Original Article

Type 1 Diabetes

Evidence for Susceptibility Loci from Four Genome-Wide Linkage Scans in 1,435 Multiplex Families

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Type 1 diabetes is a common, multifactorial disease with strong familial clustering (genetic risk ratio [λ_S] ~ 15). Approximately 40% of the familial aggregation of type 1 diabetes can be attributed to allelic variation of HLA loci in the major histocompatibility complex on chromosome 6p21 (locus-specific λ_S ~ 3). Three other disease susceptibility loci have been clearly demonstrated based on their direct effect on risk, *INS* (chromosome 11p15, allelic odds ratio [OR] ~ 1.9), *CTLA4* (chromosome 2q33, allelic OR ~ 1.2), and *PTPN22* (chromosome 1p13, allelic OR ~ 1.7). However, a large proportion of type 1 diabetes clustering remains unexplained. We report here on a combined linkage analysis of four datasets, three previously published genome scans, and one new genome scan of 254 families, which were consolidated through an international consortium for type 1 diabetes genetic studies (www.t1dgc.org) and provided a total sample of 1,435 families with 1,636 affected sibpairs. In addition to the HLA region (nominal $P = 2.0 \times 10^{-52}$), nine non–HLA-linked regions showed some evidence of linkage to type 1 diabetes (nominal $P < 0.01$), including three at (or near) genome-wide significance ($P < 0.05$): 2q31-q33, 10p14-q11, and 16q22-q24. In addition, after taking into account the linkage at the 6p21 (HLA) region, there was evidence supporting linkage for the 6q21 region (empiric $P < 10^{-4}$). More than 80% of the genome could be excluded as harboring type 1 diabetes susceptibility genes of modest effect ($\lambda_S \geq 1.3$) that could be detected by linkage. This study represents one of the largest linkage studies ever performed for any common disease. The results demonstrate some consistency emerging for the existence of susceptibility loci on chromosomes 2q31-q33, 6q21, 10p14-q11, and 16q22-q24 but diminished support for some previously reported locations. *Diabetes* 54:2995–3001, 2005

Type 1 diabetes is the third most prevalent chronic disease of childhood, affecting up to 0.4% of children in some populations by age 30 years, with an overall lifetime risk of nearly 1% (1,2). It is believed that a large proportion of cases of type 1 diabetes result from the autoimmune destruction of the pancreatic β cells, leading to complete dependence on exogenous insulin to regulate blood glucose levels (3). The etiology of type 1 diabetes is only partially characterized, but it is recognized that both genetic and environmental determinants are important in defining disease risk. Type 1 diabetes clusters in families, based on population-based twin and family studies (4) but does not segregate with a known mode of inheritance (5). The incidence and the age at onset of type 1 diabetes in some populations have changed dramatically since 1950 (6–8). These data, coupled with the incomplete concordance for the phenotype in monozygotic twins (30–70%), suggest that the penetrance of type 1 diabetes susceptibility alleles is strongly influenced by environmental factors (4).

Type 1 diabetes is strongly clustered in families with an overall genetic risk ratio (λ_S) of ~15 (9). At least one locus that contributes strongly to this familial clustering resides within the major histocompatibility complex (MHC) on chromosome 6p21. Genetic, functional, structural, and model studies all suggest that the HLA class II genes (*HLA-DRB1* and *-DQB1*) likely represent the primary determinants of *IDDM1*. The frequency of HLA class II susceptibility alleles also correlates well with the population incidence of type 1 diabetes (10). These studies suggest that the MHC (*IDDM1*) may account for nearly 40% of the observed familial clustering of type 1 diabetes, with a locus-specific λ_S of ~3 (11).

Given that HLA alone cannot explain the familial clustering of type 1 diabetes, several, perhaps many, genes remain to be identified. First, in the general population, individuals who carry the high-risk haplotypic combination DRB1*04-DQB1*0302/DRB1*03-DQB1*0201 have ~5% absolute risk of type 1 diabetes. However, within affected sibpair families, this genotype has ~20% risk (5,12). Second, three non-HLA loci have been identified based on genetic association studies: *IDDM2* [*INS*, 11p15 (13–16)], *IDDM12* [*CTLA4*, 2q33 (17)], and *LYP/PTPN22* [1p13 (18–20)]. Finally, the observed risk of type 1 diabetes in

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Additional information for this article can be found in an online appendix at http://diabetes.diabetesjournals.org.

