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INVITED EDITORIAL
The TDT and Other Family-Based Tests for Linkage Disequilibrium and Association

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The transmission/disequilibrium test (TDT) was introduced several years ago by Spielman et al. (1993) as a test for linkage between a complex disease and a genetic marker. The original intended use of the TDT was to test for linkage with a marker located near a candidate gene, in cases where disease *association* already had been found. However, even if prior evidence for association is absent, the TDT is valid and can be used to test any marker (or a set of markers) for which data are available from parents and one or more affected offspring.

Other tests that focus on association itself—but that, like the TDT, are applied to data from nuclear families—also have been proposed. In addition, several papers have appeared recently that discuss extensions and properties of these tests and of the TDT. Since the aim of both the TDT and the association tests is to locate genes that contribute to disease susceptibility, a number of questions about their differences have arisen. In this review, we compare the properties of the TDT with those of family-based tests of association, and we comment on issues regarding the use of these tests.

The Model and the Problem

The genetic model consists of both a locus D that contributes to disease susceptibility and a (possibly linked) marker locus M. The standard way to identify disease loci is to use classical (LOD) or nonparametric (affected-sib-pair [ASP]) methods to test for linkage with such a marker or a set of markers. It has been known for some time, however, that these methods may fail to detect a disease locus linked to a marker, even though the locus may be of biological significance (Cox et al. 1988; Spielman et al. 1989).

Even when standard linkage tests fail to provide evidence, however, a disease locus linked to the marker may be suggested sometimes by the presence of a "disease association," usually established by a case-control study. The underlying premise is that, if an association is found, it is likely to be due to linkage disequilibrium. (We use the term strictly to mean the presence of both linkage and association between marker and disease.) Since linkage disequilibrium is found only over very small map distances, close linkage between marker and disease susceptibility is implied. However, it is a well-known result of population genetics that admixture, heterogeneity, or stratification in a population can make it impossible to draw valid conclusions from a conventional case-control study, since these conditions ("population structure") can give rise to substantial association even for unlinked loci. Accordingly, we developed the TDT to test for linkage in the presence of association—that is, to distinguish this case (linkage disequilibrium) from associations that arise from population structure in the absence of linkage.

The TDT grew out of earlier proposals for avoiding incorrect conclusions from disease associations. Recognizing the problem, Falk and Rubinstein (1987) proposed the haplotype relative risk (HRR) as a family-based test for association, but they did not focus on linkage. Field et al. (1986), Thomson et al. (1989), and Thomson (1995) developed this approach further as a test for association. Ott's (1989) analysis of the mathematical model for the HRR was the point of departure for our development of the TDT, and Parsian et al. (1991) presented and applied a similar test without calling attention to its mathematical properties.

The TDT as a Test of Linkage: Theory and Practice

Conventional tests for linkage (e.g., LOD and ASP) require sibships with multiple offspring. In the TDT, by contrast, sibships with a single affected offspring can be used to detect linkage between disease and marker, provided that disease association with some particular marker allele is also present. We consider a marker locus M, with two alleles M_1 and M_2, and obtain genotypes for affected individuals and their parents. In the most general form, the data to be analyzed are numbers of

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"transmissions"; that is, for parents of each genotype (M_1M_1, M_1M_2, and M_2M_2), we determine the number of times that the M_1 allele or the M_2 allele was transmitted to an affected offspring. Spielman et al. (1993, table 2), denoted these counts as follows:

a, number of times that M_1M_1 transmits M_1 to affected offspring;
b, number of times that M_1M_2 transmits M_1 to affected offspring;
c, number of times that M_1M_2 transmits M_2 to affected offspring;
d, number of times that M_2M_2 transmits M_2 to affected offspring.

The counts may come from families that are simplex (i.e., data are from only one affected offspring), multiplex (data are from two or more affected sibs), or multigenerational; and the population may exhibit structure.

