Do Non–Insulin-Dependent Diabetes Mellitus (NIDDM) and Insulin-Dependent Diabetes Mellitus (IDDM) Share Genetic Susceptibility Loci? An Analysis of Putative IDDM Susceptibility Regions in Familial NIDDM

Steven C. Elbein, Michael D. Hoffman, Rachel A. Mayorga, Kelli L. Barrett, Mark Leppert, and Sandra Hasstedt

Non–insulin-dependent diabetes mellitus (NIDDM) has been viewed as genetically and physiologically distinct from insulin-dependent diabetes mellitus (IDDM), yet many of the recently suggested IDDM susceptibility loci are likely to increase the risk of diabetes through nonautoimmune mechanisms. To test the hypothesis that the IDDM susceptibility loci include important NIDDM susceptibility loci, we tested the linkage of 14 putative susceptibility regions with NIDDM among families and sibling pairs of Northern European descent. All regions were tested with highly informative microsatellite (simple tandem repeat) polymorphisms in up to 166 affected individuals from 42 families using both parametric and nonparametric methods (149 pairs for sibling pair analyses). We found no evidence for linkage to the majority of loci, including loci that appeared to be linked to IDDM in more than one study. We report some evidence for shared susceptibility for regions on chromosomes 1, 2, and 6. The best evidence based on multilocus affected pedigree member (APM) analysis of markers near D1S191 suggested linkage at *P* value .0001. This region has not yet been confirmed as an IDDM locus, and our analyses could represent a false-positive result. The role of these three regions will only be clarified by testing in additional families. In combination with other investigations in our laboratory for chromosome 11 susceptibility regions, our data generally do not provide convincing evidence that IDDM and NIDDM share common genetic factors among families of Northern European descent with ascertainment of two or more NIDDM siblings.

INSULIN-DEPENDENT DIABETES mellitus (IDDM) and non–insulin-dependent diabetes mellitus (NIDDM) have been viewed as distinct physiologic and genetic entities. Nonetheless, considerable data suggest this classification is overly simplistic. Both autoimmunity and HLA association have been reported in patients with the NIDDM phenotype,[1] and the identical mitochondrial mutation ($tRNA^{Leu(UUR)}$) has been reported in individuals with both the NIDDM and IDDM phenotypes.[2] Current evidence suggests that autoimmune pancreatic β-cell destruction may arrest before complete β-cell loss,[3] and most investigators now view NIDDM as an imbalance between diminished insulin secretory capacity and decreased insulin sensitivity.[4] Given these facts, we hypothesized that IDDM and NIDDM share non–HLA-linked components of the genetic predisposition. Recent linkage studies based on analysis of IDDM sibling pairs from three laboratories[5-7] have identified a large number of putative IDDM susceptibility loci, many of which have been duplicated in independent populations and thus appear to be legitimate secondary susceptibility loci,[8-10] although they have not yet met the criteria of confirmed loci proposed by Lander and Kruglyak.[11] The genes and mutations linked to these markers are unknown, but these loci are not currently known to be involved in the autoimmune pathogenesis of IDDM. Some of these loci may turn out to represent false-positive linkage, but they must nonetheless be viewed as strong candidates for NIDDM susceptibility.

To examine the hypothesis of shared susceptibility, we tested 22 markers from 14 chromosomal regions for linkage in NIDDM families and sibling pairs of northern European extraction. We included markers at or near proposed IDDM loci 1,3,5,6,7,8,9, and 10, in addition to regions suggested but not yet duplicated in an independent population. Although we found marginal evidence for linkage in three regions, we report that these putative IDDM loci are unlikely to be important regions of NIDDM susceptibility.

