \).

This may be parametrized by \( 0 \leq \alpha \leq 1 \) and \( 0 \leq \delta \leq \alpha \), where \( P(\text{share 2}|\text{both sibs affected}) = (1 - \alpha)/4 \), \( P(\text{share 1}|\text{both sibs affected}) = (1 - \delta)/2 \), and \( P(\text{share 0}|\text{both sibs affected}) = (1 + \alpha + 2\delta)/4 \), e.g. as in Feingold and Siegmund [1997]. Alternatively, it may be parametrized by \( \lambda_S \), the relative risk to siblings of affecteds, and \( \lambda_O \), the relative risk to offspring of affected, where \( \alpha = 1 - 1/\lambda_S \) and \( \delta = 1 - \lambda_O/\lambda_S \) [Risch 1990b]. For a single-gene two-allele model, if we let \( n_0 = [a^2 + 2a\bar{a}(1 - \rho\bar{\mu}) + \bar{a}^2\bar{\rho}]^2 \), \( n_1 = a[a + \bar{a}(1 - \rho\bar{\mu})]^2 + \bar{a}[a(1 - \rho\bar{\mu}) + \bar{a}\bar{\rho}]^2 \), and \( n_2 = a + \bar{a}\bar{\rho}^2 \), then \( \alpha = 1 - n_0/(.25n_0 + .5n_1 + .25n_2) \) and \( \delta = 1 - n_1/(.25n_0 + .5n_1 + .25n_2) \).

Alternatively, the two-allele model may be parametrized by \( K \), the population prevalence of the trait, \( V_A \), the additive variance of the trait, and \( V_D \), the dominant variance of the trait, with \( \alpha = (V_A/2 + V_D/4)/(K^2 + V_A/2 + V_D/4) \) and \( \delta = (V_D/4)/(K^2 + V_A/2 + V_D/4) \) [Suarez et al. 1978]. Feingold and Siegmund [1997] point out that the two-allele assumption is not necessary for these last formulae to hold.

References


Risch N (1990b) Linkage strategies for genetically complex traits. II. The power of affected relative pairs. Am J Hum Genet 46:229-241


Suarez BK (1978) The affected sib pair IBD distribution for HLA-linked disease susceptibility genes. Tissue Antigens 12:87-93


Table 1 Example 1: Outbred Sib Pair and First Cousin

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Null</th>
<th>$S_{pairs} - \mu_0$</th>
<th>$S_{all} - \mu_0$</th>
<th>$S_{alleles} - \mu_0$</th>
<th>$S_{everyone} - \mu_0$</th>
<th>$S_{geno} - \mu_0$</th>
<th>$S_{fewest} - \mu_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(sib,sib,cousin)</td>
<td>Prob.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$c_1$ 1 2 3 4 5 6</td>
<td>.125</td>
<td>-1.5</td>
<td>-.1</td>
<td>-1.375</td>
<td>-.125</td>
<td>-.25</td>
<td>-.0625</td>
</tr>
<tr>
<td>$c_2$ 1 2 3 4 1 5</td>
<td>.125</td>
<td>-.5</td>
<td>-.1</td>
<td>-.375</td>
<td>-.125</td>
<td>-.25</td>
<td>-.0625</td>
</tr>
<tr>
<td>$c_3$ 1 2 1 3 4 5</td>
<td>.3125</td>
<td>-.5</td>
<td>-.1</td>
<td>-.375</td>
<td>-.125</td>
<td>-.25</td>
<td>-.0625</td>
</tr>
<tr>
<td>$c_4$ 1 2 1 3 2 4</td>
<td>.125</td>
<td>.5</td>
<td>.09</td>
<td>.625</td>
<td>-.125</td>
<td>-.25</td>
<td>-.0625</td>
</tr>
<tr>
<td>$c_5$ 1 2 1 2 3 4</td>
<td>.1875</td>
<td>.5</td>
<td>.09</td>
<td>.625</td>
<td>-.125</td>
<td>-.75</td>
<td>-.0625</td>
</tr>
<tr>
<td>$c_6$ 1 2 1 3 1 4</td>
<td>.0625</td>
<td>1.5</td>
<td>.59</td>
<td>.625</td>
<td>.875</td>
<td>-.25</td>
<td>-.0625</td>
</tr>
<tr>
<td>$c_7$ 1 2 1 2 2 3</td>
<td>.0625</td>
<td>2.5</td>
<td>.84</td>
<td>1.625</td>
<td>.875</td>
<td>-.75</td>
<td>.9375</td>
</tr>
</tbody>
</table>
Table II Optimal Sharing Statistics in Special Cases

