

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

Patrick Concannon,^{1,2} Suna Onengut-Gumuscu,^{2,3} John A. Todd,⁴ Deborah J. Smyth,⁴ Flemming Pociot,⁵ Regine Bergholdt,⁵ Beena Akolkar,⁶ Henry A. Erlich,⁷ Joan E. Hilner,⁸ Cécile Julier,⁹ Grant Morahan,¹⁰ Jørn Nerup,⁵ Concepcion R. Nierras,¹¹ Wei-Min Chen,^{2,12} Stephen S. Rich,² and the Type 1 Diabetes Genetics Consortium

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]; $P = 4.4 \times 10^{-12}$).

From the ¹Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, Virginia; the ²Center for Public Health Genomics, University of Virginia, Charlottesville, Virginia; the ³Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia, Charlottesville, Virginia; the ⁴Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, U.K.; the ⁵Steno Diabetes Center, Gentofte, Denmark; the ⁶Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; ⁷Roche Molecular Systems, Pleasanton, California; the ⁸Division of Public Health Sciences, Wake Forest University Health Sciences, Winston-Salem, North Carolina; ⁹INSERM U730 et CEA, Institut de Génétique Centre National de Génotypage, Evry, France; the ¹⁰Centre for Diabetes Research, The Western Australian Institute for Medical Research, and Centre for Medical Research, University of Western Australia, Perth, Australia; the ¹¹Juvenile Diabetes Research Foundation, New York, New York; and the ¹²Department of Public Health Sciences, Division of Biostatistics and Epidemiology, University of Virginia, Charlottesville, Virginia.

Corresponding author: Patrick Concannon, pjc6n@virginia.edu.

Received 6 June 2008 and accepted 14 July 2008.

Published ahead of print at <http://diabetes.diabetesjournals.org> on 22 July 2008. DOI: 10.2337/db08-0753.

© 2008 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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

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).

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. Proband 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

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

Chromosome	SNP	Position*	P	Locus†
11	rs1004446	2126719	2.5×10^{-9}	<i>INS</i>
2	rs1990760	162949558	4.1×10^{-5}	<i>IFIH1</i>
16	rs887864	11066386	7.1×10^{-5}	<i>KIAA0350</i>
21	rs876498	42714896	1.0×10^{-4}	<i>UBASH3A</i>
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}	<i>HLA</i>
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}	<i>HLA</i>
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.

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.

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

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

Study population	Effective sample size	<i>P</i>	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 validity 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 Down 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.

ACKNOWLEDGMENTS

This research uses resources provided by the T1DGC, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. Further support was provided by a grant from the NIDDK (DK46635) to P.C. and a joint JDRF and Wellcome Trust grant to the Diabetes and Inflammation Laboratory at Cambridge, which also received support from the National Institute for Health Research Cambridge Biomedical Centre.

REFERENCES

- Vafiadis P, Bennett ST, Todd JA, Nadeau J, Grabs R, Goodyer CG, Wickramasinghe S, Colle E, Polychronakos C: Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. *Nat Genet* 15:289–292, 1997
- Pugliese A, Zeller M, Fernandez A Jr, Zalcberg LJ, Bartlett RJ, Ricordi C, Pietropaolo M, Eisenbarth GS, Bennett ST, Patel DD: The insulin gene is transcribed in the human thymus and transcription levels correlated with allelic variation at the INS VNTR-IDDM2 susceptibility locus for type 1 diabetes. *Nat Genet* 15:293–297, 1997
- Nistico L, Buzzetti R, Pritchard LE, Van der Auwera B, Giovannini C, Bosi E, Larrad MT, Rios MS, Chow CC, Cockram CS, Jacobs K, Mijovic C, Bain SC, Barnett AH, Vandewalle CL, Schuit F, Gorus FK, Tosi R, Pozzilli P,