IBD, identity-by-descent; LOD, logarithm of odds; MHC, major histocompatibility complex; SNP, single nucleotide polymorphism.

first- and second-degree relatives declines in a pattern consistent with multiplicative effects of multiple loci (11).

The first type 1 diabetes genome-wide scans for linkage, using fewer than 100 affected sibpair families, identified chromosome 6p21 (*IDDM1*) as the major type 1 diabetes risk locus (21,22). Subsequent studies supported non-HLA loci on chromosomes 11q13 (*IDDM4*) and 6q25 (*IDDM5*) in families from the U.K., the U.S., and France and on chromosome 15q26 (*IDDM3*) in families from Canada. Using both linkage and association approaches, other putative type 1 diabetes susceptibility loci were identified on chromosomes 18q12-q21 (*IDDM6*), 2q33 (*IDDM7*), 6q27 (*IDDM8*), 3q22-q25 (*IDDM9*), 10p11-q11 (*IDDM10*), 14q24-q31 (*IDDM11*), 2q31-q33 (*IDDM12*), 2q34-q35 (*IDDM13*), 6q21 (*IDDM15*), 14q32 (*IDDM16*), 10q25 (*IDDM17*), 5q33 (*IDDM18*), 7p15-p13 (*GCK*), 1q42, 16q22-q24, Xp11 (conditional on HLA-DR genotype), and 8q22-q24 (8–10,12–17). Even though statistical evidence supporting linkage for some of these regions was strong in the initial reports, most regions have not been clearly established in multiple populations (9,23).

A major barrier to type 1 diabetes gene identification, given the likely small locus-specific contribution (low λ_S) for non-HLA genes, is the relatively small number of newly ascertained affected sibpair families with type 1 diabetes. In addition, previous studies have used available samples from a variety of collections, making the compilation of linkage results difficult because of apparent overlap in families analyzed and uncertainty in the equivalence of allele coding. To facilitate the genetic analysis of type 1 diabetes, results from two previous genome scans of type 1 diabetes were merged, comprising 767 families and 831 affected sibpairs from the U.K. and U.S. (24). The combined analyses supported linkage to at least six non-HLA regions to type 1 diabetes, including *IDDM2* (*INS*, nominal $P = 6.5 \times 10^{-4}$), 2q31-q33 ($P = 5.1 \times 10^{-4}$), and 10p11 ($P = 3.2 \times 10^{-4}$). A third genome scan of 424 type 1 diabetic families with at least two affected relative pairs (464 affected pairs) from Scandinavia (25) found no evidence for linkage at these latter three loci but did support linkage on chromosomes 5q11.2 (nominal $P = 8.1 \times 10^{-4}$) and 16p13 ($P = 1.6 \times 10^{-4}$). The *IDDM15* region on chromosome 6q21 supported linkage ($P = 7.0 \times 10^{-7}$) when HLA was taken into consideration in a combined analysis of U.S., French, and Scandinavian families.

We present here a joint analysis of data from these three prior genome-wide scans (U.S., U.K., and Scandinavia) as well as 254 new families collected for this study, a total of 1,435 multiplex families, for linkage to type 1 diabetes. With an average map information content of 67% (from ~400 polymorphic microsatellite markers in each scan), this family collection provides ~95% power to detect a locus with locus-specific $\lambda_S \geq 1.3$ and $P = 10^{-4}$. In addition to HLA, there was nominal evidence for linkage of type 1 diabetes to 10 other chromosome regions, including 6q21 (*IDDM15*) and 3 that reached genome-wide levels of significance, 2q31-q33 (*IDDM12* and *IDDM7*), 10p11-q14 (*IDDM10*), and 16p12-q24. These data support the existence of non-HLA susceptibility loci for type 1 diabetes and strengthen support for a subset of loci previously proposed to contribute to type 1 diabetes risk.