SUBJECTS AND METHODS

Study Population

The study population consisted of members of 42 families ascertained for at least two siblings with NIDDM onset before age 65 years and of Northern European extraction. These families included 29 multigenerational pedigrees, two families with a typical NIDDM sibling pair but ascertained for a mixture of NIDDM and IDDM, and 11 simple sibling pair families for which offspring or parents of affected siblings were not available at the time of the study. A total of 503 individuals representing 159 affected sibling pairs were typed for all markers. Families in which both parents were known to be diabetic at the time of ascertainment were excluded. For ascertainment, affection was defined as diabetes under medical therapy or diabetes according to World Health Organization criteria. All pedigree members not known to be diabetic underwent a standard 75-g oral glucose tolerance test. For linkage studies, affection was defined as meeting one of the following criteria: medical therapy for NIDDM; fasting glucose greater than 7.8 mmol/L; or 2-hour postchallenge glucose of 7.8 mmol/L for age under 45, 11.1 mmol/L for ages 45 to 64, and 13.3 mmol/L for age over 64. These cutoffs correspond to both World Health Organization criteria for impaired glucose tolerance (age <45) or NIDDM (age 45 to 65), and take into account the age-dependence of postchallenge glucose.[12] Detailed descriptions of the population and the diagnostic criteria have been reported elsewhere.[13,14]

From the Division of Endocrinology, Diabetes and Metabolism, Department of Veterans Affairs Medical Center and University of Utah, Salt Lake City; and the Department of Human Genetics, University of Utah, Salt Lake City, UT.

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Address reprint requests to Steven C. Elbein, MD, Endocrinology 111J/LR, VAMC, 4700 W 7th St, Little Rock, AR 72205.

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Genotyping was performed for both affected and unaffected members of 19 two- and three-generation families (405 individuals), as described elsewhere.[13,14] To increase the power for nonparametric analytical methods, affected and unaffected siblings and available parents of the proband were typed from an additional 23 families (98 individuals). The maximum number of affected individuals was 166, yielding 159 sibling pairs when all possible combinations were considered (n[n-1]/2). When the suggested correction factor for multiple siblings [n-1] was used, the number of sibling pairs was 94. For chromosome 1 loci, all available members of 29 multigenerational pedigrees (618 individuals) were typed in addition to the affected siblings typed for other studies. Informed consent was obtained for all study participants.

Marker Typing

Microsatellite (dinucleotide repeat) markers were selected from IDDM linkage studies,[5-7] or were nearby markers from published linkage maps[15,16] (Table 1). Microsatellite regions were enzymatically amplified from 60 ng to 100 ng genomic DNA in a 25-μL reaction volume in 96-well microtiter dishes. Reactions contained 10 pmol of each primer, 0.5 pmol γ-^{32}P-labeled primer, 1.5 mmol/L $MgCl_2$, 50 mmol/L KCl, or 40 mmol/L NaCl, 200 μmol of each nucleotide, and 0.3 to 0.5 U Taq polymerase (Perkin-Elmer-Cetus, Norwalk, CT). Amplification was performed in a PHC-3 thermocycler (Techne, Princeton, NJ) with a 3- to 5-minute initial denaturation, 30 cycles of 30-second denaturation (94°C), 30-second annealing (55°C to 59°C), and extension for 1 minute at 72°C. Conditions were optimized, including the use of 5% dimethylsulfoxide or 5% glycerol as required. Following amplification, the reaction was denatured for 6 minutes at 94°C in 33% formamide with 3.3 mmol/L NaOH, and 8% of the reaction was separated on 6% polyacrylamide: 8.3-mol/L urea gels for 4 to 6 hours at 60 W. Gels were exposed to NEF film (NEN DuPont, Boston, MA) for 24 to 48 hours with or without an intensifying screen and scored by two readers who were blinded to affection status.

Table 1. Putative IDDM Loci

Locus	Location	Distance	No. of Alleles	Heterozygosity
D1S191*	1q	243	7	0.712
D2S326 (*IDDM7*)†	2q-ter	176	12	0.865
D3S1303 (*IDDM9*)†	13q	162	11	0.788
D6S285 (*IDDM1*)	6p (HLA region)	47	9	0.630
TNFA (*IDDM1*)†	6p (HLA region)	60	12	0.857
D6S441 (*IDDM5*)†	6q25	183	14	0.858
D6S305†	6q25	196	12	0.848
D6S264 (*IDDM8*)†	6q27	208	10	0.708
CFTR†	7q	165	10	0.687
D8S264*	8p	5	12	0.845
D8S277*	8p	12	13	0.748
D8S257†	8q	127	8	0.740
D8S556†	8q	133	10	0.800
D10S193 (*IDDM10*)†	10p	61	11	0.779
D10S220 (*IDDM10*)†	10p	72	12	0.813
D10S582 (*IDDM10*)*	10p	83	10	0.757
D13S158†	13q	99	11	0.826
D14S70†	14q	39	7	0.771
D15S107 (*IDDM3*)‡	15q26	121	8	0.712
D15S87 (*IDDM3*)‡	15q26	127	14	0.848
D18S64 (*IDDM6*)†	18q	87	10	0.731

