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Analysis of Two-locus Traits Under Heterogeneity for Recessive Versus Dominant Inheritance

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Abstract

Complex traits have been modeled under various modes of two-locus inheritance. One example of a two-locus threshold model is the situation where an individual is susceptible to a disease trait if he or she carries three or more disease alleles. Under this model, if each locus is examined individually the inheritance appears recessive for some mating types and dominant for others. We developed a heterogeneity test, the Model-heterogeneity test, where an admixture of dominant and recessive sibships can be present. The properties of the Model-heterogeneity test were examined and compared to the Admixture test. The power of the Model-heterogeneity test to detect linkage is comparable to that of the Admixture test.

Keywords

admixture; complex traits; model-heterogeneity; two-locus models

INTRODUCTION

Complex traits have been modeled to follow a two-locus mode of inheritance. For example, a two-locus threshold model has been shown to provide a good fit to schizophrenia recurrence risks and population prevalence [Newman and Rice, 1992].

Under the two-locus threshold model, each of the two disease loci has two alleles (1 = normal allele, 2 = disease allele) and an individual is susceptible to schizophrenia with a penetrance of 35% when he or she carries three or more 2 alleles (slightly modified version of Newman and Rice's model). Under such a model, penetrances for each locus can be calculated for each of the two-locus mating types and weighted over all mating types. For example, if the frequency is assumed to be 0.2 for the 2 allele at each locus, the penetrances for locus 1 or locus 2 are equal to 0.0, 0.004, 0.005 for genotypes 11 , 12 and 22 , respectively. The penetrances for genotypes 11 , 12 and 22 are the weighted sum of the penetrance for locus 1 or 2, where the weight is the probability of occurrence of each mating type. These penetrances indicate a dominant single-locus inheritance with virtually no informativeness for unaffected individuals. However, the penetrance is dependent on the mating type. For example, for mating type $12\ 11 \times 22\ 22$ (genotypes at loci 1 and 2 per individual), for locus 1 the penetrances among offspring are 0.0, 0.0 and 0.175, for genotypes 11 , 12 and 22 . On the other hand, for mating type $12\ 22 \times 22\ 22$, the corresponding penetrances are 0, 0.175 and 0.175. Thus, inheritance appears recessive for some mating types and dominant for others. Therefore, we propose that: 1) extended

pedigrees be broken into nuclear families and 2) analysis be carried out under a special type of heterogeneity testing which is described here, in which admixture of sibships with recessive and dominant inheritance is allowed for.

It has been shown for both Mendelian and multilocus traits [Clerget-Darpoux et al., 1986; Risch and Giuffra, 1992; Vieland et al., 1992] that analysis under the wrong model parameters retains much of the linkage information, but results in biased (inflated) estimates of the recombination fraction. When analyzing complex traits, analysis is often done using two-point linkage analysis and then testing for admixture [Smith, 1961; 1963; Ott, 1983]. Because, when mapping susceptibility genes for complex traits, the inheritance model is unknown, various models are often tested [Berrettini et al., 1994].

The model heterogeneity test incorporates an additional parameter into the Admixture test, the proportion of families of the autosomal recessive (or dominant) type. The properties and the ability of the Model-heterogeneity test to detect linkage were investigated and compared to the Admixture test in the situation where a disease trait is due to two loci.

METHODS

Three loci were simulated using SIMULATE [Terwilliger and Ott, 1994] for nuclear pedigrees with four offspring. The first two loci are the disease loci, where the 2 allele is the disease allele (freq = 0.3). The third locus is a marker with five alleles of equal frequency. The marker locus was simulated at $\Theta = 0.5$ and 0.02 depending on whether the data were generated under the null hypothesis of no linkage or the alternative hypothesis of linkage to the first locus.

An individual who inherits three or more copies of the disease allele, 2, is susceptible to the disease trait with penetrance 35%. Using a random number generator it was determined which susceptible individuals are affected. If a pedigree has two or more affected offspring, they were ascertained into the sample for analysis. For each replicate, sampling continued until a total of $n = 100$ pedigrees were ascertained. The likelihoods for each pedigree were calculated using MLINK [Lathrop et al., 1984] under a dominant and recessive model, for $\Theta = 0.0$ to 0.5 at steps of 0.02. For the autosomal dominant model, penetrances of 0.005, 0.5 and 0.5 were used for genotypes 11, 12 and 22. The disease gene frequency was set to 0.005. For analysis under the autosomal recessive model a disease gene frequency of 0.1 and a penetrance model of 0.005, 0.005 and 0.5 were used. When analyzing a trait where the correct penetrances are unknown it is important to choose a penetrance ratio (genetic versus nongenetic cases) which is robust to penetrance misspecification. It has been demonstrated that a penetrance ratio of 100:1 meets this criterion (Ott, personal communication). The penetrance values used in the analysis reflect a penetrance ratio of 100:1 and that the autosomal recessive and autosomal dominant models both correspond to a population disease prevalence of 1%; for example, the population prevalence of schizophrenia.

