Letters to the Editor

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Reply to Whittemore and Shih

To the Editor:

We thank Whittemore and Shih for their thoughtful discussion of our paper and are indebted to them for detecting two errors in the estimate of the *P* value in gender skewing and the calculation of the component β. The former led us to underemphasize the significance of the gender skewing, whereas the latter approximation appears to have had little effect.

We agree that both the LOD-score method and the β analysis have failings, as discussed in our paper. Whittemore and Shih appropriately point out additional limitations. Parametric linkage analysis conceivably allows for θ to be determined as a function of gender skewing. For Leri-Weill dyschondrosteosis (LWD), where there is little evidence of genetic heterogeneity, the calculated relationship is likely to remain correct. The range of θ, however, is subject not only to errors from lack of appreciation of complexity, as Whittemore and Shih remind us, but also to genetic-model misspecification and, therefore, remains highly uncertain. It is worth noting that the largest sibships concordant for Hodgkin disease (HD) (i.e., those with four or five affected children, as shown in table 3 of our article) demonstrate the greatest sex concordance, supporting the assertion that, if there were to be an HD gene situated in the pseudoautosomal region (PAR), then it is rather more likely to be centromerically situated than what is suggested from the calculated θ of the complete data set (i.e., including table 2 of our article). The β analysis suffers from the inability to measure the genetic distance between the putative locus and the marker—here, phenotypic sex. Neither approach is ideal when the marker is nothing but the sex of the patient as reported in the literature.

We wish to continue to emphasize the speculative nature of the hypothesis that an HD gene resides in the PAR. This conjecture can only be validated by studies utilizing a distribution of molecular genetic markers within the PAR. Because the PAR can easily be overlooked in genomewide screens for linkage and because two lines of evidence, gender concordance and the unique family segregating both HD and LWD, lead to the suggestion of a PAR locus, we ask that this hypothesis not be overlooked should sufficient clinical samples ultimately become available to put it to the test.

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