Letters to the Editor

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A Program for the Monte Carlo Evaluation of Significance of the Extended Transmission/Disequilibrium Test

To the Editor:

The extended transmission/disequilibrium test (ETDT) package (Sham and Curtis 1995*a*) calculates three likelihood ratio transmission/disequilibrium test (TDT) statistics for a multiallelic marker: an allelewise statistic that assumes an allele-specific effect on transmission distortion from heterozygous parents, a genotypewise statistic that allows an independent effect for each parental genotype, and a goodness-of-fit statistic that assesses the adequacy of the allelewise model compared with the genotypewise model. Since a marker with m alleles will have $m(m-1)/2$ possible heterozygous genotypes, there may be very few observations of certain genotypes when m is large, so that P values based on asymptotic χ^2 distributions may be inaccurate, especially for the latter two tests. The χ^2 approximation is more likely to be adequate for the allelewise test unless there are very few observations or very many alleles. Since we have proposed the allelewise test to be the most useful test in most circumstances, we did not at first implement a Monte Carlo approach (e.g., Sham and Curtis 1995*b;* Cleves et al. 1997; Kaplan et al. 1997*a;* Miller 1997) in the ETDT program to obtain empirical P values. We now believe that it is useful to have such an option, and we have therefore extended the ETDT package to include a program called "MCETDT," which carries out such a procedure to obtain empirical P values for all three tests.

MCETDT works by taking input to the LRTDT program of the ETDT package and then generating transmissions at random according to the null hypothesis of equal transmission, conditional on the observed parental genotypes. The three statistics are then calculated by LRTDT in the usual fashion for multiple replicates of simulated data, and the proportion of times each statistic is equal to or greater than the corresponding one from the real data provides an empirical P value for that test. If n replicates are used to estimate this P value, then the standard error (SE) of the estimate is $\sqrt{P(1-P)/n}$.

Example application. In a large collaborative linkage study of schizophrenia, data on transmissions of alleles at D22S278 to subjects affected with schizophrenia were available in 574 families (Vallada et al. 1998). Asymptotic and empirical results based on 10,000 replicates were calculated by use of MCETDT and, for comparison, the Spielman-Ewens (Spielman and Ewens 1996) and Stuart (1955) statistics were also calculated by use of MATLAB.

The results are shown in table 1; the asymptotic P values for the genotypewise and goodness-of-fit tests are anticonservative. Nevertheless, the empirical P value for the genotypewise test of ETDT is more highly significant than the results of any other method of analysis and hence provides the strongest support for transmission distortion.

There have been extensive discussions regarding the analysis of multiallelic TDT data (e.g., Kaplan et al. 1997*a,* 1997*b;* Miller 1997; Sham 1997; Lazzeroni and Lange 1998). Monte Carlo methods provide a useful way to obtain empirical P values for tests conducted on sparse data sets. (The new program is provided as part of the ETDT package, which is freely available at http://www.gene.ucl.ac.uk/users/dcurtis/software.html).

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Table 1

Comparison of Different TDT Statistics Applied to Schizophrenia and D22S278

Type	χ^2	df	Asymptotic *P* Value	Empirical *P* Value	SE (*P*)
ETDT:					
Allelewise	22.025	10	.0151	.0142	.0012
Genotypewise	66.228	30	.0002	.0009	.0003
Goodness-of-fit	44.203	20	.0015	.0085	.0009
MATLAB:					
Spielman-Ewens	22.358	10	.0134	.0115	.0011
Stuart	18.976	10	.0406	.0202	.0014

References

Cleves MA, Olson JM, Jacobs KB (1997) Exact transmission/disequilibrium tests with multiallelic markers. Genet Epidemiol 14:337–347

Kaplan NL, Martin ER, Weir BS (1997*a*) Power studies for the transmission/disequilibrium tests with multiple alleles. Am J Hum Genet 60:691–702

——— (1997*b*) Reply to Sham. Am J Hum Genet 61:778

Lazzeroni LC, Lange K (1998) A conditional inference framework for extending the transmission/disequilibrium test. Hum Hered 48:67–81

Mathworks, Inc. (1993) MATLAB version 4.0, Natick, Massachusetts

Miller MB (1997) Genomic scanning and the transmission/disequilibrium test: analysis of error rates. Genet Epidemiol 14:851–856

Sham PC, Curtis D (1995*a*) An extended transmission/disequilibrium test (TDT) for multiallelic marker loci. Ann Hum Genet 59:323–336

——— (1995*b*) Monte Carlo tests for associations between disease and alleles at highly polymorphic loci. Ann Hum Genet 59:97–105

Sham PC (1997) Transmission/disequilibrium tests for multiallelic loci. Am J Hum Genet 61:774–778

Spielman RS, Ewens WJ (1996) The TDT and other family-based tests for linkage disequilibrium and association. Am J Hum Genet 59:983–989

Stuart A (1955) A test of homogeneity of the marginal distribution in a two-way classification. Biometrika 42:412–416

Vallada H, Curtis D, Sham P, Kunugi H, Zhao JH, Murray R, McGuffin P, et al (1998) A transmission disequilibrium and linkage analysis of D22S278 marker alleles in 574 families: further support for a susceptibility locus for schizophrenia at 22q12. Schizophr Res 32:115–121

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