A Human Type 1 Diabetes Susceptibility Locus Maps to Chromosome 21q22.3

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OBJECTIVE—The Type 1 Diabetes Genetics Consortium (T1DGC) has assembled and genotyped a large collection of multiplex families for the purpose of mapping genomic regions linked to type 1 diabetes. In the current study, we tested for evidence of loci associated with type 1 diabetes utilizing genome-wide linkage scan data and family-based association methods.

RESEARCH DESIGN AND METHODS—A total of 2,496 multiplex families with type 1 diabetes were genotyped with a panel of 6,090 single nucleotide polymorphisms (SNPs). Evidence of association to disease was evaluated by the pedigree disequilibrium test. Significant results were followed up by genotyping and analyses in two independent sets of samples: 2,214 parent-affected child trio families and a panel of 7,721 case and 9,679 control subjects.

RESULTS—Three of the SNPs most strongly associated with type 1 diabetes localized to previously identified type 1 diabetes risk loci: *INS*, *IFIH1*, and *KIAA0350*. A fourth strongly associated SNP, rs876498 ($P = 1.0 \times 10^{-4}$), occurred in the sixth intron of the *UBASH3A* locus at chromosome 21q22.3. Support for this disease association was obtained in two additional independent sample sets: families with type 1 diabetes (odds ratio [OR] 1.06 [95% CI 1.00–1.11]; $P = 0.023$) and case and control subjects (1.14 [1.09–1.19]; $P = 7.5 \times 10^{-8}$).

CONCLUSIONS—The T1DGC 6K SNP scan and follow-up studies reported here confirm previously reported type 1 diabetes associations at *INS*, *IFIH1*, and *KIAA0350* and identify an additional disease association on chromosome 21q22.3 in the *UBASH3A* locus (OR 1.10 [95% CI 1.07–1.13]; $P = 4.4 \times 10^{-12}$). This gene and its flanking regions are now validated targets for further resequencing, genotyping, and functional studies in type 1 diabetes. ***Diabetes* 57:2858–2861, 2008**

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Genome-wide linkage and association studies focused on candidate genes or interval mapping in type 1 diabetes have previously identified a handful of risk loci that have been confirmed by multiple replications. Of these, the major risk factor(s) reside within the HLA region on chromosome 6p21. Other, non-HLA type 1 diabetes loci have comparatively small effects on disease risk relative to HLA but comparable effect sizes to risk loci identified in other common disorders. These include the insulin (*INS*) locus, where variation is thought to impact the transcription and expression of insulin, modulating thymic selection of T-cells specific for this autoantigen (1,2). Variants at the cytotoxic T-lymphocyte antigen (*CTLA4*) locus are implicated in type 1 diabetes risk, potentially by altering the production of differentially spliced products from the locus that affects T-cell activation (3,4). Single nucleotide polymorphisms (SNPs) in the interleukin-2 receptor α (*IL2RA*) region, which encodes one chain of the heterodimeric interleukin-2 cytokine receptor, are associated with type 1 diabetes (5). Finally, a nonsynonymous coding region SNP in the protein tyrosine phosphatase, nonreceptor type 22 (*PTPN22*) gene has been associated with type 1 diabetes as well as a number of other autoimmune disorders (6–9). This SNP, which predicts an Arg to Trp substitution at position 620, increases the activity of the *PTPN22* encoded phosphatase LYP, resulting in hyporesponsiveness of T-cells (10,11).

Recently, the approach of genome-wide association scanning has been applied to type 1 diabetes (12–14). The combination of high-density SNP coverage and large sample sizes for both initial screening and follow-up genotyping in these studies has both confirmed known type 1 diabetes loci and identified a number of novel candidate genes and regions. New associations with type 1 diabetes have been identified and replicated for SNPs in two regions on chromosome 12, 12q24 near *C12orf30* and 12q13 near erythroblastic leukemia viral oncogene homolog 3 (*ERBB3*); a region on 16p13 near C-type lectin domain family 16, member A (*CLEC16A/KIAA0350*); a region on 18p11 near protein tyrosine phosphatase, nonreceptor type 2 (*PTPN2*); and a region on 2q24 near interferon induced with helicase C domain 1 (*IFIH1*) (15,16). Detailed information about each of these type 1 diabetes–associated loci can be found at the T1DBase Web site (www.t1dbase.org).