The null hypothesis of interest is that the marker and disease are unlinked. For any specified null hypothesis and a given set of data, there is a standard procedure ("Neyman-Pearson"; e.g., see Kendall and Stuart 1979) for obtaining the most powerful statistical test. Application of this procedure, for the present data and hypothesis, yields the TDT as the optimal test. When marker and disease are unlinked, data used in the TDT for related individuals are independent. It follows that data from a large pedigree may be used (if desired) by applying the TDT to each affected individual separately.

The TDT is carried out as follows. The result obtained by applying Neyman-Pearson theory dictates that we use data (observations *b* and *c*) only from those parents who are heterozygous M_1M_2; this result holds regardless of whether there is population structure. The TDT statistic is $(b - c)^2/(b + c)$; it tests for equal numbers of transmissions of M_1 and M_2 from heterozygous parents to affected offspring. If there is linkage between marker and disease, as well as allelic association, *b* and *c* will tend to differ in value. The statistical significance of the TDT is tested by χ^2 ("McNemar Test") or by the exact binomial test (see Spielman et al. 1993); a significant difference provides evidence that the marker is linked to the disease locus.

Note that, if there is no linkage, alleles of M segregate independently of disease, so the presence of association (e.g., from population structure) will not cause *b* to differ from *c*. Thus such an association would not lead us to infer linkage incorrectly. Similarly, when there is linkage but no association, there is also, on average, no tendency for *b* to differ from *c*. Thus the TDT can detect linkage only in the presence of association.

In contrast, when tests of linkage are carried out by ASP methods, there is no requirement for association, since linkage is then detected as departure from random assortment within families. However, ASP methods do require the presence of two or more affected sibs. This restriction, which poses practical difficulties for study of diseases for which multiplex families are rare, does not apply to the TDT. Table 1 presents and compares some relevant features of the ASP approach, the TDT, and another family-based test (the *a*ffected *f*amily *ba*sed *c*ontrols [AFBAC] method) discussed below.

Tests of Association: Additional Properties of the TDT

The AFBAC Method with the 2×2 Contingency Test

The TDT was conceived from the start as a means to locate disease genes by testing for *linkage*. In contrast, the AFBAC method (Thomson 1995) was proposed as a means to locate disease genes by the well-established approach of testing for disease *association*, but with family-based studies substituted for case-control studies (table 1, last column). Unlike the TDT, this method uses data from all parents, whether homozygous or heterozygous. In each parent of an affected child, one allele is the "transmitted" allele and one is the "untransmitted" allele. The rationale for this approach and the similar HRR procedure (Falk and Rubinstein 1987) is that the transmitted and untransmitted categories are matched with respect to population of origin. The expectation was that any differences observed might therefore escape the confounding effects of possible population structure. The statistical test used with AFBAC is the classical 2×2 contingency test comparing the proportion of M_1 alleles among those transmitted and the proportion of M_1 alleles among those not transmitted. The resulting statistic is treated as a χ^2 with 1 df.

It is true of both the TDT and the AFBAC method that the test has statistical power only when linkage and association are both present. It might therefore appear that the tests are equivalent—the TDT as a test for linkage in presence of association and the AFBAC as a test for association in presence of linkage. A main point of the present review is that this symmetrical situation does not hold; the two tests are not equally valid. (We use "valid" in the standard statistical sense, to mean "always having the claimed significance level,"—i.e., type I error.") We now discuss in detail the issue of validity. Since the validity of the tests depends in part on whether the family material is simplex or multiplex, we deal with these two possibilities separately.

Tests of Association in Simplex Families

Although designed as a test of linkage, the TDT is also valid as a test of association in simplex families, even if population structure is present. In contrast, if population structure is present, the contingency test used with the AFBAC method is not valid as a test of association, even for simplex families (see Ewens and Spielman 1995, eq. [12]; table 1).

Table 1

Comparison of Three Family-Based Tests for Locating Disease Genes

	ASP	TDT Hardy-Weinberg or Structured	AFBAC Hardy-Weinberg	AFBAC Structured
Linkage	Valid (multiplex by definition)	Valid (simplex and multiplex)	Not applicable (not valid)	
Association	Not applicable	Valid (simplex only)	Valid[a] (simplex only)	Not valid
Statistic	χ^2 or binomial test	χ^2 (McNemar) or binomial	2×2 contingency test	

[a] Valid test of association with AFBAC requires Hardy-Weinberg conditions for at least two generations.

