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Necessary and sufficient conditions for equality of sibling and parent-offspring risk of a disease endophenotype in case families

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SUMMARY

A large number of linkage and association studies of complex diseases focus on analysis of a more common or more easily measured disease endophenotype. The motivation for this approach is that there is a pleiotropic locus common to both the disease and the endophenotype and that this locus is a major genetic determinant of the endophenotype. In this paper we determine the conditions in which the risk of the endophenotype in siblings of affected probands with disease equals the risk of the endophenotype in the offspring(parents) of affected parents(offspring) with disease. In doing so we prove that this equality holds if and only if the penetrance of either the endophenotype *or* the disease (but not necessarily both) is additive.

Keywords

linkage; sibpair; endophenotype; recurrence risk; additivity

INTRODUCTION

Linkage analysis based on affected sib pairs with disease has long been considered an effective and reliable approach for finding major disease loci. The power of such a linkage analysis, however, is determined by the extent to which a locus determines the disease of interest. Investigators have frequently estimated the power of these linkage analyses based on simulations. In these simulations they have assumed a major disease allele and set the penetrance values and gene frequencies to values that coincided with the disease prevalence and observed risks in siblings of affected individuals [SLINK Ott (1989) and Weeks et al. (1990)]. As an alternative to simulation, Risch (1990) derived some very straightforward and extremely useful expressions for numerically computing the power of a linkage analysis for a given number of affected sibling pairs that was based only on disease recurrence risk in siblings and the population risk. However these equations were derived based on the assumption that the disease recurrence risk in siblings equaled disease recurrence risk in parents and offspring of an affected proband. This latter assumption holds whenever the disease allele has an additive effect on the penetrance of the trait; that is, whenever the penetrance (f) of the disease for the individual with *one* disease allele (f_1), was midway between the penetrance of the disease for those with no disease alleles (f_0) and 2 disease alleles (f_2) that is, $f_1 = (f_0 + f_2) / 2$.

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More recently, the study of disease related endophenotypes has been of interest with a popular design being to ascertain the family members through an affected proband with disease and to study the distribution of marker and endophenotype in sib pairs. With this in mind, Sung et al. (2009) derived numerical expressions for the power of a linkage analysis of the endophenotype based on sib pairs in which one sibling is affected with disease and the other is chosen at random. In this case, assuming that there was one pleiotropic allele that affected both disease and endophenotype, there were three additional penetrance values to be incorporated into the computation. Assuming that the penetrance values for the disease were lower than the penetrance values for the endophenotype, calculations from Sung et al. (2009) indicated (as expected) that for a given sample size a linkage analysis based on the disease endophenotype will have substantially greater power than one based on the disease itself.

Sung et al. (2009) also noted that similarly to Risch's (1990) study, expressions for the power could also be derived and simplified greatly if the risk of the *endophenotypes* in offspring(parents) of affected parents(offspring) with disease equals risk of the *endophenotypes* in siblings of *affected individuals with disease*. Moreover, they noted that this finding holds if and only if either the penetrance of the endophenotype is additive or the penetrance of the disease is additive. It is not necessary that both sets of penetrance values be additive. The observations by Sung et al. (2009) were based on computer simulations. We now present an algebraic proof of these equalities which is considered to be a very useful finding for the field of human quantitative genetics that we have not to date noted in textbooks or other papers.

