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Reply to Laberge

To the Editor:

Dr. Laberge's reply to our letter (De Braekeleer and Melancon 1990) only deals with myotonic dystrophy (MD) in Saguenay-Lac-St-Jean, whereas our letter discussed the issue of cystic fibrosis (CF) carrier screening and not that of MD screening after 1983. Furthermore, carrier screening of an autosomal recessive disorder, such as CF, and of an autosomal dominant disease, such as MD, have completely different implications. Finally, there is no argument in Dr. Laberge's letter which weakens our conclusions. Therefore, we reaffirm that organizing a mass CF carrier screening in Saguenay-Lac-St-Jean is premature.

MARC DE BRAEKELEER*AND
MARCEL J. MELANÇON†
*Genetics, Université du Québec à Chicoutimi, and
†Groupe de Recherche en Génétique et Ethique,
Collège deChicoutimi, Québec*

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Can a Susceptibility Locus for Schizophrenia Be Excluded from Chromosome 5q11-13?

To the Editor:

McGuffin et al. (1990) reanalyzed data from five studies designed to assess evidence for linkage between markers on chromosome 5q and a susceptibility locus for schizophrenia. Overall results from this analysis are purported to exclude the existence of a major susceptibility locus from chromosome 5q and therefore consider Sherrington et al.'s (1988) previously positive findings as likely to have been due to chance. Weeks et al. (1990) show specifically, however, that multiple testing of several disease classifications and subsequent selection of the classification maximizing the evidence for linkage could not have so greatly increased the probability of falsely concluding in favor of linkage, when it was nonexistent, as to allow "chance" to be a likely explanation for Sherrington et al.'s findings. We wish to point out, however, that specification of an incorrect genetic model may lead to falsely negative evidence for linkage. In this letter we point out considerations for evaluating results from an analysis which shows exclusion of a locus from a genomic region.

The approach which has been considered by investigators attempting to isolate a gene for schizophrenia has consisted of choosing a simple genetic model based on population parameters for the disease. Williamson and Amos (1990) show that, in the absence of linkage, failure to choose a correct model does not, asymptotically, lead to falsely positive evidence for linkage. However, as shown by Clerget-Darpoux et al. (1986), for a simple Mendelian trait, failure to choose the correct penetrance of the disease allele results in both a biased estimate of the recombination fraction and a decrease of the maximum lod score. The choice of an incorrect genetic model may therefore fail to yield correct evidence for linkage. In addition, within some region of a linked marker locus, misspecification of the genetic model can lead to false exclusion of linkage, as can be seen in results from numerous analytic and simulation studies (e.g., Clerget-Darpoux et al. 1986; Rice et al. 1989; Risch et al. 1989). The size of this exclusion region is determined by the amount of information in the sample and by how closely the specified model fits the data. Results from multipoint linkage

are particularly affected by the genetic model that is chosen, and any type of misspecification of the genetic model can lead to the false exclusion of a linked marker. For instance, false exclusions occur when the gene frequency is underestimated (Risch and Giuffra 1990) and/or when genetic heterogeneity in the causation of the trait is ignored (Martinez and Goldin 1990).

For complex diseases such as schizophrenia there can be no doubt that simple Mendelian models are inadequate to describe the familial patterns of disease (McGue et al. 1985). The genetic model chosen by McGuffin et al. (1990) assumes that disease allele frequency is .005, that penetrance among heterozygous individuals is .85, and that penetrance among homozygous individuals of 1.0, with the penetrance among homozygous normal individuals (the sporadic risk) being set to .0001 (correcting an apparent error in McGuffin et al.'s paper) in order to obtain a population prevalence of .0086. This choice of parameters is inconsistent with available published data regarding recurrence (Faraone and Tsuang 1985), because the predicted recurrence risk of 42% for offspring of affected individuals (over 98% of whom are heterozygotes) is much higher than the 12% risk that has been observed empirically. To account for this discrepancy between the model and the observed risk, the sporadic risk in the model should be increased and the penetrance among heterozygotes should be decreased. Moreover, since McGuffin et al. use the broadest definition of affection for schizophrenia, the sporadic risk should be higher, to reflect the higher population frequency of schizophrenia under this definition. Finally, the sporadic risk for individuals with affected relatives is likely to be higher, because of their shared environment, than is the population sporadic risk, as can be seen by the higher risk for fraternal cotwins than for siblings (Faraone and Tsuang 1985). For small recombination fractions, the effect of misspecifying the sporadic risk is to score affected individuals as likely recombinants, thus providing possibly false evidence against linkage.

