Letters to the Editor

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Reply to Horvath et al.

To the Editor:

The letter by Horvath et al. points out that the critical value based on the asymptotic distribution of the disequilibrium maximum-binomial likelihood (DMLB) test (Huang and Jiang 1999) is anticonservative. They show, on the basis of the exact critical values that they obtained, for affected-sib-pair data and the models considered in the study by Huang and Jiang (1999), that (1) when $\delta_p = 1$, the transmission/disequilibrium test (TDT [Falk and Rubinstein 1987; Terwilliger and Ott 1992; Spielman and Ewens 1993]) is more powerful than the DMLB, except in one case; (2) when $\delta_p = .8$ and $p = m$, the TDT is more powerful than the DMLB; (3) when $\delta_p = .8$, the DMLB is, "on average," more powerful than the TDT; and (4) when $\delta_p = .5$ or .3, the DMLB is more powerful than the TDT, except in one case.

We thank Horvath et al. for carrying out the exact calculation of the critical values of the DMLB and for pointing out the anticonservativeness of the asymptotic approximation used in our report. We agree that exact calculation should be used whenever possible. There are several points on which we would like to comment in this reply. First, in our report, we did not suggest that the DMLB should replace the TDT or any other linkage test. However, we believe that, in addition to the existing methods, the DMLB is an interesting approach when the extent of linkage disequilibrium (LD) is unknown. Second, we stated in our report that, when LD is maximum or nearly so, the power of the DMLB and that of the TDT are similar. The results by Horvath et al. show that, when $\delta_p = 1$, although the TDT tends to be more powerful than the DMLB, the difference in power is often not large. The median of the differences is .035; ~75% of the differences are <.05. The largest difference is .08, which occurs in one case. Third, the letter by Horvath et al. does not give a complete picture of the comparison. They did not compare the power of the TDT versus that of the DMLB, for any values of δ_p in the range $0 \leqslant \delta_p < .3$. In this range, the DMLB is more powerful than the TDT. When the extent of LD is unknown, meaningful conclusions regarding the comparison of any two linkage tests should be drawn on the basis of the consideration of the full range of LD, not just part of the range. Fourth, both our calculation and that by Horvath et al. are approximate with respect to the original likelihood-ratio form of the DMLB (eq. [7]) in Huang and Jiang 1999), because they are based on its score test statistic.

Horvath et al. also mentioned the case of candidate-gene study and the situation when LD is very weak. If we know the amount of LD, we should build this information into the analysis. For instance, in a candidate-gene study, we can fix the mixture parameter λ at 1 and 0 for a two-sided test in the DMLB likelihood (λ is defined in Huang and Jiang 1999). If we know that LD is very weak, we can let $\lambda = .5$ in the DMLB likelihood. In either case, it results in reduced degrees of freedom and increased power. However, the point of our report is to adaptively detect linkage when the amount of LD is unknown, such as when one is conducting a genomewide screen. The extent of LD may vary across different chromosome regions. Because the DMLB tends to be more powerful than the TDT when $0 \leqslant \delta_p <\sim .8$ and only slightly less powerful than the TDT when $\sim.8 < \delta_p \leqslant 1$, we believe that the overall conclusion of our report remains valid—that is, the DMLB has relatively robust and good power behavior in comparison with the TDT, when the whole range of LD is considered.

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