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Address for correspondence and reprints: Dr. Joseph D. Terwilliger, Columbia University, Unit 109, 1150 St. Nicholas Avenue, Room 520C, New York, NY 10032. E-mail: jdt3@columbia.edu

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Interpretation of Linkage Data for a Huntington-Like Disorder Mapping to 4p15.3

To The Editor:

Kambouris et al. (2000) report on the mapping of a neurodegenerative disorder on the basis of a sibship of 10 individuals whose parents are first cousins. Using a model of autosomal recessive inheritance, linkage analysis detects a maximum two-point LOD score (Z_{max}) of 3.03 at recombination fraction (θ) 0.

The authors of the report postulate the genetic interval as a 7-cM region bounded by *D4S2366* and *D4S2983,* because all affected individuals are homozygous for the two markers (*D4S431* and *D4S394*) in between. Figure 1 in their article demonstrates a haplotype analysis in which the parents (III:2 and III:3), although first cousins, share very few alleles in the putative linked region.

First, the marker order presented in the report's figure 2*b* contradicts that presented in its haplotype analysis (fig. 1) and in the multipoint analysis (fig. 2*a*). The Marshfield sex-averaged linkage map places *D4S2366* between *D4S431* and *D4S394*. The haplotype and multipoint analyses place *D4S2366* centromeric to *D4S431* and *D4S394*. Since the parents share no alleles for *D4S2366,* interposing *D4S2366* between *D4S431* and *D4S394* would abolish this region of putative homozygosity by descent among the affected individuals. It appears more likely that it is by chance alone that the two parents share a "2" allele for *D4S431* and a "1" allele for *D4S394*. For example, the Foundation Jean Dausset CEPH genotype database reveals that the most common allele (205 bp) for *D4S394* has a frequency of 41%. Thus, if allele 1 for *D4S394* in the report's figure 1 is the 205-bp allele, the chances are 41% that parent III:2 inherited the 1 allele from the unrelated parent (II:1). Without genotype data for the parents and/or siblings of III:2 and III:3, identity by descent cannot be assumed.

Kambouris et al. make the assumption that the disorder is recessive, apparently because of the consanguinity in the family. Although they report $Z_{max} = 3.03$ at $\theta = 0$, under the assumption of 50% penetrance, the two-point LOD scores were likely calculated under a model of 100% penetrance. The two-point LOD scores would be expected to be lower under a model of 50% penetrance (two-point LOD score 2.7 at $\theta = 0$ for the four fully linked markers). The data could also support a model of autosomal dominance with reduced penetrance with the disorder segregating with the red haplotype, if the disease is not penetrant in parent III:2 and individual IV:8. The same argument could be made for parent III:3 and individual IV:10 and the purple haplotype. Testing a dominant model assuming 90% penetrance demonstrated a Z_{max} of 1.94 at $\theta = 0$, with marker *D4S412* (data not shown).

Even if it were assumed that the mode of inheritance is truly autosomal recessive, homozygous genotypes among the affected individuals are not absolutely required. If the linkage to this region is true, and if the red and purple haplotypes contain noncomplementing mutated alleles, the genetic interval would actually be defined by the telomeric recombination event in IV:2 and the centromeric recombination events in IV:4—that is, by *D4S3023* and *D4S1599,* defining a nonrecombinant region of 15 cM.

Finally, Kambouris et al. note that only chromosome 4 markers were genotyped. Testing markers at the already mapped locus on chromosome 20, for a similar Huntington-like disorder, would certainly seem pertinent. A two-point LOD score of 3.3 (not 3.0) is the generally accepted criterion for a 5% significance level (Lander and Schork 1994). A complete genome screen may well reveal another locus in which the parents are heterozygous for a common haplotype with a more convincing region of homozygosity.

MARCI M. LESPERANCE[1]
AND MARGIT BURMEISTER[2,3,4]
Departments of [1]Otolaryngology–Head and Neck Surgery, [2]Psychiatry, and [3]Human Genetics and [4]Mental Health Research Institute, University of Michigan Health System, Ann Arbor

Electronic-Database Information

The URL for data in this article is as follows:

Foundation Jean Dausset CEPH, http://www.cephb.fr

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Address for correspondence and reprints: Dr. Marci M. Lesperance, Otolaryngology–Head and Neck Surgery, F6905 Mott Box 0241, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0241. E-mail: lesperan@umich.edu

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Reply to Lesperance and Burmeister

To the Editor:

Lesperance and Burmeister rightly draw attention to a discrepancy, in the placement of D4S2366, between that presented in haplotype/multipoint analysis and that presented in the Marshfield sex-averaged linkage map. The precise position of D4S2366 in relation to D4S431 and D4S394 is open to question, in the absence of their placement on current physical maps. Our placement of D4S2366 was based on its assignment 4–5 cM and 12–13 cM from the 4p telomere in the CHLC and Marshfield sex-averaged maps, respectively. Both a LOD score (3.03) and a homozygosity LOD score (4.71) were presented, because, as pointed out by Lesperance and Burmeister, although the parents were first cousins, relatively few alleles were shared in the linkage interval. Nonparametric linkage (NPL) analysis (data not shown) based on inherited-by-descent allele sharing among affected individuals was also performed, using multiple markers and genotyping data from all pedigree members. This analytical approach is least likely to be misled through inherited-by-state allele sharing, is least sensitive to specification of allele frequencies, and is model free (Kruglyak et al. 1996). Multipoint NPL analysis of markers D4S3023, D4S2366, D4S431, D4S394, D4S2983, and D4S1599 resulted in a Z score of 5.31 or level of significance $P < .00001$ (Kruglyak et al. 1996), indicating, with a high level of confidence, that affected individuals share by descent the 15-cM region between D4S3023 and D4S1599. On the basis of such data, it is our opinion that a whole-genome scan in search of more robust linkage is not warranted. We sought to consolidate evidence that the region encompassing D4S431 and D4S394 was homozygous by descent (HBD) in affected individuals, by genotyping them for markers D4S3007 and D4S2935, which are positioned between D4S431 and D4S394, in both the Généthon and Marshfield sex-averaged linkage maps. However, D4S3007 and D4S2935 were noninformative and partially informative, respectively, in the family studied. Given ambiguity in the placement of D4S2366, the 15-cM region defined by D4S3023 and D4S1599 should be regarded as the candidate interval, with initial focus on a putative region HBD between D4S2366 and D4S2983. Given the extremely rare nature of the disease studied and the extensive consanguinity in the pedigree, we strongly believe that this is an autosomal recessive disorder. However, in consideration of the fact that 50% of individuals within the sibship are affected, we did discuss the possibility of autosomal dominant inheritance with germline mosaicism explaining the absence of disease in either parent. A 90%-penetrant autosomal dominant disease, as suggested by Lesperance and Burmeister, cannot be excluded. Finally, the parametric LOD score of 3.03 is indeed calculated on the basis of 100% penetrance. The 50% figure that appeared in the original manuscript was a typographical error.

MARIOS KAMBOURIS[1,2] AND BRIAN F. MEYER[1]
[1]*King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; and* [2]*Yale University School of Medicine, New Haven*

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Address for correspondence and reprints: Dr. Marios Kambouris, King Faisal Specialist Hospital & Research Centre, P.O. Box 3354 – MBC #03, Riyadh 11211, Saudi Arabia. E-mail: marios.kambouris@yale.edu

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