NOTATION AND ASSUMPTIONS

We consider a biallelic locus which is pleiotropic for a presence of both a disease ($D+$) and an abnormal endophenotype ($E+$). We denote by the letter A , the allele that increases the susceptibility to $D+$ and assume that A also increases the susceptibility to $E+$. We denote the allele frequency of A , by p . Thus, associated with this locus are six penetrance values, with f_{kt} denoting the penetrance of the phenotype t ($t=D+, E+$) given one has the genotype with k copies ($k=0,1,2$) of the disease/endophenotype susceptibility allele. We let G_k denote the genotype with k copies of the disease/endophenotype susceptibility allele and then let $M_{d@m}$ denote a parental mating type in which the father has genotype G_d and the mother has

genotype G_m ($d, m=0,1,2$). We let X_{D+}^R (X_{E+}^R) equal 1 if the individual has the disease (abnormal endophenotype) and 0 otherwise for an individual with position R in a family. We set $R = \text{pro}$ (proband) or sib (sibling of proband). We let K^{D+} and K^{E+} denote the population risks of $D+$ and $E+$, respectively. We also denote the risk of $E+$ conditional on an affected sibling with the disease as $K_s^{E+|D+}$. Similarly we denote the risk of $E+$ in an offspring(parents) conditional on affected parent(offspring) with the disease as $K_o^{E+|D+}$, and let $K_M^{E+|D+}$ denote the risk of $E+$ given a monozygotic twin has $D+$. Thus in terms of our notation:

$$K_s^{E+|D+} = P\left(X_{E+}^{\text{sib}} = 1 | X_{D+}^{\text{pro}} = 1\right) \quad (1)$$

Well known results from quantitative genetics are the relationships between sibling recurrence risk, parent-offspring recurrence risk, monozygotic twin recurrence risk and the number of alleles shared IBD at the locus [Pak Sham (1998)]. We refer to this latter variable, which we denote by I_L (where $I_L = 0,1,2$), as 'alleles IBD'. These relationships can be stated:

$$P(X_{E+}^{sib}=1|X_{D+}^{pro}=1, I_L=0)=P(X_{E+}^{sib}=1)=K^{E+} \quad (\text{population risk of } E+) \quad (2)$$

$$P(X_{E+}^{sib}=1|X_{D+}^{pro}=1, I_L=1)=K_O^{E+|D+} \quad (\text{risk of } E+ \text{ in offspring (patents) of } D+ \text{ parent (offspring)}) \quad (3)$$

$$P(X_{E+}^{sib}=1|X_{D+}^{pro}=1, I_L=2)=K_M^{E+|D+} \quad (\text{risk of } E+ \text{ in twin of } D+ \text{ monozygotic twin}) \quad (4)$$

Equations (2) and (4) are quite logical. That is a sibling who shares no loci IBD with the proband has the same risk of abnormal endophenotype as a random member of the population and a sibling who shares 2 alleles IBD has the same risk as a monozygotic cotwin of a proband (who also shares 2 alleles IBD). Equation (3) follows from the fact that parent and offspring always share exactly one at a locus. Thus we extend the logic of equations (2) and (4) to this situation.

We assume random mating with respect to $D+$ and $E+$. Thus, $P(M_{d\otimes m}) = P(G_d) \cdot P(G_m)$. We also assume that sibling genotypes conditional on parents' genotypes are independent:

$P(G_h^{pro}, G_k^{sib}|M_{d\otimes m}) = P(G_h^{pro}|M_{d\otimes m}) \cdot P(G_k^{sib}|M_{d\otimes m})$. We assume Hardy Weinberg Equilibrium and obtain the values of $P(G_k)$ for $k = 0, 1, 2$ as a function of p , the frequency of the disease/endophenotype predisposing allele, as $P(G_0) = (1-p)^2$, $P(G_1) = 2p(1-p)$, $P(G_2) = p^2$.

The values of $P(G_h^{pro}|M_{d\otimes m})$ and $P(G_k^{sib}|M_{d\otimes m})$ for $h, k, d, m = 0, 1, 2$ and simply the Mendelian probabilities of offspring genotypes conditional on parents' genotypes. For completeness, these are given in Table 1.