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Most of the non-HLA type 1 diabetes risk loci are characterized by ORs in the 1.15–1.3 range, and despite the recent increase in the number of such loci identified and confirmed, it is unlikely that these known loci can account for all of the genetic risk for type 1 diabetes (15). Therefore, in the current study, we took advantage of a recently completed genome-wide scan for linkage in multiplex families with type 1 diabetes to explore whether alleles at any of the 6,090 SNPs genotyped displayed evidence of association with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Families used for initial screening were selected from nine different sources: the four Type 1 Diabetes Genetics Consortium (T1DGC) networks (Asia-Pacific [$n = 228$], Europe [$n = 585$], North America [$n = 370$], and the U.K. [$n = 124$]), the Diabetes U.K. Warren Repository ($n = 429$), the Human Biological Data Interchange repository ($n = 424$), the Joslin Diabetes Center ($n = 112$), the Steno Diabetes Center ($n = 146$), and Sardinia ($n = 78$). Details on recruitment sites and the numbers of families contributed for each of the T1DGC networks are accessible from the public side of the T1DGC Web site (www.t1dgc.org). Minimum entry criteria for families included the presence of at least one affected sibling pair, and availability of one or both biological parents was preferred. Eligibility requirements for affected individuals included documented type 1 diabetes with onset earlier than 35 years of age, insulin use within 6 months of diagnosis, and the absence of any concomitant disease or disorder associated with diabetes. In total, 2,496 families were genotyped. Both parents were available for 72.9% of families; 18.8% had only a single parent. Most families (91.7%) had exactly two affected full siblings; 4.1% had three and 0.3% had four or more affected siblings. The remaining families had pairs that were either incomplete or were half siblings.

The family replication set of samples consisted of 2,214 parent-affected child trio families derived from two sources. The Genetics of Kidneys in Diabetes (GoKinD) study of diabetic nephropathy contributed 578 families. Affected offspring in these families had type 1 diabetes diagnosed before 31 years of age, had initiated insulin therapy within 1 year of diagnosis, and had continued insulin treatment uninterrupted since initiation. The remaining 1,636 families were selected from the Danish Society of Childhood Diabetes and were all of Danish Caucasoid origin. Probands in these families were diagnosed with type 1 diabetes before 15 years of age and had continued insulin treatment since diagnosis. The case-control replication set consisted of 17,400 subjects, including 7,721 type 1 diabetic case subjects recruited as part of the Juvenile Diabetes Research Foundation International/Wellcome Trust British case collection and 9,679 control subjects from the British 1958 Birth Cohort and the Wellcome Trust Case Control Blood Service (13,17).

Genotyping. Families included in the original genome-wide linkage scan were all genotyped at the Center for Inherited Disease Research using the Illumina Human Linkage-12 Genotyping Beadchip consisting of 6,090 SNPs. Genotyping of SNP rs876498 in replication samples was performed using an Eclipse genotyping assay (Nanogen). As quality control for accuracy of this assay, a blinded resampling and genotyping of 366 families with type 1 diabetes from the initial genome-wide scan was performed.

Statistical analysis. Before statistical genetic analyses, genotype data were evaluated for Mendelian errors using PedCheck (18). PREST (19) was used to estimate the likelihood of each specified relationship in pedigrees given the genotyping information. Based on these analyses, 43 families were removed from further analysis due to the presence of a duplicate family, a duplicate sample within the family, nonresolvable family errors, or missing genotype information. Allelic association with type 1 diabetes within multiplex families was assessed using the pedigree disequilibrium test (PDT) (20), which provides a valid test of association in the presence of linkage in families with multiple affected individuals. The PDT examines the discrepancy between the alleles of heterozygote parents and those transmitted to affected offspring, as well as the allelic difference between affected and unaffected siblings. Both PDT-SUM and PDT-AVE tests (21) were carried out. Because these tests are asymptotically equivalent, the PDT-AVE test, in which counts of trios and pairs for each pedigree are weighted, is primarily reported here. PLINK (v.1.02) (22) was used to assess allelic association to type 1 diabetes in trio families, via the transmission/disequilibrium test (23), and in case-control samples. A logistic regression model was used to estimate effect sizes, with familial correlations being taken into account by the generalized estimating equation method (24).

