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### Transmission Disequilibrium, Family Controls, and Great Expectations

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Transmission/disequilibrium testing (TDT) has gained popularity as a method to evaluate the linkage or association of candidate genes with disease and to screen the genome for susceptibility loci. This approach has fostered great expectations that complex human disorders will become tractable to gene mappers, and, indeed, among the many recent publications that make use of the TDT are an increasing number that extend the method to more-complex data. The time is ripe to consider the strengths and weaknesses of this methodology and its promise for the study of the complex genetics of human disorders.

#### Historical Background

Association studies of candidate genes or loci have long been popular among human geneticists. However, failure to reproduce findings has plagued this type of analysis, indicating that the disease cases and the controls may differ systematically in some manner that is inconsistent between different studies. Epidemiologists describe a factor as a “confounder” if it is correlated with both disease and a measured characteristic of interest—and so causes false-positive (or even false-negative) associations between them. Confounding factors in genetic analysis include differences in ancestral genetic composition, between cases and controls. For ethnic background to act as a confounding variable, both the genetic-marker frequency and the disease frequency must vary according to ethnic background. The tools for responding to biases that arise from ethnic background are familiar from epidemiological practice: One attempts either to estimate and then correct for known biases or to match cases and controls more closely with respect to the confounding factor. Because many populations are stratified according to ethnic subgroups and because ethnic background is difficult to measure, and

because genetic markers frequently vary across different ethnic groups, the choice of controls for genetic studies is difficult. To avoid these difficulties, Falk and Rubinstein (1987) proposed the use of the parents of disease cases, as an alternative type of control, a procedure that has become known as the “haplotype relative risk” (HRR) method. For this design, the two alleles of the parents that were not transmitted to their affected child are combined to create a pseudocontrol, and the association of disease with particular marker alleles is assessed by traditional case-control methods. Thus, the frequencies of particular marker alleles among cases and the pseudocontrols are used to derive an odds ratio (called the “HRR” when applied to the pseudocontrols). The validity of this method as a test for association or linkage depends on the structures both of the pedigrees (i.e., simplex or multiplex pedigrees) and of the populations to which it is applied (Spielman and Ewens 1996).

As an alternative to the HRR method of analysis, Spielman et al. (1993) proposed the TDT as a way to test for linkage in the presence of association (i.e., linkage disequilibrium). This was a crucial advance in the development of statistical tools to identify chromosomal regions that may harbor disease-susceptibility genes. The TDT method evaluates whether the frequency of transmission of alleles from heterozygous parents to their affected children deviates from 50%, the expected Mendelian frequency when there is no linkage. The form of the statistic is quite simple: Consider two alleles, *A* and *B*, and let *a* denote the number of times that allele *A* is transmitted from a heterozygous *A/B* parent to the affected child, and let *b* denote the number of times that allele *B* is transmitted from a heterozygous *A/B* parent to the affected child. Then,  $TDT = (a - b)^2 / (a + b)$ , which has an approximate  $\chi^2$  distribution with 1 df. The TDT method can be applied to large pedigrees with many affected subjects or even to a single disease case per family (simplex family), provided that genotypes for both parents of the affected subjects are available. However, a simplex family is informative for linkage only when linkage disequilibrium exists—that is, when the likelihood of the coupling and the repulsion linkage phases in the parents are not equal (Spielman et al.

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1994). For this reason, TDT is considered a test for linkage in the presence of linkage disequilibrium. The advantage of the TDT method is that it is not sensitive to a stratified population, so it avoids spurious associations that can arise when one is sampling cases and unrelated controls. Because the HRR and TDT methods can be applied to the same data, these two methods are often confused with each other, but they are not equally applicable in all circumstances (for an excellent review of these points, see Spielman and Ewens 1996). The TDT is statistically valid even if the population is stratified, but population stratification can cause the rate of false positives to increase under the HRR and several related methods (Schaid and Sommer 1994; Ewens and Spielman 1995).

