Letter to the Editor

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Pseudoautosomal Linkage of Hodgkin Disease

To the Editor:

We wish to thank Horwitz and Wiernik for their interesting paper "Pseudoautosomal Linkage of Hodgkin Disease" (Horwitz and Wiernik 1999), even though we disagree with some of their conclusions. The authors combined two findings from the literature to propose a new direction in the genetic epidemiology of Hodgkin disease. The first finding is that of a pair of sisters concordant for both Hodgkin disease (MIM 236000) and the rare disorder Leri-Weill dyschondrosteosis (LWD) (MIM 127300) (Gokhale et al. 1995). The second finding is that LWD results from mutations and large deletions of the SHOX homeobox gene on the pseudoautosomal region of the short arms of the X and Y chromosomes (Belin et al. 1998; Shears et al. 1998). Horwitz and Wiernik conjecture that a gene for Hodgkin disease may also lie in this region.

This conjecture predicts an excess of sex concordance among pairs of relatives with Hodgkin disease, an excess that, in fact, has been reported for sibs (Grufferman et al. 1977). To investigate this prediction in a larger data set, Horwitz and Wiernik evaluated sex concordance in 102 affected sib pairs (ASPs) gathered from the world's literature. They found that 63 (62%) of the pairs were concordant (41 male-male and 22 female-female). Part of this excess concordance is likely explained by the higher incidence of Hodgkin disease among males than among females. After allowing for this fact, the authors conclude that the excess concordance is not statistically significant. They base their conclusion on the value 4.40 of a χ^2 test on 2 df ($P > .2$). In fact, the excess is statistically significant, because the value 4.40 of the likelihood ratio statistic of the null hypothesis of no concordance, allowing for a male excess risk, should be referred to a χ^2 distribution on 1 df ($P < .05$).

To further investigate their conjecture, Horwitz and Wiernik conducted a linkage analysis of the pseudoautosomal region, using sexual phenotype as the marker and based on the sex distribution within a sample of multiple-case families obtained from the literature and from Montefiore Medical Center. On the basis of a parametric analysis, the authors report a male recombination fraction (θ) of .254, which they interpret as evidence that the putative Hodgkin disease gene is in close proximity to the SHOX locus. Using an analysis based on the beta model proposed by Morton and colleagues (Morton 1996; Collins and Morton 1996), they conclude that a putative pseudoautosomal region (PAR) gene accounts for 29% of Hodgkin disease heritability in the United States. We believe that the authors have overinterpreted the results of both these analyses.

They have overinterpreted the results of the parametric analysis, because the models they fit to the data fail to account for the probable genetic heterogeneity of the disease. Instead, the models assume that a PAR gene is solely responsible for hereditary Hodgkin disease. It is well known that failure to account for such heterogeneity leads to overestimates of θ. Evidence that more than one gene is responsible for hereditary Hodgkin disease arises not only from data implicating the HLA region (Berberich et al. 1983; Chakravarti et al. 1986), but also from the high recurrence risk in MZ twins compared with DZ twins (Mack et al. 1995). Thus the authors are attributing greater precision to the estimate $\theta_{\text{male}} = .254$ than is warranted by the data.

In an attempt to estimate the fraction of hereditary Hodgkin disease due to a putative PAR gene, Horwitz and Wiernik fit Morton's beta model (Morton 1995; Collins and Morton 1996) to the sexual phenotypes of the 102 ASPs. They combined the estimate for beta obtained in this way with sibling recurrence risks from the literature to produce their 29% estimate. To clarify why this estimate is inappropriate, it is helpful to review the beta model. Suppose that there are m unlinked genes responsible for hereditary Hodgkin disease. The model assumes that the joint probability that two relatives are both affected, given their identical-by-descent (IBD) status for each of the m genes, is

$$P(D_1 = D_2 = 1 \mid \text{IBD}_1 = j_1,\ldots,\text{IBD}_m = j_m) = K^2 \exp\left[\sum_{\ell=1}^{m} j_\ell \beta_\ell\right] . \quad (1)$$

In this equation, D_1 and D_2 are indicators for Hodgkin disease status, K is the prevalence of disease in the general population, IBD_ℓ denotes IBD status for gene ℓ,

$\ell = 1,...,m$, and $\beta_\ell \geq 0$ measures the log contribution of gene ℓ to the sibs' phenotype correlation, $\ell = 1,...,m$. Equation (1) implies that two sibs are both affected with probability

$$P(D_1 = D_2 = 1 \mid \text{sibs}) = K^2\left[\sum_{j_1=0}^{2} \cdots \sum_{j_m=0}^{2} \pi(j_1,...,j_m) \exp\left(\sum_{\ell=1}^{m} j_\ell \beta_\ell\right)\right], \quad (2)$$

where

$$\pi(j_1,...,j_m) = \left(\frac{1}{4}\right)^m \prod_{\ell=1}^{m} \binom{2}{j_\ell} \quad (3)$$

is the joint probability that two sibs share j_ℓ alleles IBD at locus ℓ, $\ell = 1,...,m$. Substituting equation (3) into equation (2) gives

$$P(D_1 = D_2 = 1 \mid \text{sibs}) = K^2 \prod_{\ell=1}^{m} \left(\frac{1 + e^{\beta_\ell}}{2}\right)^2 . \quad (4)$$