To combine results of the original genome scan and those of follow-up studies, a weighted Z score–based fixed effects meta-analysis method was used. In brief, a Z statistic summarizing the magnitude of the P value for association and direction of effect was generated for each study. An overall Z statistic was then computed as a weighted average of the individual statistics, and a corresponding P value for that statistic was computed. The weights were proportional to the square root of the number of individuals in each study and scaled such that the squared weights summed to 1. For the meta-analysis of the effect size, the inverse variance was used as the weight for each study.

TABLE 1
PDT results from 6K SNP scan at $P < 0.001$

Chromosome	SNP	Position*	P	Locus†
11	rs1004446	2126719	2.5×10^{-9}	*INS*
2	rs1990760	162949558	4.1×10^{-5}	*IFIH1*
16	rs887864	11066386	7.1×10^{-5}	*KIAA0350*
21	rs876498	42714896	1.0×10^{-4}	*UBASH3A*
11	rs2076837	14931161	2.5×10^{-4}	
10	rs877783	72985946	3.6×10^{-4}	
2	rs6767	5021488	4.4×10^{-4}	
10	rs942434	7277013	5.8×10^{-4}	
6	rs169679	28964551	6.1×10^{-4}	*HLA*
22	rs885978	17572780	6.4×10^{-4}	
2	rs1504	36977669	6.8×10^{-4}	
5	rs860732	179360006	7.0×10^{-4}	
6	rs1011094	28883961	7.9×10^{-4}	*HLA*
7	rs1543851	64250422	8.4×10^{-4}	
8	rs1872283	107880067	9.0×10^{-4}	
3	rs353087	15165591	9.9×10^{-4}	

*Nucleotide position on indicated chromosome; †most proximal locus to indicated SNP.

RESULTS

After data cleaning, PDT was performed on the data from 5,943 markers genotyped in the family collection. Table 1 lists all SNPs with $P < 0.001$ in this analysis. Only a single marker, rs1004446, displayed evidence of association with type 1 diabetes at a genome-wide significance level ($P = 2.5 \times 10^{-9}$). This SNP is located in the *INS-IGF2* region on chromosome 11p15 and has previously been reported to be associated with type 1 diabetes (14). Indeed, among the 16 SNPs listed in Table 1, 5 corresponded to previously confirmed type 1 diabetes loci identified through genome-wide scanning: rs1004446 (*INS-IGF2*), a nonsynonymous coding SNP rs1990760 (*IFIH1*), rs887864 (intron 18 of *CLEC16A/KIAA0350*), and two SNPs, rs169679 and rs1011094, that flank the *HLA* region.

Given that the top three most associated SNPs (ranked by statistical significance in Table 1) correspond to confirmed type 1 diabetes risk loci, we examined the fourth-ranked SNP, rs876498, for which there was also substantial evidence of association with type 1 diabetes ($P = 1.0 \times 10^{-4}$ for PDT-AVE test and $P = 1.0 \times 10^{-5}$ for PDT-SUM test). Further impetus for follow-up study of this SNP came from its location within the sixth intron of the gene *UBASH3A*, which is expressed predominantly in T-cells and is involved in the regulation of signaling from the antigen receptor (25). The putative disease-associated allele was relatively common, with a minor allele frequency of 0.45 in unaffected founders. Blinded validation genotyping was carried out in 366 of the original 2,496 T1DGC families by a second methodology to confirm the initial finding. A concordance rate of 100% was observed between the original and the validation study. To confirm and extend the initial finding, rs876498 was genotyped in additional independent populations, both family based and case control (Table 2). Overall, there was highly significant evidence of association between the minor

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TABLE 2
Follow-up genotyping for rs876498 in families with type 1 diabetes

Study population	Effective sample size	P	OR (95% CI)
Original genome scan: 2,496 ASP families	6,172 trios and DSPs	1.0×10^{-4}	1.09 (1.04–1.13)
Follow-up: 2,214 parent-affected child trios	890 trios	0.023	1.06 (1.00–1.11)
Follow-up: 7,721 affected individuals, 9,679 control subjects	17,400	7.5×10^{-8}	1.14 (1.09–1.19)
Overall	22,635	4.4×10^{-12}	1.10 (1.07–1.13)

ASP, affected sibling pair; DSPs, discordant sibling pairs.

allele at rs876498 and type 1 diabetes (OR 1.10 [95% CI 1.07–1.13]; $P = 4.4 \times 10^{-12}$).