NOTE. Loci reported to be linked to IDDM in previous studies. Location, approximate chromosomal location; distance, approximate distance from the most telomeric p marker; no. of alleles, the number of alleles in the Utah population (based on the current studies); heterozygosity, the heterozygosity in the study population.

*Markers reported to be linked by Hashimoto et al.[6]

†Markers reported by Davies et al.[5]

‡Markers reported to be linked to IDDM by Field et al.[7]

Linkage Analysis

Linkage analysis was performed using both parametric and nonparametric methods. Parametric analysis was performed under three models: dominant with a maximum penetrance of 0.9, recessive with a maximum penetrance of 0.9, and dominant with a maximum penetrance of 0.3. Liability classes were assigned according to age and body mass index, as described in detail elsewhere.[13,14] Analyses were made using the MLINK program from the Linkage 5.1 package,[17] run under Unix on a Sun IPX workstation. An age-dependent phenocopy frequency was included under all models to account for up to 50% of all diabetic cases.

Nonparametric analysis was performed using the affected pedigree member (APM) method.[18] For nonparametric studies, individuals with uncertain diagnosis (coded as liability classes 9 and 10[13]) were considered unaffected, which thus reduced the number of sibling pairs to 149. Marker allele frequencies were determined from 80 to 100 unrelated individuals representative of the study population. For two-point APM analyses, significance was determined both asymptotically (program output) and by simulation based on 3,000 to 5,000 repetitions. In accordance with the recommendations of Weeks and Lange,[19] we considered only the program output for the intermediate weighting factor, $f(p) = 1/\sqrt{p}$. We also determined sharing of alleles identical by descent (IBD) using the SibPal program of the SAGE package.[20] For chromosome 1p, where multiple closely spaced markers were typed, we also tested linkage with the multipoint version of the APM program (APMMULT[21]).

RESULTS

The 22 markers typed for 14 putative IDDM susceptibility regions are shown in Table 1. With the exception of D6S285 (HLA region), all markers were highly informative, with heterozygosity values in our population near or exceeding 0.7. Results of parametric and APM studies are shown in Table 2. We found no evidence for linkage by any method for most loci, including numbered IDDM loci for which linkage to IDDM was suggested in more than one study[5-7,9]: D6S285 and TNFA at *IDDM1* on chromosome 6p (HLA), *IDDM8* on chromosome 6q, *IDDM9* (D3S1303), *IDDM6* (D18S64), the two chromosome 8 regions, *IDDM10* on chromosome 10, and *IDDM3* on chromosome 15 (Table 2). We found only minimal evidence of linkage for two other numbered IDDM loci: *IDDM7* on chromosome 2q (D2S326) under recessive parametric and APM models, and slightly better evidence under dominant and APM models for *IDDM5* on chromosome 6q (D6S441). Analysis with the SibPal program of the SAGE package provided only marginal evidence for excess sharing of alleles IBD among affected siblings for D2S326 ($P < .05$), but did not suggest excess sharing of alleles among affected siblings for any other region. Considering the number of methods tested and uncertain a priori evidence for linkage, P values between .05 and .01 are likely to represent false-positive findings rather than true linkage. Analysis of other chromosome 6q markers (Tables 1 and 2) failed to confirm linkage at D6S441, although these markers are 13 to 25 centimorgan (cM) distant.

