Letter to the Editor

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Sibling Recurrence Risk Ratio as a Measure of Genetic Effect: *Caveat Emptor!*

To the Editor:

The recent paper by Altmüller et al. (2001) is a laudable attempt to characterize successful and (mostly) unsuccessful genomewide scans of complex diseases. I wish to comment on one of the major findings in their study—that is, that the magnitude of the sibling recurrence risk ratio, λ_S, is not a predictor for the success or failure of genomewide scans (Altmüller et al. 2001, p. 943).

As perhaps the most widely used measure for familial aggregation of complex diseases, λ_S is often used as a measure of genetic effect and has thus been used for genetic modeling of complex diseases and for exclusion mapping in genomewide scans (for excluding chromosomal regions that may harbor genes that confer a sibling recurrence risk ratio of at least, say, 1.5; see, e.g., Cailhier et al. 2001 and Duffy et al. 2001). Although λ_S is indeed an excellent measure for familial aggregation of complex diseases, it is quite a quantum leap to use it as a measure of genetic effect, since, for almost all complex diseases, both environmental and genetic components—all of which are yet to be identified, in many cases—contribute to the disease susceptibility.

It has been shown that λ_S is sensitive to ascertainment bias and/or overreporting (Guo 1998). Even if the disease of interest has nothing to do with any genetic component, ascertainment bias alone can artificially inflate λ_S. In addition, in the complete absence of any genetic component, multiple interacting environmental factors shared by siblings would also yield a moderate or even high value of λ_S (Guo 2000*a*). In cases in which, in addition to environmental components, a genetic component does indeed contribute to familial aggregation, λ_S is a hodgepodge of genetic and environmental contributions, and, without the identification of genetic factors, environmental factors, and their interactions, it is difficult—if not impossible—to make a balance sheet as to how much effect is due to genes or to environmental factors (Risch et al. 1993; Guo 2000*b*). This is due to the fact that, even in ideal situations (i.e., time-constancy of genetic effect, random mating, no gene-environment correlation, etc.), λ_S can be decomposed as $\lambda_S = 1 + G + E + G \times E$, where G denotes the contribution from the genetic component, E denotes the contribution from the environmental component, and $G \times E$ denotes the contribution from gene-environment interactions (Guo 2000*b*).

It can be seen from the above formula that, in order to gauge the genetic contribution to λ_S, one has to know the effects of at least two of these factors—G, E, or $G \times E$—since the overall magnitude of λ_S can be measured fairly accurately, if it is done with care. It should be noted that, in measuring E and $G \times E$, it is necessary to measure the correlation coefficients of environmental effects and of the interaction between environmental and genetic effects, in addition to the identification of the gene or genes and the environmental factor or factors (Guo 2000*b*). These measurements have, unfortunately, hardly ever been performed so far in published genetic epidemiological studies. It also can be seen that, since genetic and environmental factors are entangled together, exclusion mapping can be a meaningless, make-believe exercise for multifactorial diseases.

With this in mind, it is perhaps not surprising to see in the article by Altmüller et al. (2001) that, inconsistent with the conventional view, the magnitude of λ_S does not predict the outcome of a genomewide scan. It can be further inferred that, in the case of exclusion mapping of complex diseases known to be multifactorial, it is futile—as well as, perhaps, illusional—to exclude chromosomal regions that may harbor genes conferring λ_S greater than a certain value. Given the theoretical analyses of λ_S and the empirical findings of Altmüller et al. (2001), we should exercise extreme caution when it comes to the use of λ_S as a measure of the genetic effect for complex diseases.

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