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Am. J. Hum. Genet. 64:1246–1248, 1999

Reply to Baron

To the Editor:

Baron (1999 [in this issue]) criticizes our recent report on ascertainment strategies to detect susceptibility alleles of differing frequencies (Badner et al. 1998). In that report, we showed that, when the susceptibility allele frequency was rare, extended pedigrees had greater power to detect linkage than did nuclear families. However, when the susceptibility allele frequency was common, extended pedigrees were no more powerful than nuclear families, and the relatively densely affected pedigrees we simulated had a loss of power, probably secondary to increased homozygosity in the parents. This was true for the single-locus and the two-locus additive and multiplicative models that we simulated. Therefore, we concluded that, for rare susceptibility alleles, extended pedigrees had greater power to detect linkage. However, for common susceptibility alleles, nuclear families were at least as powerful as extended pedigrees and, because of the greater ease of ascertainment and full genotyping, were preferable to collect.

Baron's arguments are that (1) Extended pedigrees are valuable, and we claimed that they are not, (2) We simulated pedigrees that do not correspond to the real world, (3) Parametric analytical methods are valid, and we claimed they are not, and (4) Previous publications by our group are inconsistent with the 1998 report. None of these arguments have merit. Baron has also made criticisms about previous findings of our group that were not mentioned in our 1998 report.

Value of Extended Pedigrees in Complex Genetic Disorders.—Traditionally, extended pedigrees were understood to be best, always, for finding linkage to illness. We demonstrate that this is not true when the susceptibility allele is common. However, we do not say that extended pedigrees are never valuable for detection of linkage in complex genetic traits. We stated, "These [extended large pedigrees] *may not* be the best family structures for detection of linkage for a complex trait especially when parametric methods are used" (italics added), which means that we did not rule out the possibility that extended large pedigrees would be powerful under some circumstances. Even when the allele

frequency is common, extended pedigrees are not "of little benefit for detection to linkage," as Baron (1999) claims we stated. But they do not offer an advantage over nuclear families when the susceptibility allele is common, and, because they tend to be harder to collect and genotype completely, it is better to collect nuclear families when starting a new study. This does not mean throwing out the extended pedigrees already collected and genotyped; they may still be informative.

Validity of Pedigrees We Simulated.—Baron's letter criticizes the fact that only the last two generations were assumed to be genotyped in our simulations and that we fixed our pedigree structures prior to simulation. Although in some studies it may be possible to genotype more than two generations, this is hardly common, and it is often difficult to genotype the parental generation in disorders with adult ages at onset. We do mention in our discussion (Badner et al. 1998) that it is possible that larger, more-completely genotyped pedigrees would have increased power over the pedigrees that we simulated. However, it is not clear how representative these pedigrees are in linkage studies of complex genetic traits.

We did fix the pedigree structure prior to simulation. Pedigrees are not ascertained randomly for linkage studies, and usually they are genotyped only when they meet particular criteria (e.g., at least two affected sibs or two or more generations affected). In determining the power for a particular pedigree sample, it is reasonable to simulate the observed pedigree structures with the genetic model of interest. This enabled us to see the interaction of pedigree structure and susceptibility allele frequency.

Validity of Parametric Analysis.—Baron (1999) states that parametric analyses are worthwhile because they have detected several putative linkages in bipolar disorder. A particular analytical method (such as parametric linkage analysis) may not be appropriate for a particular type of genetic model and/or pedigree structure because of low power to detect linkage, relative to other methods that could be used. This does not mean that it is impossible to detect linkage with such a method, nor does it mean that evidence of linkage arising from such methods is always invalid. However, if multiple methods are used to detect linkage, some of which have low power to detect linkage for the pedigree structure and inheritance pattern of the susceptibility gene being analyzed, modest evidence of linkage may be overwhelmed by false negatives obtained by methods of low power. This may have been the case in the analysis of Knowles et al. (1998), which used multiple analytical methods to detect linkage between bipolar disorder and chromosome 18 and discounted the significant results that were observed, in single-point nonparametric analysis, because of multiple testing.

No Conflict with Previous Studies by Our Group.—Our earlier publications did report on pedigrees collected when we subscribed to the traditional consensus of collection of large pedigrees for linkage studies. In the course of analyzing these pedigrees, we came to the insight reported in Badner et al. (1998) and have concentrated our analyses on nonparametric methods, especially affected sib pair linkage studies (Detera-Wadleigh et al. 1996; Berrettini et al. 1997). In our more recent pedigree collections, we have focused on ascertaining smaller families (Detera-Wadleigh et al. 1997).

