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Maximum-Likelihood Expression of the Transmission/Disequilibrium Test and Power Considerations

To the Editor:

The classic transmission/disequilibrium test (TDT) proposed by Spielman et al. (1993) for analysis of family-based case-control studies is a matched χ^2 test referred to as "McNemar's test." However, the same data also could be analyzed by a likelihood model, as suggested by Terwilliger (1995). In the present letter, we study the maximum likelihood (ML) statistic derived from this model and show that, when a common asymptotic threshold is used, the ML statistic is expected to be slightly more powerful than the classic McNemar χ^2. We also investigate the influence of linkage disequilibrium and allelic frequencies on the power of the ML-TDT, with comparison with the results obtained by means of the classic TDT in a recent study (Risch and Merikangas 1996) .

Using the notation in Spielman et al.'s (1993) table 2, we consider a marker locus with codominant alleles M_1 and M_2, where b (c) is the number of alleles M_1 (M_2) transmitted from a heterozygous M_1M_2 parent to an affected child. The classic TDT test is $\chi^2_{TD} = (b - c)^2/n$, where $n = b + c$ is the number of informative heterozygous parents. Let π be the probability that allele M_1 is transmitted from an M_1M_2 parent to an affected child; then $L(\pi)$—the likelihood for the same data—can be written as $L(\pi) = \pi^b(1 - \pi)^c$. The ML estimator of π, denoted as "p," is equal to b/n, and, in the ML-TDT, the test of the null hypothesis $\pi = .5$ is performed by use of a standard likelihood-ratio test denoted as "Λ":

$$\Lambda = 2Ln[L(p)/L(.5)]$$
$$= 2n[pLn(p) + (1 - p)Ln(1 - p) - Ln(.5)] .$$

When the alternative hypothesis, H_1, is $\pi \neq .5$, $\Lambda_{\pi \neq .5}$ is asymptotically distributed as a χ^2 with 1 df, and this procedure allows us to assess the effect of both alleles in a single two-sided test; when H_1 is $\pi > .5$, p is bounded at .5 when $b < n/2$, and $\Lambda_{\pi \neq .5}$ is asymptotically distributed as a 50:50 mixture of χ^2(0 df) and χ^2(1 df). In this latter procedure, the effect of each allele should be assessed separately, leading to two one-sided tests.

The two statistics, $\Lambda_{\pi \neq .5}$ and χ^2_{TD}, are strictly monotonic, increasing with an increasing departure of p from .5, and are perfectly correlated in rank, and they are therefore equivalent in the sense discussed by Knapp et al. (1994). In particular, it is possible to find a critical threshold, denoted as c_{ML}, for $\Lambda_{\pi \neq .5}$, and another one, c_{TD}, for χ^2_{TD}, such that the tests derived from the two statistics have identical sizes (and consequently equal power). However, this equivalence does not necessarily imply the equality of the power of the tests when the *same* critical threshold is used for the two statistics (i.e., when $c_{ML} = c_{TD}$). This corresponds to the common situation in which an asymptotic threshold is considered; for example, for a .05 type I error, the critical value of 3.84 is used for both $\Lambda_{\pi \neq .5}$ and χ^2_{TD}. In this case, to determine the statistic producing the highest value for a given p, we are interested in the difference between $\Lambda_{\pi \neq .5}$ and χ^2_{TD}, denoted as "$d(p)$," which is equal to

