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## LETTER TO THE EDITOR

# "Power Comparisons for Genotypic vs. Allelic TDT Methods with >2 Alleles"

**To the Editor:** Family-based association methods have become increasingly popular tools for both fine mapping and candidate gene association studies. Of such methods, the transmission disequilibrium test (TDT) has received the most attention [Spielman et al., 1993; Risch and Merikangas, 1996]. This test was originally proposed as an "allelic" test of linkage and association which compares transmitted to nontransmitted alleles in parents of cases in a matched analysis [Spielman et al., 1993]. Several have pointed out that the TDT can also be framed as a genotypic test of linkage and association [Self et al. 1991; Schaid, 1999], similar to the genotype relative risk modeling of Schaid and Sommer [1993], by comparing the case's transmitted genotype to the set of all possible genotypes for that individual, given the parental genotypes. This "genotypic" TDT allows for assessment of genotype relative risks and modeling of particular risk relationships, while the allelic version must make an implicit assumption of multiplicative effects of alleles. Further, this framework allows analysis of individuals, rather than considering chromosomes as the unit of observation, which provides a natural setting for the inclusion of covariates and tests for possible interaction [Schaid and Sommer, 1993]. Schaid [1999] presented a likelihood framework for the genotypic TDT, allowing likelihood ratio (LR) testing, and showed modeling situations in which this LR test method outperforms the allelic score and LR test versions, using diallelic markers [Schaid and Sommer, 1993]. Specifically, the "genotypic" LR test provided more statistical power across recessive models and for dominant models with frequent risk alleles [Schaid and Sommer, 1993].

Recently, there has been a great deal of interest in haplotype-based association methods, considering the potential increases in statistical power to detect a disease-associated variant by considering alleles at several markers across a region

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simultaneously, rather than a single marker allele in linkage disequilibrium (LD) with an unobserved high-risk allele [Daly et al., 2001; Fallin et al., 2001]. However, most combined-locus systems (haplotypes) contain more than two common ($>1\%$) haplotypes [Daly et al., 2001], creating difficulty for both allelic and genotypic TDT strategies due to the numerous categories. The main difficulty lies in the need to either model effects of all possible haplotypes simultaneously, or sequentially evaluate the effect and significance of each individual haplotype separately. The first strategy can have limited power due to the large number of degrees of freedom, while the second must be corrected for multiple comparisons. This problem is compounded when dealing with genotypes, where $h(h+1)/2$ categories are possible (for h distinct haplotypes).

For a diallelic system, Schaid and Sommer [1993] showed the advantages of a likelihood-based genotypic TDT framework compared to the traditional allelic version. In epidemiologic studies, the genotypic TDT is intuitively appealing, given the focus on the individual as the observed unit rather than on single alleles, because covariates can be incorporated easily in this setting. However, it is important to extend the diallelic genotype TDT power findings of Schaid and Sommer [1993] to situations for multiple alleles (and therefore multiple haplotypes) to better develop an efficient testing strategy for haplotype-based tests.

We performed simulations to compare allelic and genotypic versions of this test for scenarios of multiple alleles under several genetic models, following the simulation models of Schaid [1999]. Specifically, we compared two ''allelic'' tests: A1, the multiallelic score test [Spielman and Ewens, 1996]; and A2, the LR test based on conditional logistic modeling, with 1-1 matching of transmitted-nontransmitted alleles [Maestri et al., 1997], with the ''genotypic'' LR test (G) based on conditional logistic modeling with 3-1 matching of offspring-pseudo-sibling genotypes [Schaid, 1999]. Specific scenarios used to simulate data are shown in Table I and include multiplicative, additive, dominant, and recessive risk models for different marker and trait allele frequencies.