The reason is given by Ewens and Spielman (1995). Suppose that there is in fact no association (i.e., the null hypothesis is true). If the sample of affected individuals is from a structured population, the TDT statistic is distributed as χ^2. In these circumstances, however, the contingency-test statistic does not have the χ^2 distribution attributed to it, since the denominator of the contingency statistic is inappropriately large, as shown by Ewens and Spielman (1995, p. 460, below eq. [12]). Therefore the test will not actually have the type I error chosen.

There is only one circumstance in which the contingency test *is* valid as a test of association. If there has been random mating in the population for at least two generations preceding that from which the affected offspring are drawn (so that population structure has been eliminated), the requirements for the contingency-test statistic to be distributed as χ^2 are met, and the test (with simplex data) is valid. Under these restrictive circumstances, the contingency test, as a test of association, is more powerful than the TDT (Ewens and Spielman 1995, table 4, lines 3 and 4); that is, it is more likely to detect an association if it exists. We stress, however, that, if it cannot be assumed that admixture has been absent for the previous two generations, the contingency test is not valid.

The question of validity cannot be separated completely from that of power. The contingency test has greater power than the TDT only when population structure is absent. When population structure is present, the inflated denominator of the contingency statistic leads to reduced power to detect association, if it exists. It follows that, if there is population structure, the contingency test will sometimes fail to detect a true association that is detected by the TDT. (Although the preceding explanation states the problem in principle, it is important to gauge the size of the effect in practice. The effect is illustrated by Ewens and Spielman [1995, table 4, lines 1 and 2].)

Tests of Association in Multiplex Families (Table 1, Middle Row)

Neither the contingency test nor the TDT is valid as a test of association if the families are multiplex (contain affected sibs) or have affected members in multiple generations. The problem is that any χ^2 test assumes independent observations for the data, and marker data sampled from related affected individuals are not necessarily independent, even when association is absent (i.e., under the null hypothesis for tests of association).

The lack of independence can be illustrated with an extreme example suggested by J. D. Terwilliger (personal communication). Consider one large pedigree with multiple affected members (a rare autosomal dominant, for simplicity) all descended from one affected founder individual. Suppose that we study a marker that shows no recombination with the disease. In this pedigree, all affected individuals receive the disease allele with the same marker allele (say M_1), the allele that was in coupling with disease in the founder. If the marker is highly polymorphic, there might be many informative (heterozygous) parents of affected individuals, and this single pedigree might show a great preponderance of transmissions of M_1. This is not evidence for linkage disequilibrium but is a consequence of studying a restricted sample of families, in this case just one.

A large value of the TDT or AFBAC-contingency statistic indicates association in the sample of meioses tested, but inferences about association in the population are valid only when the meioses tested are a random sample of independent meioses from the population. If multiplex families are included, not all meioses are independent, and we know of no valid simple test of association that uses the information from multiple related affected individuals. Of course, if only one trio of affected offspring and parents is used from such pedigrees or multiplex families, the situation is equivalent to that of simplex families, and the TDT is then valid as a test of association.

Use of AFBAC and the Contingency Statistic to Test for Linkage

The contingency test is not intended as a test of *linkage,* and, if incorrectly used for linkage, it will lead to an excess of false-positive results, even under circumstances (e.g., simplex families and no population structure) when it would be valid as a test of association. The

Table 2

Frequency with Which Contingency-Test Statistic Will Exceed 5%, 1%, and 0.1% Values (3.84, 6.63, and 10.82, Respectively) of χ^2 with df = 1, When Marker and Disease Are Unlinked and There Is No Population Structure

Disequilibrium Coefficient	Frequency of Type I Error When Nominal Value = (%)		
	5%	1%	0.1%
.010	5.66	1.15	.126
.015	6.17	1.37	.164
.020	7.09	1.70	.230
.025	8.34	2.25	.356

NOTE.—The frequency of the disease allele is assumed to be .05, and that of the associated marker is assumed to be .4.

statistical properties of the sampled data under the null hypothesis of no association differ from those under the hypothesis of no linkage, so that inference about one hypothesis is valid, but inference about the other is not.