When there are more than two alleles at the marker locus, several TDTs can be computed, one for each allele. In this case, one needs to correct for multiple testing, to avoid increasing the false-positive rate. The Bonferroni method can be used, by multiplication of each allele-specific  $P$  value by  $(K - 1)$ , where  $K$  is the number of marker alleles. Note that the correction factor is  $(K - 1)$ , not  $K$ , because there can be, at most,  $(K - 1)$  df when one is considering multiple alleles (Schaid 1996). Several extensions of the TDT have been proposed to account for multiple alleles (Sham and Curtis 1995; Schaid 1996; Spielman and Ewens 1996; Lazzaroni and Lange 1998), all of which compute  $\chi^2$  statistics for global allelic transmission/disequilibrium testing. A subtle point, which is often overlooked in the application of these global  $\chi^2$  statistics, is that there can be fewer than  $(K - 1)$  df (Schaid 1996); if this is ignored, the power of the test will be diminished. The power of these global methods may vary, depending on the details of the underlying genetic mechanism (Schaid 1996; Kaplan et al. 1997)—in particular, on whether a single allele or multiple alleles are preferentially transmitted to affected children. If a single allele is strongly associated, then the Bonferroni method will provide more power than the global methods (Schaid 1996), an important consideration when one is reviewing the application of the various TDT methods in reported studies. Many of the TDT methods (single-allele tests, or global tests) compute  $P$  values by means of the  $\chi^2$  distribution, which is valid only when the number of informative (i.e., heterozygous) parents in the study is large. Some investigators ignore rare alleles when applying the TDT, a questionable practice because it wastes useful information and does not guarantee the reliability of the  $\chi^2$  distribution for the alleles tested. Instead, the exact  $P$  value can be computed, or it can be approximated by simulation studies (Lazzaroni and Lange 1998).

## Application of the TDT in Linkage Studies

The TDT method has been widely applied to test for linkage between candidate-gene regions and a variety of complex disorders. Some issues regarding the interpretation of positive findings by the TDT method warrant discussion. If only affected subjects are sampled and a candidate gene is evaluated, then one would expect that the biologically high-risk allele is preferentially transmitted. For example, it has been confirmed that the high-activity form of a metabolic enzyme is preferentially transmitted in schizophrenia (Li et al. 1996). Furthermore, it can be fruitful to quantify the risk associated with an allele. The TDT method is most sensitive to allelic effects that are multiplicative for genotype relative risks (Schaid, in press); that is, if the relative risk of disease for heterozygous carriers compared with homozygous noncarriers is  $r$ , then multiplicative effects imply that homozygous carriers have a relative risk of  $r^2$ . This relative-risk parameter can be estimated as  $r = a/b$ , where  $a$  and  $b$  are the counts used to compute the TDT. Alternatively, general genotype relative risks can be computed (Schaid and Sommer 1993; Schaid, in press) without assumption of the multiplicative model. When the high-risk allele is rare, the fraction of disease attributable to the high-risk allele may be low enough to suggest that it is a minor risk factor (Li et al. 1996). When nonaffected sibs of affected cases are also sampled, one should evaluate whether the allele that is preferentially transmitted among affected cases is not preferentially transmitted among nonaffected subjects. An example in which the same allele is preferentially transmitted to both affected and nonaffected children is the association between type 1 diabetes and chromosomal region 10p11-q11 (Reed et al. 1997). This certainly confuses interpretations. Models to assess whether some alleles are high-risk and others are protective against disease may prove helpful (Self et al. 1991; Morris et al. 1997). An example in which alleles appear to be protective, because they are preferentially not transmitted, is leprosy (Cervino and Curnow 1997).

Statistical power in TDT studies depends on the number of parents heterozygous for particular alleles and becomes a critical issue when findings are negative. Even if there are a large number of heterozygous parents, a study can still have low power if only one allele is associated with disease and if there are few parents who are heterozygous for that allele. Power can be diluted when there is little linkage disequilibrium between disease and marker alleles, despite close linkage. In fact, it can be shown that the magnitude of transmission disequilibrium of a marker allele depends on the genotype relative risk of the susceptibility locus, the genetic distance between disease and marker loci, and the amount

of linkage disequilibrium (Schaid 1996). One should also consider the choice of study population (e.g., genetically isolated vs. highly mixed), as well as the ascertainment criteria (e.g., simplex vs. multiplex pedigrees).