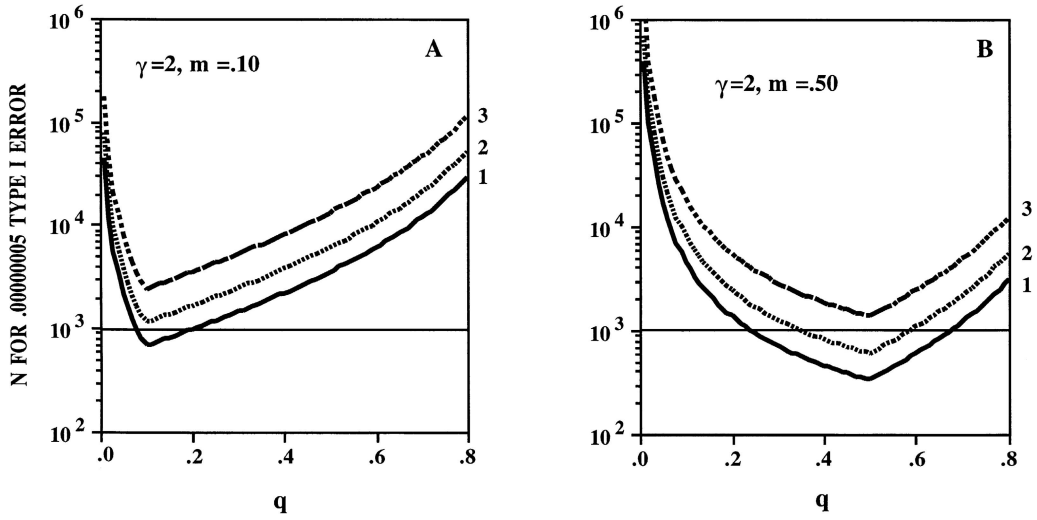

Figure 1 *N* (log scale) required for detection of association, for a type I error of 5×10^{-8} (genomewide-screening strategy) and a power of 80%, according to q, for $\gamma = 2$. The curves are drawn for $m = .10$ (*A*) and $m = .50$ (*B*), under the assumption that linkage disequilibrium is equal to its maximum, δ_{max} (curve 1), $.75\delta_{max}$ (curve 2), and $.5\delta_{max}$ (curve 3).

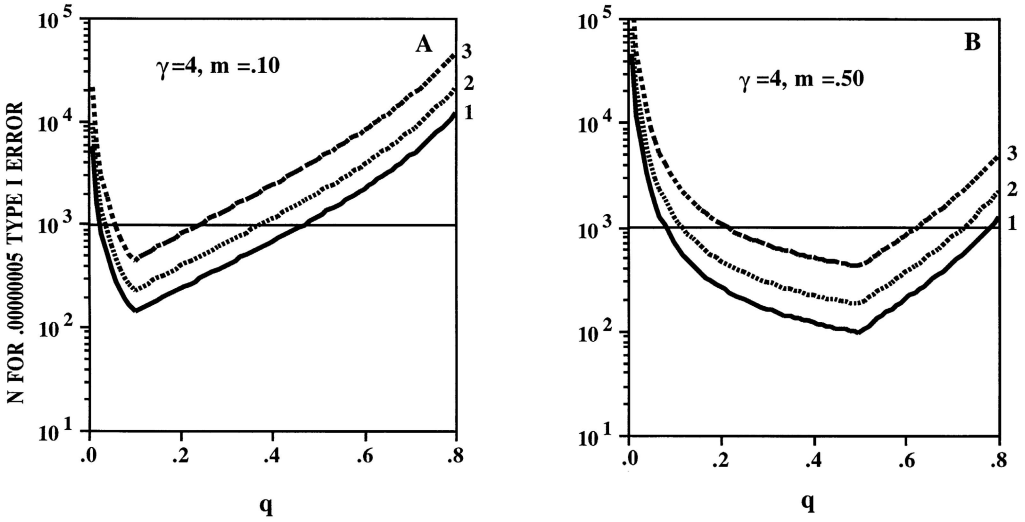

Figure 2 *N* (log scale) required for detection of association, for a type I error of 5×10^{-8} (genomewide-screening strategy) and a power of 80%, according to q, for $\gamma = 4$. The curves are as described in figure 1.

$$d(p) = 2n[pLn(p) + (1-p) \times Ln(1-p) - Ln(.5) - 2(p-.5)^2] .$$

The second derivative of $d(p)$, which is equal to $2n\{[p(1-p)]^{-1} - 4\}$, is a positive function for $p \neq .5$, since, for $p \neq .5$, $p(1-p)$ is always $<.25$. Consequently, its primitive, which is the first derivative of $d(p)$ and is equal to $2n[Ln(p) - Ln(1-p) - 4p + 2]$, is an increasing function as p departs from .5 and is also positive, since this first derivative is equal to 0 for $p = .5$. By the same reasoning, $d(p)$ is found to be a positive, increasing function as p departs from .5. This result demonstrates that, for $p \neq .5$, $\Lambda_{\pi \neq .5}$ is always $> \chi^2_{TD}$. As an example, we consider the data for insulin-dependent diabetes mellitus and the insulin-gene region, presented in Spielman et al.'s (1993) table 5, where $b = 78$ and $c = 46$. The analysis by classic TDT provided a χ^2_{TD} of 8.26, whereas $\Lambda_{\pi \neq .5}$ is equal to 8.35. This is not, of course, a large difference, but it makes the point that, when asymptotic thresholds are used, the ML-TDT is expected to be slightly more powerful that the McNemar test.

