Linkage of Genetic Markers on Human Chromosomes 20 and 12 to NIDDM in Caucasian Sib Pairs With a History of Diabetic Nephropathy

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The potential contribution of maturity-onset diabetes of the young (MODY) genes to NIDDM susceptibility in African-American and Caucasian NIDDM-affected sibling pairs with a history of adult-onset diabetic nephropathy has been evaluated. Evidence for linkage to NIDDM was found with polymorphic loci that map to the long arms of human chromosomes 20 and 12 in regions containing the MODY1 and MODY3 genes. Nonparametric analysis of chromosome 20 inheritance data collected with the MODY1-linked marker D20S197 provides evidence for linkage to NIDDM with a *P* value of 0.005 in Caucasian sib pairs using affected sibpair (ASP) analyses. Nonparametric analysis of chromosome 12 inheritance data collected with the MODY3-linked markers D12S349 and D12S86 provides evidence for linkage to NIDDM with *P* values of 0.04 and 0.006, respectively, in Caucasian sib pairs using similar analyses. No evidence for linkage of MODY1 and MODY3 markers to NIDDM in African-American sib pairs was observed. In addition, no evidence for linkage to MODY2 (glucokinase-associated MODY) was observed with either study population. Results of multipoint maximum logarithm of odds (LOD) score analysis were consistent with the ASP results. A maximum LOD score of 1.48 was calculated for linkage to MODY1-linked loci and 1.45 to MODY3-linked loci in Caucasian sib pairs. Tabulation of allele sharing in affected sib pairs with D20S197 and D12S349 suggests that affected sibling pairs may inherit susceptibility genes simultaneously from chromosome 20 and chromosome 12. The results suggest that genes contributing to NIDDM in the general Caucasian population are located in the regions containing the MODY1 and MODY3 genes. *Diabetes* 46:882–886, 1997

NIDDM, or type II diabetes, is a common chronic disorder, affecting an estimated 5% of adult Americans. In addition to environmental influences, it is now widely accepted that inherited genetic susceptibility to NIDDM plays a crucial role in development of this disorder. In an effort to locate and identify NIDDM susceptibility genes, genetic linkage searches using polymorphic DNA markers associated with candidate genes or anonymous chromosomal locations are being performed. These studies have been successful in identifying one gene, glucokinase (1–3), and two chromosomal locations: the MODY1 locus in 20q12-q13.1 (4–7) and the MODY3 locus in 12q (8,9) for maturity-onset diabetes of the young (MODY), relatively uncommon forms of NIDDM inherited in an autosomal dominant pattern.

Several barriers to identifying NIDDM susceptibility genes in the general population can be envisioned, including genetic heterogeneity (i.e., multiple different genes in the population can contribute either independently or together to the development of NIDDM). Our efforts have focused on families with a history of NIDDM-related complications, especially diabetic nephropathy, rather than on a general, potentially very heterogeneous, NIDDM population. NIDDM nephropathy is a debilitating and often lethal complication of NIDDM. There is increasing evidence that the lethal complications of NIDDM such as diabetic nephropathy also have a strong familial component (10,11). Diabetic nephropathy in these families could be due to a subpopulation of NIDDM-affected individuals with a more homogeneous genetic origin to their NIDDM. Consequently we have focused our efforts on genetically evaluating families with a history of diabetic (NIDDM) nephropathy. This manuscript describes evidence for coinheritance of NIDDM in sib pairs from these families with genetic markers on human chromosomes 20 and 12.

RESEARCH DESIGN AND METHODS

Genetic markers. All markers are highly polymorphic short sequence repeat polymorphisms (SSRs). Genotyping was carried out using conventional methods for polymerase chain reaction amplification, labeling, sequencing gel analysis, and autoradiography, as described previously (7). Thirteen genetic markers from chromosome 20q, PLC1 (12), D20S99, D20S96, ADA (13), D20S17 (7), D20S197, D20S178, D20S213 (14), D20S75, D20S176, D20S196, D20S100, and PCK1 (15), were chosen from published genetic maps and the publicly available databases and associated information maintained by the Cooperative Human Linkage Center (CHLC), Genethon, and the Centre d'Etude du Polymorphisme Humain (CEPH). The chromosome 20 markers span an interval of ~40 cM on the long arm of chromosome 20. The polymorphic marker used to evaluate linkage to glucokinase (GCK1) on chromosome 7 has been described (16). Eight genetic markers from chromosome 12q in the MODY3 region were evaluated based on their positions in published MODY3 linkages (8,9) and available databases. The chromosome 12 markers span an interval of approximately 14 cM on 12q.