RESULTING EQUATIONS

Expressions for $K_S^{E+|D+}$ and $K_O^{E+|D+}$ are obtained as a function of disease/endophenotype predisposing allele frequency (p) and the $D+$ and $E+$ penetrance values (f_{kt} , $k = 0, 1, 2$ and $t = D+, E+$) as follows.

$$\begin{aligned} & K_S^{E+|D+} \\ &= P(X_{E+}^{sib}=1|X_{D+}^{pro}=1) \\ &= \frac{1}{K^{D+}} \sum_{d,m=0}^2 \sum_{h,k=0}^2 \left[f_{hE+} \cdot f_{hD+} \cdot P(G_k^{sib}|M_{d\otimes m}) \cdot P(G_h^{pro}|M_{d\otimes m}) \cdot P(M_{d\otimes m}) \right] \end{aligned} \quad (5)$$

From equation (3) we obtain

$$\begin{aligned}
& K_o^{E+|D+} \\
&= P(X_{E+}^{sib}=1|X_{D+}^{pro}=1, I_L=1) \\
&= \frac{2}{K^{D+}} \sum_{d,m=0}^2 \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(I_L=1|G_k^{sib}, G_h^{pro}, M_{d\otimes m}) \cdot P(G_k^{sib}|M_{d\otimes m}) \cdot P(G_h^{pro}|M_{d\otimes m}) \cdot P(M_{d\otimes m}) \right]
\end{aligned}
\tag{6}$$

Above we have noted that the disease population risk, $K^{D+}=P(X_{D+}^{pro}=1)$ and that $P(I_L=1)=0.5$ to obtain equation (5) and (6). The conditional probabilities, $P(I_L|G_k^{pro}, G_h^{sib}, M_{d\otimes m})$, required to reduce the expressions in (6) are given in Table 2.

THE PROOF

As indicated in Table 2, we have $P(I_L=1|G_k^{sib}, G_h^{pro}, M_{d\otimes m})=0.5$ except when both parents are heterozygous. Thus if we note that

$$K_S^{E+|D+}=B_S+H_S \tag{7}$$

where

$$B_S = \frac{1}{K^{D+}} \sum_{d,m=0}^2 \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(G_k^{sib}|M_{d\otimes m}) \cdot P(G_h^{pro}|M_{d\otimes m}) \cdot P(M_{d\otimes m}) \right],$$

except
d=m=1

$$H_S = \frac{1}{K^{D+}} \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(G_k^{sib}|M_{1\otimes 1}) \cdot P(G_h^{pro}|M_{1\otimes 1}) \cdot P(M_{1\otimes 1}) \right]$$

and

$$K_o^{E+|D+}=B_o+H_o \tag{8}$$

where

$$B_o = \frac{2}{K^{D+}} \sum_{d,m=0}^2 \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(I_L=1|G_k^{sib}, G_h^{pro}, M_{d\otimes m}) \cdot P(G_k^{sib}|M_{d\otimes m}) \cdot P(G_h^{pro}|M_{d\otimes m}) \cdot P(M_{d\otimes m}) \right],$$

except
d=m=1

$$H_o = \frac{2}{K^{D+}} \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(I_L=1|G_k^{sib}, G_h^{pro}, M_{1\otimes 1}) \cdot P(G_k^{sib}|M_{1\otimes 1}) \cdot P(G_h^{pro}|M_{1\otimes 1}) \cdot P(M_{1\otimes 1}) \right]$$

then

$$\begin{aligned} B_o &= \frac{2}{K^{D+}} \sum_{d,m=0}^2 \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(I_L=1|G_k^{sib}, G_h^{pro}, M_{d\otimes m}) \cdot P(G_k^{sib}|M_{d\otimes m}) \cdot P(G_h^{pro}|M_{d\otimes m}) \cdot P(M_{d\otimes m}) \right] \\ &\quad \text{except} \\ &\quad d=m=1 \\ &= \frac{2}{K^{D+}} \sum_{d,m=0}^2 \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot \frac{1}{2} \cdot P(G_k^{sib}|M_{d\otimes m}) \cdot P(G_h^{pro}|M_{d\otimes m}) \cdot P(M_{d\otimes m}) \right] \\ &\quad \text{except} \\ &\quad d=m=1 \\ &= \frac{1}{K^{D+}} \sum_{d,m=0}^2 \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(G_k^{sib}|M_{d\otimes m}) \cdot P(G_h^{pro}|M_{d\otimes m}) \cdot P(M_{d\otimes m}) \right] \\ &\quad \text{except} \\ &\quad d=m=1 \\ &= B_s = B \end{aligned} \tag{9}$$