### The TDT Method and Genetic Heterogeneity

The TDT method has been used to assess heterogeneity in transmission disequilibrium, by partitioning of the data to potential sources of heterogeneity and then applying the TDT to each subgroup. Several sources of heterogeneity are (1) parent-of-origin effects, (2) allelic heterogeneity, and (3) ethnic heterogeneity. For the parent-of-origin effect, transmission of maternal alleles can be evaluated separately from transmission of paternal alleles, to examine whether the parental origin of susceptibility alleles influences the risk of disease. Type 1 diabetes is an example—albeit a controversial one—for which a susceptibility allele at the insulin gene region at 11p15.5 is transmitted at a significantly increased frequency from heterozygous fathers to their diabetic offspring, whereas transmission from heterozygous mothers does not differ from the random Mendelian expectation of 50% (Bui et al. 1996). Other examples that have a reported parent-of-origin effect are coeliac disease (Petronzelli et al. 1997) and bipolar disorder (Waldman et al. 1997). Allelic heterogeneity, such that there is more than one common allele that exhibits transmission disequilibrium, has been demonstrated in type 1 diabetes (Merriman et al. 1997). Heterogeneity across different ethnic groups, such that some groups demonstrate transmission disequilibrium whereas others do not, has also been demonstrated for type 1 diabetes (Marron et al. 1997). The advantage of the TDT method is its simplicity of application to various subsets. However, when it is necessary to assess the simultaneous influence of several factors on heterogeneity, splitting the data into many subsets can lead to sparse data and unreliable statistical tests, as well as make the interpretation difficult.

An alternative way to assess transmission/disequilibrium heterogeneity is to model the influence of multiple factors—and, possibly, their interactions—by conditional logistic regression (Schaid 1995), as Weinberg et al. (1998) have suggested for parent-of-origin effects. Thus, one treats the affected child as the case and constructs three pseudosib controls according to the parental genotypes (i.e., the two alleles from each parent can be potentially combined to create four different children, one of which is the case and the other three of which are the pseudocontrols). Gene  $\times$  environment interaction may be suggested when transmission disequilibrium varies according to the levels of an environmental factor. For example, maternal smoking interacts with the trans-

mission disequilibrium of a susceptibility allele of the *BCL3* proto-oncogene, to influence the risk of cleft lip (Maestri et al. 1997).

### Choosing among Statistical Tests

Evaluating the relative success of TDT versus other linkage methods can be difficult and even misleading. Some comparative studies have used different criteria to claim statistical significance for the TDT method than are used for linkage methods. For example, the maximum-LOD-score method for affected sib pairs (ASPs) is often considered statistically significant only if the maximum LOD score is  $>3$ , which approximately translates to  $P = .0001$ . In contrast, the TDT method is often claimed to be statistically significant if the  $P < .05$ . Hence, to compare the TDT method with the maximum-LOD-score method for ASPs, the LOD score should be transformed to a  $P$  value by first transforming the LOD score to a standard normal random variable,  $z = \sqrt{4.6 \text{ LOD}}$ , and then using a one-sided  $P$  value (because the alternative hypothesis is that the recombination fraction is  $<.5$ ; a two-sided  $P$  value is typically used for TDT, because transmission disequilibrium can be positive or negative).

Further confusion can arise when it is not clear whether the TDT  $P$  value is corrected for testing of multiple alleles at each marker locus or for testing of multiple marker loci. It is important to recognize that the screening of many marker loci, even if they are within a short chromosomal region, can increase the rate of false-positive findings by the TDT method; the Bonferroni method or simulation-based methods should be used to compute  $P$  values. Furthermore, it is difficult to judge whether, for genomewide screening, the TDT method will be more successful than ASP methods, because, to date, many of the applications of TDT have been as follow-up studies, or confirmatory analyses, for promising chromosomal regions. Nonetheless, it certainly makes sense to use the TDT method to follow up promising linkage regions, because, if linkage disequilibrium exists, the TDT will capitalize on this, to help in the fine localization of the susceptibility locus. However, one needs to be cautious when applying and interpreting the TDT method. When the TDT is used to test for linkage, it is valid to use all affected subjects who have parental data: The false-positive rate for linkage is not inflated, even if subjects are genetically related, because, under the null hypothesis of no linkage, the transmission of parental marker alleles follows Mendel's law of transmission, so that sibs are independent (Spielman and Ewens 1996). However, when the TDT is used for fine localization via linkage disequilibrium, genetic linkage causes dependencies among related subjects, which can

