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Analysis of 55 autoimmune disease and type II diabetes loci: further confirmation of chromosomes 4q27, 12q13.2 and 12q24.13 as type I diabetes loci, and support for a new locus, 12q13.3–q14.1

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Abstract

A candidate gene study was conducted on 10 established type II diabetes genes and 45 genes associated with autoimmune diseases, including type I diabetes (T1D), in a maximum of 1410 affected sib-pair families assembled by the Type I Diabetes Genetics Consortium. Associations at P values < 10^{-3} were found for three known T1D regions at chromosomes 4q27, 12q13.2 and 12q24.13 (http://www.T1DBase.org). Support was obtained for a newly identified T1D candidate locus on chromosome 12q13.3–12q14.1 (rs1678536/KIF5A: P=8.1 × 10^{-3}; relative risk (RR) for minor allele=0.89, 95% CI=0.82–0.97), which has a separate association from the previously reported T1D candidate locus ERBB3/12q13.2–q13.3. Our new evidence adds to that previously published for the same gene region in a T1D case–control study (rs1678542; P=3.0 × 10^{-4}; odds ratio (OR)=0.92, 95% CI=0.88–0.96). This region, which contains many genes, has also been associated with rheumatoid arthritis.

Keywords

autoimmune disease; type I diabetes; type II diabetes; SNPs; T1DGC

Introduction

The advent of genome-wide association studies has highlighted the commonality and differences between diseases. Genes found to be associated in one disease are now routinely genotyped in related diseases, providing a more focused and often more informative candidate gene approach.[1,2] A candidate gene study was performed using a panel of 216 SNPs from 10 known T2D loci (including *HHEX* and *SLC30A8*), 126 SNPs from 5 known T1D regions (including *CTLA4* and *IL2*) and 239 SNPs from 40 known other autoimmune disease regions (including *IL23R* and *PADI4*). Although T1D and T2D are considered etiologically distinct, characterized by autoimmune destruction of the pancreatic β cells and by impaired β cell function, respectively, T2D loci were included in the study as they may share a common pathophysiological etiology, suggested by the similarities in their clinical manifestation.[3] The

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Conflict of interest
The authors declare no conflict of interest.

five known T1D loci were included for further confirmation. All SNPs were genotyped in a maximum of 1410 T1D affected sib-pair families assembled by the Type I Diabetes Genetics Consortium (T1DGC), providing 2198 parent–child trios. A complete list of SNPs, genes and regions is provided in Supplementary Table 1.

Results

A total of 581 SNPs was selected from T2D genes related to β-cell function, T1D and other autoimmune candidate genes and genotyped at the Broad Institute of Harvard/MIT in Cambridge, MA, USA (http://www.broad.mit.edu/) using the Illumina Golden Gate platform. In addition to the standard sample and SNP quality control, we visually inspected the SNP signal intensity plots for each of the family groups (see accompanying paper4), resulting in 334 SNPs that passed quality control (Supplementary Table 1).[8]

Fifty-one SNPs exhibited some evidence ($P < 0.05$) of association with T1D (Table 1),[8] 16 of which were from known T1D regions. Only four SNPs reached the required level of significance for this study ($P<0.001$) and these SNPs were all from known T1D regions: rs11171747 on chromosome 12q13.2 ($P=7.1 \times 10^{-6}$), located 21 kb telomeric of *ERBB3*;[5] rs4767364 ($P=1.6 \times 10^{-4}$) and rs17696736 ($P=6.2 \times 10^{-4}$) on 12q24.13 in the *C12orf30* region, located 597 kb telomeric of *SH2B3*;[5] and rs12510683 ($P=7.1 \times 10^{-4}$) on 4q27 in the *KIAA1109* region, located 393 kb centromeric of *IL2-IL21*.

Gene regions showing some evidence of association ($0.05> P> 0.001$) with T1D included SNPs in two T2D genes thought to be involved with β-cell function (Table 1): *CDKAL1* on chromosome 6p22.3 ($P=1.6 \times 10^{-3}$) and *SLC30A8* on 8q24.11 ($P=1.6 \times 10^{-3}$). Recent studies of *SLC30A8* have identified an association of T2D with the non-synonymous SNP, rs13266634 (Arg325Trp), an SNP also genotyped in this study. This SNP has also been reported to determine ZnT8 autoantibody specificity in T1D;[6] however, no association with T1D was found with this SNP in this study of T1D affected sib-pair families (data not shown) in agreement with an earlier study of 7680 British T1D cases and 7200 controls.7 Similarly, the most strongly associated *CDKAL1* SNP with T2D was not associated with T1D in this large British case–control study.[7]