To calculate the critical values for the Model-heterogeneity and Admixture tests at three significance levels ($p = 0.05$, 0.01 and 0.001), 10,000 replicates of $n=100$ pedigrees were simulated under the null hypothesis of no linkage. Utilizing the resulting critical, values the

power was estimated for the Model-heterogeneity and Admixture tests by simulating 500 replicates of $n = 100$ pedigrees under the alternative hypothesis of linkage ($\Theta = 0.02$). Each replicate was analyzed as described below.

Model-heterogeneity Test

For each replicate the likelihood was maximized over α_1 = the proportion of linked families of the recessive type, Θ_1 = the estimate of theta for the families of the autosomal recessive type, Θ_2 = the proportion of linked families of the dominant type and Θ_2 = the estimate of theta for families of the autosomal dominant type. The proportion of autosomal recessive families, r was set to 0.5, since approximately 50% of the mating types have an autosomal recessive penetrance structure at locus 1. In an additional analysis the likelihoods were maximized over r as well as $\alpha_1, \Theta_1, \alpha_2$ and Θ_2 (results not shown). The likelihood under the alternative hypothesis, H_1 is:

$$r\alpha_1 L_r(\Theta_1) + (1-r)\alpha_2 L_d(\Theta_2) + r\alpha_1 L_r(1/2) + (1-r)\alpha_2 L_d(1/2)$$

and under the null hypothesis of no linkage, H_0 is:

$$rL_r(1/2) + (1-r)L_d(1/2)$$

where L_r and L_d are the likelihoods under the recessive and dominant model, respectively. The likelihood ratio of H_1 and H_0 was calculated for each replicate.

Admixture Test: Recessive and Dominant Model

For each replicate the likelihoods calculated under the recessive model were tested for linkage under admixture where under H_0 : $\Theta=1/2$ and H_1 : ($\alpha<1, \Theta<1/2$). This scenario was repeated employing the likelihoods which were calculated under the dominant model.

Admixture Test: Recessive/Dominant Model

Since it is often the case that investigators will analyze the data under a recessive model and then a dominant model, each replicate was analyzed under the recessive model and then the dominant model as described above (Admixture test: recessive and dominant model). The two resulting maximum likelihood ratios were compared and the highest maximum likelihood ratio was taken as the result from the test for each replicate.

RESULTS AND DISCUSSION

Table I presents the critical values in $\log_{10}$ likelihoods for significance levels: 0.001, 0.01 and 0.05, for the four analyses using the Model-heterogeneity test and the Admixture test using three models: recessive/dominant; recessive; and dominant.

Table II displays the power to detect linkage for each of the four analyses at three significance levels ($p = 0.001, 0.01$ and 0.05). The Model-heterogeneity and the Admixture

test using the recessive/dominant model were equally powerful. Both the Model-heterogeneity test and Admixture test using the recessive/dominant model were moderately more powerful than testing for admixture using either the recessive or dominant model alone. The Model-heterogeneity test was compared to the Admixture test under a variety of recombination fraction values between the marker and locus 1. The results were similar to the ones presented here.

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TABLE I.

Critical Values

Analysis type	p-Values		
	0.001	0.01	0.05
Model-heterogeneity test	2.47	1.55	0.90
Admixture test: recessive/dominant model	2.48	1.47	0.86
Admixture test: recessive model	2.29	1.27	0.69
Admixture test: dominant model	2.03	1.23	0.60

TABLE II.

Power to Detect Linkage

Analysis type	p-Values		
	0.001	0.01	0.05
Model-heterogeneity test	0.75	0.93	0.97
Admixture test: recessive/dominant model	0.74	0.92	0.97
Admixture test: recessive model	0.71	0.91	0.97
Admixture test: dominant model	0.60	0.82	0.95