falsely inflate the evidence for linkage disequilibrium. To handle this problem, one can randomly sample a single affected subject per family and then apply the TDT. Because this wastes information, a better alternative for ASPs is to apply a method that correctly accounts for dependencies among sibs when one is testing for linkage disequilibrium (Martin et al. 1997).

Whether the TDT method will be more successful than other linkage methods will very likely depend on the population studied (e.g., whether linkage disequilibrium is large in the target population, which depends on the genetic history of the population), on the sampled pedigrees, and on the density of the genetic markers. In some reports, the evidence for linkage differs dramatically between the TDT and other linkage methods. Nonsyndromic cleft lip provides an example in which there is, on the basis of a parametric LOD score, a lack of evidence for linkage (maximum LOD score 0.41;  $P = .08$ ) yet, on the basis of a global TDT that assesses transmission disequilibrium for all alleles simultaneously, striking evidence for linkage/linkage disequilibrium ( $P = .0005$ ) with the *BCL3* locus (Wyszynski et al. 1997). These results are a bit surprising, because the sample was not from an isolated population but, rather, was a collection of families throughout the United States, so that the sample likely represents a mixture of different ethnic groups. Another example for which the TDT results appear to add linkage information over and above that added by ASP methods is a study of multiple sclerosis (Ebers et al. 1996). This particular study presented results for a genomewide linkage screen based on ASP methods and concluded that there was modest evidence for linkage on several chromosomes. Application of the TDT to the HLA region, which harbors alleles associated with multiple sclerosis, failed to detect transmission disequilibrium, but a marker locus ~4 cM from the HLA region did demonstrate strong transmission disequilibrium. The families for this study were collected throughout all of Canada, and so they likely represent a mixture of ethnic backgrounds. In contrast to these two reports, a study of rheumatoid arthritis demonstrated that the evidence for linkage with HLA-A was much stronger with the ASP method ( $P < .0001$ ) than with the TDT method ( $P = .033$ ; but this value is not corrected for the testing of multiple alleles) (Marlow et al. 1997). For the rheumatoid arthritis study, the families were obtained from a national registry in the United Kingdom, so one could infer that ethnic heterogeneity could cause allelic heterogeneity, thereby diminishing the likely success of the TDT method. Lack of linkage disequilibrium could also cause the TDT method to fail to identify linkage. On the basis of these anecdotal reports, it appears difficult to anticipate whether the TDT method or the ASP will be the better approach for localization of susceptibility loci for complex disorders, at least for the present

genetic-marker maps. It can be shown that the TDT will have greater power than ASP methods when there is strong linkage disequilibrium (Risch and Merikangas 1996). However, the amount of linkage disequilibrium is unknown in most populations. Population genetics suggests that linkage-disequilibrium mapping of disease genes will prove most fruitful in genetically isolated populations or in recently admixed populations. The latter populations may be particularly suitable for TDT analysis if there are large differences, in both disease risk and marker-allele frequencies, between the founding populations (Kaplan et al. 1998). The challenge for the geneticist will be to identify these types of idealized populations.

The positive TDT results reported from Canada and the United States may appear surprising, because of the ethnically mixed populations in both countries. However, the amount of linkage disequilibrium depends, in a complex manner, on the ancestral history of a population, including the age of the disease-causing mutation; younger mutations can demonstrate stronger linkage disequilibrium (Jorde 1995). So, despite excellent theoretical arguments why the TDT and other linkage-disequilibrium mapping strategies can lack power to detect susceptibility genes for complex disorders in heterogeneous populations (Xiong and Guo, in press), empirical evidence will likely offer keen insights into the real benefits of this mapping strategy.