Linkage between Bipolar Disorder and Chromosome 18.—The report of the linkage of chromosome 18 and bipolar disorder as a "confirmed" finding (Berrettini et al. 1997) in our series of extended pedigrees does not conflict with Badner et al. (1998), for the reasons mentioned above. Although how to determine what constitutes a confirmed linkage finding in a complex genetic trait may be argued, the fact is that two independent studies (Berrettini et al. 1994; Stine et al. 1995) show moderate evidence of linkage in the same region, and other independent pedigree sample analyses have shown modest evidence of linkage, using nonparametric methods (Badner and Goldin 1997). It is debatable whether, as shown by Berrettini et al. (1997), having a small proportion of tests from multiple analytic methods exceed thresholds delineated by Lander and Kruglyak (Lander and Kruglyak 1995) denotes significant evidence of linkage. However, it has been shown that, when multiple genome scans show modest evidence of linkage in the same region, this can be very significant statistically when taken as a whole, even when nonreplicating studies are included (Badner and Goldin, in press).

Baron's letter cites Rice (1997) in support of the lack of general acceptance of the linkage findings between bipolar disorder and chromosome 18. What Rice (1997) actually stated was this: "Taken as a whole, the results would appear suggestive, but not definitive for linkage to a bipolar susceptibility locus on chromosome 18." Although this does not indicate support of the linkage as a confirmed finding, it does not indicate a complete lack of acceptance of linkage either. Although it is true that there is no one "correct" strategy for linkage detection in complex genetic traits, nontraditional strategies may detect linkage where strategies developed for simple genetic traits have failed.

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Am. J. Hum. Genet. 64:1248–1252, 1999

Down-Weighting of Multiple Affected Sib Pairs Leads to Biased Likelihood-Ratio Tests, under the Assumption of No Linkage

To the Editor:

In large nuclear families with several affected siblings, affected-sib-pair analyses are often based on all the possible pairs of affected siblings that can be formed. Because of concern about dependence between sibling pairs from the same family, it has been recommended that, when tests for linkage are constructed, pairs from families with a large number of affected siblings be given less weight (e.g., see Daly and Lander 1996; Davis and Weeks 1997). Various weighting schemes have been proposed (Hodge 1984; Suarez and Van Eerdewegh 1984; Sham et al. 1997). However, several authors have shown in simulations that likelihood-ratio tests weighted according to the proposal of Suarez and Van Eerdewegh (1984) are quite conservative (Meunier et al. 1997; Abel and Müller-Myhsok 1998). Likelihood-ratio tests behave differently from other tests for linkage in sibling pairs, such as the means test, and therefore should be treated differently.

It is important to distinguish between the performance of a test statistic under the null hypothesis of no linkage (type I error) and the performance when there is linkage (power). Sham et al. (1997), Blackwelder and Elston (1985), and Suarez and Van Eerdewegh (1984) have shown that, for any weighting function, the means test statistic is unbiased and that, for large numbers of families, the test has the expected type I error under the null hypothesis of no linkage. Different weighting functions can, however, improve the power of the linkage tests. Sham et al. (1997) also have shown that the most powerful weighting function for the means test will be a function of the true genetic model.

However, linkage tests based on the likelihood ratio, such as the maximum-likelihood score (MLS) described by Risch (1990), Holmans (1993), and Kruglyak and Lander (1995), can have a biased distribution (i.e., one that is not χ^2) when there are multiple affected sib pairs per family, even under the null hypothesis. Unweighted likelihood-ratio tests can be slightly anticonservative (Kong et al. 1997; Abel and Müller-Myhsok 1998), and, as noted elsewhere, the commonly used weights of Suarez and Van Eerdewegh (1984), which weight each pair by $2/k$, where k is the number of affected siblings, can be extremely conservative.

The deviation from the expected distribution for likelihood-ratio tests under the null hypothesis is due to the distribution of the identity by descent (IBD) scores from multiple sibling pairs. Although it has been shown that the IBD statuses of any two sib pairs from the same family are independent (Suarez and Hodge 1979; Hodge 1984; Blackwelder and Elston 1985), the pairs are not jointly independent (Kong et al. 1997). Also, the distribution of IBD sharing in large sibships will be highly skewed. When small numbers of sibships are analyzed by the means test, the skewness of the IBD distribution can lead to P values that are too small (Kong et al. 1997; Sham et al. 1997), but the impact of skewness decreases as the sample size increases and the central-limit theorem