Equation (4) determines the sibling recurrence risk λ_S as

$$\begin{aligned}\lambda_S &= K^{-1}P(D_2 = 1 \mid D_1 = 1, \text{sibs}) \\ &= K^{-2}P(D_1 = D_2 = 1 \mid \text{sibs}) \\ &= \prod_{\ell=1}^{m} \left(\frac{1 + e^{\beta_\ell}}{2}\right)^2 . \end{aligned} \quad (5)$$

According to equation (5), the fractional contribution of the PAR gene (gene 1) to the recurrence risk λ_S is

$$F_{\text{PAR}} = \frac{[(1 + e^{\beta_1})/2]^2}{\lambda_S} . \quad (6)$$

The parameter β_1 is estimable from IBD sharing data in affected sibs, because from equation (2) and Bayes's Rule the probability that two affected sibs share j alleles IBD at the PAR locus 1 is given by

$$z_j = \frac{\alpha_j e^{j\beta_1}}{\sum_{i=0}^{2} \alpha_i e^{i\beta_1}}, \; j = 0,1,2 . \quad (7)$$

In this equation, $\alpha_0 = 1/4$, $\alpha_1 = 1/2$, and $\alpha_2 = 1/4$ are the Mendelian probabilities that the sibs share 0, 1, and 2 alleles IBD at the PAR locus. Thus, in principle, one could (1) estimate β_1 from linkage data in the PAR, (2) estimate the sibling recurrence risk from epidemiological data, and (3) combine these two estimates in equation (6) to attribute a fractional contribution F_{PAR} of hereditary Hodgkin disease to the putative PAR gene. For example, the estimate $\hat{\beta}_1 = .562$, obtained by Horwitz and Wiernik, gives $F_{\text{PAR}} = .01$, using the recurrence risk $\lambda_S = 210$ of Hafez et al. (1985), and it gives $F_{\text{PAR}} = .27$, using the value $\lambda_S = 7$ of Grufferman et al. (1977). When β_1 is close to zero, $[(1 + e^{\beta_1})/2]^2 \sim e^{\beta_1}$ and equation (6) becomes $F_{\text{PAR}} \sim \exp(\beta_1 - \ln\lambda_s)$. This approximation gives $F_{\text{PAR}} = .01$ for $\lambda_S = 210$ and $F_{\text{PAR}} = .25$ for $\lambda_S = 7$. (Inexplicably, Horwitz and Wiernik used the ratio $\hat{\beta}_1/\ln\lambda_S$ for the fraction of hereditary Hodgkin disease due to a gene in the PAR. Thus, with $\hat{\beta}_1 = .562$, they estimated this fraction as .11 for $\lambda_S = 210$ and as .29 for $\lambda_S = 7$.)

In practice, however, such attribution is inappropriate. It requires the assumption that IBD status at the PAR gene equals IBD status at the marker (which is an arbitrary sex-specific locus). In fact, the unknown genetic distance between marker and PAR gene and the unknown penetrance of the PAR gene (which determines β_1) are completely confounded: highly penetrant genes more distal from the marker will yield the same estimates $\hat{\beta}_1$ as less-penetrant genes close to the marker.

In summary, IBD status at the PAR gene cannot be inferred from sexual phenotypes of ASPs, and thus equation (7) cannot be used to estimate β_1. This also can be seen by considering the usual nonparametric ASP test, which evaluates the mean number of alleles shared at the marker. ASPs of the same sex share an average of 1.5 marker alleles IBD, whereas ASPs of the opposite sex share an average of 0.5 such alleles. Letting n denote the number of sex-concordant pairs among the 102 sib pairs described by Horwitz and Wiernik, the ASP test is based on the score $1.5n + 0.5(102 - n) = n + \text{constant}$. The ASP test statistic is

$$T^2 = \frac{(n - 102p)^2}{102p(1 - p)} ,$$

where p denotes the null frequency of sex-concordant sib pairs. Using the estimate $P = (.593)^2 + (.407)^2 = .5173$, where .593 and .407 are the proportions of males and females, respectively, among the 204 sibs, we have $T^2 = 4.11$ for $n = 63$ sex-concordant pairs. This ASP test simply evaluates the statistical significance of the observed sex concordance among the 102 ASPs, allowing for excess Hodgkin disease risk in males. In conclusion, without genotype data for multiple markers in the p-terminal PAR, the only inferences possible are those concerning the magnitude of any excess sex concordance among ASPs; it is not possible to infer the location or relative importance of a PAR gene for Hodgkin disease.

These comments notwithstanding, we are grateful to the authors for their seminal and potentially important observations. Further progress in our understanding of the genetic etiology of Hodgkin disease clearly requires more detailed marker data among multiple-case families, both in the PAR and elsewhere in the genome.

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ALICE S. WHITTEMORE AND MEI-CHIUNG SHIH
Stanford University School of Medicine
Department of Health Research and Policy
Stanford

Electronic-Database Information

The URL for data in this article is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Hodgkin disease [MIM 236000] and LWD [MIM 127300])

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Address for correspondence and reprints: Dr. Alice Whittemore, Stanford University School of Medicine, Department of Health Research and Policy, Redwood Building, Room T204, Stanford, CA 94305. E-mail: alicesw@leland.stanford.edu

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