Statistica Sinica **14**(2004), 1021-1036

USING KULLBACK-LEIBLER INFORMATION FOR MODEL SELECTION WHEN THE DATA-GENERATING MODEL IS UNKNOWN: APPLICATIONS TO GENETIC TESTING PROBLEMS

Gang Zheng[1], Boris Freidlin[2] and Joseph L. Gastwirth[2,3]

[1]*National Heart, Lung and Blood Institute,* [2]*National Cancer Institute and* [3]*George Washington University*

Abstract: In genetic studies of complex diseases the underlying genetic model is usually unknown. Thus, a family of locally optimal statistics is obtained for testing association or linkage. Utilizing two new measures based on Kullback-Leibler information, we are able to define a family of admissible genetic models and obtain the corresponding two optimality criteria to select robust models. The model selection procedures described in this paper are valid regardless of sample size. The results are applied to genetic linkage analysis using affected sibs and candidate-gene association tests using the case-parents design. Our results provide insight into some commonly used statistics in the genetic linkage analysis of affected sib-pairs.

Key words and phrases: Admissible genetic model, association and linkage, Kullback-Leibler information, maximin, minimax, robustness.

1. Introduction

In many genetic testing problems, the alternative hypothesis is indexed by a nuisance parameter which is not defined under the null hypothesis. For example, in linkage analysis for affected sib-pairs, the probabilities that a sib-pair shares i alleles identical-by-descent (IBD) p_i, $i = 0, 1, 2$, are a mixture of two trinomial distributions given by (e.g., Holmans (1993) and Whittemore and Tu (1998)):

$$(p_0, p_1, p_2) = (1 - \lambda)(1/4, 1/2, 1/4) + \lambda(0, \psi, 1 - \psi), \tag{1}$$

where $\psi \in \Psi = [0, 1/2]$ and $\lambda \in [0, 1]$. Here one tests $H_0 : \lambda = 0$ (no linkage) against $H_1 : \lambda > 0$ (linkage), where $\psi \in \Psi$ is unknown and determined by the underlying genetic model, e.g., under the alternative hypothesis, $\psi = 0$ corresponds to a rare recessive disease and $\psi = 1/2$ corresponds to the disease that follows an additive genetic model. The second example comes from candidate-gene association tests using parents and their diseased offspring (Schaid and Sommer

(1993)), in which

$$H_0 : f(x;\lambda) = f(x;0) = f_0(x) \text{ versus } H_1 : f(x;\lambda) \in \Psi = \{f_1(x;\lambda), \ldots, f_k(x;\lambda)\}, \tag{2}$$

where $f_i(x;\lambda) = f_0(x)$ if and only if $\lambda = 0$ for $i = 1, \ldots, k$ and k is known. In this case, the alternative consists of a finite number of different distributions (genetic models). In both examples, we test a null hypothesis against a family of alternatives indexed by a one-dimensional parameter ψ which appears in the model only under the alternative hypothesis.

Generally, let $X = (X_1, \ldots, X_n)$ be a random sample of size n with a density (mass) function $f(x;\lambda,\psi)$, where ψ is a vector of parameters. We test $H_0 : \lambda = 0$ against $H_1 : \lambda > 0$. Under the null hypothesis H_0, $f(x;0,\psi) = f_0(x)$ is independent of ψ. Thus, ψ is not defined under H_0. Davies (1977) considered this problem when Ψ is a closed interval. This method was used by Shoukri and Lathrop (1993) and Lemdani and Pons (1995) for testing linkage in genetics, under the model $f(x;\lambda,\psi) = (1-\lambda)f(x;1/2) + \lambda f(x;\psi)$, where $\psi = \theta \in [0, 1/2]$ is a recombination fraction. The asymptotic distributions of their test statistics are either not available or intractable. Hence, Liang and Rathouz (1999) studied another approach by estimating the recombination fraction ψ under an arbitrary alternative model, i.e., $\lambda = \lambda_0 > 0$. However, their approach cannot be directly applied to the two problems described above. Since they require that the null hypothesis can be specified by $H_0 : \psi = 1/2$, while in our problems the null model is uniquely defined by $\lambda = 0$, i.e., the alternative is true if $\lambda > 0$ for any ψ.

On the other hand, for problem (1), Whittemore and Tu (1998) studied the score statistic Z_ψ for a fixed ψ, given by

$$Z_\psi = n^{-1/2} \sum_{i=1}^{n} \left[\frac{\partial}{\partial\lambda} \{\log f(x_i;\lambda,\psi)\} / i(\psi) \right]_{\lambda=0}, \tag{3}$$

where $f(x_i;\lambda,\psi)$ is the likelihood function for the i sib-pair and

$$\{i(\psi)\}^2 = \mathrm{Var}_{\mathrm{H}_0} \left[\frac{\partial}{\partial\lambda} \{\log f(x_i;\lambda,\psi)\} \right].$$

They replaced ψ in Z_ψ with a fixed value $\psi^{(0)} \in \Psi$ that minimizes the maximum relative efficiency loss when an incorrect ψ is used under the alternative. Gastwirth and Freidlin (2000) showed that the robust score test $Z_{\psi^{(0)}}$ of Whittemore and Tu (1998) can be easily obtained as the maximin efficiency robust test (MERT) (Gastwirth (1985)), under which ψ is selected to maximize the minimum asymptotic relative efficiency of Z_ψ relative to Z_{ψ^*} when ψ^* is the true value.

The purpose of this paper is to define two new measures using Kullback-Leibler information (Kullback (1959)) to obtain a family of admissible genetic models. We also obtain two optimality criteria to select a robust genetic model for testing $H_0 : \lambda = 0$ against $H_1 : \lambda > 0$, when the null hypotheses can be uniquely determined by $\lambda = 0$. The methods are applied to the genetic testing problems described above.

The rest of the paper is organized as follows. In Section 2, two measures based on Kullback-Leibler information are introduced. Two robust criteria and their properties are given in Section 3. In Section 4, the insight into commonly used tests in the linkage analysis of affected sib-pairs provided by the measures is presented. The results are also applied to model selection for linkage analysis using affected sib triples and for the candidate-gene association tests using parents and their diseased offspring.

2. Kullback-Leibler Information and Related Measures

2.1. Kullback-Leibler information

Let H_i, $i = 1, 2$ be two hypotheses with corresponding density (mass) functions $f_i(x)$. The expected information contained in a single random variable X in favor of H_2 against H_1 is given by

$$K(H_2 : H_1) = \int \log\left\{\frac{f_2(x)}{f_1(x)}\right\} dF_2(x) = \int f_2(x) \log\left\{\frac{f_2(x)}{f_1(x)}\right\} d\mu(x)$$

with respect to some measure μ. Here $K(H_2 : H_1)$ is called the Kullback-Leibler information (KLI) for discriminating H_2 from H_1 when the hypothesis H_2 is true; it measures the divergence or distance between two hypotheses H_1 and H_2. Note that $K(H_2 : H_1) \geq 0$, where the equality holds if and only if $H_1 = H_2$. Korol, Ronin and Kirzhner (1996) and Chernoff (1999) have applied KLI to problems in genetics.