<table>
<thead>
<tr>
<th>Model</th>
<th>Outbred Pedigree</th>
<th>Outbred Pedigree</th>
<th>Inbred Pedigree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((S_{#\text{geno}}, S_{#\text{prs}} \text{ can vary}))</td>
<td>((S_{#\text{geno}}, S_{#\text{prs}} \text{ cannot vary}))</td>
<td></td>
</tr>
<tr>
<td>1. dominant, (f_0 \rightarrow 0, a \rightarrow 0)</td>
<td>(S_{\text{everyone}})</td>
<td>(S_{\text{everyone}})</td>
<td>(S_{\text{everyone}})</td>
</tr>
<tr>
<td>2. dominant, (f_0 \rightarrow 0, a \rightarrow 1)</td>
<td>(S_{#\text{geno}})</td>
<td>(S_{\text{pairs}} - S_{#\text{all triples}})</td>
<td>(S_{#\text{all HBD}})</td>
</tr>
<tr>
<td>3. dominant (a \rightarrow 0, f_0 \rightarrow f_2), single or multigene</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{# \text{all HBD}})</td>
</tr>
<tr>
<td>4. dominant, (f_0 \rightarrow f_2, a \rightarrow 1), single or multigene</td>
<td>(S_{#\text{prs}})</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{# \text{all HBD}})</td>
</tr>
<tr>
<td>5. recessive, (f_0 \rightarrow 0, a \rightarrow 0)</td>
<td>(S_{\text{fewest}})</td>
<td>(S_{\text{fewest}})</td>
<td>(S_{\text{fewest}})</td>
</tr>
<tr>
<td>6. recessive, (f_0 \rightarrow 0, a \rightarrow 1)</td>
<td>(S_{#\text{alleles}})</td>
<td>(S_{#\text{alleles}})</td>
<td>(S_{#\text{alleles}})</td>
</tr>
<tr>
<td>7. recessive, (f_0 \rightarrow f_2, a \rightarrow 0), single or multigene</td>
<td>(S_{#\text{prs}})</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{# \text{all HBD}})</td>
</tr>
<tr>
<td>8. recessive, (f_0 \rightarrow f_2, a \rightarrow 1), single or multigene</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{# \text{all HBD}})</td>
</tr>
<tr>
<td>9. additive, (f_0 \rightarrow f_2), single or multigene</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{\text{pairs}})</td>
<td>(S_{\text{pairs}})</td>
</tr>
</tbody>
</table>
**Figure Legends**

Figure 1a: Sib pair plus parent: power of various sharing statistics $S$ against a dominant alternative with varying predisposing allele frequency and no phenocopies

Figure 1b: Sib pair plus parent: power of various sharing statistics $S$ against a dominant alternative with varying phenocopy rate and predisposing allele frequency .02

Figure 1c: Sib pair plus parent: power of various sharing statistics $S$ against an additive alternative with varying predisposing allele frequency and no phenocopies

Figure 1d: Sib pair plus parent: power of various sharing statistics $S$ against an additive alternative with varying phenocopy rate and predisposing allele frequency .02

Figure 1e: Sib pair plus parent: power of various sharing statistics $S$ against a recessive alternative with varying predisposing allele frequency and no phenocopies

Figure 1f: Sib pair plus parent: power of various sharing statistics $S$ against a recessive alternative with varying phenocopy rate and predisposing allele frequency .02

(Legend for all of Figure 1):

In Figures 1 a)-f), sample size $= 30$, power is computed at a single point assumed to have no recombination with the gene, significance level $= 2 \times 10^{-5}$, and exact p-values are computed
using $Z^{tot}$ or equivalently $\log(LR^{exp})$.