RESEARCH DESIGN AND METHODS

Four sets of Caucasian families provided genome scan data for the combined analyses. Three sets of families have been previously published—U.K. (21,26), U.S. (24,26), and Scandinavia (25)—and one set of 254 families that were newly assembled for this study. The new collection of DNA samples from 254 families was obtained from several sources. DNA samples from 47 U.K. families were identified from the Diabetes U.K. Warren repository (28) that had not been genotyped previously. Families not previously used in published genome scans from the U.S. were contributed by the Joslin Diabetes Center (121 families) and from the Human Biological Data Interchange (76 families). Ten families from Australia were collected by investigators at the Walter and Eliza Hall Institute as previously described (29). In total, there were 1,435 families containing 6,899 individuals (6,358 with genome scan data). A total of 3,109 individuals were affected (with type 1 diabetes), and of these, 3,072 had genotype data (for details of the samples, see table in online appendix [available at http://diabetes.diabetesjournals.org]).

Genotyping. Microsatellite marker genotyping technologies and allele scoring conventions varied between the different laboratories providing the data for previously published type 1 diabetic families. Details of genotyping of the U.K. (21), U.S. (27), and Scandinavian (25) families have been previously described. The 254 new families were genotyped by the Center for the Inheritance of Disease Research (http://www.cidr.jhmi.edu/) using a panel of 405 microsatellite markers. Because direct merging of genotypes (by standardized allele size) was not possible, within-family recoded genotype data from all four sources were merged into a single database. Family-naming conventions between the samples were normalized, and individual marker names were modified to indicate the laboratory of origin for the genotyping. After elimination of marker inconsistencies (see below), genetic markers were selected to form the analysis panel. Multiple independent genotyping occurred for some markers on a subset of individuals by different laboratories. In these cases, only one marker was used for the current analysis. Unless a marker showed inconsistencies in identity-by-descent (IBD) sharing, the marker that was included for analysis was the one scored in the most samples. A total of 1,190 markers were included in the combined analyses. Markers that previously had been added to maps because of association with type 1 diabetes were excluded to avoid bias in the multipoint linkage results. The excluded markers were located on chromosome 2 (alpha4, *ND1*, *D2S152*, *CTLA4*, and *IGFBP5*) and chromosome 11 (*INS*, *TH*).

Statistical analysis. Before integration of the genetic data, marker error detection and pedigree structure within each dataset were made using PREST software (30). This method uses the genome scan data to determine the likelihood of each specified relationship given the genetic data. Unlikely marker genotypes were resolved by recoding the specific genotype to "unknown." Occurrences of nonpaternity were resolved by changing the pedigree structure to that which was most likely and then repeating the analysis to confirm appropriate relationships. An integrated marker map was developed by using public databases (Mammalian Genotyping Service, http://research.marshfieldclinic.org/genetics/Genotyping_Service/mgsver2.htm; Southampton, http://cedar.genetics.soton.ac.uk/public_html/; Cooperative Human Linkage Center, http://gai.nci.nih.gov/CHLC/; deCODE, http://www.decode.is) as well as physical map and genome sequence information from the University of California at Santa Cruz (http://genome.ucsc.edu/) using primer sequences in BLAST searches against the genome sequence. All analyses were based on this "consensus" map. Single and multipoint linkage analyses (based on the consensus map order and distances) were performed using GeneHunter-plus [$S_{(pairs)}$ option (31–33)]. Examination of double recombinants was performed using Merlin software (34). Information content was estimated using Allegro (35).

Estimation of IBD statistics and resulting likelihoods under the null and alternative hypotheses were computed within each dataset. These dataset-specific likelihoods were then combined for the combined linkage analyses. Multipoint linkage analyses were performed, and maximized logarithm of odds (LOD) scores were calculated under an exponential model with δ constrained between 0 and 2 (32). Genome-wide empirical P values were determined by simulating Mendelian transmission with families maintaining the patterns of missing data observed in the sample (36). The fraction of LOD scores observed greater than the nominal value, based on simulations of 10,000 replicates across the genome, provided the estimated genome-wide P value. Exclusion mapping was performed using the MapMaker/SIBS program (37).