This conclusion is illustrated in table 2, which reproduces and extends results from table 5 of our recent paper (Ewens and Spielman 1995). In this example there is association, at the level of the disequilibrium coefficient shown, but no linkage. The results show the actual rate of false-positive findings, when the nominal value is .05, .01, or .001. It is clear that use of the contingency test leads to a false-positive rate substantially higher than the nominal value. (In contrast, use of the TDT results in the nominal value.) The proportional inflation of the false-positive frequency with the contingency test is greatest when the nominal type I error is small; this effect is relevant to the problem, discussed below, of testing many marker loci and using a small type I error at each.

Generalizations and Extensions

Mode of Inheritance

The formulas (e.g., eqq. [16]–[19]) in our recent paper (Ewens and Spielman 1995) demonstrating the properties of the TDT assume that the contribution of the locus being investigated is recessive. However, all the properties of the TDT as a test of linkage hold regardless of the mode of inheritance (Spielman et al. 1993; Ewens and Spielman 1995). Schaid and Sommer (1994) have proposed several TDT-like tests, each of which assumes some specific mode of inheritance, which have power greater than that of the TDT when the assumed mode of inheritance is correct.

More than Two Alleles at the Marker Locus

There is considerable current research on the appropriate extension of the two-allele TDT discussed above to the case of an arbitrary number k of marker alleles. We consider first this extension when the TDT is used as a test of linkage.

We focus on the case in which no information is available on the mode of inheritance: if such information is available, a procedure that extends the approaches discussed by Schaid and Sommer (1994) might be appropriate. We propose a simple statistic that reduces to the two-allele TDT when $k = 2$ and that also allows us to use information on the relative levels of association of the various marker alleles. As with the two-allele TDT, and for the same reasons, we consider only parents heterozygous for marker alleles; and the discussion below assumes this throughout.

Various authors have considered a statistic that compares, for each heterozygous parent genotype M_iM_j, the number of times that M_i is transmitted to affected offspring with the number of times that M_j is transmitted to such offspring. This statistic has a χ^2 distribution with $k(k-1)/2$ df when there is no linkage, but, because of the large number of df, it lacks power when k is large. (A real effect associated with one allele may be undetectable, "swamped" by negligible effects for several or many other alleles.) Since the data matrix for this test is usually sparse, the test, on the whole, is agreed not to be useful.

The preferred approach is to use as data both the total number of times $n_{i.}$ that marker allele M_i is transmitted to affected offspring and the number of times $n_{.i}$ that it is not. The natural extension of the two-allele TDT test statistic is then $[(k-1)/k]\Sigma_i(n_{i.}-n_{.i})^2/(n_{i.}+n_{.i}-2n_{ii})$, where summation is over all k alleles. The use of this formula ensures that only data from heterozygous parents are included. This statistic has very nearly a χ^2 distribution with $k-1$ df when the null hypothesis of no linkage is true (N. L. Kaplan, E. R. Martin, and B. S. Weir, personal communication; W. J. Ewens and R. S. Spielman, unpublished data). It is thus easily computed and simple to use. Numerical evidence suggests that its use is asymptotically equivalent to use of the logistic-function approach of Harley et al. (1995), the Grizzle-Starmer-Koch weighted-least-squares procedure of Duffy (1995), and the logistic-regression procedure of Sham and Curtis (1995), when these methods also use data from heterozygous parents only.

Although use of the aforementioned statistic largely avoids the "swamping" effect inherent in the statistic with $k(k-1)/2$ df, the number of df used (i.e., $k-1$) still might be uncomfortably large, and we might seek a χ^2 testing procedure having only a small number of df, corresponding to a test of only the marker allele(s) most closely associated with the disease. In practice, of course, we usually do not know in advance which these alleles are.

