*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*

### References

Farrall M (1997) LOD wars: the affected-sib-pair paradigm strikes back! Am J Hum Genet 60:735–737 (in this issue)

Greenberg DA, Hodge SE, Vieland VJ, Spence MA (1996) Affecteds-only linkage methods are not a panacea. Am J Hum Genet 58:892–895

Knapp M, Seuchter SA, Baur MP (1994) Linkage analysis in nuclear families. II. Relationship between affected sib-pair tests and lod score analysis. Hum Hered 44:44–51

Whittemore AS (1996) Genome scanning for linkage: an overview. Am J Hum Genet 59:704–716

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



0002-9297/97/6003-0034$02.00

---

*Am. J. Hum. Genet. 60:738–740, 1997*

## 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

**Table 1**

**Maternal-Paternal Sharing of HLA DR Antigens and History of Miscarriage in Women Who Develop Rheumatoid Arthritis Postpartum**

| No. of HLA DR Antigens Shared | History of Miscarriage | | | Risk |
|---|---|---|---|---|
| | Yes | No | Total | |
| 2 or 1 | 10 | 26 | 36 | .28 |
| 0 | 6 | 49 | 55 | .11 |

NOTE.—Risk ratio = 2.54; 95% confidence interval (1.01, 6.39).

represent a marker for sharing of other closely linked susceptibility genes (Gill 1992).

Jin et al. (1995) recently corroborated these findings of HLA sharing among 123 couples in which the woman had a history of RSA and 76 couples with unexplained infertility. Sharing of HLA DR antigens was found to be in excess among couples with a history of RSA, whereas sharing of DQ antigens was of importance among couples with unexplained infertility. Jin et. al. (1995) also hypothesized that some associations between reproductive factors and autoimmune diseases may be due to a combined association with susceptibility genes in the HLA region (i.e., maternal possession of particular susceptibility genes increased the risk of autoimmune disease, and maternal-paternal sharing of the same genes was associated with a greater frequency of reproductive abnormalities). For example, rheumatoid arthritis (RA) has a well-characterized association with the HLA DR gene, in particular HLA DR4 (Ollier and Thomson 1992). Women with RA have also been found to be more likely to report a reduced fecundity (Nelson et al. 1993) and also be at increased risk of spontaneous abortions (Kaplan 1986; Shelton et al. 1994), although this latter finding has not been found in all studies in which it was investigated (Silman et al. 1988; Spector and Silman 1990; Nelson et al. 1992).

We have recently hypothesized that HLA sharing may also be associated with maternal onset of RA (Brennan et al. 1996). To investigate this hypothesis, we recruited 91 couples where the woman developed her first symptoms of RA within 12 mo of a livebirth pregnancy. Fifty-five of the couples shared no DR type, 34 shared one DR type, and 2 shared both DR types. Using the shared-allele test (Jin et al. 1995), we found that these were almost exactly the same frequencies as would be expected by chance, thus refuting the hypothesis that sharing of HLA DR antigens influenced the onset of RA. We did, however, detect a relationship between sharing of HLA DR antigens and reporting at least one miscarriage prior to the onset of RA (table 1). The percentage of women who reported at least one of their pregnancies ending in a miscarriage was greater among those who shared at least one HLA DR type with the father (28%) than among women with completely dissimilar DR type (11%). The risk ratio associated with sharing at least one DR antigen and reporting a miscarriage prior to the onset of RA was 2.5, 95% confidence interval (1.01, 6.39). Because of the high prevalence of women who were HLA DR4 positive (76%), it was not possible to investigate whether sharing of particular DR types explained this increased risk.

These 91 women are an atypical RA group, in that all were fertile and developed RA after a livebirth pregnancy. Also, none of the women had experienced three or more spontaneous abortions prior to the onset of disease. It is therefore not possible to discuss whether a simultaneous association exists between particular disease-susceptibility genes for RA and sharing of these genes causeing reduced fecundity or RSA. However, the observation of an increased prevalence of HLA DR sharing among women who report just one miscarriage, an effect not previously reported, does suggest that such associations may be particularly common among women with RA. Information from studies investigating reproductive outcome and RA that also incorporate data on maternal and paternal sharing of HLA DR alleles would therefore be of much interest.

PAUL BRENNAN
*Arthritis and Rheumatism Council Epidemiology Research Unit*
*University of Manchester Medical School*
*Manchester*

## References

Brennan P, Payton T, Ollier B, Silman A (1996) Maternal exposure to paternal HLA does not explain the postpartum increase in rheumatoid arthritis. Genet Epidemiol 13:411–418

Gill TJ III (1992) Influence of MHC and MHC-linked genes on reproduction. Am J Hum Genet 50:1–5

Jin K, Hong-Nerng H, Speed TP, Gill TJ III (1995) Reproductive failure and the major histocompatibility complex. Am J Hum Genet 56:1456–1467

Kaplan D (1986) Fetal wastage in patients with rheumatoid arthritis. J Rheumatol 135:875–877

Nelson JL, Koepsell TD, Dugowson CE, Voigt LF, Daling JR, Hansen JA (1993) Fecundity before disease onset in women with rheumatoid arthritis. Arthritis Rheum 36:7–14

Nelson JL, Voigt LF, Koepsell TD, Dugowson CE, Daling JR (1992) Pregnancy outcome in women with rheumatoid arthritis before disease onset. Br J Rheumatol 19:18–21

Ober C, Elias S, Kostyu DD, Hauck WW (1992) Decreased fecundability in Hutterite couples sharing HLA-DR. Am J Hum Genet 50:6–14