The KLI assumes that the underlying model (F_2) is known. In our applications, however, the true model is indexed by a nuisance parameter. We define two new measures using KLI when the true model is unknown. Let H_0, H_1 and H_1^* be the null model, the selected alternative model, and the true model, respectively. In the following, $H_1 \in \Psi$ means that the value of the parameter ψ corresponding to H_1 is contained in Ψ.

2.2. Kullback-Leibler information difference for three hypotheses

Given three hypotheses H_0, H_1 and H_1^*, the difference of two KLI, denoted by $\Delta(H_1, H_0|H_1^*)$, is defined as

$$\Delta(H_1, H_0|H_1^*) = K(H_1^* : H_0) - K(H_1^* : H_1) = \int \log\left\{\frac{f_1(x)}{f_0(x)}\right\} dF_1^*(x), \qquad (4)$$

where $dF_1^*(x)/d\mu(x) = f_1^*(x) = f(x;\lambda,\psi^*)$, $\lambda > 0$, is the corresponding density (mass) function under the true model H_1^*. Note that λ and ψ^* specify the true density function f_1^*. From (4), $\Delta(H_1, H_0|H_1^*)$ is the expected value of the logarithm of the likelihood ratio with respect to the (unknown) true model. Note that (4) reduces to the KLI when $f_1^* = f_1$. If $f_1^* \neq f_1$, $\Delta(H_1, H_0|H_1^*)$ need not have two properties of KLI, i.e., in some situations, $\Delta(H_1, H_0|H_1^*) < 0$ when $f_1^* \neq f_1$ and $\Delta(H_1, H_0|H_1^*) = 0$ does not imply $H_1 = H_0$.

Example 2.1. Consider testing for a mixture of trinomial distributions:

$$\begin{aligned} H_0 :\ & \mathbf{p}_0 = (p_1^0, p_2^0, p_3^0) \ \text{ against} \\ H_1 :\ & \mathbf{p}_1 = (1-\lambda)(p_1^0, p_2^0, p_3^0) + \lambda\left(\pi_1(\psi), \pi_2(\psi), \pi_3(\psi)\right), \end{aligned}$$

where $\psi \in \Psi$ and $\lambda \in [0,1]$, and $\pi_i(\psi) \geq 0$ with $\sum \pi_i(\psi) = 1$. Then we have

$$\Delta(H_1 : H_0|H_1^*) = n\sum_{i=1}^{3}\left\{(1-\lambda)p_i^0 + \lambda\pi_i(\psi^*)\right\}\log\left[\{(1-\lambda)p_i^0 + \lambda\pi_i(\psi)\}/p_i^0\right],$$

where $n = n_1 + n_2 + n_3$ and n_i is the count for the ith category. The testing problem (1) is a special case with $(p_1^0, p_2^0, p_3^0) = (1/4, 1/2, 1/4)$ and $(\pi_1(\psi), \pi_2(\psi), \pi_3(\psi)) = (0, \psi, 1-\psi)$. In (1), let $\lambda = 0.5$ and $\psi^* = 0.5$ and $n = 1$, say. If we select a model with $\psi = 0$, then $\Delta(H_1 : H_0|H_1^*) = -0.08961 < 0$. Thus, $\Delta(H_1 : H_0|H_1^*)$ can be negative in contrast to the usual KLI.

Example 2.2. For discriminating $N(\psi, 1)$ from $N(0,1)$, when $N(\psi^*, 1)$ is true, $\Delta(H_1 : H_0|H_1^*) = \psi(\psi^* - \psi/2)$. If $0 \notin \Psi$, $\Delta(H_1 : H_0|H_1^*) = 0$ if and only if $\psi = 2\psi^*$. This shows that $\Delta(H_1 : H_0|H_1^*) = 0$ does not necessarily imply that $H_1 = H_0$.

Note that $\Delta(H_1, H_0|H_1^*)$ measures how much closer H_1 (that we select) is to the true model H_1^* than H_0 is. The upper bound of $\Delta(H_1, H_0|H_1^*)$ is reached when $H_1 = H_1^*$. Given $H_1^* \neq H_0$, the aim is to select a model H_1 as close to H_1^* as possible. Thus, intuitively, if H_1 is a good model, it should satisfy $\Delta(H_1 : H_0|H_1^*) > 0$ for all possible $H_1^* \in \Psi$. This leads to the following definition of an admissible model.

Definition 2.1. For fixed $\lambda > 0$, a model $H_1 \in \Psi$ is called λ-admissible if $\Delta(H_1 : H_0|H_1^*) \geq 0$ is non-negative for any $H_1^* \in \Psi$.

Denote the set of all λ-admissible models as A_λ, called the λ-admissible set. Obviously, $A_\lambda \subset \Psi$. The λ-admissible set might be empty for a specific testing problem. Moreover, for some $\lambda > 0$, the true model H_1^* itself may not be in

the λ-admissible set unless $A_\lambda = \Psi$ for all $\lambda > 0$. An example illustrating this phenomenon will be given in Section 4.

2.3. Kullback-Leibler information ratio for three hypotheses

In addition to the difference between two KLI, we consider the ratio of two KLI, denoted by $R(H_1 : H_0|H_1^*)$, which is defined as follows:

$$R(H_1 : H_0|H_1^*) = \frac{K(H_1^* : H_1)}{K(H_1^* : H_0)}, \tag{5}$$

when $H_1^* \neq H_0$. When $H_1 \neq H_0 = H_1^*$, $R(H_1 : H_0|H_1^*)$ is defined to be ∞. Similarly, $R(H_1 : H_0|H_1^*) = 0$ if $H_1 = H_0 = H_1^*$.

Given $H_1^* \neq H_0$, we want to select H_1 with $R(H_1 : H_0|H_1^*) < 1$. The two measures $\Delta(H_1 : H_0|H_1^*)$ and $R(H_1 : H_0|H_1^*)$ are related by

$$R(H_1 : H_0|H_1^*) = \frac{\Delta(H_1^* : H_0|H_1^*) - \Delta(H_1 : H_0|H_1^*)}{\Delta(H_1^* : H_0|H_1^*)}. \tag{6}$$

Thus, $R(H_1 : H_0|H_1^*) = 0$ if the true model is selected. Hence $R(H_1 : H_0|H_1^*)$ can be thought as a relative loss due to selecting a wrong model $H_1 \neq H_1^*$. It is easy to see $R(H_1 : H_0|H_1^*) \geq 0$ with equality holding if and only if $H_1 = H_1^*$. For $H_1 \in A_\lambda$, $0 \leq R(H_1 : H_0|H_1^*) \leq 1$, where $R(H_1 : H_0|H_1^*) = 1$ if and only if $K(H_1^* : H_0) = K(H_1^* : H_1) \neq 0$. Using (5), a model is λ-admissible if and only if $R(H_1 : H_0|H_1^*) \leq 1$.