This difficulty is overcome by breaking down the total

χ^2 statistic displayed above into separate χ^2 components, each corresponding to one marker allele, and then using the largest such component as the test statistic. The testing procedure must of course allow for both the nonindependence of these components and the fact that the largest component of the total χ^2 has been chosen. Amended χ^2 significance points for this purpose are available from the authors. This procedure is very similar to the well-known use of Bonferroni corrections (Feller 1968) when multiple alleles at a marker locus are tested for disease association.

The test statistic above may also be used as a test of association for data from simplex families and, as in the case of $k = 2$, is then the appropriate test of association when population stratification exists. (Note that, as in the case of testing for linkage, only data from heterozygous parents may be used.)

Rice et al. (1995) and Thomson (1995) propose, as a test statistic for association, a direct extension, to an arbitrary number of marker alleles, of the two-marker allele-contingency test of association discussed above. As for the case of a marker with two alleles, this statistic is a valid χ^2 only if there has been no population structure for at least two generations and if, furthermore, only simplex data are used.

Terwilliger (1995) has proposed a test of association, having 1 df only, that is appropriate if only one (unknown) marker allele might be positively associated with the disease. Further research is necessary on the relationship between this procedure and that following from the χ^2 decomposition discussed above.

Segregation Distortion

Suppose the TDT detects an effect, say an observed excess of allele M_1 in transmissions from heterozygous parents to affected offspring. In the model given above, this finding is taken as evidence for linkage. In principle, however, the finding could result, instead, from some preferential transmission in the meiotic process itself. Segregation distortion would be expected to produce excess transmissions of the M_1 allele to the unaffected offspring as well as to the affected. This possibility can be tested by examining transmissions from heterozygous parents to unaffected offspring (Parsian et al. 1991), ideally the sibs of the same affected individuals studied with the TDT.

Incomplete Genotype Data

Curtis and Sham (1995) have pointed out a problem that arises when genotype data are unavailable for one parent. Consider the case in which there are only two alleles at M, so that the available parent, if informative, is heterozygous (M_1M_2). If the offspring is M_1M_1, we can conclude that the available heterozygous parent transmitted M_1. If the offspring is M_2M_2, it is clear that the available parent transmitted M_2. It thus appears that even data from some incomplete families can be used. However, if the offspring is heterozygous, it is not possible to determine which allele was transmitted from the available parent, so the data are discarded.

Curtis and Sham have shown that discarding uninformative families this way leads to bias in the TDT. Under the null hypothesis (no linkage), M_1 and M_2 are equally likely to be transmitted by the available parent; but, the more common M_1 is in the population, the more likely it is to be the allele transmitted by the unavailable parent. When this happens, data on transmission from the available M_1M_2 parent will be used if that parent transmits M_1, whereas such data will be discarded if that parent transmits M_2. The net result is that the higher the frequency of M_1 in the population, the greater the *apparent* transmission of M_1 from heterozygotes.

The families that give rise to the problem are those in which the child is homozygous or heterozygous for the alleles in the available parent. However, if the offspring has an allele (e.g., M_3) not present in the available parent, no combination will be discarded, and no bias will occur if the data are used. (If neither parent is available, there is no way to obtain information for the TDT from the child's genotype.) On the other hand, even when the child has no allele different from those in the parent, it is sometimes possible to use the data. When there is more than one offspring in the sibship, it sometimes will be possible to deduce that the unavailable parent has genotype M_1M_2, and, in these cases, we may proceed as though this genotype were known directly.

Further Comments

Many Marker Loci

When the TDT was introduced, the intended use was as a test for linkage with a particular marker—for example, one at or very near a candidate gene. Since then, the TDT also has been used as a screening test (by us and by others; e.g., see contributions to Genetic Analysis 9 [Goldin et al. 1995]). In this approach, the TDT is applied to data from many markers throughout the genome, without prior evidence of either population association or proximity to candidate genes.