We also compare the numbers of families that the ML-TDT requires for detection of an association in different situations versus those given in a recent paper by Risch and Merikangas (1996), who used the classic McNemar test. We use the same genetic model as was used by Risch and Merikangas (1996), which includes (1) a disease locus with two alleles, A and a, with population frequencies q and $1 - q$, and a multiplicative model with genotypic relative risk γ and γ^2 for Aa and AA subjects, respectively; and (2) a closely linked diallelic marker (recombination fraction 0) with alleles M_1 and M_2 with respective frequencies m and $1 - m$. For reasons of comparability, we consider the one-sided $\Lambda_{\pi \neq .5}$ test and denote as "Z_α" and "$Z_{1-\beta}$" the standard normal deviates corresponding to a type I error of α and a power of $1 - \beta$, respectively (e.g., $Z_{1-\beta} = .842$ to achieve a power of 80%). If it is assumed that, under H_1, p follows a normal distribution with expectation p_1 and variance $\sigma^2 = p_1(1-p_1)/n$, then the number of heterozygous M_1M_2 parents, n, is obtained by solving the following equation:

$$2n[p_\beta Ln(p_\beta) + (1-p_\beta) \times Ln(1-p_\beta) - Ln(.5)] = (Z_\alpha)^2 ,$$

where $p_\beta = p_1 - \sigma Z_{1-\beta}$. This equation, which has no simple analytical solution, can be solved by a straightforward iterative procedure. From n, the number of necessary families, denoted as "N," is obtained as $N = n/2h$, where h, the probability that a parent with an affected child is M_1M_2, is computed by use of formulas developed by Risch and Merikangas (1996). For example, when $\gamma = 4$ and α is fixed at 5×10^{-8} ($Z_\alpha = -5.33$), we obtain, with the ML-TDT, $N = 139$ for $q = m = .10$ and $N = 96$ for $q = m = .50$, compared with 150 and 103, respectively, for the classic TDT (Risch and Merikangas 1996); the corresponding numbers for $\gamma = 2$ are 680 and 334 for the ML-TDT, compared with 695 and 340.

However, as we have pointed out in a comment elsewhere (Müller-Myhsok and Abel 1997), all computations performed by Risch and Merikangas (1996) were