3. Two Robustness Criteria Based on Kullback-Leibler Information

3.1. The maximin criterion

From (4), the KLI $K(H_1^* : H_0)$ is an upper bound for $\Delta(H_1 : H_0|H_1^*)$, i.e., $\Delta(H_1 : H_0|H_1^*) \leq K(H_1^* : H_0)$ for any H_1 and H_1^*. Given the true model H_1^*, a larger value of $\Delta(H_1 : H_0|H_1^*)$ indicates that H_1 is closer to the true model (H_1^*) than H_0. However, the true model is unknown. Thus, we may consider selecting a value of ψ (or an alternative model) such that it maximizes the minimum $\Delta(H_1 : H_0|H_1^*)$.

Definition 3.1.(Maximin criterion). For fixed $\lambda > 0$ and any $H_1 \in \Psi$, a λ-maximin model, denoted by $H_1^{\text{MAXMIN}} \in \Psi$ (or $\psi^{\text{MAXMIN}} \in \Psi$), satisfies

$$\inf_{H_1^* \in \Psi} \Delta(H_1^{\text{MAXMIN}} : H_0|H_1^*) \geq \inf_{H_1^* \in \Psi} \Delta(H_1 : H_0|H_1^*). \tag{7}$$

Recall that $\Delta(H_1 : H_0|H_1^*)$ is a function of both λ and ψ^* so when λ is fixed, one is concerned with choice of ψ. If there exists $\epsilon > 0$ and (7) holds for any $H_1 \in \Psi$ and for $0 < \lambda < \epsilon$, then the model is called a local maximin model, also denoted

by H_1^{MAXMIN}. Note that the local maximin model is a λ-maximin model with $0 < \lambda < \epsilon$ for some small $\epsilon > 0$.

In practice, λ is not known, so we are only interested in selecting a local maximin model. The local maximin model can be found numerically as shown later. Denote the complement of A_λ by A_λ^C. The following result, proved in Appendix A, gives the properties of the admissible set of models and the maximin model.

Theorem 3.1. *Assume A_λ is not empty for a fixed $\lambda > 0$. Then any model $H_1 \in A_\lambda$ has greater minimum $\Delta(H_1 : H_0|H_1^*)$ than models in A_λ^C. Thus, a maximin model is admissible. Further*

$$\sup_{H_1 \in \Psi} \inf_{H_1^* \in \Psi} \Delta(H_1 : H_0|H_1^*) \geq 0. \tag{8}$$

Equality holds if and only if there is a sequence of alternatives $H_{1,k}^* \in \Psi$, $k = 1, 2, \ldots$, such that $K(H_{1,k}^* : H_0) \to 0$ as $k \to \infty$.

Theorem 3.1 shows that the λ-maximin model in Ψ is only contained in the subset A_λ. Further, for any model contained in A_λ^c, there exists a true model such that $\Delta(H_1 : H_0|H_1^*)$ is negative, i.e., models in A_λ^c are not robust. Moreover, the conclusions of Theorem 3.1 hold for a local maximin model. We are not interested in selecting a model where equality in (8) holds, as this would imply that the optimal robust model selected is as close to the true model as the null model is. An example for which equality in (8) holds is $H_0 \in \bar{\Psi}$, the compact closure of Ψ. In this case, $\inf_{H_1^* \in \Psi} \Delta(H_1 : H_0|H_1^*) \leq \Delta(H_1 : H_0|H_0) = -\Delta(H_0 : H_1|H_0) \leq 0$. Thus $H_1^{\text{MAXMIN}} = H_0$ by Definition 3.1 when equality in (8) holds, which shows the λ-maximin model can be used only if $H_0 \notin \bar{\Psi}$. Hence the equality in (8) does not hold for the two testing problems described in Section 1.

3.2. The minimax criterion

Minimax models based on the ratio of two KLI in (5) are defined as follows:

Definition 3.2.(Minimax criterion). When the true model H_1^* is not known and $H_1^* \neq H_0$, for any $H_1 \in \Psi$ and fixed $\lambda > 0$, a model, $H_1^{\text{MINMAX}} \in \Psi$ (or $\psi^{\text{MINMAX}} \in \Psi$), is called a λ-minimax model if it satisfies

$$\sup_{H_1^* \in \Psi} R(H_1^{\text{MINMAX}} : H_0|H_1^*) \leq \sup_{H_1^* \in \Psi} R(H_1 : H_0|H_1^*).$$

A local minimax model, also denoted by H_1^{MINMAX}, can be defined analogously to the local maximin model.

In practice, we only interested in a local minimax model. If $H_0 \in \bar{\Psi}$, we show that $H_1^{\text{MINMAX}} = H_0$ in Appendix B. As in the case of the maximin models, the

minimax models can be used only if there is a neighborhood of H_0 contained in the complement of Ψ. For the relative loss (6), the analog of Theorem 3.1 is proved similarly.

Theorem 3.2. *If A_λ is not empty for a fixed $\lambda > 0$, then any model $H_1 \in A_\lambda$ has smaller maximum relative loss than the models in A_λ^C. This implies that a minimax model is admissible.*

Like Theorem 3.1, Theorem 3.2 shows that the λ-minimax model is only contained in A_λ. Generally, for statistical estimation, explicit minimax estimates are not easy to obtain and each problem must be treated on its own merits (Lehmann (1987)). The same is true for finding the maximin and minimax model for testing. Numerical computation is required to find the local maximin and minimax models for each problem. Note that ψ^{MAXMIN} and ψ^{MINMAX} only depend on the set of models and do not depend on test statistics, data or sample size. The test statistics $Z_{\psi^{\text{MAXMIN}}}$ and $Z_{\psi^{\text{MINMAX}}}$ follow an asymptotic standard normal distribution under the null hypothesis.

4. Applications to Genetic Testing Problems

In this section, we consider applications of robust model selection for testing association (Section 4.1), testing genetic linkage using affected sib pairs (Section 4.2) and using affected sib triples (Section 4.3). These results provide insight into commonly used test statistics.

4.1. Candidate-gene association study using parents and their diseased offspring

Association studies using parents and their diseased offspring offer a powerful approach for studying the association of a disease with a candidate gene when there is linkage (Spielman, McGinnis and Ewens (1993), Schaid and Sommer (1993), Curnow, Morris and Whittaker (1998) and Ewens (1999)). In these studies the family is ascertained by first obtaining an affected child.