Ober C, Weitkamp L (1990) The immunogenetics of normal and abnormal pregnancy. In: Andreani D, Bompiani GD, DiMario U, Faulk WP, Galluzo A (eds) Immunobiology of

normal and abnormal pregnancy. John Wiley & Sons, London, pp 3–21

Ollier W, Thomson W (1992) Population genetics of rheumatoid arthritis. Rheum Dis Clin North Am 18:741–759

Shelton AJ, Harger JH, Dorman JS, Kuller LH, LaPorte RE, Gill TJ (1994) Association between familial autoimmune diseases and recurrent spontaneous abortions. Am J Reprod Immunol 32:82–87

Silman AJ, Roman E, Beral V, Brown A (1988) Adverse reproductive outcomes in women who subsequently develop rheumatoid arthritis. Ann Rheum Dis 47:979–981

Spector TD, Silman AJ (1990) Is poor pregnancy outcome a risk factor in rheumatoid arthritis? Ann Rheum Dis 49:12–14

Address for correspondence and reprints: Dr. Paul Brennan, ARC Epidemiology Research Unit, School of Epidemiology and Health Sciences, Stopford Building, The University of Manchester, Oxford Road, Manchester M13 9PT, United Kingdom. E-mail: paul@fsl.er.man.ac.uk



0002-9297/97/6003-0035$02.00

---

*Am. J. Hum. Genet. 60:740–742, 1997*

## The Phenotypic Difference Discards Sib-Pair QTL Linkage Information

*To the Editor:*

Kruglyak and Lander (1995) provide an important synthesis of methods for identity-by-descent (IBD) sib-pair linkage mapping, with an emphasis on the use of complete multipoint inheritance information for each sib pair. These procedures are implemented in the computer program MAPMAKER/SIBS, which performs interval mapping for dichotomous and quantitative traits. The authors present three methods for mapping quantitative trait loci (QTLs): a variant of the commonly used Haseman-Elston regression approach (Haseman and Elston 1972), a maximum-likelihood procedure involving variance components, and a rank-based nonparametric procedure. These approaches and related work (Amos and Elston 1989; Fulker and Cardon 1994; Olson 1995) use the magnitude of the difference in the sibling phenotype values for each sib pair as the observation for analysis. Linkage is detected if siblings sharing more alleles IBD have similar phenotypes (i.e., a small difference in the phenotype values), while siblings sharing fewer alleles IBD have less similar phenotypes. Such techniques have been used to detect linkage for a number of quantitative traits (e.g., Cardon et al. 1994; DeMeester et al. 1995). However, the exclusive reliance on the phenotypic differences may be due in large part to historical inertia. A likelihood argument is presented here to show that, under certain classical assumptions, the phenotypic differences do not contain the full likelihood information for QTL mapping. Furthermore, considerable gains in power to detect linkage can be achieved with an expanded likelihood model. The development here is related to previous work (Amos 1994; Amos et al. 1996), which incorporates the full set of phenotypic data using likelihood and robust quasi-likelihood methods. The purpose of this letter is not to endorse a particular approach but to spur research in alternative and perhaps more powerful linkage tests.

Using the notation from Kruglyak and Lander (1995), for the $i$th sib pair let $v_i$ be the number of alleles (0, 1, or 2) shared IBD by the siblings at a marker locus. For simplicity, the arguments here are initially developed under the assumption that the $v_i$ are known exactly—i.e., the marker is fully informative for each individual. However, the overall conclusions do not depend strongly on this assumption. The phenotypes of siblings 1 and 2 (arbitrarily ordered) in the $i$th pair are denoted $\phi_{1i},\phi_{2i}$, with difference $D_i=\phi_{1i} - \phi_{2i}$. The differences have mean zero, and are assumed to be normally distributed with variances $\sigma^2_{v_i} = \mathrm{Var}(D_i \mid v_i)$. The power to detect linkage derives from the fact that a marker linked to the QTL should exhibit $\sigma^2_0 > \sigma^2_1 > \sigma^2_2$, and Kruglyak and Lander (1995) recommend a test based on maximum-likelihood estimation of these variances. Note that from the value $D_i$ alone one cannot recover the original pair $\{\phi_{1i},\phi_{2i}\}$, and it is reasonable to speculate that the original phenotypes may carry additional information for linkage.

We assume that the phenotype pair is bivariate normally distributed, with $E(\phi_{1i}) = \mathrm{E}(\phi_{2i}) = \mu$, and $\mathrm{Var}(\phi_{1i}) = \mathrm{Var}(\phi_{2i}) = \xi^2$, regardless of IBD status. Here it is the correlation $\rho_{v_i} = \mathrm{corr}(\phi_{1i},\phi_{2i} \mid v_i)$ that varies with $v_i$, and a linked marker should exhibit $0 \leq \rho_0 < \rho_1 < \rho_2$. The use of correlations is a convenient reparameterization of the difference variances, with $\sigma^2_{v_i} = 2\,\xi^2\,(1 - \rho_{v_i})$.

With the bivariate normal density f, the likelihood for the full data is

$$L = \prod_i f(\phi_{1i}, \phi_{2i}; \mu, \xi^2, \rho_{v_i}) \,. \qquad (1)$$

This likelihood is relatively simple in form, and under the distributional assumptions the LOD score will provide the asymptotically most powerful test for linkage to the locus. The LOD score is computed by maximizing over the parameters, with the denominator subject to the null hypothesis constraint that the correlations are all equal. Unfortunately, this LOD based on the full likelihood is rarely used when performing sib-pair QTL linkage analysis, and it is important to understand the consequences of relying solely on the differences $D$. We proceed by noting that the difference $D_i$ and the *sum* of the phenotypes $S_i = \phi_{1i} + \phi_{2i}$ together completely specify the phenotype pair, and so the full data likelihood may be equivalently rewritten in terms of the pairs $\{D_i,S_i\}$.