Study subjects. DNA samples have been collected and genotyped from families with multiple NIDDM-affected members and with a history of diabetic nephropathy. The family set included 44 African-American and 21 Caucasian families encompassing 93 African-American and 53 Caucasian NIDDM affected sib pairs for a total of 146 affected sib pairs. The African-American families had the following numbers of NIDDM-affected members: 2 affected,

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GCK, glucokinase; IBD, identical by descent; LOD, logarithm of odds; MLS, maximum LOD score; MODY, maturity-onset diabetes of the young; PCK1, phosphoenolpyruvate carboxykinase; SSR, short sequence repeat polymorphism.

30 families; 3 affected, 7 families; 4 affected, 4 families; 5 affected, 2 families; 10 affected, 1 3-generation family. The Caucasian families had the following numbers of NIDDM affected members: 2 affected, 15 families; 3 affected, 2 families; 4 affected, 2 families; and 5 affected, 2 families. The Caucasian NIDDM patients had an average BMI of 30.3 and average age of diagnosis of 45.6 years, and the African-American NIDDM patients had an average BMI of 30.67 and an average age of diagnosis of 39.7 years.

The affected sib pairs were originally identified through a proband with end-stage renal disease or chronic renal insufficiency due to NIDDM. NIDDM was diagnosed in patients developing diabetes after the age of 35 years or receiving oral hypoglycemic agents. Twenty-three of the African-American families had two or more family members with nephropathy, while the balance of the African-American families and all of the Caucasian families had one member with diabetic nephropathy. Medical records from renal failure patients were reviewed to verify the etiology of the nephropathy. Renal failure was attributed to diabetes in the presence of serum creatinine ≥1.5 mg/dl, diabetes for >10 years, evidence of proliferative diabetic retinopathy (when available), the presence of proteinuria >3 g/24 h or >100 mg/dl, and the absence of other known causes of renal failure.

Genetic analysis. Genotypic data collected using SSR markers from chromosomes 7, 12, and 20 were analyzed using nonparametric linkage analysis methods: affected sib-pair analysis with the SIBPAL program of S.A.G.E. (17) and the MAPMAKER/SIBS program for maximum logarithm of odds (LOD) score (MLS) calculations developed by Kruglyak and Lander (18). To have sufficient power to test linkage with MAPMAKER/SIBS, the option for using all sibling pairs was used for calculations. While this could introduce some biases in families with more than two affected siblings, we have used this analytical method as a confirmatory rather than as a primary linkage analysis method. This set of NIDDM sib pairs was accumulated through addition of new families and subjects to a sib-pair set that has previously been evaluated for its statistical power to detect linkage (19) in a series of simulation tests incorporating different models of inheritance using the computer program SIMLINK (20).

Caucasian allele frequencies were calculated using the alleles from one member of each family. Allele frequencies for African-Americans were determined using DNA collected from 90 unrelated African-Americans from our local population. Results of the SIBPAL analysis of the Caucasian and African-American populations were combined to produce *P* values for the pooled data by calculation of a weighted (mean) sharing of marker alleles IBD (identical by descent) statistic, computation of a pooled standard deviation, and summing individual degrees of freedom.

Allele sharing of D20S197 and D12S349 in affected sib pairs was evaluated by identifying affected pairs that share zero, one, or two alleles D20S197, and then examining whether the same sibpair shared zero, one, or two alleles from the other locus (D12S349).

It should be noted that the results presented here are not derived from a whole genome screen but are specific tests of the hypothesis that MODY gene alleles contribute to NIDDM in the general population. Rather than using the conservative thresholds for interpreting linkage results from a whole genome screen, a value of $P = 0.01$ has been proposed to be applicable for tests of markers that have previously been linked to genes (29). It should be noted, however, that the issue of significance values has yet to be resolved.