Equations (7) and (8) imply that what remains is to show an equivalence for the case where both parents are heterozygous. That is, we substitute the results of (9) into (7) and (8) and obtain the following expressions

$$\begin{aligned} K_s^{E+|D+} &= B_s + H_s \\ &= B + \frac{1}{K^{D+}} \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(G_k^{sib}|M_{1\otimes 1}) \cdot P(G_h^{pro}|M_{1\otimes 1}) \cdot P(M_{1\otimes 1}) \right] \\ &= B + \frac{P(M_{1\otimes 1})}{K^{D+}} \left[\begin{aligned} &\left(f_{0E+} \cdot f_{0D+} \cdot \frac{1}{4} \cdot \frac{1}{4} \right) + \left(f_{1E+} \cdot f_{0D+} \cdot \frac{1}{2} \cdot \frac{1}{4} \right) + \left(f_{2E+} \cdot f_{0D+} \cdot \frac{1}{4} \cdot \frac{1}{4} \right) \\ &+ \left(f_{0E+} \cdot f_{1D+} \cdot \frac{1}{4} \cdot \frac{1}{2} \right) + \left(f_{1E+} \cdot f_{1D+} \cdot \frac{1}{2} \cdot \frac{1}{2} \right) + \left(f_{2E+} \cdot f_{1D+} \cdot \frac{1}{4} \cdot \frac{1}{2} \right) \\ &+ \left(f_{0E+} \cdot f_{2D+} \cdot \frac{1}{4} \cdot \frac{1}{4} \right) + \left(f_{1E+} \cdot f_{2D+} \cdot \frac{1}{2} \cdot \frac{1}{4} \right) + \left(f_{2E+} \cdot f_{2D+} \cdot \frac{1}{4} \cdot \frac{1}{4} \right) \end{aligned} \right] \end{aligned} \tag{10}$$

$$\begin{aligned} K_o^{E+|D+} &= B_o + H_o \\ &= B + \frac{2}{K^{D+}} \sum_{h,k=0}^2 \left[f_{kE+} \cdot f_{hD+} \cdot P(I_L=1|G_k^{sib}, G_h^{pro}, M_{1\otimes 1}) \cdot P(G_k^{sib}|M_{1\otimes 1}) \cdot P(G_h^{pro}|M_{1\otimes 1}) \cdot P(M_{1\otimes 1}) \right] \\ &= B + \frac{2 \cdot P(M_{1\otimes 1})}{K^{D+}} \left[\begin{aligned} &\left(f_{1E+} \cdot f_{0D+} \cdot 1 \cdot \frac{1}{2} \cdot \frac{1}{4} \right) + \left(f_{1E+} \cdot f_{2D+} \cdot 1 \cdot \frac{1}{2} \cdot \frac{1}{4} \right) \\ &+ \left(f_{0E+} \cdot f_{1D+} \cdot 1 \cdot \frac{1}{4} \cdot \frac{1}{2} \right) + \left(f_{2E+} \cdot f_{1D+} \cdot 1 \cdot \frac{1}{4} \cdot \frac{1}{2} \right) \end{aligned} \right] \end{aligned} \tag{11}$$