Previous studies have identified a potential type 1 diabetes susceptibility locus near (but not within) the HLA complex (*IDDM15*) (25,27,38). In the presence of strong support for linkage due to *IDDM1*, determining the support for *IDDM15* is complex because of the positive correlation among the IBD proportions for linked loci. Without accounting for this positive correlation, statistical tests are biased toward inferring an epistatic relationship. A simple approach when IBD is known is to compare the observed correlation, r, between the IBD estimates at two loci (i.e., *IDDM1* and *IDDM15*) with the theoretical correlation, $\rho = (1–2\theta)^2$, for two loci separated by recombination fraction, θ. The statistic $t = (z - \zeta)\sqrt{n-3}$, where $z = \frac{1}{2} \ln\left(\frac{1+r}{1-r}\right)$ and

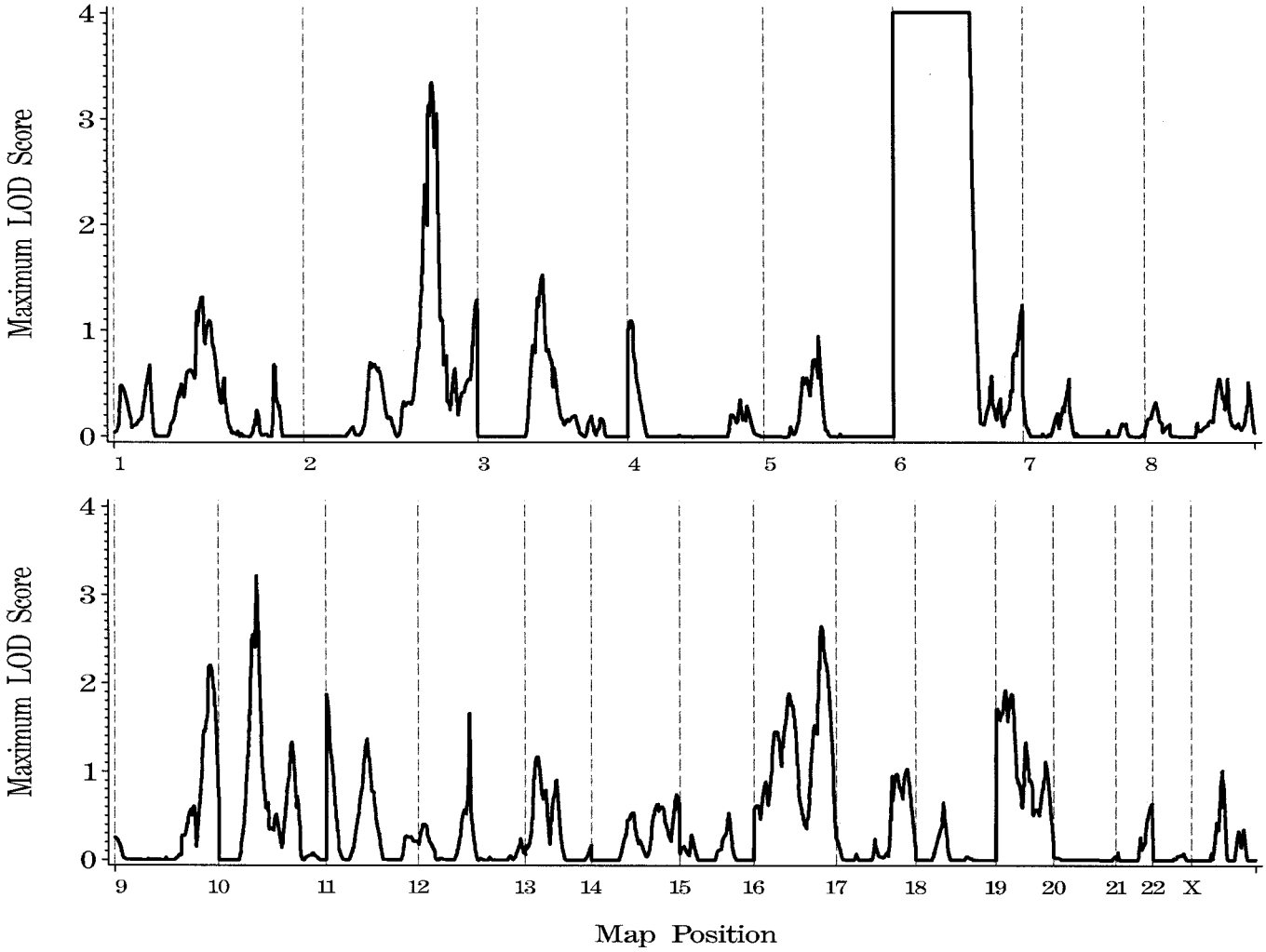

FIG. 1. Genome-wide linkage analysis of type 1 diabetes in 1,435 multiplex families.