RESULTS

As one focus of our laboratory has been the analysis of chromosome 20–linked MODY1 in the RW family (5–7,14,21,22), a family with many NIDDM members, markers linked to MODY1 were evaluated in this collection of NIDDM-affected sib pairs. Thirteen different SSR markers covering the MODY1 region and extending to the phosphoenolpyruvate carboxykinase (PCK1) gene were used in the evaluation. Of the MODY1-linked markers tested, D20S178 and D20S197 are both tightly linked to MODY1 with MLSs of 15.98 and 13.13, respectively, at recombination fraction 0.00 (21). D20S178 and D20S197 have physically been located on yeast artificial chromosome clones that are linked or also contain the D20S16 locus (data not shown), which, in our studies, has the highest LOD score with MODY1, ($z_{max} = 17.00$ at $\Theta = 0.00$ [21]) and has been physically assigned to 20q12–q13.1 (22).

One set of candidate genes under study are the genes whose products carry out critical rate limiting steps in glycolysis and gluconeogenesis. One such gene, *PCK1*, codes for phosphoenolpyruvate carboxykinase, which carries out a rate-limiting step in glycolysis (23), also maps to chromosome 20, and was included in the evaluation of the NIDDM sib pairs. The SSR associated with the PCK1 gene maps ~25 cM distal to D20S75 (15) and has been physically assigned to 20q13.2 (24). In addition to MODY1 linked markers, we also tested a marker linked to the GCK1 gene (16), in which mutations lead to MODY2, and markers from chromosome 12q that are linked to MODY3 (8,9).

The results of analyses of the collected genotypic data in African-American sib pairs, Caucasian sib pairs, and the two sets combined are shown in Table 1. Results of the SIBPAL analysis are reported as proportion of alleles IBD, and the corresponding statistic *t* and *P* values. For the chromosome 20 markers, no evidence of linkage to NIDDM is seen in the African-American sib pairs, but evidence for linkage is seen in Caucasian sib pairs with D20S197; and a low, though not significant, *P* value is seen with the closely linked but less informative marker D20S178. Both show mild evidence for linkage with the combined data, but this is due primarily to the Caucasian data. D20S197 and D20S178 are in the middle of the approximately 10 cM interval thought to encompass the MODY1 gene (7,21).

No evidence for significant linkage is seen with the GCK1 polymorphism to NIDDM in either group, but there is evidence for linkage to markers in the MODY3 region of chromosome 12 in Caucasian sib pairs. D12S349 and D12S86 show evidence for linkage in Caucasian sib pairs, and D12S321 has a *P* value of 0.10. Each of these three markers is in the 5 cM interval thought to encompass the MODY3 gene (9). As with the MODY1 locus, there is no significant evidence for linkage of these markers to NIDDM in the African-American sib pairs.

With evidence for linkage of NIDDM in Caucasian sib pairs to markers on chromosome 20 and 12, a second nonparametric linkage analysis approach was carried out to complement the results of the SIBPAL analysis. Multipoint linkage analysis of marker data from chromosomes 20 and 12 was done using MAPMAKER/SIBS (18). This program carries out multipoint sib-pair analysis computing an MLS. For chromosome 20 marker analysis (Fig. 1*A*), the MLS curve has several local maxima, but the peak LOD score, consistent with the SIBPAL results, is seen at D20S197 and D20S178 (MLS of 1.5). For chromosome 12 markers (Fig. 1*B*), the MLS curve has one maximum (LOD of 1.45 at D12S349 and D12S86) at markers that are not separated by recombination (9).

These results provide evidence for linkage of both chromosome 12 and chromosome 20 markers to NIDDM in the Caucasian affected sib pairs. A logical extension of this observation is to evaluate whether the NIDDM susceptibility loci on chromosomes 20 and 12 are inherited together in the affected sib pairs or are inherited independently. We have evaluated allelic sharing in affected sib pairs for the most informative linked markers, D20S197 and D12S349. Affected sib pairs that inherited identical genotypes, i.e., shared two, one, or zero alleles for either D20S197 or D12S349, were identified. These sib pairs were then scored for sharing of two, one, or zero alleles for the other marker. For example, if the sibs of an affected sibpair had the same genotypes for D20S197, it was then determined whether the sibs inherited zero, one, or two alleles in common from D12S349. The results of this analysis (Table 2) reveal skewed distribution of sharing two