Thus, if $K_S^{E+|D+} = K_O^{E+|D+}$ or equivalently $K_S^{E+|D+} - K_O^{E+|D+} = 0$, substituting into (10) and (11), we have

$$\begin{aligned}
 & K_S^{E+|D+} \\
 &= \frac{P(M_{1\otimes 1})}{K^{D+}} \left[\begin{aligned} & (f_{0E+} \cdot f_{0D+} \cdot \frac{1}{4} \cdot \frac{1}{4}) + (f_{1E+} \cdot f_{0D+} \cdot \frac{1}{2} \cdot \frac{1}{4}) + (f_{2E+} \cdot f_{0D+} \cdot \frac{1}{4} \cdot \frac{1}{4}) \\ & (f_{0E+} \cdot f_{1D+} \cdot \frac{1}{4} \cdot \frac{1}{2}) + (f_{1E+} \cdot f_{1D+} \cdot \frac{1}{2} \cdot \frac{1}{2}) + (f_{2E+} \cdot f_{1D+} \cdot \frac{1}{4} \cdot \frac{1}{2}) \\ & (f_{0E+} \cdot f_{2D+} \cdot \frac{1}{4} \cdot \frac{1}{4}) + (f_{1E+} \cdot f_{2D+} \cdot \frac{1}{2} \cdot \frac{1}{4}) + (f_{2E+} \cdot f_{2D+} \cdot \frac{1}{4} \cdot \frac{1}{4}) \end{aligned} \right] \\
 & - \frac{2 \cdot P(M_{1\otimes 1})}{K^{D+}} \left[\begin{aligned} & (f_{1E+} \cdot f_{0D+} \cdot 1 \cdot \frac{1}{2} \cdot \frac{1}{4}) + (f_{1E+} \cdot f_{2D+} \cdot 1 \cdot \frac{1}{2} \cdot \frac{1}{4}) \\ & + (f_{0E+} \cdot f_{1D+} \cdot 1 \cdot \frac{1}{4} \cdot \frac{1}{2}) + (f_{2E+} \cdot f_{1D+} \cdot 1 \cdot \frac{1}{4} \cdot \frac{1}{2}) \end{aligned} \right] \\
 &= \frac{P(M_{1\otimes 1})}{16 \cdot K^{D+}} \left[\begin{aligned} & f_{0E+} (f_{0D+} + 2f_{1D+} + f_{2D+} - 4f_{1D+}) \\ & + f_{1E+} (2f_{0D+} + 4f_{1D+} + 2f_{2D+} - 4f_{0D+} - 4f_{2D+}) \\ & + f_{2E+} (f_{0D+} + 2f_{1D+} + f_{2D+} - 4f_{1D+}) \end{aligned} \right] \\
 &= \frac{P(M_{1\otimes 1})}{16 \cdot K^{D+}} (f_{0E+} - 2f_{1E+} + f_{2E+}) (f_{0D+} - 2f_{1D+} + f_{2D+}) = 0
 \end{aligned}$$

Therefore, if $K_S^{E+|D+} = K_O^{E+|D+}$, then $f_{0E+} - 2f_{1E+} + f_{2E+}$, or $f_{0D+} - 2f_{1D+} + f_{2D+} = 0$, or equivalently $f_{1t} = (f_{0t} + f_{2t}) / 2$ for either $t = E+$ or $D+$, but not necessarily both.

Alternatively that is, if either the endophenotype is additive or disease is additive (but not necessarily both), we have $K_S^{E+|D+} = K_O^{E+|D+}$.

