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)

<table>
<thead>
<tr>
<th>Under model</th>
<th>Test</th>
<th>Test</th>
<th>Test</th>
<th>Test</th>
<th>Test</th>
<th>Test</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( Z_{\text{DOM}} )</td>
<td>( Z_{\text{REC}} )</td>
<td>( Z_{\text{ADD}} )</td>
<td>( \text{MERT(D,R,T)} )</td>
<td>( \text{MAX(D,R,T)} )</td>
<td>( \text{MERT(D,T)} )</td>
<td>( \text{MAX(D,T)} )</td>
</tr>
<tr>
<td>Null</td>
<td>.049</td>
<td>.047</td>
<td>.049</td>
<td>.050</td>
<td>.046</td>
<td>.049</td>
<td>.050</td>
</tr>
<tr>
<td>DOM(^1)</td>
<td>.812</td>
<td>.068</td>
<td>.720</td>
<td>.535</td>
<td>.734</td>
<td>.790</td>
<td>.870</td>
</tr>
<tr>
<td>REC(^2)</td>
<td>.067</td>
<td>.862</td>
<td>.492</td>
<td>.663</td>
<td>.797</td>
<td>.233</td>
<td>.429</td>
</tr>
<tr>
<td>ADD(^3)</td>
<td>.778</td>
<td>.258</td>
<td>.811</td>
<td>.734</td>
<td>.756</td>
<td>.820</td>
<td>.812</td>
</tr>
<tr>
<td>MUL(^4)</td>
<td>.669</td>
<td>.433</td>
<td>.799</td>
<td>.775</td>
<td>.743</td>
<td>.762</td>
<td>.778</td>
</tr>
</tbody>
</table>

\(^1\) Model Dominant \( f_0=.02 \) \( f_1=.045 \) \( f_2=.045 \)

\(^2\) Model Recessive \( f_0=.02 \) \( f_1=.02 \) \( f_2=.077 \)

\(^3\) Model Additive \( f_0=.02 \) \( f_1=.0425 \) \( f_2=.065 \)

\(^4\) Model Multiplicative \( f_0=.02 \) \( f_1=.038 \) \( f_2=.0722 \)
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)

<table>
<thead>
<tr>
<th>Test</th>
<th>Under model</th>
<th>( Z_{DOM} )</th>
<th>( Z_{REC} )</th>
<th>( Z_{ADD} )</th>
<th>MERT ( (D,R,T) )</th>
<th>MAX ( (D,R,T) )</th>
<th>MERT ( (D,T) )</th>
<th>MAX ( (D,T) )</th>
<th>MERT ( (R,T) )</th>
<th>MAX ( (R,T) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>.051</td>
<td>.044</td>
<td>.052</td>
<td>.047</td>
<td>.049</td>
<td>.052</td>
<td>.053</td>
<td>.047</td>
<td>.047</td>
<td>.044</td>
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<tr>
<td>DOM(^1)</td>
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<td>.065</td>
<td>.703</td>
<td>.509</td>
<td>.719</td>
<td>.777</td>
<td>.777</td>
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<td>.613</td>
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</tr>
<tr>
<td>REC(^2)</td>
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<td>.813</td>
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<td>.605</td>
<td>.738</td>
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<td>.391</td>
<td>.737</td>
<td>.765</td>
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<tr>
<td>ADD(^3)</td>
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<td>.814</td>
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<td>.732</td>
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<tr>
<td>MUL(^4)</td>
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<td>.372</td>
<td>.726</td>
<td>.699</td>
<td>.662</td>
<td>.692</td>
<td>.698</td>
<td>.635</td>
<td>.669</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Model Dominant \( f_0 = .02 \) \( f_1 = .053 \) \( f_2 = .053 \)
\(^2\) Model Recessive \( f_0 = .02 \) \( f_1 = .02 \) \( f_2 = .1 \)
\(^3\) Model Additive \( f_0 = .02 \) \( f_1 = .051 \) \( f_2 = .082 \)
\(^4\) Model Multiplicative \( f_0 = .02 \) \( f_1 = .042 \) \( f_2 = .0882 \)

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