$\zeta = \frac{1}{2}\ln\left(\frac{1+\rho}{1-\rho}\right)$ allows for the test of "interaction" that contrasts the observed IBD at *IDDM15* based on the distance of *IDDM15* from *IDDM1* and the expected IBD given that distance. Using a sex-averaged map, IBD estimates for each sibpair in the data were computed, and a single IBD estimate was selected from each pedigree. Thus, each of these IBD estimates is independent. Under the null hypothesis of no interaction between these loci, t approximately has a standard normal distribution. Observed correlations greater than ρ reflect increased sharing at *IDDM15* over that expected from IBD at *IDDM1* and the hypothesized genetic distance of *IDDM15* from *IDDM1*. A series of 10,000 simulations were performed as described above (36), with the correlation in IBD computed between *IDDM1* and *IDDM15*. The empirical P value for significance of *IDDM15* was based on the number of simulated correlations greater than that observed in the original data.

RESULTS

Linkage analysis. Analysis of 1,190 genetic markers in 1,435 families revealed that the strongest evidence for linkage to type 1 diabetes was on chromosome 6p21 (nominal $P = 2.0 \times 10^{-52}$) in the MHC (Fig. 1).There were nine non–HLA-linked regions with nominal evidence supporting linkage to type 1 diabetes ($P < 0.01$), including 2q31-q33 (*IDDM7* and *IDDM12*; $P = 9.0 \times 10^{-5}$; genome-wide $P = 0.016$), 10p14-q11 (*IDDM10*, $P = 1.2 \times 10^{-4}$; genome-wide $P = 0.021$), and 16q22-q24 ($P = 4.9 \times 10^{-4}$; genome-wide $P = 0.075$). The estimates of genetic relative risk varied by region, with *IDDM1* having the largest locus-specific effect ($\lambda_S \sim 3.3$) and the other sites having low locus-specific effects ($\lambda_S \sim 1.1$–1.2). Individual linkage plots by chromosome are provided in the online appendix (supplementary figures, upper curves).

Exclusion mapping. Each of the four datasets had the equivalent of an ~9-centiMorgan (cM) map, providing an average marker information content of ~ 66%. The range of information from the markers was 62% for chromosome 15 to 73% for chromosome 16. In the combined data, 82% of the genome could be excluded at LOD < -2 for loci of effect size $\lambda_S \geq 1.3$ (supplementary figures, lower curves), and >95% could be excluded for $\lambda_S \geq 1.5$. Several entire chromosomes could be excluded (chromosomes 7, 8, 18, 20, 21, and 22). The majority of chromosome 6 (due to the strongly linked 6p21/MHC region) and <50% of chromosomes 16, 19, and X could be excluded for $\lambda_S \geq 1.3$. For effects of $\lambda_S \geq 1.1$, only 6% of the genome could be excluded. The extent of exclusion for each chromosome is shown in Table 1.

IDDM15. The t-statistic was computed to determine the increase in sharing at *IDDM15*, beyond that expected from sharing at *IDDM1* and expected decay in sharing due to genetic distance. In the current data, the test statistic was computed for *IDDM15* at a position 37 cM from *IDDM1* (at 47 cM on chromosome 6), using a sex-averaged map. The test statistic was also computed for a range of map positions within 5 cM (32–42 cM) with similar results. At