Among the six parental mating types, only (a) $MM \times MN$, (b) $MN \times MN$, and (c) $MN \times NN$, where M is the disease allele and N is the normal allele, are informative, i.e., the offspring genotype conditional probabilities differ for these mating types. Denote the probabilities of disease, conditional on genotypes at the candidate-gene locus, as $f_0 = \Pr(\text{disease}|NN)$, $f_1 = \Pr(\text{disease}|MN)$, and $f_2 = \Pr(\text{disease}|MM)$. Define relative risks $r_1 = f_1/f_0$ and $r_2 = f_2/f_0$. Using relative risks, four basic genetic models are (i) recessive ($r_1 = 1, r_2 = r$), (ii) multiplicative ($r_1 = r^{1/2}, r_2 = r$), (iii) additive ($r_1 = (1+r)/2, r_2 = r$), and (iv) dominant ($r_1 = r_2 = r$). Let $\lambda = r - 1$. From (2), the null hypothesis becomes $H_0 : r = 1$ against $H_1 : r > 1$. Under H_0, $r_1 = r_2 = 1$ for each of

the four models, which implies that $f_0 = f_1 = f_2$. Under the alternative, the four genetic models are different. We use symbols MT for mating type, D for disease and O for offspring. From Schaid and Sommer (1993), for mating type (a), the genotype of diseased offspring is either MM or MN and, conditional on the mating type, $\Pr(\mathrm{O} = MM|\mathrm{MT} = (a), \mathrm{O} = \mathrm{D}) = r_2/(r_1 + r_2)$. Similarly, for mating type (c), the genotype of diseased offspring (MN or NN) conditional on the mating type has $\Pr(\mathrm{O} = MN|\mathrm{MT} = (c), \mathrm{O} = \mathrm{D}) = r_1/(1 + r_1)$. For mating type (b), the conditional distribution of NN, MN, or MM is trinomial with $p_0 = \Pr(\mathrm{O} = NN|\mathrm{MT} = (b), \mathrm{O} = \mathrm{D}) = 1/(r_2 + 2r_1 + 1)$, $p_1 = \Pr(\mathrm{O} = MN|\mathrm{MT} = (b), \mathrm{O} = \mathrm{D}) = 2r_1/(r_2 + 2r_1 + 1)$, and $p_2 = 1 - p_0 - p_1$. For either mating type (a) or (c), the efficient score tests for $r = 1$ against $r > 1$ are identical for the four models (Zheng, Freidlin and Gastwirth (2002)), so there is no need for model selection for these two mating types. However, the score tests are different under different models for mating type (b) (see below). Conditional on the mating type, data from mating types (a), (b) and (c) are independent. Thus each mating type can be regarded as a stratum. The remainder of the section focuses on model selection for mating type (b). Once an optimal test statistic is obtained for mating type (b), it is combined with the optimal test statistics for the other two mating types. Note that in Zheng, Freidlin and Gastwirth (2002), MERT is a linear combination of Z_{rec} and Z_{dom}, which is identical to Z_{add} for mating type (b).

Under the null $r = 1$, $(p_0, p_1, p_2) = (1/4, 1/2, 1/4)$ for all four models as the disease is not related to the gene. Let $n = n_0 + n_1 + n_2$, where n_i is the count of cases with i M alleles, $i = 0, 1, 2$. The likelihood function under the null is $L_0 \propto (1/4)^{n_2}(1/2)^{n_1}(1/4)^{n_0}$, and under the alternative it is $L_1 \propto p_2^{n_2} p_1^{n_1} p_0^{n_0}$, where p_0, p_1, and p_2 are functions of $r > 1$. Thus, from (3), the efficient score tests under four models are given by $Z_{\mathrm{add}} = Z_{\mathrm{mul}} = n^{1/2}(\hat{p}_0 - \hat{p}_2)/(1/2)^{1/2}$, $Z_{\mathrm{rec}} = n^{1/2}(3\hat{p}_2 - \hat{p}_1 - \hat{p}_0)/3^{1/2}$, and $Z_{\mathrm{dom}} = n^{1/2}(\hat{p}_1 + \hat{p}_2 - 3\hat{p}_0)/3^{1/2}$, where $\hat{p}_i = n_i/n$ for $i = 0, 1, 2$, and where "add" stands for additive, etc. Hence the optimal test depends on the underlying genetic model, which usually is unknown for complex diseases. Thus, the results of Section 3 can be applied to the testing problem.

Under the alternative, we calculate $\Delta(H_1 : H_0|H_1^*)$. For example, if we select the dominant model but the true model is recessive, then using (4) one obtains $\Delta(H_1 = \mathrm{dom} : H_0|H_1^* = \mathrm{rec}) = n[\log\{4/(3r + 1)\} + \{(r + 2)/(r + 3)\}\log r]$ and $\Delta(H_1 = \mathrm{rec} : H_0|H_1^* = \mathrm{rec}) = n[\log\{4/(r + 3)\} + \{r/(r + 3)\}\log r]$. Thus, the relative loss, denoted by $R(\mathrm{dom}|\mathrm{rec}) = R(H_1 = \mathrm{dom} : H_0|H_1^* = \mathrm{rec})$, is

$$R(\mathrm{dom}|\mathrm{rec}) = \frac{\log\{(3r + 1)/(r + 3)\} - \{2/(r + 3)\}\log r}{\log\{4/(r + 3)\} + \{r/(r + 3)\}\log r},$$

where the numerator is the absolute loss. For the four different models, we have a total of twelve expressions for the relative (absolute) loss in terms of KLI.

To find a local minimax model for each selected model H_1, we first want to choose the true model H_1^* with the maximum relative loss $R(H_1|H_1^*)$ as $r \to 1$. Then we select the alternative H_1 that minimizes this relative loss. For example, when $1 < r < 2$ and H_1 is additive, the model H_1^* maximizing the relative loss is the recessive model. In fact, the (H_1, H_1^*) pairs yielding the maximum relative loss are (dom, mul), (rec, dom), (add, rec) and (mul, dom). Then, from these pairs, we find H_1 with the smallest relative loss $R(H_1|H_1^*)$ as $r \to 1$. This is the minimax model. For $1 < r < 2$, $R(\text{add}|\text{rec})$ is the smallest among the four pairs. Thus, the additive model is the minimax one. However, as $r \to 1$, $\lim R(\text{add}|\text{rec}) = \lim R(\text{mul}|\text{dom})$. It can also be shown that the relative loss converges to zero as $r \to 1$ if we select the multiplicative model when the additive model is actually true, and vice verse. This is not surprising since $Z_{\text{add}} = Z_{\text{mul}}$. Similarly, one can show that the maximin model for this problem is also additive. Thus the minimax and maximin models yield the same locally optimal test statistic Z_{add}, which is also Z_{mul}. It can be verified that the additive and multiplicative models are admissible as $r \to 1$, but $\Delta(H_1 = \text{dom} : H_0|H_1^* = \text{rec})$ and $\Delta(H_1 = \text{rec} : H_0|H_1^* = \text{dom})$ are negative as $r \to 1$. Thus the dominant and recessive models are not locally admissible.

