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References

Kambouris M, Bohlega S, Al-Tahan A, Meyer BF (2000) Localization of the gene for a novel autosomal recessive neurodegenerative Huntington-like disorder to 4p15.3. Am J Hum Genet 66:445–452

Lander ES, Schork NJ (1994) Genetic dissection of complex traits. Science 265:2037–2048

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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.

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References

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

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