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Transmission-Ratio Distortion at Xp11.4-p21.1 in Type 1 Diabetes

To the Editor:

Naumova et al. (1998) reported a deviation from the expected Mendelian 1:1 ratio of grandpaternal/grandmaternal alleles at loci in Xp11.4-p21.1 in the children of 47 families not selected on the basis of the disease status of the children. The transmission-ratio distortion (TRD) was found only among male offspring and was manifested as a bias in favor of the inheritance of the alleles of the maternal grandfather. The critical region, containing the putative TRD locus, named "*DMS1,*" was mapped to an interval bounded by DXS538 and DXS7 and peaking at DXS1068.

These observations might have an impact on the results of a study in which we have provided evidence of linkage to type 1 diabetes mellitus (MIM 222100), in the same region of chromosome X (Cucca et al. 1998). The possibility of TRD at chromosome Xp gives rise to the question of whether the diabetes-linkage results are indeed disease specific. The following evidence suggests that it is highly unlikely that the *DMS1* locus is responsible for the chromosome Xp linkage to type 1 diabetes.

We genotyped DXS1068 (a marker that was at the peak of our linkage curve) in two sample sets of control families not ascertained on the basis of the disease status of the children. These control families were from the Centre d'Etude du Polymorphisme Humaine (Fondation Jean Dausset/CEPH) and from a population-based sam-

ple from the town of Busselton, Australia, and included 61 large pedigrees with 603 children and 220 families with 525 children, respectively (Hill et al. 1995). Single-point allele sharing in these families with multiple sibships was corrected by means of the method proposed by Hodge (1984), as implemented in the software GENOME ANALYSIS SYSTEM, version 2.0. We obtained 51% sharing, by sib pairs, of one allele identical by descent (252.6 sharing one allele and 243.4 sharing no alleles; $P = .68$). This compares with 60.5% sharing for DXS1068 in 580 type 1 diabetic sib pair families (193 sharing one allele identical by descent and 126 sharing no alleles in a single-point analysis; $P = 2 \times 10^{-4}$). Hence, there is no evidence of TRD in these nondiabetic families that were analyzed in the same way that we analyzed the diabetic families.

We typed both 255 discordant (affected/unaffected) independent sib pairs from the United Kingdom and Sardinian families for DXS1068. We obtained identity-by-descent values of 77 and 86 for sharing one and no alleles, respectively, for all discordant pairs (47.6%); the corresponding values were 25 and 29 for male/male pairs only (46.3%). The trend toward <50% allele sharing in discordant sib pairs is consistent with a type 1 diabetes–specific effect.

The putative *DMS1* TRD locus near the DXS1068 locus affects only male progeny, whereas the strongest linkage that we observed for DXS1068 was in male/female pairs (Cucca et al 1998). The linkage of the DXS1068 region to type 1 diabetes was strongly concentrated in the 97 of 580 families that had human leukocyte antigen (HLA) DR3/X (X is not DR4) sib pairs (multipoint MLS = 3.5 at DXS1068). Some weak evidence of linkage was present also in the 195 DR3/4 sib pairs (multipoint MLS = .75 at DXS1068), and no evidence of linkage was obtained in the other 288 families with affected sib pairs (Cucca et al. 1998). We evaluated linkage on chromosome X, conditioning the data according to the genotype at the HLA *IDDM1* major locus on chromosome 6p21, because, in a large data set from Sardinia, the United Kingdom, and the United States, there was a strong increase in the male:female (M:F) ratio, which was almost exclusively restricted to patients with the DR3/X genotype (M:F ratio = 1.7; $P = 4.7 \times 10^{-7}$), compared with a ratio of 1.0 in the DR4/Y category (Y is not DR3), with a small effect in DR3/4 patients (M:F ratio = 1.2; $P = .03$) (Cucca et al. 1998). Hence, both the evidence of linkage and the bias in the M:F ratio were concentrated in the families with patients positive for the HLA-DR3, which is one of the two main predisposing haplotypes at the HLA/*IDDM1* major locus. These data suggest an interaction between HLA-DR3 haplotypes and the diabetes locus on chromosome X, which is unlikely to be caused by an effect of the putative *DMS1* locus. Furthermore, both in the unaffected parents and siblings of the United Kingdom and in the Sardinian families who were DR3/3 homozygotes, the ratio was reversed: 56 males and 80 females (0.7; $P = .04$) compared with an M:F ratio of 2.2 in DR3/3 patients ($P = 1.3 \times 10^{-6}$), thereby providing another control for our results (Cucca et al. 1998).