4.2. Linkage analysis using affected sib-pairs

Nonparametric linkage analysis based on IBD sharing of affected sib-pairs is known to be robust to the inherent uncertainty about the precise underlying genetic model for diseases. For the mixture model (1), let n_i be the observed numbers of pairs sharing $i = 0, 1, 2$ alleles IBD, and $n = n_0 + n_1 + n_2$. One family of nonparametric test statistics consists of the weighted averages of the observed frequencies $(n_i/n, i = 0, 1, 2)$ of sib-pairs sharing alleles IBD. The likelihood function is proportional to $p_0^{n_0} p_1^{n_1} p_2^{n_2}$. From (3), the efficient score test for $H_0 : \lambda = 0$ is $Z_\psi = \{n_2(3 - 4\psi) - n_1(1 - 2\psi) - n_0\}/\{n(6\psi^2 - 8\psi + 3)\}^{1/2}$, where $\psi \in [0, 1/2]$ is unknown. Several tests have been proposed for testing H_0. The means test $Z_{.5} = n^{1/2}(2\hat{p}_2 + \hat{p}_1 - 1)/(1/2)^{1/2}$, obtained by setting $\psi = 0.5$, where $\hat{p}_i = n_i/n$, compares the observed $(2n_2 + n_1)/n$ of alleles shared IBD by sib-pairs with its null expectation, $2(1/4) + 1/2 = 1$. The proportions test $Z_0 = n^{1/2}(4\hat{p}_2 - 1)/3^{1/2}$ compares the proportion $\hat{p}_2$ of sib-pairs sharing two alleles IBD to $1/4$. Both the means test and proportions tests were studied by Suarez, Rice and Reich (1978), Blackwelder and Elston (1985) and Schaid and Nick (1990). Recent research is summarized in Shih and Whittemore (2001). The robust minimax or MERT (Whittemore and Tu (1998) and Gastwirth and

Freidlin (2000)) corresponds to $\psi = (3 - 6^{1/2})/(4 - 6^{1/2}) \approx 0.355$. Feingold and Siegmund (1997) suggested another robust test by setting $\psi = 0.25$.

First, we numerically find the *local* admissible models. We compute the values of $\Delta(H_1 : H_0|H_1^*)$ for $\lambda = 0.00001$, 0.0001, and from 0.001 to 0.999 with a step size of 0.001 and both ψ^* and ψ from 0.01 to 0.50 with a step size of .01, and find A_λ for these values. It seems that the admissible set is an interval $A_\lambda = [L, 0.50]$, where L is a decreasing function of $\lambda > 0$. When $\lambda = 0.00001, 0.0001, 0.001$, $A_\lambda = [0.22, 0.50]$. It follows that any selected model H_1 with $\psi \geq 0.22$ will be admissible for $\lambda \geq 0.00001$. Therefore, as $\lambda \to 0$, $A_\lambda = [0.22, 0.50]$ defines a family of locally optimal robust tests for genetic linkage using affected sib-pairs. Note tests specified by $\psi = 0.25$, $\psi = 0.355$, and $\psi = 0.50$, are admissible. The proportions test, corresponding to $\psi = 0 \in A_\lambda^C$, is not. This is because $\Delta(H_1 : H_0|H_1^*) < 0$ when the recessive model is selected (H_1) and the true model (H_1^*) is additive. This is consistent with the results in Whittemore and Tu (1998) and Gastwirth and Freidlin (2000) indicating that the proportions test has low power when the additive model holds.

The results of Section 3 can now be applied to select a value of ψ for the robust Z_ψ. To find ψ^{MAXMIN}, it is easy to show that, under the alternative hypothesis, $(1 + \lambda)p_1 < 2p_2$ for $\lambda > 0$. For any fixed alternative model, $\Delta(H_1 : H_0|H_1^*)$ only depends on ψ^*. It can be shown that $\partial\Delta(H_1 : H_0|H_1^*)/\partial\psi^* = n\lambda \log\{p_1/(2p_2)\} < 0$. Thus $\inf_{\psi^*} \Delta(H_1 : H_0|H_1^*) = \Delta(H_1 : H_0|H_1^*)|_{\psi^*=0.5}$. Then for $\psi \in [0, 1/2]$, we have $\partial\{\Delta(H_1 : H_0|H_1^*)|_{\psi^*=0.5}\}/\partial\psi = n\lambda\{2/p_1 - (1 + \lambda)/p_2\}/4 > 0$. Thus $\psi^{\text{MAXMIN}} = 0.5$ for any $\lambda \in (0, 1]$. Hence the means test, $Z_{0.5}$, is the optimal test under the maximin criterion. This result may underlie those of Blackwelder and Elston (1985), Schaid and Nick (1990) and Knapp, Seuchter and Baur (1994), who found that the means test is quite powerful for a wide variety of genetic models.

Next we find ψ^{MINMAX} for the relative loss criterion. In most cases, the explicit ψ^{MINMAX} is not available (see discussion in Section 3.2). However, for the trinomial distribution, one can show (Appendix C) that the local ψ^{MINMAX} satisfies $10\psi^2 - 12\psi + 3 = 0$, which has only one root in $[0, 1/2]$. The valid root is $\psi^{\text{MINMAX}} = (3 - 6^{1/2})/(4 - 6^{1/2})$. Thus, $Z_{\psi^{\text{MINMAX}}}$ coincides with the MERT.

Using KLI and two robust criteria, we show that the means test is optimal under the maximin criterion and that the MERT is optimal under the minimax criterion while the proportions test is not admissible based on the KLI criteria.

4.3. Linkage analysis using affected sib-triples

For n affected sib-triples, there are four possible IBD configurations for three affected sibs. Following Whittemore and Tu (1998), let p_i be true IBD probability for affected sib-triples, $i = 0, 1, 2, 3$, where $\sum_{i=0}^{3} p_i = 1$. Note that three possible

sib-pairs can be obtained from one sib-triple. Let p_0 be the probability that one sib-pair shares two alleles IBD and that the remaining two sib-pairs share one allele each, p_1 the probability that all three sib-pairs share two alleles IBD, p_2 the probability that two sib-pairs share one allele IBD and that the remaining one sib-pair shares zero allele IBD, and p_3 the probability that one sib-pair shares two alleles IBD and that the remaining two sib-pairs share zero allele IBD. Under the null hypothesis of no linkage, $\mathbf{p} = (p_0, p_1, p_2, p_3) = (3/8, 1/16, 3/8, 3/16)$. Whittemore and Tu (1998) considered the following family of distributions for possible linkage,

$$F_{a,b} = \left\{\mathbf{p} : \mathbf{p} = (1-\lambda)(\frac{3}{8}, \frac{1}{16}, \frac{3}{8}, \frac{3}{16}) + \lambda(a, b, 0, 1-a-b); \lambda \in [0,1]\right\}, \quad (9)$$

where a and b are nuisance parameters determined by the underlying genetic model and satisfy the constraints (i) $0 \le a \le 3/4$, (ii) $7/40 \le b \le 1$, (iii) $a+b \le 1$, and (iv) $6a + 8b \ge 5$. These constraints form the nuisance parameter space Ψ, a closed convex set in R^2 with five vertices: $(a_1, b_1) = (0, 1)$, $(a_2, b_2) = (0, 0.625)$, $(a_3, b_3) = (0.6, 0.175)$, $(a_4, b_4) = (0.75, 0.175)$ and $(a_5, b_5) = (0.75, 0.25)$.

