Letters to the Editor

The Sib Transmission/Disequilibrium Test is a Mantel-Haenszel Test

To the Editor:

Spielman and Ewens's (1998) proposed extension of the transmission/disequilibrium test (TDT), using discordant sibships, provides a simple and elegant way to apply the TDT in instances in which parents are not available. It is easy to see that the adapted test, called the "sib TDT" (S-TDT), is numerically equivalent to a Mantel-Haenszel test of trend, also known as the "Mantel extension test" (Rosner 1995).

The original Mantel-Haenszel test is used routinely in matched case-control studies, to test for association between disease and exposure. When exposure is expressed as a quantitative risk factor with C levels, the Mantel extension test allows the investigator to obtain a 1-df test against the alternative of a monotone trend. For each matched set, a 2 × C table classifying subjects according to disease and exposure status is formed. The statistic is determined by assigning the columns quantitative values corresponding to exposure level. The statistic also may be derived as a score test for no association within each matched set, by use of a model for the log odds of disease, which is linear in exposure level.

To obtain the S-TDT by use of the Mantel extension test, sibship is used as the stratifying variable, and for each sibship a 2 × 3 table cross-classifying sibs on the basis of disease status and genotype is formed. The quantitative value of exposure that yields the S-TDT assigns to each genotype the number of putative disease-associated alleles that a sib has (i.e., 2, 1, or 0) for genotypes AA, AB, or BB.

The advantages of viewing the S-TDT as a Mantel extension test are threefold. First, the test is already widely available on commercial software. For example, SAS currently implements the Mantel extension test as part of its Cochran-Mantel-Haenszel procedure. This version of the test allows user-specified scores for the levels of the quantitative variable but does not provide a continuity correction. Another program, StatXact, provides an exact P value for the Mantel extension test, as well as the asymptotic P value.

Second, it immediately is obvious how to use the test with other genetic models. For example, for an arbitrary genetic model, an investigator may want to use the 2-df Mantel-Haenszel test, which makes no assumption about how risk varies with number of A alleles. To test a dominant model, a value of 1 would be assigned to genotype AA or AB and a value of 0 to genotype BB; to test a recessive model, exposure values of 1 for AA and of 0 for all other genotypes would be used.

Third, if the marker is actually a candidate gene, the investigator may wish to estimate risk ratios. Collapsing over sibships and estimating risk ratios by use of the 2 × 3 margin results in biased estimates, which may be confounded because sibships may come from different populations with different disease risks and allele distributions. Instead, to estimate risk ratios, a Mantel-Haenszel estimate of odds ratio—or, in the general case, conditional logistic regression (Breslow and Day 1980)—should be used.

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