### Recent Developments

The advantages of the TDT method—that is, its simplicity and its insensitivity to population stratification—have motivated methodological research into its properties, particularly as it and its variants are applied to more complicated data. Because the TDT uses only affected sibs, and because, in nuclear families, unaffected sibs often outnumber affected sibs, it appears that there should be valuable information among unaffected children, because they should demonstrate negative transmission of any alleles positively transmitted among their affected sibs. However, for complex disorders with low penetrance, the inclusion of unaffected sibs in TDT analyses can lead to a decrease in power, primarily because the amount of transmission-disequilibrium information that they add is small relative to the amount of random noise that they introduce (Boehnke and Langefeld 1997).

A serious limitation of the TDT method and its extensions is that they all require genotype information on both parents, which limits their applications to diseases with an early age at onset. Biases can occur when one parent is missing (Curtis and Sham 1995), and, although models can be used to infer the genotype of one or both missing parents (Schaid and Li 1997), the models often assume a homogeneous population, which may be un-

realistic. An alternative approach is to use unaffected sibs as a type of control (Boehnke and Langefeld 1998; Schaid and Rowland 1998; Spielman and Ewens 1998), to avoid problems of population stratification. Although the TDT method measures transmission disequilibrium of alleles, one could first measure deviation of genotypes from their Mendelian expectation and then transform the genotypic disequilibrium into allelic disequilibrium by means of allele-counting methods. Allele counts are linear combinations of genotype counts, which implies that allelic deviations from equilibrium are linear combinations of genotypic deviations from equilibrium. If both parents are available, the Mendelian genotype probabilities for their children are easily computed. If both parents are missing, the genotype probabilities for the children can be estimated on the basis of the observed genotype frequencies among all sibs within a sibship. Then, the discrepancy between observed and expected genotype counts can be transformed into allelic disequilibrium, to allow both for missing parents and for combination with transmission-disequilibrium data when parents are available (Schaid and Rowland 1998). Not surprisingly, there is a loss of power when, in place of the more exact Mendelian probabilities provided by parental information, sibs are used to estimate the expected genotype distribution (Schaid and Rowland 1998; Spielman and Ewens 1998). Given that other family members, such as cousins, may be available, work is in progress to evaluate the contribution of other types of controls.

Several methods have been proposed to assess the association between quantitative traits and transmission disequilibrium (Allison 1997; Rabinowitz 1997). Similar to the case for binary traits, the objective is to evaluate whether the transmission disequilibrium of parental alleles is associated with the magnitude of the child's trait. For example, if large trait values were found to correlate with the transmission of particular alleles, this would suggest both linkage and linkage disequilibrium. When parents are missing, an approach similar to that outlined above, for the use of sib controls, can be used. (Schaid and Rowland, in press).

### Future Hopes

It has recently been proposed that the TDT method could provide direction into the future mapping of complex human disorders (Risch and Merikangas 1996), by performing genomewide TDT screens. This differs from the applications discussed above, which have applied TDTs to candidate-gene regions. This proposal is based on the assumptions that (1) genetic markers will be so dense that each gene will have several (biallelic) markers and (2) the markers will be in strong linkage disequilibrium with the susceptibility gene(s). Whether this be-

comes feasible depends not only on the availability of such a dense marker map but also on the likelihood that linkage disequilibrium will be strong enough for the TDT to detect both linkage and linkage disequilibrium. If linkage disequilibrium is less than maximal, and if allele frequencies greatly differ between disease and marker loci, then power will be diminished (Muller-Myhsok and Abel 1997). Furthermore, the assumed model of risk for the susceptibility locus, as indirectly measured on the basis of the marker genotype, will influence power (Camp 1997; Schaid, in press). However, if linkage disequilibrium is strong, then the power of the TDT method will be greater than that of the ASP methods (Risch and Merikangas 1996). Application of the TDT approach to sib pairs, rather than to a single affected child per family, increases the chance that the parents are heterozygous and results in an increase in power. Hence, sampling strategies, both as they apply to individual pedigrees and to the choice of populations to be studied, are crucial to the success of genomewide association tests.