- Todd JA, Belgian Diabetes Registry: The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. *Hum Mol Genet* 5:1075–1080, 1996
4. Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, Rainbow DB, Hunter KM, Smith AN, Di Genova G, Herr MH, Dahlman I, Payne F, Smyth D, Lowe C, Twells RC, Howlett S, Healy B, Nutland S, Rance HE, Everett V, Smink LJ, Lam AC, Cordell HJ, Walker NM, Bordin C, Hulme J, Motzo C, Cucca F, Hess JF, Metzker ML, Rogers J, Gregory S, Allahabadia A, Nithyananthan R, Tuomilehto-Wolf E, Tuomilehto J, Bingley P, Gillespie KM, Undlien DE, Ronningen KS, Guja C, Ionescu-Tirgoviste C, Savage DA, Maxwell AP, Carson DJ, Patterson CC, Franklyn JA, Clayton DG, Peterson LB, Wicker LS, Todd JA, Gough SC: Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 423:506–511, 2003
 5. Lowe CE, Cooper JD, Brusko T, Walker NM, Smyth DJ, Bailey R, Bourget K, Plagnol V, Field S, Atkinson M, Clayton DG, Wicker LS, Todd JA: Large-scale genetic fine mapping and genotype-phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. *Nat Genet* 39:1074–1082, 2007
 6. Bottini N, Musumeci L, Alonso A, Rahmouni S, Nika K, Rostamkhani M, MacMurray J, Meloni GF, Lucarelli P, Pellicchia M, Eisenbarth GS, Comings D, Mustelin T: A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet* 36:337–338, 2004
 7. Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, Ardlie KG, Huang Q, Smith AM, Spoerke JM, Conn MT, Chang M, Chang SY, Saiki RK, Catanese JJ, Leong DU, Garcia VE, McAllister LB, Jeffery DA, Lee AT, Batliwalla F, Remmers E, Criswell LA, Seldin MF, Kastner DL, Amos CI, Sninsky JJ, Gregersen PK: A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet* 75:330–337, 2004
 8. Kyogoku C, Langefeld CD, Ortmann WA, Lee A, Selby S, Carlton VE, Chang M, Ramos P, Baechler EC, Batliwalla FM, Novitzke J, Williams AH, Gillett C, Rodine P, Graham RR, Ardlie KG, Gaffney PM, Moser KL, Petri M, Begovich AB, Gregersen PK, Behrens TW: Genetic Association of the R620W Polymorphism of Protein Tyrosine Phosphatase PTPN22 with Human SLE. *Am J Hum Genet* 75:504–507, 2004
 9. Criswell LA, Pfeiffer KA, Lum RF, Gonzales B, Novitzke J, Kern M, Moser KL, Begovich AB, Carlton VE, Li W, Lee AT, Ortmann W, Behrens TW, Gregersen PK: Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. *Am J Hum Genet* 76:561–571, 2005
 10. Vang T, Congia M, Macis MD, Musumeci L, Orru V, Zavattari P, Nika K, Tautz L, Tasken K, Cucca F, Mustelin T, Bottini N: Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nat Genet* 37:1317–1319, 2005
 11. Rieck M, Arechiga A, Onengut-Gumuscu S, Greenbaum C, Concannon P, Buckner JH: Genetic variation in PTPN22 corresponds to altered function of T and B lymphocytes. *J Immunol* 179:4704–4710, 2007
 12. Smyth DJ, Cooper JD, Bailey R, Field S, Burren O, Smink LJ, Guja C, Ionescu-Tirgoviste C, Widmer B, Dunger DB, Savage DA, Walker NM, Clayton DG, Todd JA: A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nat Genet* 38:617–619, 2006
 13. Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447:661–678, 2007
 14. Hakonarson H, Grant SF, Bradfield JP, Marchand L, Kim CE, Glessner JT, Grabs R, Casalunovo T, Taback SP, Frackelton EC, Lawson ML, Robinson LJ, Skraban R, Lu Y, Chiavacci RM, Stanley CA, Kirsch SE, Rappaport EF, Orange JS, Monos DS, Devoto M, Qu HQ, Polychronakos C: A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. *Nature* 448:591–594, 2007
 15. Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, Bailey R, Nejentsev S, Field SF, Payne F, Lowe CE, Szeszkó JS, Hafler JP, Zeitels L, Yang JH, Vella A, Nutland S, Stevens HE, Schuilenburg H, Coleman G, Maisuria M, Meadows W, Smink LJ, Healy B, Burren OS, Lam AA, Ovington NR, Allen J, Adlem E, Leung HT, Wallace C, Howson JM, Guja C, Ionescu-Tirgoviste C, Simmonds MJ, Heward JM, Gough SC, Dunger DB, Wicker LS, Clayton DG: Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. *Nat Genet* 39:857–864, 2007