TABLE 1
SIBPAL analysis of linkage to NIDDM

	Sib pairs								
	All (n = 146)			African-American (n = 93)			Caucasian (n = 53)		
Locus	IBD	t	P	IBD	t	P	IBD	t	P
PLC1	0.47	−0.91	0.82	0.47	−0.76	1.00	0.48	−0.497	1.00
D20S99	0.51	0.50	0.31	0.50	0.00	0.50	0.53	0.94	0.18
D20S96	0.53	1.23	0.11	0.53	0.76	0.22	0.54	1.16	0.13
ADA	**0.54**	**1.69**	**0.047**	0.55	1.60	0.06	0.53	0.66	0.26
D20S17	0.51	0.59	0.28	0.50	−0.04	1.00	0.52	0.41	0.34
D20S197	**0.55**	**1.76**	**0.040**	0.51	0.25	0.27	**0.60**	**2.65**	**0.0054**
D20S178	0.54	1.48	0.07	0.52	0.78	0.40	0.56	1.32	0.096
D20S213	0.51	0.33	0.37	0.50	0.11	0.45	0.52	0.47	0.32
D20S75	0.49	0.33	0.59	0.45	0.04	1.00	0.55	1.04	0.15
D20S176	0.48	−0.92	0.82	0.47	−1.14	1.00	0.50	−0.09	1.00
D20S196	0.46	−1.33	0.91	0.45	−1.63	1.00	0.49	−0.10	1.00
D20S100	0.50	−0.17	0.57	0.47	−0.94	1.00	0.54	1.05	0.15
PCK1	0.52	1.00	0.16	0.53	1.11	0.14	0.51	0.21	0.42
GCK1	0.51	0.33	0.37	0.49	−0.08	1.00	0.52	0.65	0.26
D12S369	0.52	0.58	0.28	0.49	−0.25	1.00	0.56	1.49	0.07
D12S366	0.51	0.22	0.41	0.50	−0.10	1.00	0.53	0.63	0.27
D12S349	**0.54**	**1.61**	**0.05**	0.52	0.79	0.21	**0.56**	**1.76**	**0.04**
D12S86	**0.57**	**2.16**	**0.017**	0.52	0.52	0.30	**0.63**	**2.60**	**0.006**
D12S321	0.52	0.65	0.26	0.50	−0.06	1.00	0.55	1.29	0.10
D12S395	0.49	−0.35	1.00	0.50	−0.07	1.00	0.48	−0.44	1.00
D12S807	0.48	−1.73	0.96	0.48	−0.51	1.00	0.47	−0.53	1.00
D12S378	0.51	0.47	0.32	0.53	0.65	0.26	0.50	0.02	0.49

IBD, percentage of alleles identical by descent; t, t statistic. Statistically significant data are in **boldface**.

alleles at each locus. Consistent with the evidence for linkage seen with S.A.G.E. and GENEHUNTER analysis, a conventional chi-square analysis of Table 2 data results in a χ^2 of 49.5 (df = 8; $P = 2 \times 10^{-6}$). Although the test of interaction was not significant, χ^2 of 7.82 (df = 4; $P = 0.098$), these results suggest that chromosome 20 and chromosome 12 markers may be jointly important for NIDDM susceptibility in this population of NIDDM sib pairs with a history of nephropathy.

DISCUSSION

The genetic factors that determine susceptibility to NIDDM are likely to be multiple, with some genes of large effect that will be suitable for mapping (25). We have evaluated a collection of African-American and Caucasian NIDDM sib pairs with a history of diabetic nephropathy for linkage of NIDDM to SSR markers closely linked to the MODY1, MODY2, and MODY3 genes. This report presents evidence that NIDDM as expressed in Caucasian sib pairs is linked to markers on the long arms of chromosomes 20 and 12. There is equivocal evidence for linkage in African-Americans. We found that there is no evidence for linkage to the GCK1 gene (MODY2) in either data set. Analysis of the genotypic data using two nonparametric analysis approaches (SIBPAL and MAPMAKER/SIBS) results in a consistent picture of linkage to NIDDM as expressed in Caucasian sib pairs with a history of diabetic nephropathy.

