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STATISTICAL ASPECTS OF THE TRANSMISSION/DISEQUILIBRIUM TEST (TDT)

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The transmission/disequilibrium test (TDT) was introduced as a direct test of linkage which is not affected by the problem of population stratification. Such a test is needed since much of the data used currently for linkage tests does come, or might be suspected to come, from stratified populations. Also, the test is valid when the data include relatives, since it overcomes the dependence properties usually associated with such data. In practice, the main purpose of the procedure is to test for linkage between a marker locus and a purported disease locus - a link in the chain of activities whose ultimate aim is to locate disease loci. The test differs from frequently used tests based on sharing of marker alleles between affected relatives and, unlike sharing tests, is related to the population concept of association. These differences are discussed. Many interesting questions arise in the statistical theory of the TDT, some of which are still unresolved. One of the aims of this paper is to raise and discuss these.

1. Introduction. The aim of this paper is to discuss both genetical and statistical aspects of the so-called transmission/disequilibrium test (TDT) of Spielman et al. (1993). The TDT is a test for linkage between a marker locus and a disease locus, and may also, for some forms of data, be used as a test of association between these loci. However, the properties of the test when used for these two purposes are different. Although the test is naturally of more interest to geneticists than statisticians, there are several statistical aspects of the test that deserve attention, and also several for which the statistical theory is still not complete. A discussion of some of these will be given in this paper.

2. Genetical background. Since this presentation is intended for statisticians, we first give a brief definition of key genetical terms that will be used in the sequel, as well as some population genetics theory.

Many characteristics which we have are controlled by the genes that we carry. Genes may be thought of as beads on a string, the string in this case being the chromosome, or gamete. Just as specific beads have given locations on the string, so also genes occur at specific positions, or loci, on the chromosome. Thus we might say: "The genes controlling eye color occur on chromosome 16, at a locus in such and such a position on this chromosome."

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