Linkage of D1S191 and NIDDM was detected initially in 27 multigenerational families under APM analysis ($P = .00063$, asymptotic; $P = .002$, simulated). We thus tested additional markers flanking D1S191 at 1 to 2-cM intervals: D1S158-(.01)-

Table 2. Linkage Results for Putative IDDM Loci

Locus	Excluded Region, Low-Penetrance Model (θ)	Maximum Z	Maximum θ	Maximum Model	APM (*P*)	Mean Allele Sharing
D1S191	0.02	0.45	0.20	Recessive	.001	0.525
D2S326	0	0.67	0.30	Recessive	.045	0.549
D3S1303	0.15	0	0.50	—	.336	0.489
D6S285	0.15	0	0.50	—	.727	0.492
TNFA	0.14	0	0.50	—	.493	0.502
D6S441	0.01	1.03	0.30	Dominant*	.014	0.523
D6S305	0.09	0.14	0.40	Dominant	.654	0.509
D6S264	0	0	0.50	—	.101	0.502
CFTR	0.13	0	0.50	—	.370	0.483
D8S264	0.17	0	0.50	—	.791	0.490
D8S277	0.06	0	0.50	—	.493	0.481
D8S257	0.07	0	0.50	—	.144	0.489
D8S556	0.04	0.18	0.40	—	.446	0.512
D10S193	0.16	0	0.50	—	.877	0.473
D10S220	0.12	0	0.50	—	.592	0.472
D10S582	0.07	0	0.50	—	.500	0.487
D13S158	0	0	0.50	—	.272	0.497
D14S70	0.01	0.06	0.40	Dominant, low penetrance	.637	0.487
D15S107	0.08	0	0.50	—	.855	0.501
D15S87	0.16	0	0.50	—	.344	0.493
D18S64	0.07	0	0.50	—	.395	0.524

NOTE. The region excluded under the least restrictive model (dominant, low penetrance with high sporadic frequency), the maximum LOD score (Z) and recombination fraction (θ), and the parametric model under which the maximum occurred are shown. APM *P* is reported as the asymptotic value.

*Z = 0.60 at θ = 0.2, low-penetrance model.

D1S466-(.02)-D1S191-(.01)-D1S202. Both D1S158 and D1S202 were somewhat confirmatory (simulated $P = .06$ and .01, respectively), but no evidence for linkage was found at D1S466. We subsequently tested markers D1S191, D1S202, and D1S158 in all 42 families and sibships ascertained for Northern European descent and NIDDM onset before age 65 years. Some evidence for linkage was still noted on two-point APM analyses ($P = .001$ asymptotic and $P = .004$ simulated for D1S191; $P = .007$ asymptotic and $P = .012$ simulated for D1S202; $P = .055$ asymptotic and $P = .06$ simulated for D1S158), but neither parametric nor affected sibling pair analyses suggested linkage. However, multilocus APM analysis more strongly suggested a susceptibility locus near D1S191 ($P = .00010$).

DISCUSSION

Despite the considerable advance realized by distinguishing early-onset, autoimmune β-cell–destruction diabetes (IDDM) from late-onset diabetes (NIDDM), overlap is likely. Clinically, many individuals are not easily classified as either NIDDM or IDDM. Within families, the two diseases often coexist,[1] and impaired insulin secretion clearly contributes to NIDDM susceptibility.[4] Furthermore, two putative IDDM loci include the insulin gene (*IDDM2*) on chromosome 11p[6] and glucokinase on chromosome 7,[22] both of which probably act by decreasing insulin secretion rather than by autoimmune mechanisms.[23] We thus anticipated shared genetic susceptibility between IDDM and NIDDM. We have previously tested glucokinase by both linkage and screening of exons for mutations with 19 of the families reported here, and found no evidence for a major susceptibility locus.[24,25] Likewise, we found no evidence for linkage at *IDDM2*[14,26] and only marginal evidence for linkage at *IDDM4*.[14] Thus, we have tested all currently proposed autosomal susceptibility loci for IDDM. An additional putative locus has been described on the X chromosome, but this is not within the pseudoautosomal region. Additional loci certainly may exist that have not yet been detected, and further testing may determine that some or many of the loci tested here represent false-positive linkage. Also, we are not currently certain of the distance of the marker loci tested from the actual IDDM loci. A greater distance than expected from published studies would reduce our power to detect linkage in NIDDM families. Thus, our conclusions must be viewed in the context of the preliminary nature of the proposed linkage in IDDM.

