Brief Genetics Reports

Mapping NIDDM Susceptibility Loci in French Families

Studies With Markers in the Region of *NIDDM1* on Chromosome 2q

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Hanis et al. (1) have recently reported the mapping of a major susceptibility locus for NIDDM to human chromosome 2q37 in Mexican-Americans through a genomewide linkage scan. They have provided evidence that this locus is linked to NIDDM and may account for 30% of the familial clustering of NIDDM in this population. They have proposed that this locus be designated *NIDDM1*. Lander and Kruglyak (2) have recently suggested that in complex disorders, stringent significance levels and replication studies in independent data sets are required to validate a true linkage (2). The findings in Mexican-Americans at the *NIDDM1* locus satisfy the statistical levels for a positive linkage. Therefore, it is interesting to assess the role of *NIDDM1* by linkage analyses in other ethnic groups.

Here we report the analyses of the markers D2S125 and D2S140, located in the vicinity of *NIDDM1*, in NIDDM sib pairs from 172 Caucasian families from France. Families were ascertained if they comprised at least two siblings with NIDDM (3). Affected status was determined by clinical and biological examinations, including oral glucose tolerance testing. Two different categories of affected status based on severity of hyperglycemia were considered for linkage studies. We used both conservative criteria for NIDDM (referred to as "overt NIDDM") as defined by the World Health Organization (WHO), which yielded 466 affected individuals, of whom 88% were being treated with oral hypoglycemic agents or insulin, and less-stringent criteria for affected status (referred to as "all-affected"), including overt NIDDM (466 subjects), impaired glucose tolerance according to WHO criteria (44 subjects), and mild fasting hyperglycemia defined by a fasting plasma glucose value of >6.1 mmol/l on two separate measurements (73 subjects), which yielded 573 affected individuals. The resulting maximum numbers of affected sib pairs were 260 and 450 when using the stringent and less-stringent diagnostic criteria, respectively. Genotypes were determined using a nonradioactive STRP (simple tandem repeat polymorphism) genotyping procedure (3). Analyses were performed using the maximum logarithm of odds (LOD) score (MLS) method as proposed by Risch (4). The likelihood of the observed marker data among affected sib pairs is maximized as a function of identity by descent (IBD) (0, 1, or 2) probabilities (z0, z1, z2) and compared to the likelihood of the marker data with IBD probabilities equal to 1/4, 1/2, and 1/4 under the null hypothesis of no linkage by an LOD score test (MLS). Power of the MLS test can be increased by imposing constraints on the z parameters, and 2ln10MLS follows a mixture of χ^2 tests with 1 and 2 df (5). This approach can account for nonindependent sib pairs from multiplex sibships with s affected individuals by multiplying the LOD score of each pair by $2/s$. This method has recently been extended to multipoint analysis and is implemented in the program MAPMAKER/SIBS (6).

D2S125, the marker most linked to NIDDM in Mexican-Americans, showed no evidence for linkage with either overt NIDDM (among 256 sib pairs) or all-affected (among 412 sib pairs) using the MLS method (Table 1). In contrast, D2S140, located 3 cM from D2S125, showed an excess of allele sharing both among 256 overt NIDDM sib pairs (MLS 1.196, P = 0.016) and among the 449 all-affected sib pairs (MLS 1.65, P = 0.005) (Table 1). When weighting nonindependent sib pairs from multiple affected sibships, the indication for linkage at D2S140 was less significant (P = 0.04; Table 1). Multipoint analyses led to MLSs of 0.58 (P = 0.07) and 0.94 (P = 0.031) with overt NIDDM and all-affected status, respectively; when using weight, these values were 0.31 (NS) and 0.32 (NS), respectively.

We did not find evidence for linkage between the D2S125 locus and NIDDM in affected sib pairs of French origin. Analyses of the D2S140 locus, which is located 3 cM from D2S125, provided some evidence suggestive of linkage with overt NIDDM and with affected status under a broader definition. Discrepancies between the results for the two markers cannot be explained by differences in marker information

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IBD, identity by descent; LOD, logarithm of odds; MLS, maximum LOD score; WHO, World Health Organization.

TABLE 1
Results of linkage analyses of NIDDM with markers at D2S125 and D2S140 using the MLS method

		Without weight					With weight				
	n	z0	z1	z2	MLS	*P* value	z0	z1	z2	MLS	*P* value
Overt NIDDM											
D2S125	239	0.248	0.500	0.251	0.001	NS	0.250	0.500	0.250	0.000	NS
D2S140	256	0.181	0.500	0.319	1.196	0.016	0.181	0.500	0.318	0.809	0.042
All-affected											
D2S125	384	0.241	0.482	0.277	0.238	NS	0.243	0.500	0.257	0.014	NS
D2S140	449	0.195	0.490	0.315	1.651	0.005	0.206	0.478	0.316	0.833	0.039

n, number of affected sib pairs included in the analysis. z0, z1, z2 are the estimated probabilities of sharing 0, 1, or 2 alleles IBD among affected sibpairs. All-affected and overt NIDDM refer to the definitions of affected status. The all-affected group includes NIDDM patients and other individuals with either glucose intolerance or mild fasting hyperglycemia (large sense of definition of the affected status); in the overt NIDDM group, diagnosis of NIDDM was in a narrow sense and only sibpairs with NIDDM were considered affected.

(the estimation of the heterozygosity in our data was 0.71 for D2S140 and 0.84 for D2S125) or by the proportion of genotyped individuals among parents and affected and unaffected siblings. Lander and Kruglyak (2) have suggested that replication of a positive linkage requires a *P* value of ≤0.01, which could be reached in our data only at the D2S140 locus, although not when weighting nonindependent sib pairs. However, as shown in a recent simulation study, weighting the LOD scores of each pair by 2/*s* in sibships with *s* affected individuals can be too conservative (7). Multipoint analyses did not give conclusive evidence for linkage with the *NIDDM1* locus in our population. Moreover, linkage could not be excluded at a λ_s (ratio of risk in sibs of an affected individual to the risk in the general population) value of 1.36, which corresponds to the estimated genetic effect attributable to *NIDDM1* in Mexican-Americans (1), but only at the upper limit of the 1-LOD confidence interval with all affected sib pairs (MLS < −2 for λ_s = 1.7). Uncertainties in the reference linkage map with respect to the order and distance between markers have prevented precise localization of *NIDDM1*. In the Mexican-American data set, *NIDDM1* maps closest to D2S125 under some assumptions, whereas under others, it is nearer to D2S140 (N.J. Cox, personal communication). The results of our studies in French families suggest that *NIDDM1* may be closer to D2S140 than to D2S125.

In conclusion, it is unlikely that *NIDDM1* is a major diabetogenic locus in French Caucasians, but our data do not exclude the involvement of this locus in a subset of our NIDDM patients. The discrepancies of the linkage results between French and Mexican-American populations regarding the *NIDDM1* locus may reflect the clinical heterogeneity of human NIDDM, due to genetic heterogeneity between ethnic groups. Whether the gene *NIDDM1* plays a role at all in French Caucasians needs further studies that include analyses of additional markers in the region and analyses of additional affected sib pairs.

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