TABLE 1
Exclusion mapping of the type 1 diabetes multiplex family data

Chromosome	Excluded λ_S (%)			
	~1.1	~1.3	~1.5	~1.7
1	3.52	82.17	100	100
2	1.15	73.76	94.68	100
3	8.93	84.96	99.12	100
4	6.90	95.61	100	100
5	9.74	96.45	100	100
6	0.00	30.77	39.49	41.54
7	0.00	100	100	100
8	0.00	100	100	100
9	12.27	84.76	96.34	100
10	0.00	75.88	100	100
11	4.14	81.63	97.96	100
12	0.00	98.24	100	100
13	0.00	73.33	100	100
14	13.67	82.27	100	100
15	0.86	95.76	100	100
16	0.00	24.24	87.12	100
17	0.00	79.53	100	100
18	23.81	100	100	100
19	0.00	47.83	100	100
20	56.7	100	100	100
21	0.00	100	100	100
22	0.00	100	100	100
X	0.00	39.00	83.00	97.00
Total	5.57	81.64	95.34	96.68

the 37-cM distance from *IDDM1* and *IDDM15*, the expected correlation coefficient between the IBD estimates under the null hypothesis was estimated as $\rho = 0.2276$. The observed Pearson's correlation coefficient between the IBD estimates at *IDDM1* and *IDDM15*, using 1,401 informative pedigrees, was $r = 0.3132$ (empirical $P < 1.0 \times 10^{-4}$). These results support an HLA-independent effect in the *IDDM15* region.

DISCUSSION

In a previous combined analysis of U.K. and U.S. families (24), it was concluded that an effort to merge and jointly analyze existing families would be required to clarify the role of non–HLA-linked loci in type 1 diabetes. In the present study, this effort has been achieved under the auspices of the Type 1 Diabetes Genetics Consortium (http://www.t1dgc.org). We have assembled families and merged data from three large genome scans and added new data from 254 families not previously scanned. This increased sample size has allowed the exclusion of >80% of the human genome for locus-specific, but population-independent, effects of $\lambda_S \geq 1.3$. In addition to continued support for type 1 diabetes susceptibility related to the MHC (*IDDM1*) and *INS* (*IDDM2*), we identified eight regions that supported non–HLA-linked susceptibility. Furthermore, we identified three chromosomes that contained extensive areas for which linkage could not be excluded—chromosomes 16, 19, and X—that could benefit from further genotyping to increase information content and the analysis of additional families.

Three non–HLA-linked regions provided support for linkage at, or near, the genome-wide level of significance ($P < 0.05$): chromosome 2q31-q33 (*IDDM7* and *IDDM12*), 10p14-q11 (*IDDM10*), and 16q22-q24. These locations were unlikely to have occurred by chance, based on our simulations. Together with the six other non–HLA-linked regions that exhibited evidence of linkage at nominal $P < 0.01$ (Table 2) and the 10-cM map, the data indicate a strong non-HLA genetic effect for type 1 diabetes (39). Furthermore, none of the three most strongly linked regions exhibited support for linkage in the 408 families from Scandinavia (25).

Strong support for linkage (nominal $P = 7.0 \times 10^{-7}$), after taking into account linkage to HLA) to the *IDDM15* locus (6q21), was observed previously in a combined analysis of French, U.S., and Scandinavian families (25,38). In the present study, we have obtained support for *IDDM15* (empirical $P < 1.0 \times 10^{-4}$). The ability to further define the effects of this locus will be facilitated by increased information content in the HLA region and in the region surrounding *IDDM15* to better estimate the observed IBD sharing and model the residual linkage to the HLA region, including taking into account sex-specific genetic map differences.

The *IDDM12* locus lies within the 2q31-q33 region and has been attributed to single nucleotide polymorphisms (SNPs) in the 3′-untranslated region of *CTLA4* (15); however, the modest λ_S value predicted from the odds ratios (ORs) (1.1–1.2) of the disease-associated SNPs at *CTLA4* (λ_S ~1.01) in type 1 diabetes seems unlikely to fully account for the magnitude of the observed evidence for linkage (regional λ_S ~1.19). This result suggests the presence of other loci in the 2q31-q33 region, if this linkage is confirmed in other future studies. Originally, *IDDM7* at

TABLE 2
Multipoint linkage analysis of four genome scans for type 1 diabetes ($P < 0.01$)