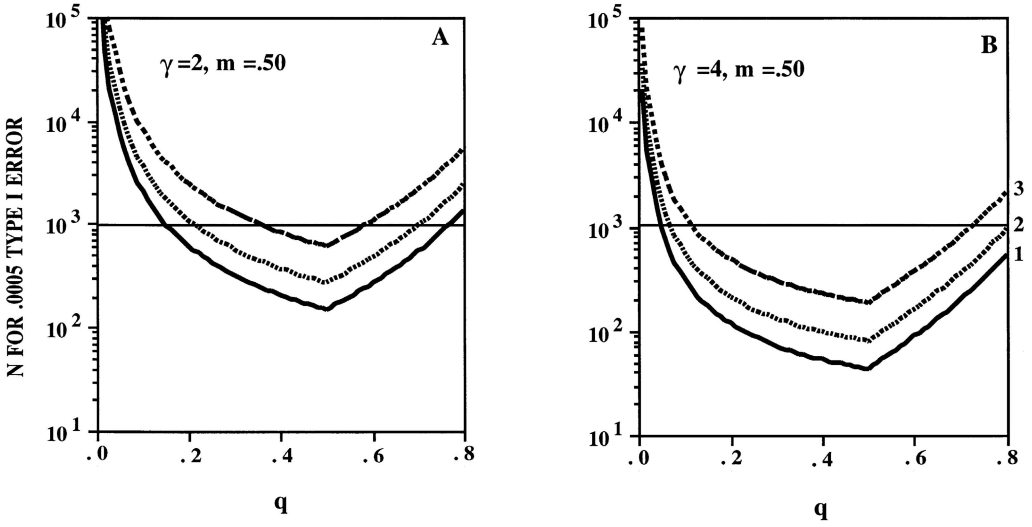

Figure 3 *N* (log scale) required for detection of an association, for a type I error of 5×10^{-4} (candidate-gene strategy) and a power of 80%, according to *q*, for $\gamma = 2$ (*A*) and $\gamma = 4$ (*B*). The curves are drawn for $m = .50$, under the assumption that linkage disequilibrium is equal to δ_{max}, (curve 1), $.75\delta_{max}$ (curve 2), and $.5\delta_{max}$ (curve 3).

based on the optimal assumption that the analyzed allele is the disease allele itself, whereas a more common situation is the analysis of polymorphisms that have a low prior probability of being the disease allele. In this case, we showed by theoretical means that the power of TDT is highly dependent not only on the linkage disequilibrium between the disease allele and the analyzed allele but also on the relative frequencies of both these alleles. In the present paper we illustrate these findings when using the ML-TDT. The coefficient of linkage disequilibrium, δ, is defined as $\text{freq}(AM_1) - qm$, and the maximum value of δ, denoted as "δ_{max}," is reached when $\text{freq}(AM_1)$ is the lowest of the two frequencies *m* and *q*. When the formulas of Müller-Myhsok and Abel (1997) are used, p_1, the expectation of *p*, and *h*, the proportion of heterozygous parents, have the following expressions:

$$p_1 = [1 + (\gamma - 1)\alpha_1]/[2 + (\gamma - 1)(\alpha_1 + \alpha_2)] ,$$

where $\alpha_1 = q + (\delta/m)$ and $\alpha_2 = q - [\delta/(1 - m)]$, and

$$h = u/\{u + m^2[1 + (\gamma - 1)\alpha_1] + (1 - m)^2[1 + (\gamma - 1)\alpha_2]\} ,$$

where $u = m(1 - m)[2 + (\gamma - 1)(\alpha_1 + \alpha_2)]$.

In the context of a genomewide search, as proposed by Risch and Merikangas (1996)—that is, $\alpha = 5 \times 10^{-8}$—figures 1 and 2 show the variations of *N* as a function of *q* for two values of *m* (.10 and .50), with various strengths of linkage disequilibrium. When $\gamma = 2$ (fig. 1), the required sample size is generally significantly >1,000 families, except for situations close to the optimal case ($m = q$ and $\delta = \delta_{max}$), representing not only a technological challenge but also a major fieldworking effort. A more pronounced gene effect ($\gamma = 4$; fig. 2) allows detection of an association for a larger range of disease-allele frequencies in samples of realistic size (e.g., for $m = .5$, a sample of 1,000 families will lead to the detection of deleterious alleles having frequencies .12–.72 when δ is $\geqslant$75% of δ_{max}). We also examined the strategy of a candidate-gene approach investigating 10 genes with five diallelic markers per gene, which leads to 100 one-sided tests and, consequently, to a required nominal type I error of .0005 for each test, for an overall type I error of .05. Results for $m = .5$ are presented in figure 3 and show that a sample of 1,000 families will allow detection of most alleles when $\gamma = 4$ and $\delta \geqslant .75\delta_{max}$ and also will allow detection of a large number of alleles when $\gamma = 2$, either having a frequency close to *m* or presenting a δ close to δ_{max}. Therefore, at present, unless there is a high chance that the disease allele is among the alleles analyzed in a genomewide search, the candidate-gene approach is a more promising strategy for TDT association studies. Alternatively, the initial use of a lower critical threshold in a genomewide setting (e.g., use of a two-stage strategy, as is commonly done in linkage analysis) can indicate follow-up regions of interest to be tested and can reduce both the genotyping efforts and the necessary sample sizes. It is also important to note that the power of such studies can be greatly influenced by both the dominance model at the disease locus and the resulting genotypic relative risks (Camp 1997). In any case, the ML-TDT appears to be an in-

teresting alternative that can take into account multiallelic markers (Terwilliger 1995) and that easily can be extended to introduce different π parameters, according to some measured factors such as parent gender.

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