Letters to the Editor

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A Note on the Application of the Transmission Disequilibrium Test When a Parent Is Missing

To the Editor:

The transmission disequilibrium test (TDT) is useful for detecting a susceptibility locus in linkage and linkage disequilibrium with a marker locus (Spielman et al. 1993). Unlike association studies, which use unrelated controls, it is not prone to produce false-positive results in the presence of hidden population stratifications. We wish to point out a situation that may have escaped the attention of some readers when there may be a risk of misapplying the test in a way that can produce false-positive results.

The situation where problems may arise is when marker information from one parent is missing although the other parent is heterozygous and so potentially informative for the TDT. If we denote this parent's marker genotype as "AB," then, if the affected child is also AB, it is clear that either allele could have been passed on, and the pair must be discarded as uninformative after all. However, if the child is, for example, AA, then the parent must have passed the A allele and must have not passed the B allele, and it may be tempting to score this meiosis accordingly. Under these circumstances, the test will be biased by the allele frequencies of A and B in the population. To make clear intuitively why this should be, consider what will happen if there are only two alleles at the marker locus and the B allele is extremely rare: on almost every occasion the missing parent will have genotype AA and pass on an A allele. Then, if the heterozygous parent passes on the B allele, the child will be AB and the pair is discarded as uninformative; whereas, if the A allele is passed, this will be included in the TDT. This will obviously lead to the accumulation of evidence apparently supporting the preferential transmission of allele A over allele B, but the result is in reality due to the difference in frequency between the alleles.

It is easy to quantify the apparent preferential transmission of allele A over allele B in this situation. Let the frequency of allele A be p, and let the frequency of allele B be $1 - p$, such that $p > \frac{1}{2}$. One of the parents is known to have genotype AB, while the other can have genotypes AA, AB, and BB, with probabilities p^2, $2p(1 - p)$, and $(1 - p)^2$, respectively. If offspring with genotype AA are used to infer that an A allele has been transmitted from the known parent, and if offspring with genotype BB are used to infer that a B allele has been transmitted from the known parent, and if offspring with genotype AB are ignored, then the probability of inferring that an A allele is transmitted is $(\frac{1}{2})p^2 + (\frac{1}{4})2p(1 - p)$, while that of inferring that a B allele is transmitted is $(\frac{1}{2})(1 - p)^2 + (\frac{1}{4})2p(1 - p)$, even when both alleles are actually equally likely to be transmitted. From these probabilities, the apparent ratio of transmission of allele A to allele B can be calculated to be $p{:}1 - p$.

We therefore conclude that, when a parental genotype is missing, the remaining parent-child pair should be discarded not only when the child has the same genotype as the parent but also if the child is homozygous. For markers with only two alleles, this means that all cases in which one parental genotype is missing must be discarded. In principle, it would be possible to generalize the TDT to include such families, but this would require the allele frequencies to be specified correctly, and this might be undesirable, since an attractive feature of the TDT is its independence from such parameters. For markers with more than two alleles, no bias will arise by including information from single parent-child pairs where the child is heterozygous but has a genotype different from that of the parent—for example, where the parent is AB and the child is AC or BC—and such pairs may be included in the TDT even if the marker genotype for the other parent is missing.

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Reference

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mtDNA D-Loop 6-bp Deletion Found in the Chilean Aymara: Not a Unique Marker for Chibcha-Speaking Amerindians

To the Editor:

Santos and Barrantes (1994) reported a 6-bp deletion between nt 106 and nt 111 of the mitochondrial DNA D-loop (Anderson et al. 1981), noting that it appeared to be specific for Chibcha-speaking groups (or, at least present in the ancestral population for Chibcha speakers). Merriwether (1993) described this deletion in two Aymara individuals (one from the Lluta Valley and one from Visviri) in northernmost Chile, indicating that this deletion extends considerably beyond lower Central America. The village of Visviri is located at 4,100 meters altitude in the Altiplano, while the Lluta Valley sample is from a coastal Aymara population. We obtained D-loop sequences on >200 Huilliche, Pehuenche, Atacameno, and Quechua Indians from Chile and Peru and did not detect the 6-bp deletion in any of these populations. The second hypervariable region of the D-loop (where this 6-bp deletion occurs) is not sequenced as often as is the first hypervariable region in population studies, and only the lab of D. C. Wallace (Torroni et al. 1992, 1993*a*, 1993*b*, 1994*a*, 1994*b*) has consistently surveyed for the *Msp*I-site loss at nt 104 (an *Msp*I-site loss is caused by this deletion). Many populations surveyed by others (Ward et al. 1991, 1993; Ginther et al. 1993; Horai et al. 1993; Shields et al. 1993; Bailliet et al. 1994; Lorenz and Smith 1994; Merriwether et al. 1994) were not screened for this deletion. While Torroni et al.'s (1993*a*, 1994*a*, 1994*b*) putative 6-bp deletion haplotypes 51, 52, and 53 are found on a lineage A background (characterized by a *Hae*III 663 site gain and an *Msp*I 104 site loss), our 6-bp deleted Aymara individuals are lineage D (*Alu*I 5,176 site loss, *Hae*III 663 site loss, and *Msp*I 104 site loss). Kolman et al. (in press) and O. Batista, C. J. Kolman, and E. Bermingham (personal communication) report that this deletion is present at >10% frequency in two Chibchan populations (Ngobe and Kuna) but is absent in two Choco populations (Embera and Waunaan) in Panama. The deletions observed by Kolman et al. (in press) and O. Batista, C. J. Kolman, and E. Bermingham (personal communication) all occurred on a lineage A background. Santos and Barrantes's Chibchan deletions also occur against a lineage A background (at nearly 60%). The occurrence of the 6-bp deletion on both lineage A and lineage D backgrounds could be indicative of multiple origins for the 6-bp deletion. Given the present data, one could consider the combination of a *Hae*III 663 site gain (or other definitive lineage A markers) plus the 6-bp deletion (or an *Msp*I 104 site loss) to be a Chibcha-specific combination. One should not use the 6-bp deletion alone as a marker indicating shared ancestry with the Chibchan or proto-Chibchan populations.

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