DISCUSSION

It has been well known for quite a while that additivity in allele penetrance results in equality of parent/offspring recurrence risk and sibling recurrence risk [Risch (1990), Pak Sham (1998)]. However, this extension to two traits determined by a single pleiotropic locus did not necessarily follow and needed to be documented. What is particularly noteworthy is the finding that the parent/offspring recurrence risk equals the sibling recurrence risk if and only if *either* the penetrance of the disease is additive *or* the penetrance of the abnormal endophenotype is additive, but not necessarily both [Sung et al. (2009)]. It is also a potentially very useful result. The motivation for investigating a complex disease via an endophenotype is the idea that while many genes may contribute to the complex disease, the genetics of the abnormal endophenotype involves a major gene. The criteria for a disease endophenotype to be useful for genetic analysis have been defined in the literature [Gottesman and Gould (2003), Cannon and Keller (2006)] as follows: 1) The endophenotype should be heritable. 2) The endophenotype is associated with causes of the disease. 3) The endophenotype appears independently whether or not disease is in effect. 4) The endophenotype and disease cosegregate within families. 5) The endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population. Given these criteria, one would not want to be confined to the assumption of additive penetrance in the case of the endophenotype. However, it might be reasonable to assume that this same gene may have a minor effect with an additive low *disease* penetrance value considering that the population risk of endophenotype is higher than the population risk of disease. Additionally, the multifactorial mode of inheritance which has been proposed for several complex diseases [Murphy and Chase (1975)] involves the assumption of many genes with small equal and *additive* effects. It is reassuring to note that additive penetrance in the case of the disease is sufficient in order to be able to assume equality of parent-offspring and siblings' risk of the abnormal endophenotype in relatives of affected probands with disease. For example, Sung et al. (2009), noted that upon assuming this equality, the power of a linkage study based on the distribution of the endophenotype in siblings of D+ probands could be expressed as an explicit function of the difference between

$K_s^{E+|D+}$ (the risk of abnormal endophenotype conditional on a sibling having the disease) and K^{E+} (the population risk of abnormal endophenotype).

The purpose of Sung et al. (2009) was to give a general expression for the calculation of the identity by descent distribution in siblings of probands, with and without the abnormal endophenotypes. Thus if the disease and the endophenotype are not additive one needs to use their general equations and/or have estimates of the risk of the endophenotype in offspring(parents) of disease affected parents(offspring) as well as the sibling risk of abnormal endophenotype. However, Sung et al (2009) did explore several situations where neither the disease nor the endophenotype has additive penetrance. They noted that for those cases where the risk of the abnormal endophenotype in offspring(parents) of the disease affected parents(offspring) did not equal the sibling risk, their findings on the relationship between power and risk difference, i.e. $K_s^{E+|D+} - E^{E+}$ observed for the case of additive either disease or endophenotype penetrance were still observed for those situations where the pleiotropic allele frequency is less than 0.06.

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TABLE 1

Values for $P(G_h^{offspring} | M_{d \otimes m})$ for $M_{d \otimes m} = G_d \otimes G_m$, $d, m, h = 0, 1, 2$

$M_d \otimes m$	h	$P(G_h^{offspring} M_{d \otimes m})$
$G_0 \otimes G_0$	0	1
$G_0 \otimes G_2$	1	1
$G_2 \otimes G_2$	2	1
$G_0 \otimes G_1$	0,1	0.5
$G_1 \otimes G_2$	1,2	0.5
$G_1 \otimes G_1$	1	0.5
$G_1 \otimes G_1$	0,2	0.25
OTHERWISE	OTHERWISE	0

TABLE 2

Values for $P(I_L|G_h^{pro}, G_k^{sib}, M_{d\otimes m})$ for $M_d\otimes_m = G_d \otimes G_m$, $d, m = 0,1,2$

Parents' Mating Type	Proband and Sibling Genotypes	I _L		
$M_d \otimes_m$	$(G_k^{sib}, G_h^{pro}) = (G_h^{pro}, G_k^{sib})$	0	1	2
$G_1 \otimes G_0$	(G_1, G_0)	0.5	0.5	0
	$(G_1, G_1), (G_0, G_0)$	0	0.5	0.5
$G_1 \otimes G_2$	(G_1, G_2)	0.5	0.5	0
	$(G_1, G_1), (G_2, G_2)$	0	0.5	0.5
$G_1 \otimes G_1$	$(G_0, G_0), (G_2, G_2)$	0	0	1
	$(G_1, G_0), (G_1, G_2)$	0	1	0
	(G_0, G_2)	1	0	0
	(G_1, G_1)	0.5	0	0.5