D20S178 and D20S197 provide the strongest evidence of linkage on chromosome 20 in Caucasian NIDDM sib pairs, and these two markers are tightly linked to MODY1 (21). It is attractive to speculate, therefore, that alleles of the MODY1 gene, presumably different from the allele that causes autosomal-dominant MODY in the RW family, segregate in the general population and contribute to NIDDM susceptibility. MODY1 appears to be an uncommon form of MODY, with the RW family being the only documented case of chromosome 20–linked MODY, but negative evaluations of D20S197 and D20S178 have not been reported in NIDDM families from the general population. It should be noted that our results cannot rule out the possibility that more than one NIDDM susceptibility gene lies in this region of the long arm of chromosome 20. In contrast to the RW MODY family, as outlined above, our sib pairs are obese (average BMI of 30.3) and have a significantly later age of diagnosis (45.6 years).

Zouali et al. (26) recently reported evidence for linkage of chromosome 20 markers in a large collection of French NIDDM families from the general population. There are both similarities and differences between this report and our own results. In the study of Zouali et al. (26), evidence for linkage to NIDDM was seen with the SSR associated with the PCK1 locus using affected sib-pair analysis, while only weak evidence of linkage with PCK1 was apparent in our study. Two other markers, D20S100 and D20S196, reported to be 5.2 and 14.4 cM proximal to PCK1, respectively, also showed evidence in favor of linkage. It is possible that D20S100 and D20S196 could be detecting inheritance of NIDDM at the same locus in the general population, which we are hypothesizing to contribute to NIDDM susceptibility in our nephropathy sib pairs. A similarity in the family sets studied is that the strongest evidence for linkage in the French families was seen in families with age at onset of NIDDM of <45 years. The average age of diagnosis for our Caucasian NIDDM patients was 45.7 years.