We additionally point out that the data provided by McGuffin et al. provides significant evidence for genetic heterogeneity. As seen in table 3 of McGuffin et al. (1990), mild support for linkage is provided for the newly reported data outside the region for which multiple markers were available. When the admixture test (McGuffin et al. 1990, table 4) is applied to the combined data, both the homogeneous and the heterogeneous linkage tests are significant with the same type I error (.001), with the susceptibility locus being outside the region of the two linked markers when genetic homogeneity among the families is assumed and being within this linkage map when genetic heterogeneity is allowed. The observed admixture among families in the pooled sample could have resulted from a variety of sources, including (1) variation in ascertainment schemes, which would affect how well the chosen model fit the data, (2) clinical heterogeneity in assessments, as well as (3) true genetic heterogeneity. It is obvious, however, that disregarding families having positive lod scores will lead to the rejection of linkage in the resulting subsample of families. If the study protocols are similar enough to allow combined analysis of all the data, then identification of the "linked" and "unlinked" families can be performed objectively, independently of their study origin. This assignment can be made, for instance, on the basis of their posterior probability of being of the "linked" type (Ott 1985). McGuffin et al's finding is consistent with the cosegregation of a disease locus and a linked marker(s) in some of the families.

Although two-point linkage analysis is asymptotically robust to misspecification of the genetic model when the disease locus and a marker locus segregate independently, the inverse has not been proved, and, moreover, misspecification of the genetic model can lead to false exclusion for some genomic region(s). An approach that would allow a valid LOD score test for linkage for schizophrenia can be accomplished by maximimizing the likelihood over the segregation parameters and the recombination fraction and by then comparing this likelihood with that obtained by maximizing the likelihood over the segregation parameters, under the assumption that the recombination fraction is .5 (Ott 1985). For complex diseases such as schizophrenia, the modeling should ideally include parameters allowing for an increase in disease liability conferred by the affection status of one's relatives, as well as the effects of age and any other important covariables on an individual's disease liability. The regressive approach for the analysis of pedigree data was extended (Bonney et al. 1988) to allow the analysis of a trait and a linked marker, with allowance for the effects that family members' phenotypes may have on an individual's genotype-specific risk for a disease. Although this approach requires further theoretical studies, a recent application in the study of cutaneous malignant melanoma (Demenais et al. 1990) shows that allowing the genotypic-specific risk to depend on the

phenotypes of an individual's relatives may have major importance for the detection of linkage.

When the data are not used to estimate relevant segregation parameters, and when exclusion of linkage between a putative marker and a susceptibility locus occurs, the interpretation of the results must include the possibility that the proposed genetic model could not adequately describe the familial pattern of the disease, as well as the possibility that the marker and disease-susceptibility loci are unlinked. For complex diseases, results from multipoint analyses must be interpreted with caution, because the methods are strongly affected by any misspecification of the genetic model.

C. I. Amos, M. Martinez, and S. J. Bale
Family Studies Section, National Cancer Institute, and Clinical Neurogenetics Branch, National Institute of Mental Health Bethesda, MD

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Reply to Amos et al.

To the Editor:

We are grateful to Amos et al. for their interest in our paper (McGuffin et al. 1990). While we agree with much of what they say, we are concerned that, in focusing on certain technical details, they may have become so preoccupied with the trees that they are failing to see the forest. Although the details are complicated, the gist of our paper was simple; the most likely interpretation of disparities between published results on linkage of a schizophrenia susceptibility gene to markers in the chromosome 5q11-q13 region is that no linkage is present and that the sole positive study of Sherrington et al. is mistaken. Indeed, since the submission of our paper there has now been one further published study (Aschauer et al. 1990), which again fails to find chromosome 5q linkage and provides negative results which are completely consistent with our own and all other negative studies.

The problem for psychiatric genetics is that linkage between a schizophrenia gene and chromosome 5q markers has become psychiatry's version of cold nuclear fusion; both were dramatic and appealing findings which everyone would like to be true but which no one can replicate. However, the singular merit of