In addition, some evidence of association with T1D (Table 1) was found for rs231727 in *CTLA4* on chromosome 2q33.2 ($P=1.2 \times 10^{-3}$), a known T1D region;[7] rs1678536 in *KIF5A* on 12q13.3 ($P=8.11 \times 10^{-3}$) and rs701008 in *AGAP2* on 12q14.1 ($P=2.5 \times 10^{-3}$). The *KIF5A* and *AGAP2* SNPs are not independently associated with T1D: using logistic regression, adding rs1678536/*KIF5A* to rs701008/*AGAP2* gave $P=0.37$ and rs701008/*AGAP2* to rs1678536/*KIF5A* gave $P=0.08$. The two SNPs are 138 kb apart and in the same linkage disequilibrium block ($D' =0.78$ and $r^2=0.42$ in parents).[7] The associated 12q13.3–q14.1 region is approximately 1.6Mb. Nevertheless, the association of the rs1678536/*KIF5A* and rs701008/*AGAP2* SNPs is independent of the established *ERBB3*/12q13.2–q13.3 region:[8] using logistic regression, adding rs11171747/*ERBB3* (most associated SNP found in this study) to rs1678536/*KIF5A* gave $P=1.4 \times 10^{-3}$ and adding rs1678536/*KIF5A* to rs11171747/*ERBB3* gave $P=7.3 \times 10^{-3}$. *KIF5A* is about 2Mb centromeric of *ERBB3* with a single recombination hotspot between these genes.

Discussion

In addition to the previously reported T1D-associated *ERBB3*/12q13.2–q13.3 region,[5] we provide evidence of an independent T1D locus within the 12q13.3–q14.1 region, which contains 47 protein-coding genes, including *KIF5A, AGAP2, PIP4K2C* and also the vitamin D-associated gene *CYP27B1*, which has been reported to show some evidence of an association

with T1D.[9] However, rs1678542/*KIF5A* (an SNP associated with rheumatoid arthritis)[10] and rs10877012/*CYP27B1* are not independently associated with T1D in 7455 cases and 9089 controls: using logistic regression, adding rs1678542/*KIF5A* to rs10877012/*CYP27B1* gave P=0.018 and rs10877012/*CYP27B1* to rs1678542/*KIF5A* gave P=0.10. The 12q13.3–q14.1 region has been earlier associated with rheumatoid arthritis (rs1678542/*KIF5A*)[10] and most recently with T1D in 8010 cases and 9733 controls (rs1678542/*KIF5A*, $P=3.0 \times 10^{-4}$; OR=0.92, 95% CI=0.88–0.96).[2] Hence, we have obtained further support for the 12q13.3–q14.1 region in T1D affected sib-pair families. As this region contains 47 protein-coding genes, further sequencing and genotyping will be required to ascertain the contribution of these genes to T1D. We found no convincing evidence of commonality between type I and type II diabetes.

Materials and methods

Subjects

The DNA samples were genotyped at the Broad Institute of Harvard/MIT in Cambridge, MA, USA (http://www.broad.mit.edu/). The samples were assembled by the T1DGC and consist of affected sib-pair families of two parents and two affected offspring. The families were obtained from nine cohorts: Diabetes UK (DUK), Human Biological Data Interchange (HBDI), T1DGC Asia Pacific (AP) Network, T1DGC European (EUR) Network, T1DGC United Kingdom (UK) Network, T1DGC North America (NA) Network, Joslin (JOS) Diabetes Center, Sardinia (SAR) and Denmark (DAN). The AP, EUR, NA and UK collections were newly recruited by the T1DGC, whereas the remainder where part of established collections; 2074 families had at least 1 member who passed sample quality control, 1410 families provided 2798 parent–child trios.

SNP selection

A total of 581 SNPs were selected from T2D genes related to β-cell function, recent T1D and other autoimmune candidate genes (Table 1; www.T1DBase.org). SNPs were genotyped using the Illumina Golden Gate platform at the Broad Institute of Harvard/MIT in Cambridge, MA, USA (http://www.broad.mit.edu/). In addition to standard sample and SNP quality control, SNP signal intensity plots for each of the family groups were visually inspected (see accompanying paper4). This process provided 334 SNPs with well-separated signal clouds—148 of 239 SNPs from autoimmune disease regions, 114 of 216 SNPs from T2D regions and 72 of 126 SNPs from T1D regions. Genotype signal intensity cluster plots are available in T1DBase.8

Statistics

All analyses were carried out in the R statistical environment using the snpMatrix package from the bioConductor project.[11] Family groups were analyzed using the transmission/disequilibrium test configured as a score test. The scores and their variances were summed over family groups and genotyping centers to pool information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

