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Nonparametric Linkage Tests Are Model Free

To the Editor:

I followed with interest the recent exchange between Greenberg et al. (1996, 1997) and Farrall (1997). A major point of contention is whether affected-sib-pair (ASP) and other nonparametric linkage tests are really model free. Greenberg et al. (1997) contend that, because such tests are equivalent to LOD score tests under particular genetic models, they in fact implicitly assume a model and are "hardly model free in the usual understanding of that phrase." Farrall argues that the tests are nonparametric in the sense that they do not require that a particular model be specified a priori. Who is right?

The argument can be settled by referring to standard statistical literature on nonparametric statistics. Lindgren (1968, p. 400) defines "distribution free" (or "model free," or "nonparametric") tests as "procedures involving a statistic whose distribution (at least under the null hypothesis) does not depend on the particular form of the population distribution" (also see Cox and Hinkley 1974; Kendall and Stuart 1979); that is, such tests are *valid* regardless of the true (unknown) genetic parameters, in the standard sense that they give the correct false-positive rate. ASP and other nonparametric linkage tests are certainly model free by this definition (as are parametric LOD score tests under a single model). In order for nonparametric tests to be useful, they should also maintain reasonable power to detect an effect (in our case, linkage) under a broad range of alternative hypotheses (in our case, genetic parameters). ASP and other nonparametric linkage tests have been designed with this in mind, and some tests have been explicitly shown to maintain high power under a broad range of genetic models (Kruglyak et al. 1996).

Greenberg et al. (1996, 1997) correctly point out that a particular nonparametric test can be equivalent to a parametric test with a specific choice of parameters. However, this *does not* mean that the nonparametric test *assumes* this choice of parameters—key properties of the test hold for *any* choice of a genetic model. The equivalence simply means that the nonparametric test is most sensitive to a particular alternative hypothesis, while its model-free nature assures reasonable power under all alternatives. The ASP mean test may be equivalent to a LOD score test under a recessive model, but it still has high power to detect a dominant-acting locus, and its validity does not depend on the genetic model at all.

Nonparametric linkage tests, including those based on ASPs, are thus certainly model free in the classic sense of the term. The debate between parametric and nonparametric statistics is not new, and the trade-offs are well known (Cox and Hinkley 1974). Researchers using parametric methods when the correct model is unknown face the following choices: guess right and you win; guess wrong and you can lose big; or fish over all possible models and pay the statistical price. Nonparametric methods are designed to provide protection against the last two choices, at the cost of some loss of power relative to the correct guess. The interesting issue in the design of such methods is how to achieve a minimal loss of power while retaining robustness to a maximal range of alternatives.

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