Brief Genetics Report

Investigation of Linkage of Chromosome 8 to Type 1 Diabetes

Multipoint Analysis and Exclusion Mapping of Human Chromosome 8 in 593 Affected Sib-Pair Families From the U.K. and U.S.

Francesco Cucca, Laura Esposito, Juliet V. Goy, Marilyn E. Merriman, Amanda J. Wilson, Peter W. Reed, Stephen C. Bain, and John A. Todd

Type 1 diabetes is a common multifactorial disease that is strongly clustered in families: the sibling risk-to-population prevalence ratio (λ_s) is 15 (6%/0.4%) (1). Two loci, *IDDM1* in the major histocompatibility complex (MHC) on chromosome 6p21 and *IDDM2* in the insulin gene (*INS*) region of chromosome 11p15.5 can account for ~50% of the observed familial clustering (1). Locus-specific λ_s values (1) in 356 U.K. affected sib-pair families (2) for *IDDM1* and *IDDM2* are 3.0 and 1.3, respectively, or 41 and 8%, assuming a multiplicative model (J.A.T., unpublished observations). The rapid reduction in risk from first- to second- to third-degree relatives of type 1 diabetic patients (3) and whole genome scanning of a spontaneous mouse model of autoimmune type 1 diabetes (4,5) suggest that other genes may account for the rest of the familial clustering (1,4,5). In humans, two genome-wide scans, both based on the analysis of affected sib pairs, have been published so far (6,7), with the larger scan evaluating 290 markers in 96 U.K. families (data were analyzed in 93 of these families, so henceforth, this scan will be referred to as the 93 U.K. family scan) (6). The main conclusions of these studies were that the presence elsewhere in the genome of a second gene with an effect similar to *IDDM1* ($\lambda_s = 3$) is unlikely, and that other genes with $\lambda_s < 3$ are involved. Subsequently, additional evidence for linkage to some of these and other regions has been reported (8–10).

From the Wellcome Trust Centre for Human Genetics (F.C., L.E., J.V.G., M.E.M., A.J.W., P.W.R., J.A.T.), Nuffield Department of Surgery, University of Oxford, Headington, Oxford; and the Department of Medicine (S.C.B.), University of Birmingham, Birmingham Heartlands Hospital, Birmingham, U.K.

Address correspondence and reprint requests to Prof. John Todd, Wellcome Trust Centre for Human Genetics, Windmill Road, Headington, Oxford, OX3 7BN, U.K. E-mail: john.todd@well.ox.ac.uk.

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L.E. and J.V.G. contributed equally to this work. J.A.T. has received consulting fees and research grant support from Merck.

λ_s, sibling risk-to-population prevalence ratio; LOD, logarithm of odds; MHC, major histocompatibility complex; MLS, maximum LOD score.

In our previous genome scan using 93 U.K. families, apart from *IDDM1* and *IDDM2*, chromosome 8q had the highest maximum logarithm of odds (LOD) score (maximum LOD score [MLS] = 2.6 at marker *D8S556*) (6). However, our initial map contained 61 intervals of ≥20 centimorgans (cM) that contained no markers, and the linkage data were analyzed in a single pointwise fashion. In the present report, we have reduced the number of these intervals from 61 to 9 by typing an additional 76 markers, giving a total of 366 markers at an average density of 9.8 cM and average information content of 68%. The results from the 93 U.K. families were evaluated by multipoint analysis using MAPMAKER/SIBS (11). (Raw data are available at http://www.well.ox.ac.uk/~plyons.) Eleven chromosome regions had multipoint MLS ≥1.0: MHC *TNFa* (*IDDM1*, MLS = 11; multipoint estimate of $\lambda_s = 2.87$), *D6S311-D6S441* (*IDDM5*, MLS = 2.4; $\lambda_s = 1.8$), *D11S922-INS* (*IDDM2*, MLS = 2.3; $\lambda_s = 2.1$), *D13S71-D13S159* (MLS = 2.0; $\lambda_s = 1.27$), *D8S88-D8S198* (MLS = 1.7; $\lambda_s = 1.25$), *D6S281-DK6Q27* (*IDDM8*, MLS = 1.7; $\lambda_s = 1.23$), *D17S926-D17S513* (MLS = 1.7; $\lambda_s = 1.85$), *D10S193-D10S220* (*IDDM10*, MLS = 1.3; $\lambda_s = 1.19$), *D3S1303-D3S1279* (MLS = 1.2; $\lambda_s = 1.44$), D17S784 (MLS = 1.1; $\lambda_s = 1.66$), and *D13S192-D13S120* (MLS = 1.0; $\lambda_s = 1.16$).

Given these chromosome 8 results and that linkage of chromosome 8p has been reported by another group (7), chromosome 8 was therefore chosen for follow-up analysis, using 17 markers, in an additional 500 affected sib-pair families (Fig. 1). All subjects in this study were Caucasian and had at least two affected siblings per family; both parents were included and typed. U.K. families ($n = 339$) had one sibling diagnosed at <17 years of age and the other at <29 years of age. In another 18 U.K. families, both siblings were >16 years of age at diagnosis but <29 years of age. All grandparents were Caucasian and born in the U.K. (2). U.S. multiplex families ($n = 218$) had at least one sibling diagnosed at <17 years of age and the other at <29 years of age. In 18 other U.S. families, both siblings were >16 years of age at diagnosis but <29 years of age (12). In the 30 U.K. and U.S. families containing more than two affected siblings, only the first two diagnosed were included in this study. Most of chromosome