Under (9), we test $H_0 : \lambda = 0$ against $H_1 : \lambda > 0$ (with linkage), where the alternative is indexed by two nuisance parameters a and b, undefined under the null. The locally optimal test statistic for $H_0 : \lambda = 0$ for the family $F_{a,b}$, when a and b are fixed, can be written (Whittemore and Tu (1998))

$$Z_{a,b} = \frac{n^{1/2}[w_0(\hat{p}_0 - 3/8) + (\hat{p}_1 - 1/16) + w_2(\hat{p}_2 - 3/8)]}{[15(w_0^2 + w_2^2)/64 - 9w_0w_2/32 - 6(w_0 + w_2)/128 + 15/256]^{1/2}}, \quad (10)$$

where $\hat{p}_i = n_i/n$, $i = 0, 1, 2, 3$, are observed frequencies, $w_0 = (3a/2 + b - 1)/(a + 4b - 1)$ and $w_2 = (a + b - 1)/(a + 4b - 1)$, $(a, b) \in \Psi$. Several common test statistics can be obtained from (10). If $(a, b) = (a_5, b_5)$, $Z_{a_5,b_5} = n^{1/2}(\hat{p}_0/2 + \hat{p}_1 - 1/4)/(3/32)^{1/2}$ is the means test, and if $(a, b) = (a_1, b_1)$, $Z_{a_1,b_1} = n^{1/2}(\hat{p}_1 - 1/16)/(15/256)^{1/2}$ is the proportions test. Whittemore and Tu (1998) obtained the robust test with $(a^{WT}, b^{WT}) = (0.532, 0.307)$, which is also the MERT (Gastwirth and Freidlin (2000)). Under the null, $Z_{a,b}$ has an asymptotic standard normal distribution for fixed a and b.

Let $v_1(a) = \lambda a + (3/8)(1-\lambda)$, $v_2(b) = \lambda b + (1/16)(1-\lambda)$ and $v_3(a, b) = \lambda(1 - a - b) + (3/16)(1-\lambda)$. Then

$$\Delta(H_1 : H_0|H_1^*) = \mathrm{E}_{H_1^*}\left\{\log(\frac{L_\lambda}{L_0})\right\} = nv_1(a^*)\log[\frac{8}{3}v_1(a)] + nv_2(b^*)\log[16v_2(b)]$$
$$+n[\frac{3}{8}(1-\lambda)]\log(1-\lambda) + nv_3(a^*, b^*)\log[\frac{16}{3}v_3(a, b)]. \quad (11)$$

Hence the KLI can be obtained as

$$K(H_1 : H_0) = \Delta(H_1 : H_0|H_1^*)|_{(a^*=a, b^*=b)}. \quad (12)$$

From (11) and (12) with H_1 replaced by H_1^* in (12), and the identity $K(H_1^* : H_1) = K(H_1^* : H_0) - \Delta(H_1 : H_0|H_1^*)$, we have

$$K(H_1^* : H_1) = nv_1(a^*)\log[v_1(a^*)/v_1(a)] + nv_2(b^*)\log[v_2(b^*)/v_2(b)] + nv_3(a^*, b^*)\log[v_3(a^*, b^*)/v_3(a, b)]. \tag{13}$$

Hence, we can also obtain the relative loss $R(H_1 : H_0|H_1^*)$ from (11), (12) and (13).

Numerical results show that the local maximin and minimax models correspond to $(a, b) = (a_3, b_3) = (0.6, 0.175)$ and $(a, b) = (0.508, 0.323)$, respectively (based on $\lambda = 0.001, 0.0001, 0.00001$). Note that the minimax model is close to that of Whittemore and Tu (1998) with $(a, b) = (0.532, 0.307)$. Further, for $\lambda = 0.00001$ and an increment of 0.005 for both a^* and b^* for $(a^*, b^*) \in \Psi$, numerical results show that (a, b) corresponds to the MERT and means test is admissible but not admissible for the proportions test. As in Whittemore and Tu (1998), we calculate the sample size required by the proportions test (PROP), means test (MEAN), MERT, minimax test and maximin test to achieve the same asymptotic power as that achieved by the locally optimal test based on 100 sib-triples for each vertex of Ψ and two inner points of Ψ. The columns for proportions test, means test and MERT are the same as those of Whittemore and Tu (1998). The results are reported in Table 1.

Table 1. Sample size required for the same asymptotic power as is shown by the optimal 1df test, based on 100 affected sib-triples.

	Sample size required for				
	PROP	MEAN	MERT	Minimax	Maximin
	$a = 0$	$a = 0.75$	$a = 0.532$	$a = 0.508$	$a = 0.6$
True value (a^*, b^*)	$b = 1$	$b = 0.25$	$b = 0.307$	$b = 0.323$	$b = 0.175$
$(a_1, b_1) = (0, 1)$	100	250	137	130	333
$(a_2, b_2) = (0, 0.625)$	111	400	147	137	243
$(a_3, b_3) = (0.6, 0.175)$	333	133	123	128	100
$(a_4, b_4) = (0.75, 0.175)$	472	106	146	158	121
$(a_5, b_5) = (0.75, 0.25)$	250	100	126	132	133
Inner point: (0.3, 0.6)	102	190	117	113	222
Inner point: (0.375, 0.375)	118	188	109	106	156

From Table 1, we see that the sample sizes required by the minimax test are similar to those of the MERT. The MERT requires smaller sample sizes in the part of parameter space near the three vertices (a_3, b_3), (a_4, b_4) and (a_5, b_5), while the minimax test requires smaller sample sizes in the other part of the parameter space. The sample sizes for the maximin test are smaller than the MERT and the

minimax test when the underlying genetic models are specified by (a_3, b_3) and (a_4, b_4). If we compare the largest sample size required by these tests, the MERT has the smallest (147) followed by the minimax (158), maximin (333), means test (400) and proportions test (472). Thus, when there is no knowledge of the underlying mode of inheritance, the MERT can be used to design the study.

5. Conclusion

We applied the Kullback-Leibler information to the selection of a robust model for testing problems when the true model is unknown, and examined the robustness properties of statistical tests. The approach can handle non-standard testing problems where the null model can be uniquely expressed but the family of alternative models is indexed by a nuisance parameter (continuous or discrete). For either criteria, given a family of models, we obtain a corresponding family of robust procedures (those based on the admissible set in the nuisance parameter space). The results provide insight into the commonly used tests in genetic linkage analysis for affected sib-pairs or sib-triples, and robust candidate-gene association tests. For linkage analysis using affected sib-pairs, both the means test and MERT, are admissible. For candidate-gene association studies, the additive and multiplicative models, which are locally equivalent, are admissible.

Acknowledgements

The research of Joseph Gastwirth was supported in part by grant SES-031956 from NSF. We would like to thank the referee for helpful comments and suggestions that improved the presentation of the paper.