Transmission-disequilibrium methods have proved useful not only for detection of linkage but also for the gaining of insights into genetic heterogeneity, as well as into gene  $\times$  environment interaction. For genes of small effect, these novel approaches may prove to be most fruitful in the unraveling of the genetic etiology of complex disorders. Both theory and applied results seem to indicate that, when used with other linkage-based methods, transmission-disequilibrium methods are useful tools for the identification of susceptibility genes. The full range of the utility of these methods has not yet been explored, but continued applications will increase experience and provide genetic insights into complex human disorders.

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### References

- Allison DB (1997) Transmission-disequilibrium tests for quantitative traits. *Am J Hum Genet* 60:676–690
- Boehnke M, Langefeld CD (1997) A transmission/disequilibrium test that uses both affected and unaffected offspring. *Am J Hum Genet Suppl* 61:A269
- (1998) Genetic association mapping based on discordant sib pairs: the discordant-alleles test. *Am J Hum Genet* 62:950–961
- Bui MM, Luo DF, She JY, Maclaren NK, Muir A, Thomson G, She JX (1996) Paternally transmitted IDDM2 influences diabetes susceptibility despite biallelic expression of the insulin gene in human pancreas. *J Autoimmun* 9:97–103
- Camp NJ (1997) Genomewide transmission/disequilibrium