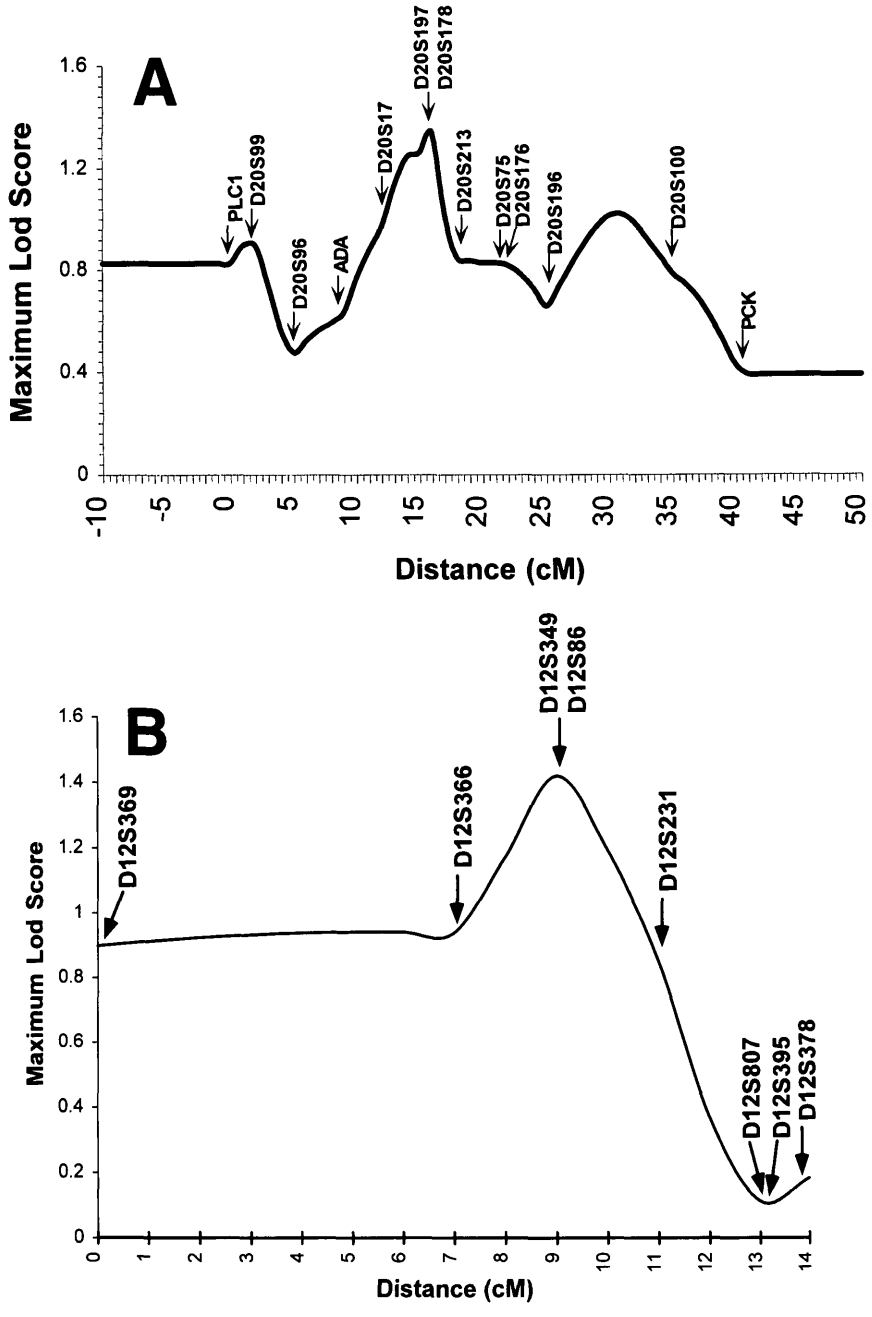

FIG. 1. Multipoint MLS linkage analysis in Caucasian NIDDM sib pairs. *A*: MLSs across the 20q genetic interval are shown. Genetic distances in centimorgans are calculated from the arbitrary origin of PLC1 (the most centromere proximal marker in the map). The MODY1 gene has been mapped to the interval encompassed by ADA to D20S213 (21). *B*: MLSs across the 12q genetic interval are shown. Genetic distances in centimorgans are calculated from the arbitrary origin of D12S369 (the most centromere proximal marker in the map). MODY3 maps within an interval bounded by D12S366 and including D12S395 (9).

In addition to the study of Zouali et al. (26), analysis of NIDDM families from the Joslin Diabetes Center supports linkage to chromosome 20 in the MODY1 region (A. Krolewski, J. Warram, personal communication). Taken in their entirety, these three reports support the hypothesis that a gene (or genes) contributing to NIDDM susceptibility in the general population lies on the long arm of chromosome 20. This gene is likely to be located in the same region as the MODY1 gene and could represent alleles of the MODY1 gene contributing to NIDDM in the general population of NIDDM-affected individuals or a separate NIDDM susceptibility gene.

No evidence for linkage to NIDDM in either racial group was seen with a GCK1 polymorphism. This does not exclude GCK1 mutations from contributing to NIDDM susceptibility, but it suggests that this gene does not play a substantial role in NIDDM when members are selected for a history of diabetic nephropathy. In addition, African-American sib pairs showed little evidence for linkage with markers from any of the three MODY loci. The African-American collection of sib pairs contains a substantial number of families in which the sibling pairs are concordant for both diabetes and nephropathy (in contrast to the Caucasian families, which uniformly have a single diabetic nephropathy proband). We have evaluated the African-American sib pairs after stratification into sib pairs containing a single diabetic nephropathy case and sib pairs with multiple diabetic nephropathy cases. Neither of these groups individually shows evidence for linkage to the markers tested (data not shown).

In addition to the evidence for linkage with MODY1-linked loci, we observed evidence for linkage to MODY3-linked markers on chromosome 12 to NIDDM in our Caucasian sib pairs. In contrast to MODY1, Lesage et al. (27) reported no evidence for linkage in a large collection of French NIDDM families from the general population. While this study was in the

TABLE 2
Evaluation of Caucasian affected sib pairs for identity by state (IBS) allele sharing with D20S197 and D12S349

	Sib pairs sharing 0 alleles at D20S197	Sib pairs sharing 1 allele at D20S197	Sib pairs sharing 2 alleles at D20S197
Sib pairs sharing 0 alleles at D12S349	0	2	1
Sib pairs sharing 1 allele at D12S349	2	13	2
Sib pairs sharing 2 alleles at D12S349	1	12	14

process of review, Mahtani et al. (28) described linkage of MODY3-linked markers to a set of NIDDM families from a population isolate in western Finland. Consistent with the study of Mahtani et al. (28), our patient group represents a subpopulation rather than a general collection of NIDDM families, which is one possible explanation of the discordant results. Additional studies with closely spaced polymorphic markers in a larger set of Caucasian sib pairs with diabetic nephropathy will be necessary to confirm our observations.

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