**TABLE I. Simulating Scenarios**[a]

| Simulating scenario | Pr(A) | $r_1$ | $r_2$ | Pr(M1) | No. of families |
|---|---|---|---|---|---|
| 1. (multiplicative) | 0.5 | 2 | 4 | 0.5 | 103 |
| 2. (additive) | | 2 | 3 | | 183 |
| 3. (dominant) | | 4 | 4 | | 209 |
| 4. (recessive) | | 1 | 2 | | 295 |
| 5. (multiplicative) | 0.1 | 2 | 4 | 0.1 | 209 |
| 6. (additive) | | 2 | 3 | | 243 |
| 7. (dominant) | | 2 | 2 | | 288 |
| 8. (recessive) | | 1 | 9 | | 315 |

[a]Pr(A), frequency of high-risk allele A; $r_1$, relative risk for heterozygotes (ratio of penetrance of Aa vs. penetrance of aa); $r_2$, relative risk for homozygotes (ratio of penetrance of AA vs. penetrance of aa); Pr(M1), frequency of marker allele 1; recombination rate between M and A = 0; linkage disequilibrium is set to maximum between marker allele 1 and high-risk allele, 0 for alleles 2 to n−1. Scenarios 1–4 assume equal marker allele frequencies. Scenarios 5–8 assume the marker allele frequency is 0.1 except for the $(n-1)^{th}$ allele. Simulations were generated under random mating assumption.

