assume, therefore, that the proportion of unilaterally affected patients with mutations in leukocyte DNA approximates the prevalence of hereditary retinoblastoma among patients with isolated unilateral tumors. The percentage obtained from our conjoint studies is now in accord with a previous estimate by Vogel (1979) that was based on epidemiological data.

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Electronic-Database Information

URL for data in this article is as follows:

RB1 gene mutation database, http://home.kamp.net/home/dr.lohmann

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TDT Clarification

To the Editor:

A potentially misleading statement occurs in the invited editorial "The TDT and other family-based tests for linkage disequilibrium and association" by Spielman and Ewens (59:983–989), published in the November 1996 issue of the *Journal*. We wish to make the following clarification.

In discussing some issues that arise when the transmission/disequilibrium test (TDT) is used in families where genotype data are unavailable for one parent, we noted the finding of Curtis and Sham (1995) that, when there is a single affected offspring who is homozygous for an allele present in the available (heterozygous) parent, the TDT gives a biased result and should not be used. We then stated that "[w]hen there is more than one offspring in the sibship, it sometimes will be possible to deduce that the unavailable parent [is also heterozygous], and, in these cases, we may proceed as though this [reconstructed] genotype were known directly" (Spielman and Ewens 1996, p. 987).

We should have emphasized that this claim assumes that the reconstruction is done from the genotypes of unaffected offspring. A bias will usually arise in the TDT statistic if the reconstruction uses, in whole or in part, genotype data from affected offspring whose genotypes are then used in the TDT. A bias can also arise when both parental genotypes are reconstructed from the genotypes of the offspring.

The bias resulting from reconstruction occurs for a reason different from that noted by Curtis and Sham

(1995). Since reconstruction is possible only with certain offspring genotype combinations, families in which parental genotypes can be reconstructed are not random as far as offspring genotypes are concerned. This restriction leads to a bias if the offspring genotype data that were used for reconstruction are also used in the TDT.

Knapp (in press) has calculated the size of this bias in a number of important cases and has thus been able to establish more general TDT tests where this bias is allowed for.

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