Evidence for a Novel Type 1 Diabetes Susceptibility Locus on Chromosome 8

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Type 1 diabetes results from a combination of genetic susceptibility and environmental exposures. Susceptibility loci other than HLA and the insulin gene remain to be identified to account for the degree of familial clustering observed in this disorder. Early genome-wide scans provided suggestive evidence of linkage on chromosome 8q, prompting detailed analysis of this region. A total of 20 microsatellite markers spanning an 88-cM region of 8q11-24 were genotyped in 24 type 1 diabetes pedigrees from Wisconsin that contained 39 affected sib-pairs. Multipoint linkage analyses provided close to suggestive evidence of linkage, with a multipoint logarithm of odds score (MLS) of 2.4 and Genehunter nonparametric logarithm of odds score (NPL) of 2.7 (P = 0.003). There is also evidence of linkage disequilibrium at peak marker D8S1823 for the 217-bp allele (P = 0.037) using the pedigree disequilibrium test. Although our sample size was small, the multiple tests were consistent and our preliminary results suggested that 8q24 may harbor a novel population-specific type 1 diabetes susceptibility gene. Continued investigation of this region for a novel type 1 diabetes susceptibility gene appears justified. Diabetes 51 (Suppl. 3): S316–S319, 2002

RESULTS AND DISCUSSION

Multipoint linkage analyses of 39 ASPs from 24 Wisconsin pedigrees provided close to suggestive evidence of linkage, with an MLS of 2.4 (Fig. 1) and Genehunter NPL of 2.7 (P = 0.003) (Fig. 2). Reversing the order of markers D8S1823 and D8S269 did not change these values (data not shown). There is also evidence of LD at marker D8S1823 (the location of the linkage peak) for the 217-bp allele (P = 0.037) using the PDT (Table 1). This allele was present in the founder individuals (parents) from the Wisconsin population.

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Received for publication 1 March 2002 and accepted in revised form 21 May 2002.

M.L.S. has received research funding from Cerylid Biosciences.

ASP, affected sib-pair; LD, linkage disequilibrium; LOD, logarithm of odds; MLS, multipoint logarithm of odds score; NPL, nonparametric logarithm of odds; PDT, pedigree disequilibrium test.

The symposium and the publication of this article have been made possible by an unrestricted educational grant from Servier, Paris.
population at a frequency of 0.43. There was no evidence of LD with any of the remaining microsatellite markers. Our preliminary data therefore suggest that 8q24 may harbor a novel population-specific type 1 diabetes susceptibility gene.

The linkage peak of Davies et al. (1) at D8S556, located between our typed markers D8S88 and D8S2320, is 9 cM proximal to our peak marker D8S1823. The peak of Concannon et al. (4) at D8S1779 (genetically mapped between D8S2320 and D8S1694) is 2.5 cM proximal to D8S1823. The more distal peak of the two peaks detected by Cucca et al. (3), located between D8S198 (1.7 cM proximal to D8S1823) and D8S281 (1.2 cM distal to D8S1823), lies within our region of linkage. Additional conditional multipoint analyses of the U.K. data from Professor John Todd’s group (http://www-gene.cimr.cam.ac.uk/todd) indicate that their evidence for linkage across a broad 50-cM region from D8S273 to D8S198, which encompasses the linkage peak observed in this analysis, is greatest in HLA-identical sibs (MLS 2.2) and those sharing a DR3/DR4 genotype (MLS 1.5). It is interesting to note that on stratification of this admittedly small dataset, 23 (59%) of the 39 Wisconsin ASPs shared an HLA-A/-B/-DR haplotype, and 21 ASPs (54%) shared the DR3/DR4 combination. The latter is considerably higher than the proportion of DR3/DR4 heterozygotes in a population-based sample of type 1 diabetes case subjects (38%) and control subjects (5%) from Wisconsin (9), suggesting that the putative locus on 8q24 may interact with the HLA region.

The sample size used for our study is small, especially when compared with other recent type 1 diabetes studies. The estimated locus-specific λs for D8S1823 (the marker closest to the linkage peak) is 1.6 and, based on the work of Risch (10–12), this result suggests that we would require ~300–400 ASPs for 95% power to detect a LOD score of 3.

The families studied were all recruited from Wisconsin. In 1989 (when the families in this investigation were recruited), the Wisconsin population could be described as fairly homogeneous, primarily middle-class, small-town or rural, and of northern European Caucasian descent (9). Additionally, in 1970–1979, southern Wisconsin had one of the highest rates of type 1 diabetes in the U.S., with an incidence of 18.2 cases (under 15 years of age) per 100,000 individuals (13). The patients and relatives studied are thus likely to possess overall reduced genetic heterogeneity, especially when compared with large published heterogeneous studies using resources such as the Human
Biological Data Interchange and U.K. Warren Repository, possibly explaining the relatively modest linkage scores achieved by other studies of this region (1,3,4). It is conceivable that expanding the original 96 Caucasian U.K.-born families (1) to 357 U.K. and 236 U.S. families (3) or 250 U.K. and 366 U.S. families (4) may have increased heterogeneity sufficiently to diminish the previously suggestive multipoint linkage value.

In the future, we intend to investigate the association in already-collected Wisconsin-born case and control subjects (14). Evaluation of other Midwest U.S. populations for comparison with this region of linkage may also be fruitful. Independent confirmation in a second dataset from a comparable population would provide considerable support for this locus. Because our results are close to suggestive linkage using the strict criteria of Lander and Kruglyak (15) and multiple approaches provide consistent evidence for a susceptibility locus, continued investigation of this region for a novel type 1 diabetes susceptibility gene is warranted.

ACKNOWLEDGMENTS
This work was funded by a Juvenile Diabetes Research Foundation Grant 1-1999-139.

We wish to thank the study participants and the late Dr. Michael Sheehy. We also thank Dr. Grant Morahan for initiating our investigation of chromosome 8q and Joanne Pendleton for technical assistance.

REFERENCES
3. Cucca F, Esposito L, Goy JV, Merriman ME, Wilson AJ, Reed PW, Bain SC, Todd JA: Investigation of linkage of chromosome 8 to type 1 diabetes:

### TABLE 1
PDT results for microsatellite marker DSS1823

<table>
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<th>Allele (bp)</th>
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<tr>
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<tr>
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</tr>
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FIG. 2. Genehunter 2.1 NPL results, using founder allele frequencies.