DISCUSSION

In the current study, we took advantage of available SNP genotyping data from a linkage study of 2,496 multiplex families with type 1 diabetes–affected sibling pairs. The ability to use family-based testing for association allowed the combined analysis of subjects selected from multiple different geographic areas while reducing concerns regarding the potential effects of population stratification. Two approaches were used as an additional check for potential heterogeneity from family collection in the nine T1DGC regions. First, a meta-analysis combining the nine individual PDT results provided a $P = 2.8 \times 10^{-5}$, the same magnitude of significance as our combined data analysis. Second, a Q statistic based on the association effect and SE was computed. The association heterogeneity test (Q 5.15, 7 d.f. [one group has missing estimates]; $P = 0.64$) indicates no statistically significant heterogeneity across the regions of the T1DGC data. The validness of our test for association can also be shown from the genomic control number 1.02 obtained when the whole-genome scan results were examined (26).

Although SNP coverage was extremely sparse for genome-wide association testing, an advantage was that the SNP selection in the linkage panel of markers differs from the higher density panels used in previous genome-wide association studies. Three of the top four markers, ranked by P value, corresponded to previously established type 1 diabetes risk loci. The fourth-ranked SNP mapped to chromosome 21q22.3; no locus associated at genome-wide significance levels with type 1 diabetes or any other autoimmune disorder has previously been mapped to this chromosome. The region had, however, been previously linked to type 1 diabetes in Scandinavian families (27), and a region ~10 Mb centromeric to rs876498 has been fine-mapped in Danish families (28). Furthermore, a type 1 diabetes risk locus on chromosome 21 might have been anticipated given the increased frequency of Downs syndrome, caused by trisomy for chromosome 21, among type 1 diabetic patients (29). The findings reported here for rs876498 were validated by a blinded 15% resample using an alternative genotyping approach and then replicated in independent sets of parent-affected child trio families and case-control subjects. These studies provide compelling evidence for association of the minor allele at this SNP, rs876498, with type 1 diabetes.

The SNP rs876498 is located within the sixth intron of a gene variously referred to as ubiquitin associated and SH3 domain containing, A (*UBASH3A*) (30), T-cell ubiquitin ligand (*TULA*) (31), and suppressor of T-cell signaling 2 (*Sts-2*) (32). Based on the available data in HapMap (release 23a), rs876498 is centrally located in a haplotype block of ~14 kb contained entirely within *UBASH3A*. Flanking genes in the region are not obvious candidates, on functional grounds, for involvement in type 1 diabetes etiology, and they include the trefoil domain containing family members *TFF1* and *TFF2*; the transmembrane serine protease *TMPRSS3*; *RSPH1*, which encodes a male meiotic metaphase chromosome associated protein; and the glycerol 3-phosphate transporter *SLC37A1*.

UBASH3A is expressed predominantly in T-cells, where it interacts with c-CBL through its SH3 domain and binds to ubiquitin and ubiquitylated proteins via its ubiquitin-associated domain ((25). In T-cells, it acts in part by inhibiting c-CBL–mediated downregulation of protein tyrosine kinases such as ZAP70 that are activated upon T-cell receptor stimulation (32). In this regard, *UBASH3A* is reminiscent of another identified type 1 diabetes risk locus, *PTPN22*, whose product, LYP, also interacts with c-CBL but directly downregulates some of the same protein tyrosine kinases by dephosphorylation (6,33). UBASH3A has other functions in T-cells, including participation in proapoptotic pathways (34). The functions of UBASH3A make it an appealing candidate to contribute to type 1 diabetes risk. While it may be premature to focus exclusively on this single gene based upon the present data, the significant and replicated findings of association reported here strongly suggest that a gene or genes in this region contributes to risk for type 1 diabetes.

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