**TABLE II. Type I Error Rates and Power for Each TDT Method With 2, 3, 5, 7, and 10 Alleles Per Locus[a]**

| | | Type 1 Error | | | Power | | |
|---|---|---|---|---|---|---|---|
| Scenario | No. alleles | A1 | A2 | G | A1 | A2 | G |
| 1 | 2 | 0.0075 | 0.0080 | 0.0115 | 0.8120 | 0.8165 | 0.7110 |
| | 3 | 0.0120 | 0.0135 | 0.0095 | 0.4605 | 0.4785 | 0.3250 |
| | 5 | 0.0120 | 0.0135 | 0.0175 | 0.3600 | 0.3715 | 0.2080 |
| | 7 | 0.0085 | 0.0105 | 0.0300 | 0.1745 | 0.1800 | 0.0600 |
| | 10 | 0.0055 | 0.0055 | 0.0995 | 0.0780 | 0.0870 | 0.0980 |
| 2 | 2 | 0.0095 | 0.0105 | 0.0115 | 0.7860 | 0.7895 | 0.7460 |
| | 3 | 0.0115 | 0.0120 | 0.0145 | 0.4640 | 0.4675 | 0.3410 |
| | 5 | 0.0050 | 0.0065 | 0.0100 | 0.1690 | 0.1810 | 0.0880 |
| | 7 | 0.0050 | 0.0060 | 0.0125 | 0.0825 | 0.0920 | 0.0505 |
| | 10 | 0.0080 | 0.0105 | 0.0420 | 0.0430 | 0.0465 | 0.0735 |
| 3 | 2 | 0.0090 | 0.0090 | 0.0060 | 0.7980 | 0.7995 | 0.9950 |
| | 3 | 0.0060 | 0.0060 | 0.0080 | 0.3875 | 0.3925 | 0.5905 |
| | 5 | 0.0090 | 0.0105 | 0.0120 | 0.1240 | 0.1260 | 0.1240 |
| | 7 | 0.0085 | 0.0090 | 0.0150 | 0.0560 | 0.0595 | 0.0505 |
| | 10 | 0.0080 | 0.0095 | 0.0410 | 0.0270 | 0.0305 | 0.0675 |
| 4 | 2 | 0.0080 | 0.0080 | 0.0095 | 0.7900 | 0.7915 | 0.9075 |
| | 3 | 0.0095 | 0.0010 | 0.0070 | 0.4650 | 0.4655 | 0.4865 |
| | 5 | 0.0095 | 0.0095 | 0.0115 | 0.1880 | 0.1925 | 0.1205 |
| | 7 | 0.0110 | 0.0135 | 0.0120 | 0.0800 | 0.0825 | 0.0505 |
| | 10 | 0.0100 | 0.0110 | 0.0280 | 0.0355 | 0.0395 | 0.0385 |
| 5 | 2 | 0.0110 | 0.0110 | 0.0120 | 0.8065 | 0.8120 | 0.7055 |
| | 3 | 0.0105 | 0.0100 | 0.0165 | 0.6460 | 0.6935 | 0.5385 |
| | 5 | 0.0120 | 0.0115 | 0.0160 | 0.5865 | 0.6010 | 0.3425 |
| | 7 | 0.0100 | 0.0125 | 0.0225 | 0.4950 | 0.5025 | 0.2350 |
| | 10 | 0.0105 | 0.0125 | 0.0500 | 0.4300 | 0.4265 | 0.2380 |
| 6 | 2 | 0.0080 | 0.0080 | 0.0130 | 0.7900 | 0.7910 | 0.7060 |
| | 3 | 0.0125 | 0.0095 | 0.0105 | 0.6545 | 0.7075 | 0.5720 |
| | 5 | 0.0130 | 0.0120 | 0.0125 | 0.5635 | 0.5835 | 0.3460 |
| | 7 | 0.0100 | 0.0100 | 0.0160 | 0.4750 | 0.4790 | 0.2635 |
| | 10 | 0.0130 | 0.0110 | 0.0375 | 0.4180 | 0.4165 | 0.2055 |
| 7 | 2 | 0.0135 | 0.0140 | 0.0105 | 0.7975 | 0.8015 | 0.7955 |
| | 3 | 0.0100 | 0.0085 | 0.0075 | 0.6600 | 0.7190 | 0.6195 |
| | 5 | 0.0160 | 0.0160 | 0.0075 | 0.5650 | 0.5875 | 0.4070 |
| | 7 | 0.0080 | 0.0090 | 0.0205 | 0.4715 | 0.4850 | 0.2795 |
| | 10 | 0.0115 | 0.0120 | 0.0255 | 0.4225 | 0.4180 | 0.2165 |
| 8 | 2 | 0.0145 | 0.0145 | 0.0095 | 0.7945 | 0.7970 | 0.9980 |
| | 3 | 0.0080 | 0.0095 | 0.0120 | 0.6645 | 0.7125 | 0.9880 |
| | 5 | 0.0125 | 0.0115 | 0.0105 | 0.5915 | 0.6135 | 0.9510 |
| | 7 | 0.0120 | 0.0135 | 0.0195 | 0.4980 | 0.4980 | 0.8885 |
| | 10 | 0.0100 | 0.0110 | 0.0295 | 0.4705 | 0.4640 | 0.7445 |

[a]2000 simulations, significance level = 0.01.

Our results are shown in Table II. The type I error rates for each test were within reasonable limits for most scenarios, suggesting the appropriateness of the chi-square approximation for each of these tests. For diallelic loci, our results were similar to those of Schaid [1999], demonstrating the increased power of the genotypic

TDT for recessive models. Dominant models for a common marker allele also showed more power in the genotypic setting. However, as the number of alleles per locus increases, the relative increase in statistical power for the genotype-based test decreased. In fact, for scenarios involving $\geq 5$ alleles per locus, the allelic framework was more powerful.

This point is worth noting, as it has consequences for haplotype-based TDT methods where $> 5$ haplotypes are likely for many situations. While the genotypic framework allows greater flexibility in modeling and can more readily include covariates, this modeling may greatly reduce power for multiple allele (or haplotype) systems due to increased degrees of freedom. This reduction in power may be too great to justify the increased flexibility in modeling. Pursuit of permutation approaches to estimate empirical *P*-values for each test statistic may provide a solution, and comparisons of statistical power for allelic vs. genotypic tests based on empirical *P*-values in situations with multiple alleles are warranted. In any case, each investigator should consider the number of additional alleles (haplotypes), the appropriateness of a multiplicative assumption, and the importance of additional covariates when choosing the best testing approach for a particular project.

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