Letters to the Editor

Am. J. Hum. Genet. 64:1246, 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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References

Badner JA, Gershon ES, Goldin LR (1998) Optimal ascertainment strategies to detect linkage to common disease alleles. Am J Hum Genet 63:880–888

Badner JA, Goldin LR (1997) Bipolar disorder and chromosome 18: an analysis of multiple data sets. Genet Epidemiol 14:569–574

———. Meta-analysis of linkage studies. Genet Epidemiol (in press)

Baron M (1999) Optimal ascertainment strategies to detect linkage to common disease alleles. Am J Hum Genet 64: 1243–1246 (in this issue)

Berrettini WH, Ferraro TN, Goldin LR, Detera-Wadleigh SD, Choi H, Muniec D, Guroff JJ, et al (1997) A linkage study of bipolar illness. Arch Gen Psychiatry 54:27–35

Berrettini WH, Ferraro TN, Goldin LR, Weeks DE, Detera-Wadleigh S, Nurnberger JI Jr, Gershon ES (1994) Chromosome 18 DNA markers and manic-depressive illness: evidence for a susceptibility gene. Proc Natl Acad Sci USA 91: 5918–5921

Detera-Wadleigh SD, Badner JA, Goldin LR, Berrettini WH, Sanders AR, Rollins DY, Turner G, et al (1996) Affected-sib-pair analyses reveal support of prior evidence for a susceptibility locus for bipolar disorder, on 21q. Am J Hum Genet 58:1279–1285

Detera-Wadleigh SD, Badner JA, Yoshikawa T, Sanders AR, Goldin LR, Turner G, Rollins DY, et al (1997) Initial genome scan of the NIMH genetics initiative bipolar pedigrees: chromosomes 4, 7, 9, 18, 19, 20, and 21q. Am J Med Genet 74:254–262

Knowles JA, Rao PA, Cox-Matise T, Loth JE, de Jesus GM, Levine L, Das K, et al (1998) No evidence for significant linkage between bipolar affective disorder and chromosome 18 pericentromeric markers in a large series of multiplex extended pedigrees. Am J Hum Genet 62:916–924

Lander ES, Kruglyak L (1995) Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 11:241–247

Rice J (1997) Genetic analysis of bipolar disorder: summary of GAW10. Genet Epidemiol 14:549–561

Stine OC, Xu J, Koskela R, McMahon FJ, Gschwend M, Friddle C, Clark CD, et al (1995) Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. Am J Hum Genet 57:1384–1394

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