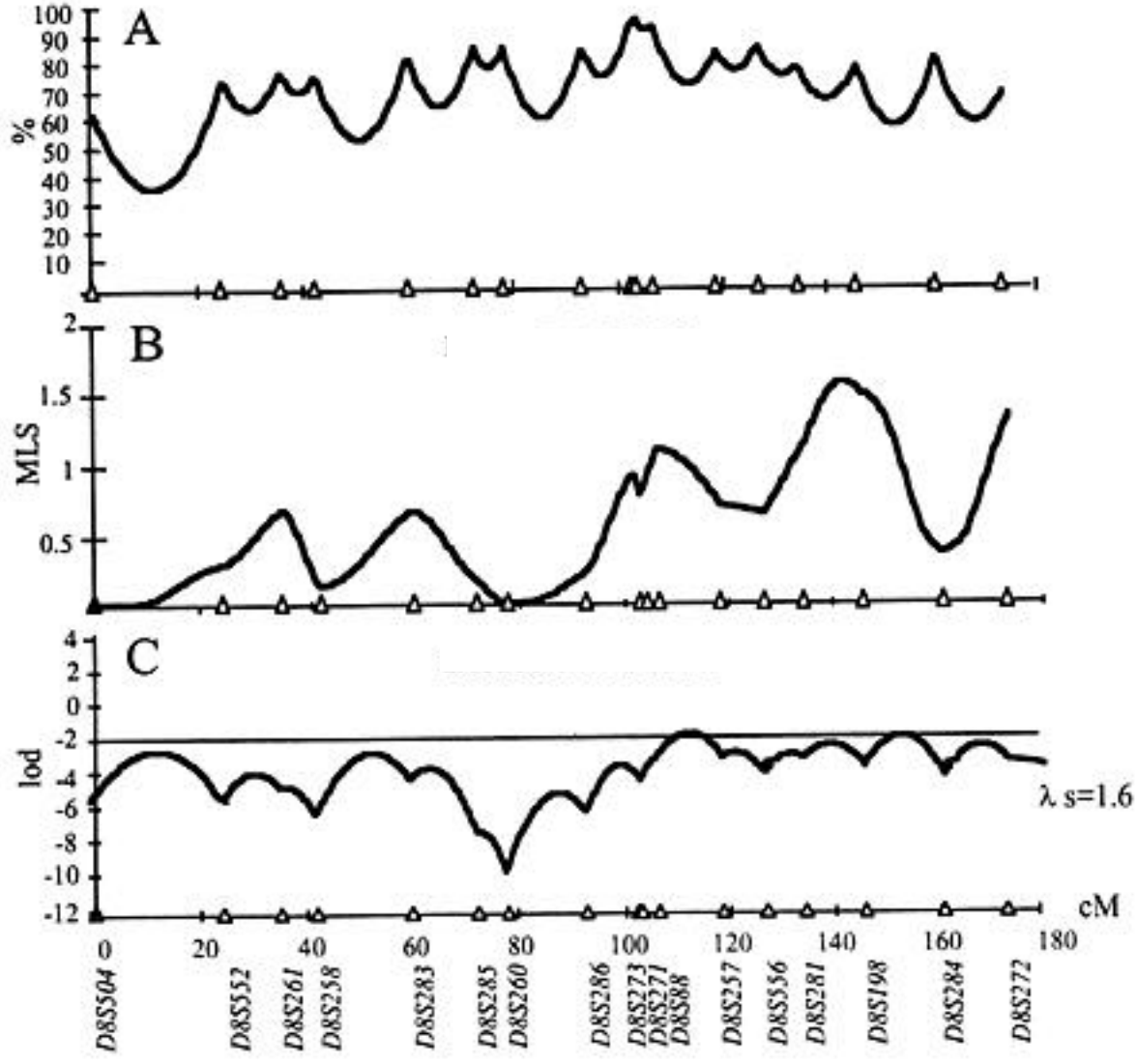

FIG. 1. Information content of families (*A*), multipoint linkage analysis (with dominance variance) (*B*), and exclusion mapping (*C*) of chromosome 8 in 593 affected sib-pair families using MAPMAKER/SIBS (11). LOD scores for exclusion mapping were computed under the assumption of no dominance variance for the hypothesis λ_s = 1.6. △, position of markers on map.

8 was at least 60% informative, with the main exception being the 8pter-8p22 region (*D8S504-D8S552*), which had only 47% average informativeness (Fig. 1*A*). Increased evidence of linkage was not obtained, however, with a peak MLS of 1.6 at *D8S198* (Fig. 1*B*; λ_s = 1.09) and all of chromosome 8 excluded at LOD –2 for gene effects at λ_s = 1.6 in the 593 families (Fig. 1*C*). It is unlikely that a diabetes gene with λ_s ≥1.6 exists on chromosome 8 in these families. There were no significant differences in linkage results between U.K. and U.S. families (not shown).

It appears, therefore, that in families from the U.K., *IDDM1*/MHC is the major locus. Nevertheless, analyses of the NOD mouse model of type 1 diabetes indicate that the MHC gene region is necessary, but not sufficient, to cause the disease (4,5). Other genes must be involved, but they are likely to have modest individual contributions to familial clustering. To detect non-MHC genes with modest effects using standard affected sib-pair linkage strategies, enormous, if not impractical, clinical resources would be required. It is evident that association-based or haplotype sharing methods, both at the genome-wide level and within intervals of potential interest identified by genome scanning, must be employed, including the identification and analysis of gene variants that could affect expression or activity of their products in pathways relevant to the etiology of type 1 diabetes.

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