Lander and Schork (1994) and Lander and Kruglyak (1995) have called attention to the large increase in the type I error (false-positive) rate when many marker loci are tested for linkage to a disease; the result is that, for each individual marker, a significance level smaller (more extreme) than the nominal level should be required. These authors point out that, when standard ASP or LOD analysis is used, there is a high correlation of the evidence for linkage at closely linked markers. As a result of this correlation, the necessary reduction in the per-locus significance level, although substantial, is

nevertheless achievable in practice. The actual per-locus significance levels required for certain customary genomewide rates, as well as the general formula for the relationship, have been provided by Lander and his colleagues.

However, TDT scores for closely linked markers do not necessarily exhibit high correlations, so there is no corresponding formula for the TDT. Instead, for the TDT it appears necessary to use the standard correction for multiple independent tests deriving from the Bonferroni inequalities. These show that, in order to achieve a specified genomewide significance level, the per-locus significance level must be essentially equal to the genomewide rate divided by the number of marker loci. When the number of markers is large, this more extreme level of significance might be very difficult to reach in practice, posing a serious problem for the use of the TDT with data from a large-scale genome screen.

"Within-Family Transmission Disequilibrium"

The phrase "transmission disequilibrium" is sometimes used as though the TDT detected, by means of family studies, a distinctive kind of disequilibrium. The implication is that what the TDT detects is not the same as linkage disequilibrium in the population. But there is no separate within-family phenomenon for which "transmission disequilibrium" would be an appropriate name. The name "TDT"—transmission/disequilibrium test—was chosen (Spielman et al. 1993) to emphasize that this test uses observations on transmission in families to test for linkage disequilibrium in the population, in contrast to a case-control study, which uses observations on unrelated individuals. When used with simplex families, the TDT is a valid test for linkage disequilibrium (association as well as linkage) in the population. However, as discussed above, if there are multiple affected individuals in some families, the inference about linkage is still valid, but that about disequilibrium is not.

Use of Both the TDT and the Contingency Test in the Same Analysis

Some investigators have been tempted to present analyses of the same data by both the TDT and the contingency test, apparently in the hope that the one with the more striking significance level will provide the more convincing conclusion. There is no justification for this procedure. First, the contingency test is never valid as a test of linkage. Second, unless there has been random mating (no population structure) for at least two generations, the contingency test is also not valid as a test of association. Since it often will not be realistic to assume random mating, the TDT usually will be preferable (see also table 1).

Conclusions

The idea of locating disease genes by linkage disequilibrium came from the observation of disease associations in case-control studies; these studies included some undisputed successes involving HLA. It was clear from the start, however, that some cases of population association might not involve linkage, being due, instead, entirely to population structure or other causes of mismatch between patients and controls. This problem led to the use of "family-based" data, rather than conventional "population-based" data. The family data for the test of linkage are the numbers of times that a specified marker allele present in a parent is or is not transmitted to an affected offspring (see Spielman et al. 1993, table 2). *For these data, standard statistical theory leads to the TDT as the optimal test of linkage between marker and disease.* The TDT is valid as a test of linkage in structured populations, and it is immaterial whether the families are simplex, multiplex, or multigenerational. The latter property is of practical value, since multiplex (and multigeneration) data already are being collected for many diseases.

In contrast to the TDT, the AFBAC method is a test for *association* that is also intended as a means for locating disease genes when population structure is present. The AFBAC method compares marker-allele frequencies in affected offspring with frequencies in control "individuals" consisting of parental alleles not transmitted to affected offspring. Standard statistical theory shows, however, that, if there is population structure, the contingency statistic used with AFBAC is not a valid test for association, although AFBAC was designed specifically to eliminate the effects that are due solely to population structure. If there is population structure, the TDT, in contrast, *is* valid as a test for association in simplex families, as well as for linkage. Although the main goal in developing the TDT was to provide a test for linkage, the TDT as a test for association is thus also likely to prove valuable for fine localization of disease genes, when linkage is not in question.

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