Robust TDT-type Candidate-Gene Association Tests

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In studies of association between genetic markers and a disease, the transmission disequilibrium test (TDT) is a well-established procedure. It avoids spurious association due to population stratification by using non-transmitted parental alleles as controls. The power of the TDT test depends on the underlying genetic model. Indeed it is optimal when an additive model holds. Related methods have been obtained for a given mode of inheritance (e.g., dominant or recessive). Quite often, however, the true model is unknown and selection of a single method of analysis is problematic since use of any one optimal test usually leads to a loss of power under another model. The general approach of efficiency robustness has suggested two types of robust procedures, which we apply to TDT-type association tests. When the plausible range of alternative models is wide (e.g. dominant through recessive) our results indicate that the maximum of several test statistics has good power under all genetic models. In the situations where the set of possible models can be narrowed (e.g., dominant through additive) a simple linear combination (MERT) performs well. These results are illustrated in the following two tables, where the disease penetrances for individuals with zero, one or two copies of allele A are denoted by f_0, f_1 and f_2, respectively. The full paper is available from the authors.

Table I Empirical power estimates: HWE holds, p=.2 (sample size 100, 5000 replications)

	Test								
Under model	Z_{DOM}	Z_{REC}	Z_{ADD} TDT	MERT (D,R,T)	MAX (D,R,T)	MERT (D,T)	MAX (D,T)	MERT (R,T)	MAX (R,T)
Null	.049	.047	.049	.050	.046	.049	.050	.048	.051
DOM[1]	.812	.068	.720	.535	.734	.790	.790	.356	.625
REC[2]	.067	.862	.492	.663	.797	.233	.429	.787	.821
ADD[3]	.778	.258	.811	.734	.756	.820	.812	.613	.732
MUL[4]	.669	.433	.799	.775	.743	.762	.778	.715	.749

[1] Model Dominant f0= .02 f1=.045 f2=.045
[2] Model Recessive f0=.02 f1=.02 f2=.077
[3] Model Additive f0=.02 f1=.0425 f2=.065
[4] Model Multiplicative f0=.02 f1=.038 f2=.0722

Table II Empirical power estimates: HWE does not hold an equal mixture of populations with p=.2 and p=.01, (sample size 100, 5000 replications)

	Test								
Under model	Z_{DOM}	Z_{REC}	Z_{ADD} TDT	MERT (D,R,T)	MAX (D,R,T)	MERT (D,T)	MAX (D,T)	MERT (R,T)	MAX (R,T)
Null	.051	.044	.052	.047	.049	.052	.053	.047	.044
DOM[1]	.800	.065	.703	.509	.719	.778	.777	.330	.613
REC[2]	.057	.813	.448	.605	.738	.217	.391	.737	.765
ADD[3]	.782	.229	.801	.717	.764	.821	.814	.600	.732
MUL[4]	.587	.372	.726	.699	.662	.692	.698	.635	.669

[1] Model Dominant f0= .02 f1=.053 f2=.053
[2] Model Recessive f0=.02 f1=.02 f2=.1
[3] Model Additive f0=.02 f1=.051 f2=.082
[4] Model Multiplicative f0=.02 f1=.042 f2=.0882

Key words: association tests, transmission disequilibrium, efficiency robust tests.