Appendix. Proofs

A. Proof of Theorem 3.1

Since $A_\lambda^C = \{H_1 : \Delta(H_1 : H_0|\tilde{H}_1^*) < 0,$ for some true model $\tilde{H}_1^* \in \Psi\}$, for any $H_1^{(1)} \in A_\lambda$ and any $H_1^{(2)} \in A_\lambda^C$, $\Delta(H_1^{(1)} : H_0|H_1^*) \geq 0 > \Delta(H_1^{(2)} : H_0|\tilde{H}_1^*)$ for any $H_1^* \in \Psi$ and some $\tilde{H}_1^* \in \Psi$. This implies

$$\inf_{H_1^* \in \Psi} \Delta(H_1^{(1)} : H_0|H_1^*) \geq 0 > \inf_{H_1^* \in \Psi} \Delta(H_1^{(2)} : H_0|H_1^*). \tag{14}$$

Thus $H_1^{\text{MAXMIN}} \in A_\lambda$ and (8) follows from (14). If the equality in (8) holds, then $\inf_{H_1^* \in \Psi} \Delta(H_1 : H_0|H_1^*) \leq 0$ for any $H_1 \in \Psi$. Thus for any $\epsilon > 0$, there exists $H_1^*(\epsilon) \in \Psi$ such that $\Delta(H_1 : H_0|H_1^*(\epsilon)) < \epsilon$ for any $H_1 \in \Psi$, which implies that $\Delta(H_1^*(\epsilon) : H_0|H_1^*(\epsilon)) \to 0$ as $\epsilon \to 0$. On the other hand, let $H_{1,k}^* \in \Psi$ be such that $K(H_{1,k}^* : H_0) \to 0$ as $k \to \infty$. Then $\inf_{H_1^*} \Delta(H_1 : H_0|H_1^*) \leq \Delta(H_1 : H_0|H_{1,k}^*) \leq$

$K(H_{1,k}^* : H_0)$, for any $H_1 \in \Psi$. This implies that $\inf_{H_1^* \in \Psi} \Delta(H_1 : H_0|H_1^*) \leq 0$ for any $H_1 \in \Psi$. Thus the equality in (8) holds.

B. Proof that $H_1^{\text{MINMAX}} = H_0$ when $H_0 \in \bar{\Psi}$

Suppose there is at least one $H_1 \in \Psi$ such that $H_1 \neq H_0$. If we select $H_1 \neq H_0$, then $\sup_{H_1^* \in \Psi} R(H_1 : H_0|H_1^*) \geq R(H_1 : H_0|H_0) = \infty$ by definition. Thus $\sup_{H_1^* \in \Psi} R(H_1 : H_0|H_1^*) = \infty$ if $H_1 \neq H_0$. If we select $H_1 = H_0$, then, by definition, $R(H_1 : H_0|H_1^*) = 1$ if $H_1 = H_0 \neq H_1^*$ and 0 if $H_1 = H_0 = H_1^*$. Thus $\sup_{H_1^* \in \Psi} R(H_1 : H_0|H_1^*) = 1$ for $H_1 = H_0$ and the lower bound of $\sup_{H_1^* \in \Psi} R(H_1 : H_0|H_1^*)$ is reached when $H_1 = H_0$. Thus $H_1^{\text{MINMAX}} = H_0$.

C. Find minimax model

Theorem. *Let trinomial probabilities $\pi_i(\psi)$, $i = 1, 2, 3$, be parameterized as linear functions of ψ. Under the null hypothesis, $(\pi_1(\psi), \pi_2(\psi), \pi_3(\psi)) = (p_1^0, p_2^0, p_3^0)$ is independent of ψ. Assume that A_λ is not empty for a fixed $\lambda > 0$. Let $\psi^* \in [L, U]$ be the true value, $\psi \in [L, U]$ be the value selected under the alternative, and $\psi^{\text{MINMAX}} \in [L, U]$ be the local minimax model. Then, for the fixed $\lambda \in (0, 1]$, we have the following*

(a) *$\partial R(\psi|\psi^*)/\partial\psi^* \leq (=, \geq) 0$ when $\psi^* < (=, >) \psi$ for $\psi \in A_\lambda$. Moreover, $R(\psi|\psi^*)$ is a strictly convex function of ψ for $\psi^* \in [L, U]$ and the minimum relative loss is reached when $\psi = \psi^*$.*

(b) *There exist L_1 and U_1: $L \leq L_1 \leq U_1 \leq U$ such that $A_\lambda = [L_1, U_1]$.*

(c) *The minimax model ψ uniquely exists and is the unique root of*

$$R(H_1 : H_0|H_1^*)|_{\psi^*=U} = R(H_1 : H_0|H_1^*)|_{\psi^*=L}. \tag{15}$$

(d) *As $\lambda \to 0$, the local $\psi^{\text{MINMAX}} \in [L, U]$ satisfies the quadratic equation*

$$\frac{\sum_i \{\pi_i(\psi) - p_i^0\}\{2\pi_i(U) - p_i^0 - \pi_i(\psi)\}/p_i^0}{\sum_i \{\pi_i(U) - p_i^0\}^2/p_i^0} = \frac{\sum_i \{\pi_i(\psi) - p_i^0\}\{2\pi_i(L) - p_i^0 - \pi_i(\psi)\}/p_i^0}{\sum_i \{\pi_i(L) - p_i^0\}^2/p_i^0}. \tag{16}$$

Proof.

(a) Denote $R(\psi|\psi^*) = R(H_1 : H_0|H_1^*)$. First we prove $R(\psi|\psi^*)$ is convex about ψ^*. Denote $a_i(\psi) = \{(1-\lambda)p_i^0 + \lambda\pi_i(\psi)\}/p_i^0$, where $\lambda \in (0, 1]$. Then $\Delta(H_1 : H_0|H_1^*) = n\sum_i p_i^0 a_i(\psi^*) \log a_i(\psi)$ and $K(H_1^* : H_0) = \Delta(H_1 : H_0|H_1^*)|_{\psi=\psi^*}$. For a fixed $\psi \in [L, U]$, we have $\partial\Delta(H_1 : H_0|H_1^*)/\partial\psi^* = n\sum_i p_i^0 a_i'(\psi^*) \log a_i(\psi)$ and $\partial K(H_1^* : H_0)/\partial\psi^* = \partial\Delta(H_1 : H_0|H_1^*)/\partial\psi^*|_{\psi=\psi^*}$. Then $\partial R(\psi|\psi^*)/\partial\psi^* = -R_2(\psi|\psi^*)/K^2(H_1^* : H_0)$, where

$$R_2(\psi|\psi^*) = K(H_1^* : H_0)\frac{\partial}{\partial\psi^*}\Delta(H_1 : H_0|H_1^*) - \Delta(H_1 : H_0|H_1^*)\frac{\partial}{\partial\psi^*}K(H_1^* : H_0).$$

Note that $R_2(\psi|\psi^*)|_{\psi^*=\psi} = 0$ and

$$\partial R_2(\psi|\psi^*)/\partial\psi^* = -n\Delta(H_1 : H_0|H_1^*)\sum_i p_i^0 \frac{\{a_i'(\psi^*)\}^2}{a_i(\psi^*)} \leq 0,$$

for $\psi \in A_\lambda$. Thus we obtain $\partial R(\psi|\psi^*)/\partial\psi^* \leq (=, \geq) 0$ when $\psi^* < (=, >)\psi$ for $\psi \in A_\lambda$.