Figure 2a: Sib quartet: power of $S_{alt}$ against a recessive alternative using different testing methods

Figure 2b: Sib quartet: power of $0.85 \times S_{fewest} + 0.15 \times S_{-\#alleles}$ against a recessive alternative using different testing methods

(Legend for all of Figure 2):

In both Figures 2a and 2b, sample size = 20, phenocopy rate = 0, power is computed at a single point assumed to have no recombination with the gene, significance level = $2 \times 10^{-5}$, exact p-values computed.

Figure 3

Optimal weight of sib quartet relative to sib pair for different models, using the optimal sharing statistic $S$

For both the dominant and recessive cases, the risk to a homozygote carrier relative to a homozygote non-carrier is assumed to be 10. The results are for $Z^{tot}$ or, equivalently, $\log(LR^{exp})$. 
Figure 1a

The plot shows the power to detect an alternative hypothesis as a function of the predisposing allele frequency. The x-axis represents the predisposing allele frequency, ranging from 0.0 to 0.25. The y-axis represents the power to detect the alternative hypothesis, ranging from 0.0 to 1.0.

Legend:
- Solid line: Srob dom
- Dotted line: Sall
- Dashed line: Spairs
- Dash-dotted line: S-#alleles

The curves demonstrate that the power decreases as the predisposing allele frequency increases.
Figure 1 c

The graph shows the power to detect alternative hypotheses across different predisposing allele frequencies. The x-axis represents the predisposing allele frequency, while the y-axis represents the power to detect alternative hypotheses. The graph includes four lines, each representing a different measure:

- **Srob dom**: Solid line
- **Sall**: Dotted line
- **Spairs**: Dash-dotted line
- **S-#alleles**: Dashed line

The power decreases sharply as the predisposing allele frequency increases, indicating a higher difficulty in detecting alternatives at higher frequencies.
Figure 1 d

The graph shows the power to detect alternative phenocopy/penetrance levels for different alleles. The x-axis represents the phenocopy/penetrance values ranging from 0.0 to 0.20, and the y-axis represents the power to detect alternative values ranging from 0.0 to 1.0.

- **Srob dom**
- **Sall**
- **Spairs**
- **S-#alleles**

The lines on the graph represent the power for each allele type, with different line styles for each category.
Figure 1 e

Power to detect alternative

predisposing allele frequency

Srob dom
Sall
Spairs
S-#alleles
Figure 1: Graph showing the power to detect alternative phenocopy/penetrance. The x-axis represents the phenocopy/penetrance, ranging from 0.0 to 0.2, and the y-axis shows the power to detect alternative, ranging from 0.0 to 1.0. The graph includes different lines representing different alleles: Srob dom, Sall, Spairs, and S-#alleles.
Figure 2 a

The graph shows the power to detect alternative predisposing allele frequencies against the Ztot and log(LRexp) compared to log(LRlin).
Figure 2 b

- **Ztot and log(LRexp)**
- **log(LRlin)**

The graph represents the power to detect alternative predisposing allele frequencies. The x-axis denotes the predisposing allele frequency, while the y-axis shows the power to detect alternative.

- The solid line represents **Ztot and log(LRexp)**.
- The dotted line represents **log(LRlin)**.
Figure 3: Optimal weight of sib quartet relative to sib pair
optimal S, \( \rho = .9, Z_{tot} \)