Am. J. Hum. Genet. 60:738, 1997

Reply to Farrall

To the Editor:

Farrall (1997 [in this issue]), in his comments about our previous letter (Greenberg et al. 1996), eloquently points out some of the advantages of affected-sib-pair (ASP) analysis. It may surprise him to learn that we do not disagree with most of his comments, but we do feel that a few of them could be potentially misleading.

Farrall (1997) says that "ASP tests are 'nonparametric' in the limited sense that the investigator does not have to declare (or have prior knowledge of) an explicit set of genetic parameters before undertaking a meaningful analysis" (p. 735). He could have added that one does not have the *option* of changing genetic parameters. One does not have to declare genetic parameters, because the design of the test is such that certain assumptions are *inherent* in the method. These assumptions are not obvious—and even may not be known—in the nonparametric methods. However, they are still there.

This critical point is illustrated in the Knapp et al. (1994) work that we cited in our previous letter (Greenberg et al. 1996). Knapp et al. showed that a particular ASP test (the mean test) has the same statistical properties as does an analysis assuming recessive inheritance. The test may be nonparametric in the sense that Farrall describes (i.e., in not having the option of changing the assumptions), but it is hardly model free in the usual understanding of that phrase.

Whittemore (1996) has gone beyond the Knapp et al. (1994) work and has demonstrated that implicit assumptions underlie *all* the nonparametric tests. The point of Whittemore's paper is that all these methods have built-in assumptions about the genetic model and that the efficiency and power of the methods of finding linkage will depend on how closely the origin of the data matches the assumptions of the method. From our point of view, we prefer the option of explicitly knowing or specifying what the assumptions are before undertaking an analysis—hence, our preference for LOD-score analysis.

Part of the intent of our letter was not to "raise the specter" (Farrall 1997) of an unhealthy obsession with ASP methods but to bring to the attention of the genetics community that this specter is already haunting us. We know of manuscripts that have not been published and of grants that have not been funded, simply because they failed to include ASP analysis, even though the characteristics of the diseases or populations under study did not warrant them. One of our correspondents said, of a grant that he was writing, that he knew that the ASP strategy that he was proposing was not the best approach for this study but that one had to "talk the talk" if one wanted to have a chance of getting funded. This kind of zeitgeist is not merely a specter but a malevolent spirit to be exorcised!

We appreciate Farrall's (1997) thoughtful comments, and we hope that this interchange will stimulate more people to think seriously about their analysis methods and to consciously select the best analysis method for the particular disease being studied and for their particular study design. The goal is to strive for the most rigorous science, not the most convenient science.

DAVID A. GREENBERG,[1] SUSAN E. HODGE,[2] VERONICA J. VIELAND,[3] AND M. ANNE SPENCE[4]

[1]*Departments of Psychiatry and Biomathematics, Mount Sinai Medical Center, and* [2]*New York State Psychiatric Institute and Columbia University, New York;* [3]*Departments of Preventive Medicine and Environmental Health and Psychiatry, University of Iowa College of Medicine, Iowa City; and* [4]*Department of Pediatrics, University of California, Irvine, Medical Center, Orange*

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Address for correspondence and reprints: Dr. David A. Greenberg, Department of Psychiatry, Box 1229, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: dag@shallot.salad.mssm.edu

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HLA Sharing and History of Miscarriage among Women with Rheumatoid Arthritis

To the Editor:

An increased frequency of recurrent spontaneous abortions (RSA), defined as three or more pregnancy losses without an identifiable cause, has been reported among women who share HLA alleles with their partner (Ober and Weitcamp 1990). A similar association has also been reported for women who have decreased fecundity (Ober et al. 1992). No specific HLA alleles have been identified as being the important etiological factor, raising the possibility that the observed sharing may