Lander and Kruglyak[27] recently suggested *P* less than 2×10^{-5} as the appropriate level of significance to ensure a false-positive rate of 5% or less given the dense map required to detect susceptibility genes for complex traits. This value is well below the levels of significance obtained in the present study. Furthermore, with the exception of TNFA in the HLA region, none of the IDDM loci proposed in the initial genome-wide searches met the level of significance proposed for "suggestive linkage" ($P < 7.4 \times 10^{-4}$)[27] when all IDDM families were considered together without regard for HLA status, although subsequent studies have provided support for at least four loci. Thus, some of the original proposed linkage to IDDM and our results for markers D1S191, D2S326, and D6S441 may represent false-positive linkage. Multilocus APM analysis of the region near D1S191 is near the range of criteria proposed by Lander and Kruglyak[27] for suggestive linkage, although the corresponding value for this method is uncertain.

In studies of IDDM, significance was improved for several

loci when the contribution of HLA was taken into account.[9] For NIDDM, no major susceptibility locus comparable to HLA in IDDM has been identified. Consequently, simultaneous analysis of two or more susceptibility loci is currently impractical. Genetic heterogeneity might partially mask an important role for one of the loci tested here, and would certainly reduce significance levels attained. To address this possibility, we performed sibling pair analyses using the SAGE program for the youngest-onset, leanest subgroup of families based on liability class (a combination of age of onset and obesity) of affected members. This subgroup analysis did not alter our conclusions based on the full pedigree set (data not shown), although the early-onset subgroup contained only 50 to 60 sibling pairs. We also tested the more general hypotheses of a linked subset against no linkage using the log of odds (LOD) score (parametric) method under all models. In no case did this test approach significance ($P > .05$).

In the present study, we tested nearly 150 affected sibling pairs, which is comparable to the number screened in published IDDM studies.[5,6] Thus, the power to detect an effect on genetic susceptibility for these loci could be comparable between this study and those. However, the impact of these loci in IDDM was relatively modest, with only a 1.5-fold increase in risk for a sibling ($\lambda_s = 1.5$). Duplication of linkage with a locus of similar impact in NIDDM might require a much larger number of sibling pairs. In both recent IDDM studies and studies of schizophrenia, putative susceptibility loci have not been linked in all populations studied.[9,28] Risch[29] examined the power to detect linkage for a locus that increased the risk to siblings by threefold over the risk to the general population ($\lambda_s = 3.0$) and predicted 80% power in 100 sibling pairs with a fully informative marker located at the disease locus.

Several factors would reduce our power to detect linkage relative to both the IDDM studies and the power estimates by Risch. First, no real marker is fully informative, and the actual distance of these markers from the disease locus is unknown. Second, unlike IDDM families, parents are generally deceased in NIDDM pedigrees. Thus, a fully informative analysis of allele sharing IBD was not possible. While LOD score analysis can infer many missing genotypes, both the sibling pair and APM analyses used in this study are less powerful than the IBD studies performed in IDDM sibships.[30] Finally, we sought to limit heterogeneity by selecting carefully on age of onset and ancestral origin and by limiting the number of independent families studied. Thus, our studies are based on a relatively small number of large multigenerational families rather than large numbers of independent sibling pairs. Whether the more homogeneous population would improve or detract from our ability to detect susceptibility loci is uncertain. Some investigators have argued that an appropriately conservative correction is to count only n-1 sibling pairs for n affected siblings, rather than all possible pairs as independent (n[n-1]/2). In this case, the number of effective sibling pairs in our studies decreases to less than 100. With this correction and using sibling pair analyses, we would have greatly reduced power to detect linkage to a locus, with an impact on NIDDM susceptibility similar to that estimated for IDDM susceptibility.

Our study design has been optimized to detect clinically important susceptibility loci that act in a high proportion of families ascertained from a uniform population under uniform criteria, or loci that play a large role in a subset of such families. The proposed IDDM susceptibility loci described to date do not meet these criteria, although three regions warrant additional study in familial NIDDM. These studies reject the hypothesis that an apparently minor IDDM susceptibility locus might represent a major NIDDM disease locus. However, power considerations, the possibility that the loci we tested will not represent true IDDM loci, the difficulty in duplicating linkage for minor susceptibility loci, and the possibility that heterogeneity masked NIDDM families with shared susceptibility raise the possibility that shared susceptibility loci may be found in the future.

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