 16. Hakonarson H, Qu HQ, Bradfield JP, Marchand L, Kim CE, Glessner JT, Grabs R, Casalunovo T, Taback SP, Frackelton EC, Eckert AW, Annaiah K, Lawson ML, Otiemo FG, Santa E, Shaner JL, Smith RM, Onyiah CC, Skraban R, Chiavacci RM, Robinson LJ, Stanley CA, Kirsch SE, Devoto M, Monos DS, Grant SF, Polychronakos C: A novel susceptibility locus for type 1 diabetes on Chr12q13 identified by a genome-wide association study. *Diabetes* 57:1143–1146, 2008
 17. Power C, Elliott J: Cohort profile: 1958 British birth cohort (National Child Development Study). *Int J Epidemiol* 35:34–41, 2006
 18. O'Connell JR, Weeks DE: PedCheck: a program for identification of genotype incompatibilities in linkage analysis. *Am J Hum Genet* 63:259–266, 1998
 19. Sun L, Wilder K, McPeck MS: Enhanced pedigree error detection. *Hum Hered* 54:99–110, 2002
 20. Martin ER, Monks SA, Warren LL, Kaplan NL: A test for linkage and association in general pedigrees: the pedigree disequilibrium test. *Am J Hum Genet* 67:146–154, 2000
 21. Martin ER, Bass MP, Kaplan NL: Correcting for a potential bias in the pedigree disequilibrium test. *Am J Hum Genet* 68:1065–1067, 2001
 22. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC: PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 81:559–575, 2007
 23. Spielman RS, McGinnis RE, Ewens WJ: Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus. *Am J Hum Genet* 52:506–516, 1993
 24. Zeger SL, Liang KY: Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 42:121–130, 1986
 25. Tsygankov AY: Multidomain STS/TULA proteins are novel cellular regulators. *IUBMB Life* 60:224–231, 2008
 26. Devlin B, Roeder K: Genomic control for association studies. *Biometrics* 55:997–1004, 1999
 27. Nerup J, Pociot F: A genomewide scan for type 1-diabetes susceptibility in Scandinavian families: identification of new loci with evidence of interactions. *Am J Hum Genet* 69:1301–1313, 2001
 28. Bergholdt R, Nerup J, Pociot F: Fine mapping of a region on chromosome 21q21.11-q22.3 showing linkage to type 1 diabetes. *J Med Genet* 42:17–25, 2005
 29. Bergholdt R, Eising S, Nerup J, Pociot F: Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: A nationwide population-based study. *Diabetologia* 49:1179–1182, 2006
 30. Wattenhofer M, Shibuya K, Kudoh J, Lyle R, Michaud J, Rossier C, Kawasaki K, Asakawa S, Minoshima S, Berry A, Bonne-Tamir B, Shimizu N, Antonarakis SE, Scott HS: Isolation and characterization of the UBASH3A gene on 21q22.3 encoding a potential nuclear protein with a novel combination of domains. *Hum Genet* 108:140–147, 2001
 31. Feshchenko EA, Smirnova EV, Swaminathan G, Teckchandani AM, Agrawal R, Band H, Zhang X, Annan RS, Carr SA, Tsygankov AY: TULA: an SH3- and UBA-containing protein that binds to c-Cbl and ubiquitin. *Oncogene* 23:4690–4706, 2004
 32. Carpino N, Turner S, Mekala D, Takahashi Y, Zang H, Geiger TL, Doherty P, Ihle JN: Regulation of ZAP-70 activation and TCR signaling by two related proteins, Sts-1 and Sts-2. *Immunity* 20:37–46, 2004
 33. Cohen S, Dadi H, Shaoul E, Sharfe N, Roifman CM: Cloning and characterization of a lymphoid-specific, inducible human protein tyrosine phosphatase, Lyp. *Blood* 93:2013–2024, 1999
 34. Collingwood TS, Smirnova EV, Bogush M, Carpino N, Annan RS, Tsygankov AY: T-cell ubiquitin ligand affects cell death through a functional interaction with apoptosis-inducing factor, a key factor of caspase-independent apoptosis. *J Biol Chem* 282:30920–30928, 2007