These results indicate that it is unlikely that the type 1 diabetes linkage that we have observed is explained by the *DMS1* locus. TRD could, however, have a significant effect on the interpretation of linkage studies of polygenes in common diseases in which increases in allele sharing at the disease locus may be very small. The possibility of TRD should be ruled out in disease studies (Eaves et al. 1999).

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Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for type 1 diabetes mellitus [MIM 222100])

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Predominance of the T14484C Mutation in French-Canadian Families with Leber Hereditary Optic Neuropathy Is Due to a Founder Effect

To the Editor:

The Leber hereditary optic neuropathy (LHON) phenotype was first defined, more than 125 years ago, as a maternally inherited optic neuropathy that primarily affects young adult men (Leber 1871). Loss of central vision may be acute or subacute, and peripheral vision is preserved. Slow delayed recovery can occur, but relative central scotomata usually remain (Johns et al. 1993). The chronic stage of LHON is characterized by optic atrophy (MIM 535000).

LHON is associated with three primary mtDNA mutations, all of which occur in genes coding for subunits of complex I of the mitochondrial respiratory chain: G3460A in *ND1,* G11778A in *ND4,* and T14484C in *ND6* (MIM 516006.0001) (Howell et al. 1995). All three of these mutations alter evolutionarily conserved amino acids and are not found in control individuals. The relative frequency of the three primary LHON mtDNA mutations varies considerably in different populations, although G11778A is the most common worldwide. We have recently found that T14484C is by far the most common mutation in French-Canadian families with LHON (Macmillan et al. 1998). The results of previous studies of mutation profiles of several metabolic disorders have demonstrated founder effects, including phenylketonuria (Rozen et al. 1994) and familial hyperchylomicronemia (De Braekeleer et al. 1991), in the French-Canadian population.

To test the hypothesis that the predominance of the T14484C mutation in French-Canadian families with LHON is caused by a founder effect, we sequenced a segment of the mtDNA displacement (D) loop and a segment of the control region from French-Canadian families with the T14484C mutation. Variation in these noncoding regions has been used extensively to study the evolution of modern populations. The regions sequenced included hypervariable regions (HVR) I and II (Vigilant et al. 1989). The D-loop region extends from nucleotide (nt) 189 backward through 0 to nt 16024 of the 16,569-bp mtDNA. The control region extends from nt 189 forward, toward the tRNAs. These two regions contain the fastest-evolving regions of mtDNA (Upholt and Dawid 1977), which have an estimated rate of evolution that is 2.8–5 times that of the remainder of the mitochondrial genome (Aquadro and Greenberg 1983; Cann et al. 1984). The average nucleotide-sequence variation in this region has been calculated to be 1.7% (Aquadro and Greenberg 1983). We reviewed the records of patients with suspected LHON who were independently referred, for molecular diagnosis, to the Montreal Neurological Hospital DNA Diagnostic Laboratory. By cycle sequencing with the use of a New England Biolabs kit (manual) or dye-labeled dideoxy terminators on an ABI system (automated), we sequenced regions that included HVR I and HVR II in the following individuals: one member of each French-Canadian family with the T14484C mutation, one member of a French-Canadian family with the G11778A mutation, and one member of a French-Canadian family without a family history of LHON and with none of the three primary LHON mutations. Sequencing was done in two reactions, by use of the following primer pairs: L15996 and H16401 (which includes HVR I) and L29 and H408 (which includes HVR II; Vigilant et al. 1989). "L" refers to "light" strand and "H" refers to "heavy" strand, and the numbers refer to the Cambridge sequence (Anderson et al. 1981). The institutional review boards of the Montreal Neurological Hospital and the University of Illinois at Chicago approved this study.

We analyzed 27 independently referred French-Canadian families with LHON and the T14484C mutation, all of which were homoplasmic for the T14484C mutation. We found eight homoplasmic transition mutations (C16069T, T16126C, G16213A, A73G, G185A, G228A, A263G, and C295T; table 1), compared with the Cambridge sequence, in the families with the T14484C mutation. Of the 27 families analyzed, 26 shared identical substitutions at all eight sites that were different from the Cambridge sequence. Six of these mutations were found only in families with the T14484C mutation and not in either the family with the G11778A family or the family without LHON (table 1). The mutated sites were distributed throughout the D-loop and control region: one was located in the large central conserved sequence block (CSB; A73G), one (G228A) was in CSB 1, two (T16126C and G16213A) were in HVR I, three (G185A, A263G, and C295T) were in HVR II, and one (C16069T) was just outside HVR I.

In addition, 22/27 families with LHON and the T14484C mutation had a C insertion in the homopolymeric stretch of C's before the T at position 310. All 27