- testing—consideration of the genotypic relative risks at disease loci. *Am J Hum Genet* 61:1424-1430
- Cervino AC, Curnow RN (1997) Testing candidate genes that may affect susceptibility to leprosy. *Int J Lepr Other Mycobact Dis* 65:456-460
- Curtis D, Sham PC (1995) A note on the application of the transmission disequilibrium test when a parent is missing. *Am J Hum Genet* 56:811-812
- Ebers GC, Kukay K, Bulman DE, Sadovnick AD, Rice G, Anderson C, Armstrong H, et al (1996) A full genome search in multiple sclerosis. *Nat Genet* 13:472-476
- Ewens WJ, Spielman RS (1995) The transmission/disequilibrium test: history, subdivision, and admixture. *Am J Hum Genet* 57:455-464
- Falk CT, Rubinstein P (1987) Haplotype relative risks: an easy reliable way to construct a proper control sample for risk calculations. *Ann Hum Genet* 51:227-233
- Jorde LB (1995) Linkage disequilibrium as a gene-mapping tool. *Am J Hum Genet* 56:11-14
- Kaplan NL, Martin ER, Morris RW, Weir BS (1998) Marker selection for the transmission/disequilibrium test, in recently admixed populations. *Am J Hum Genet* 62:703-712
- Kaplan NL, Martin ER, Weir BS (1997) Power studies for the transmission/disequilibrium tests with multiple alleles. *Am J Hum Genet* 60:691-702
- Lazzeroni LC, Lange K (1998) A conditional inference framework for extending the transmission/disequilibrium test. *Hum Hered* 48:67-81
- Li T, Sham PC, Vallada H, Xie T, Tang X, Murray RM, Liu X, et al (1996) Preferential transmission of the high activity allele of COMT in schizophrenia. *Psychiatr Genet* 6:131-133
- Maestri NE, Beaty TH, Hetmanski J, Smith EA, McIntosh I, Wyszynski DF, Liang KY, et al (1997) Application of transmission disequilibrium tests to nonsyndromic oral clefts: including candidate genes and environmental exposures in the models. *Am J Med Genet* 73:337-344
- Marlow A, John S, Hajeer A, Ollier WER, Silman AJ, Worthington J (1997) The sensitivity of different analytic methods to detect disease susceptibility genes in rheumatoid arthritis sibling pair families. *J Rheumatol* 24:208-211
- Marron MP, Raffel LJ, Garchon HJ, Jacob CO, Serrano-Rios M, Martinez Larrad MT, Teng WP, et al (1997) Insulin-dependent diabetes mellitus (IDDM) is associated with CTLA4 polymorphisms in multiple ethnic groups. *Hum Mol Genet* 6:1275-1282
- Martin ER, Kaplan NL, Weir BS (1997) Tests for linkage and association in nuclear families. *Am J Hum Genet* 61:439-448
- Merriman T, Twells R, Merriman M, Eaves I, Cox R, Cucca F, McKinney P, et al (1997) Evidence by allelic association-dependent methods for a type 1 diabetes polygene (IDDM6) on chromosome 18q21. *Hum Mol Genet* 6:1003-1010
- Morris AP, Whittaker JC, Curnow RN (1997) A likelihood ratio test for detecting patterns of disease-marker association. *Ann Hum Genet* 61:335-350
- Muller-Myhsok B, Abel L (1997) Genetic analysis of complex diseases. *Science* 275:1328-1329
- Petronzelli F, Bonamico M, Ferrante P, Grillo R, Mora B, Mariani P, Gemme G, et al (1997) Genetic contribution of the HLA region to the familial clustering of coeliac disease. *Ann Hum Genet* 61:307-317
- Rabinowitz D (1997) A transmission disequilibrium test for quantitative trait loci. *Hum Hered* 47:342-350
- Reed P, Cucca F, Jenkins S, Merriman M, Wilson A, McKinney P, Bosi E, et al (1997) Evidence for a type 1 diabetes susceptibility locus (IDDM10) on human chromosome 10p11-q11. *Hum Mol Genet* 6:1011-1016
- Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. *Science* 273:1516-1517
- Schaid DJ (1995) Relative-risk regression models using cases and their parents. *Genet Epidemiol* 12:813-818
- (1996) General score tests for associations of genetic markers with disease using cases and their parents. *Genet Epidemiol* 13:423-449
- Likelihoods and TDT for the case-parents design. *Genet Epidemiol* (in press)
- Schaid DJ, Li H (1997) Genotype relative-risks and association tests for nuclear families with missing parental data. *Genet Epidemiol* 14:1113-1118
- Schaid DJ, Rowland CR (1998) The use of parents, sibs, and unrelated controls to detect associations between genetic markers and disease. *Am J Hum Genet* 63 (in press)
- Quantitative trait transmission disequilibrium testing with regression analysis and allowance for missing parents (in press)
- Schaid DJ, Sommer SS (1993) Genotype relative risks: methods for design and analysis of candidate-gene association studies. *Am J Hum Genet* 53:1114-1126
- (1994) Comparison of statistics for candidate-gene association studies using cases and parents. *Am J Hum Genet* 55:402-409
- Self SG, Longton G, Kopecky KJ, Liang K-Y (1991) On estimating HLA/disease association with application to a study of aplastic anemia. *Biometrics* 47:53-61
- Sham PC, Curtis D (1995) An extended transmission/equilibrium test (TDT) for multi-allele marker loci. *Ann Hum Genet* 59:323-336
- Spielman RS, Ewens WJ (1996) The TDT and other family-based tests for linkage disequilibrium and association. *Am J Hum Genet* 59:983-989
- (1998) A sibship test for linkage in the presence of association: the sib transmission/disequilibrium test. *Am J Hum Genet* 62:450-458
- Spielman RS, McGinnis RE, Ewens WJ (1993) Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet* 52:506-516
- (1994) The transmission/disequilibrium test detects cosegregation and linkage. *Am J Hum Genet* 54:559-560
- Waldman ID, Robinson BF, Feigon SA (1997) Linkage disequilibrium between the dopamine transporter gene (DAT1) and bipolar disorder: extending the transmission disequilibrium test (TDT) to examine genetic heterogeneity. *Genet Epidemiol* 14:699-704
- Weinberg CR, Wilcox AJ, Lie RT (1998) A log-linear approach to case-parent-triad data: assessing effects of disease genes that act either directly or through maternal effects and that may be subject to parental imprinting. *Am J Hum Genet* 62:969-978

Wyszynski DF, Maestri N, McIntosh I, Smith EA, Lewanda AF, Garcia-Delgado C, Vinageras-Guarneros E, et al (1997) Evidence for an association between markers on chromosome 19q and non-syndromic cleft lip with or without cleft

palate in two groups of multiplex families. Hum Genet 99: 22-26

Xiong M, Guo S-W. The power of linkage detection by the transmission/disequilibrium tests. Hum Hered (in press)