Chromosome	Position (cM)	Closest marker	Nominal LOD	Nominal *P* value	λ_S	Genome-wide *P* value*
2q31-q33	192	*D2S2167*	3.34	9.0×10^{-5}	1.19	0.016
3p13-p14	98	*D3S1261*	1.52	8.2×10^{-3}	1.15	0.649
6p21	47	*TNFA*	116.30	4.9×10^{-52}	3.35	$<1.0 \times 10^{-4}$
6q21	80	*D6S283*	22.39	7.0×10^{-7}	1.56	†
9q33-q34	150	*D9S260*	2.20	1.5×10^{-3}	1.13	0.191
10p14-q11	61	*D10S1426*	3.21	1.2×10^{-4}	1.12	0.021
11p15	2	*D11S922*	1.87	3.4×10^{-3}	1.16	0.371
12q14-q12	81	*D12S375*	1.66	5.8×10^{-3}	1.10	0.528
16p12-q11.1	56	*D16S3131*	1.88	3.3×10^{-3}	1.17	0.363
16q22-q24	108	*D16S504*	2.64	4.9×10^{-4}	1.19	0.075
19p13.3-p13.2	25	*INSR*	1.92	3.0×10^{-3}	1.15	0.338

*All genome-wide empiric *P* values are based on simulations of 10,000 replicates. †Empirical *P* value determined by simulation and estimated correlation of IBD between HLA and *IDDM15*, not genome-wide (see RESEARCH DESIGN AND METHODS); empirical $P < 1.0 \times 10^{-4}$.

chromosome 2q33 was assigned on the basis of evidence of allelic association of the *D2S152* microsatellite marker, but this association has not been substantiated. The evidence supporting linkage in the current study does not include the putative *IDDM13* locus at chromosome 2q34-q35 (29). Linkage of type 1 diabetes to 10p14-q13 (*IDDM10*) is well supported by the current and past studies (24,26); however, there has been little follow-up other than association analyses of the functional candidate gene *GAD2*, suggesting that this gene is not a type 1 diabetes susceptibility locus (40,41). The observed locus-specific effects for 2q31-q33 ($\lambda_S \sim 1.19$) and 10p14-q11 ($\lambda_S \sim 1.12$) suggest that a single common susceptibility allele would have an allelic association (OR) ~3. This effect should be identifiable in a fine-mapping association study using dense SNP maps across the regions.

Support for a type 1 diabetes susceptibility locus on chromosome 16p12-q11.1, which was observed independently in both the combined U.K. and U.S. families (nominal $P = 4.5 \times 10^{-3}$) and in the Scandinavian families ($P = 2 \times 10^{-4}$), remained in the present study ($P = 3.3 \times 10^{-3}$). A recent analysis of four rheumatoid arthritis genome scans (42) reported evidence for linkage at chromosomes 6p21 (HLA; $P = 2 \times 10^{-5}$) and 16p-cen ($P = 0.004$). Because rheumatoid arthritis, antithyroid autoimmune disease, and type 1 diabetes cluster in families more often than expected by chance (43), evidence for linkage for any one of these autoimmune diseases could be informative for others. Evidence for linkage in U.K. families with early-onset rheumatoid arthritis (44) to chromosome 16p has previously been demonstrated ($P = 3.2 \times 10^{-4}$). The comparison between linkage scan results for type 1 diabetes and rheumatoid arthritis provides other interesting similarities. The largest, single, combined scan of rheumatoid arthritis families (45) reported significant linkage of rheumatoid arthritis to chromosome 6p21 (HLA; $P = 5 \times 10^{-12}$), and some evidence ($P < 0.005$) of rheumatoid arthritis linked to six other regions (1q43, 6q21, 10q21, 12q12, 17p13, and 18q21). This overlap with potential type 1 diabetes susceptibility at 6q21, 12q12, and 16p-cen may not be coincidental in the etiology of these autoimmune diseases.