SNPs from known T1D, T2D and autoimmune disease regions with evidence of T1D association, $P<0.05$, ordered by genomic position

rs number	Chromosome	Gene region	Parent–child trios	MAF	1-df P	T1D, T2D or autoimmune
rs6745050	2q33		2764	0.392	0.023	T1D
rs12990970	2q33		2750	0.394	0.045	T1D
rs231727	2q33	*CTLA4*	2763	0.359	0.00122	T1D
rs10197319	2q33		2644	0.469	0.0378	T1D
rs17268364	2q33		2756	0.459	0.0268	T1D
rs4294983	2q33		2500	0.072	0.0278	T1D
rs12640179	4q13	*GC*	886	0.078	0.0167	Autoimmune
rs16847054	4q13	*GC*	1657	0.062	0.0129	Autoimmune
rs12510683	4q27		2774	0.225	0.000713	T1D
rs6827444	4q27	*KIAA1109*	2726	0.181	0.0199	T1D
rs12511287	4q27		2767	0.307	0.0349	T1D
rs11567751	5p13	*IL7R*	2704	0.297	0.0147	Autoimmune
rs6897932	5p13	*IL7R*	2674	0.247	0.0424	Autoimmune
rs3194051	5p13	*IL7R*	2736	0.298	0.0196	Autoimmune
rs10214237	5p13		2751	0.246	0.0338	Autoimmune
rs700162	5p13	*UGT3A1*	2563	0.402	0.0436	Autoimmune
rs2447876	5p13	*UGT3A1*	241	0.188	0.0302	Autoimmune
rs3792876	5q31	*SLC22A4*	2762	0.073	0.0157	Autoimmune
rs2073838	5q31	*SLC22A4*	2778	0.073	0.0196	Autoimmune
rs7739974	6p22	*CDKAL1*	2709	0.206	0.0195	T2D
rs1569699	6p22	*CDKAL1*	2750	0.325	0.0195	T2D
rs2206736	6p22	*CDKAL1*	2784	0.172	0.0174	T2D
rs9356747	6p22	*CDKAL1*	2768	0.234	0.0356	T2D
rs7741604	6p22	*CDKAL1*	2782	0.141	0.0208	T2D
rs9465873	6p22	*CDKAL1*	2749	0.386	0.032	T2D
rs12211466	6p22	*CDKAL1*	557	0.062	0.00157	T2D
rs7738382	6p22	*CDKAL1*	2752	0.281	0.0433	T2D
rs11970030	6p22	*CDKAL1*	2765	0.124	0.04	T2D
rs4712569	6p22	*CDKAL1*	2756	0.163	0.00371	T2D
rs201351	6p22	*CDKAL1*	2739	0.119	0.00874	T2D
rs201300	6p22	*CDKAL1*	2765	0.387	0.0422	T2D
rs4389757	6p22	*CDKAL1*	2763	0.125	0.00234	T2D
rs9465994	6p22	*CDKAL1*	2764	0.473	0.0402	T2D
rs4710965	6p22	*CDKAL1*	2690	0.462	0.0422	T2D
rs6942273	6p22	*CDKAL1*	2755	0.44	0.0213	T2D
rs4876369	8q24	*SLC30A8*	1646	0.153	0.00162	T2D
rs10811661	9p21	*CDKN2B*	2750	0.171	0.0182	T2D
rs10876864	12q13		2691	0.449	0.00109	T1D

rs number	Chromosome	Gene region	Parent–child trios	MAF	1-df P	T1D, T2D or autoimmune
rs2271194	12q13	*ERBB3*	2653	0.447	0.00892	T1D
rs705708	12q13	*ERBB3*	2763	0.488	0.000125	T1D
rs11171747	12q13		2744	0.356	7.12E-06	T1D
rs1678536	12q13	*KIF5A*	2756	0.278	0.00811	Autoimmune
rs2640629	12q14		2705	0.331	0.0439	Autoimmune
rs701008	12q14	*AGAP2*	2742	0.353	0.00252	Autoimmune
rs2301551	12q14	*AGAP2*	2651	0.295	0.0253	Autoimmune
rs11172349	12q14		2722	0.307	0.0172	Autoimmune
rs12298022	12q24	*C12orf30*	2759	0.077	0.00102	T1D
rs17696736	12q24	*C12orf30*	2742	0.468	0.000618	T1D
rs4767364	12q24	*C12orf30*	2745	0.273	0.000164	T1D
rs6110460	20p13	*DEFB129*	2669	0.47	0.0302	Autoimmune
rs729749	22Q12	*NCF4*	2658	0.248	0.049	Autoimmune

MAF, minor allele frequency in unaffected parents; T1D, type I diabetes; T2D, type II diabetes.