Next we show $R(\psi|\psi^*)$ is strictly convex about ψ. For fixed $\psi^* \in [L, U]$, $\partial\Delta(H_1 : H_0|H_1^*)/\partial\psi = n\lambda\sum_i\{a_i(\psi^*)/a_i(\psi)\}\pi_i'(\psi)$, which implies $\{\partial\Delta(H_1 : H_0|H_1^*)/\partial\psi\}|_{\psi=\psi^*} = 0$ and

$$\partial^2\Delta(H_1 : H_0|H_1^*)/\partial\psi^2 = -n\lambda\sum_i a_i(\psi^*)\frac{\{\pi_i'(\psi)\}^2}{p_i^0 a_i^2(\psi)} < 0.$$

Hence $\Delta(H_1 : H_0|H_1^*)$ is strictly concave and is maximized at $\psi = \psi^*$. This implies that $R(\psi|\psi^*)$ is strictly convex about ψ and is minimized at $\psi = \psi^*$.

(b) The justification of $A_\lambda = [L_1, U_1]$ is based on the fact that $\Delta(H_1, H_0|H_1^*)$ is strictly concave about $\psi \in [L, U]$ and has a positive maximum value when $\psi = \psi^* \in [L, U]$. Thus for each $\psi^* \in [L, U]$, we can find an admissible set, which is a closed interval, $I_{\psi^*} \subset [L, U]$. Then $A_\lambda = \bigcap_{\psi^*} I_{\psi^*}$ must be $[L_1, U_1]$ since it is not empty.

(c) Since $R(\psi|\psi^*)$ is strictly convex about ψ and has a minimum value when $\psi = \psi^*$, $R(\psi|\psi^*)|_{\psi^*=U}$ is strictly decreasing for $\psi \in [L, U]$ and $R(\psi|\psi^*)|_{\psi^*=L}$ is strictly increasing for $\psi \in [L, U]$. Consider function $F(\psi) = R(\psi|\psi^*)|_{\psi^*=U} - R(\psi|\psi^*)|_{\psi^*=L}$. We have $F(L) > 0$, $F(U) < 0$ and $F'(\psi) < 0$. So $F(\psi) = 0$ must have a unique root, call it ψ_1. For $\psi \in A_\lambda$, from (a), we have $\sup_{\psi^*\in[L,U]} R(\psi|\psi^*) = \max\{R(\psi|\psi^*)|_{\psi^*=U}, R(\psi|\psi^*)|_{\psi^*=L}\}$. Obviously $R(\psi|\psi^*)|_{\psi^*=U}$ and $R(\psi|\psi^*)|_{\psi^*=L}$ cross only at $\psi = \psi_1$, which is the unique minimax model and $\psi_1 \in A_\lambda$.

(d) follows from taking limit on both sides of (15) as $\lambda \to 0$.

References

Blackwelder, W. C. and Elston, R. C. (1985). A comparison of sib-pair linkage tests for disease susceptibility loci. *Genet. Epidem.* **2**, 85-97.

Chernoff, H. (1999). Kullback-Leibler information for marker detection in the presence of association. Technical Report, Department of Statistics, Harvard University.

Curnow, R. N., Morris, A. P. and Whittaker, J. C. (1998). Locating genes involved in human diseases. *Appl. Statist.* **47**, 63-76.

Davies, R. B. (1977). Hypothesis testing when a nuisance parameter is present only under the alternative. *Biometrika* **64**, 274-254.

Ewens, W. J. (1999). Statistical aspects of the transmission/disequilibrium test (TDT). In *Statistics in Molecular Biology and Genetics* (Edited by Seilier-Moiseiwitsch). IMS.

Feingold, E. and Siegmund, D. O. (1997). Strategies for mapping heterozygous recessive traits by allele-sharing methods. *Amer. J. Hum. Genet.* **60**, 965-978.

Holmans, P. (1993). Asymptotic properties of affected-sib-pair linkage analysis. *Amer. J. Hum. Genet.* **52**, 362-374.

Gastwirth, J. L. (1985). The use of maximin efficient robust tests in combining contingency tables and survival analysis. *J. Amer. Statist. Assoc.* **80**, 380-384.

Gastwirth, J. L. and Freidlin, B. (2000). On efficiency and power robust linkage tests for affected sibs. *Ann. Hum. Genet.* **64**, 443-453.

Knapp, M., Seuchter S. A. and Baur, M. P. (1994). Linkage analysis in nuclear families. I: Optimality criteria for affected sib-pairs tests. *Hum. Hered.* **44**, 37-43.

Korol, A. B., Ronin, Y. I. and Kirzhner, V. M. (1996). Linkage between quantitative trait loci and marker loci: resolution power of three statistical approaches in single marker analysis. *Biometrics* **52**, 426-441.

Kullback, S. (1959). *Information Theory and Statistics.* Wiley, New York.

Lehmann, E. L. (1983). *Theory of Point Estimation.* Wiley, New York.

Lemdani, M. and Pons, O. (1995). Tests for genetic linkage and homogeneity. *Biometrics* **51**, 1033-1041.

Liang, K.-Y. and Rathouz, P. J. (1999). Hypothesis testing under mixture models: application to genetic linkage analysis. *Biometrics* **55**, 65-74.

Schaid, D. J. and Nick, T. G. (1990). Sib-pair linkage tests for disease susceptibility loci: Common tests vs. the asymptotically most powerful test. *Genet. Epidem.* **7**, 359-370.

Schaid, D. J. and Sommer, S. S. (1993). Genotype relative risks: Methods for design and analysis of candidate-gene association studies. *Amer. J. Hum. Genet.* **53**, 1114-1126.

Shih, M. and Whittemore, A. S. (2001). Allele-sharing among affected relatives: nonparametric methods for identifying genes. *Statist. Meth. Medical Research* **10**, 27-55.

Shoukri, M. M. and Lathrop, G. M. (1993). Statistical testing of genetic linkage under heterogeneity. *Biometrics* **49**, 151-161.

Spielman, R. S., McGinnis, R. E. and Ewens, W. J. (1993). Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes melitus (IDDM). *Amer. J. Hum. Genet.* **52**, 506-516.

Suarez, B. K., Rice, J. and Reich, T. (1978). The generalized sib pair IBD distribution: its use in the detection of linkage. *Ann. Hum. Genet.* **42**, 87-94.

Whittemore, A. S. and Tu, I.-P. (1998). Simple, robust linkage tests for affected sibs. *Amer. J. Hum. Genet.* **62**, 1228-1242.

Zheng, G., Freidlin, B. and Gastwirth, J. L. (2002). Robust TDT-type candidate-gene association tests. *Ann. Hum. Genet.* **66**, 145-155.

Office of Biostatistics Research, Division of Epidemiology and Clinical Applications, National Heart, Lung and Blood Institute, 6701 Rockledge Drive, Room 8223, MSC 7938, Bethesda, MD 20892-7938, U.S.A.

E-mail: zhengg@nhlbi.nih.gov

Biometric Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Executive Plaza North, MSC 7434, Bethesda, MD 20892, U.S.A.

E-mail: freidlinb@ctep.nci.nih.gov

Biostatistics Branch, Division of Epidemiology and Genetics, National Cancer Institute, and, Department of Statistics, George Washington University, Washington, DC 20052, U.S.A.

E-mail: jlgast@gwu.edu

(Received November 2002; accepted January 2004)