Recently, evidence for association of type 1 diabetes with alleles in the *PTPN22* locus (chromosome 1p13) has been reported (18), and this association has been confirmed (19,20). *PTPN22* encodes a lymphoid-specific tyrosine phosphatase (LYP) and is also associated with autoimmune thyroid disease, rheumatoid arthritis, and SLE (46). The absence of evidence supporting linkage of type 1 diabetes to chromosome 1p13 (*D1S206*) in the 1,435 families studied here is not surprising given the magnitude of the *PTPN22* association with type 1 diabetes. The OR of *PTPN22* is large (~1.7) but the λ_S is ~1.05. Thus, to detect linkage at $P < 0.001$ with 50% power, a sample of >8,000 affected sibpair families would be required, using a fully informative genetic map. Assuming a multiplicative model, the contribution of *PTPN22* to type 1 diabetes (based on the observed OR) is ~2%, much lower than HLA (40–50%). Nevertheless, the knowledge that *PTPN22* may be involved in risk to type 1 diabetes, as well as in other autoimmune diseases, is significant and could provide insight into modulating T-cell activity for disease prevention.

Several previously supported regions of linkage have diminished support in the current analyses. Type 1 diabetes susceptibility locus on chromosome 1q42 was strongly supported (nominal $P = 9.8 \times 10^{-5}$) in a study of 679 U.K. and U.S. families (24,47) but exhibited decreasing linkage support in a follow-up analysis of 616 families using a denser map in the region ($P = 4.0 \times 10^{-4}$). The evaluation of previously supported regions is difficult, even in the present study with over 1,600 affected sibpairs, particularly for regions with low λ_s (e.g., $\lambda_s \sim 1.1$). For example, the region on 1q42 was originally supported with MLS = 3.31 and $\lambda_s \sim 1.5$ (27). Although the current sample excludes this region at the reported $\lambda_s \sim 1.5$, support for linkage in this region has decreased with increasing sample size from a LOD = 2.20 (24), to the current LOD = 0.87 (nominal $P = 1.4 \times 10^{-2}$) with $\lambda_s \sim 1.05$. At the current estimated magnitude of genetic effect, the 1q42 region could not be excluded.

In a combined analysis of animal model and human linkage data from a number of autoimmune diseases, chromosome 18q12-q21 demonstrated evidence of linkage, which has now been supported by the analysis of congenic strains in NOD mice (48). There was no support for loci on chromosome 18 at $P < 0.05$ in the current study. Three independent studies of type 1 diabetes have reported linkage to chromosome 8q (49–51), but there was no support for 8q in this study. Additional previously reported loci with relatively little support for linkage in the current study include *IDDM4* (11q13), *IDDM6* (18q12-q21), *IDDM9* (3q22-q25), *IDDM11* (14q24-q31), *IDDM16* (14q32), *IDDM17* (10q25), and *IDDM18* (5q33). These data suggest that these putative type 1 diabetes susceptibility loci represent either false-positive results or have very small effects that may be more readily detected in certain populations because of variation in allele frequencies or other factors, including the possibility of population-specific genetic or environmental effects.

Linkage and fine mapping studies in mouse models of SLE (52) and of type 1 diabetes (53) have demonstrated that a single linkage peak may be composed of several susceptibility loci. In human populations, a linkage signal may be observed by the chance clustering of several disease loci, each with relatively weak locus-specific effects. The presence of multiple susceptibility loci may also account, in part, for broad linkage peaks often observed in studies of complex, common diseases. This underlying complexity would also increase the difficulty to obtain convincing results in future fine-mapping association studies. Both development of novel analytical approaches and increased sample size will be necessary to resolve this apparent complexity (54,55). Through the efforts of consortia (such as our international effort), it will be possible to increase the number of families for type 1 diabetes (http://www.t1dgc.org), which would increase power and allow exclusion of loci $\lambda_s \geq 1.2$, as well as provide standardized samples and reagents for future fine-mapping studies.

These results suggest two parallel tracks for the identification of type 1 diabetes susceptibility loci. First, systematic fine mapping of all the variants responsible for the HLA linkage to type 1 diabetes is justified, especially within the 4-Mb HLA region. Second, further exploration of potential non-HLA regions described here is now justified, including chromosomes 2q31-q33, 6q21, 10p14-q11, and 16q22-q24. Because sample sizes in linkage and association studies have historically been small and few genes (out of ~25,000) have been studied in depth, future collaborative efforts and establishment of accessible re-

sources for study should increase the yield of true disease susceptibility loci.

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APPENDIX

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