SUPPORTING ONLINE MATERIAL

MATERIALS AND METHODS

DNA pools experiment

We measured DNA concentration in samples of T1D patients and controls using Picogreen reagent in three replicates and normalized it to 10 ng/μl. Then we made 10 pooled samples each comprising equal amounts of DNA from 48 T1D patients and 10 pooled samples each comprising equal amounts of DNA from 48 healthy controls. Thus, altogether we resequenced DNA of 480 T1D patients and 480 healthy controls from Great Britain.

We designed oligonucleotide primers to amplify 144 target regions that covered exons and regulatory sequences of the ten genes (Table S1 and T1Dbase: http://www.t1dbase.org/page/PosterView/454Resequencing). Oligonucleotide primers were synthesized to include region-specific primers at 3' ends (Table S1), with common overhangs at 5' ends to allow for direct introduction into the 454 Sequencing system (overhang 5'GCCTCCCTCGCGCCATCAG3' on all forward primers and overhang 5'GCCTTGCCAGCCCGCTCAG3' on all reverse primers). We amplified each pooled sample in 144 separate PCR reactions using PfuUltra™ High-Fidelity DNA Polymerase (Stratagene, La Jolla, CA, USA). We checked presence of a band of expected size on 2% agarose gel and then mixed together 144 PCR products amplified from the same pooled DNA sample, taking 5 μl of each product. Samples were purified on Qiaquick column and eluted in Qiagen Elution Buffer (http://www1.qiagen.com/). These purified samples

were further cleaned with SPRI beads (Agencourt AMPure kit; http://www.agencourt.com/products/spri_reagents/ampure/) to remove low molecular weight DNA. Purified sample concentrations were measured by fluorescence using Picogreen reagent (http://www.invitrogen.com/site/us/en/home/Products-and-Services/Applications/Nucleic-Acid-Purification-and-Analysis/) and diluted to $2x10^5$ molecules/μl. Each sample was sequenced separately on a GS FLX instrument/ 100 cycle / 70x75 PTP 2Pad format, loading 750K beads per region.

For each of the 20 pooled DNA samples we obtained between 281,270 and 579,102 reads with average length of 250 bases, 9,416,365 reads in total:

T1D samples	reads, (n)	Control samples	reads, (n)
CS201b	575,009	B58-1b	432,071
CS202a	519,752	B58-2a	560,756
CS202b	281,270	B58-2b	528,943
CS203a	549,490	B58-3a	490,731
CS214a	552,040	B58-3b	408,084
CS214b	509,358	B58-4b	402,734
CS215a	456,437	B58-5a	429,673
CS215b	469,428	B58-5b	383,972
CS219a	437,871	B58-6a	449,821
CS219b	579,102	B58-6b	399,823

We extracted reads in the fasta format from the .sff files using sffinfo command. The following sequence analyses were done using pregap4 and gap4 programs in the Staden package (http://staden.sourceforge.net/). We converted reads into .exp format using pregap4. Then we screened all reads against the sequence of 144 target regions using "Screen only" command in gap4 and recorded reads that matched to each target region. Then we assembled reads into 144 contigs using "Normal shotgun assembly" command in gap4 and ran "Shuffle pads" command on all contigs to improve alignment. After that we dumped contigs into text files and used a script to count number of reads carrying

nucleotides A, C, G, T, unknown nucleotides (N) or missing nucleotides (deletions) in each contig position, separately for reads generated from pooled DNA samples of T1D cases or controls. We calculated frequency of reads carrying nucleotides A, C, G, T or missing nucleotides. In each contig reads generated from each pooled DNA sample represented 96 chromosomes, which facilitated distinction of true polymorphisms from artifacts. In the pooled samples it was impossible to distinguish rare insertion/deletion polymorphisms from sequencing errors and here we have analyzed nucleotide substitutions only. We visually analyzed read alignments in the contigs in all putatively polymorphic positions to exclude misalignment.

We calculated allele frequencies separately for reads generated from 960 chromosomes of T1D patients and 960 chromosomes of controls and then estimated the number of chromosomes in the original pools that carry different allelic nucleotides.

To test how read output estimated allele frequency among samples in the DNA pool we analyzed eight SNPs from the sequenced regions that have been genotyped previously (rs1990760, rs3184504, rs2476601, rs1046355, rs3747517, rs5215, rs759011 and rs942200). We calculated correlation only if individual genotypes for at least 47 subjects that contributed to the DNA pool of 48 subjects were available (Fig. S1).

Statistically, resequencing 960 subjects provides 100% probability of detecting a variant at 1% frequency and 98% probability of detecting variants as low as 0.2% frequency. We have empirically assessed our false-negative detection rate for SNPs with confirmed allele frequencies and found that we detected all 37 SNPs that map in our resequenced regions and have known minor allele frequency ≥1% in subjects of the European descent, including eleven with 1% - 5% frequency (dbSNP build 128).

Association test based on 480 cases and 480 controls theoretically has 72% power to detect association at false-positive rate $\alpha = 0.05$ for allele frequency 2% and OR = 2 or 45% power for allele frequency 1% and OR = 2 (Fig. S5). Given this statistical power, we cannot exclude that low frequency variants with smaller effects in the other nine genes, or that very rare variants in any of the ten genes, might also contribute to T1D. Since 480 cases and 480 controls do not provide statistical power to detect association of very rare variants with minor allele frequency << 1% for effects with OR < 2, we have not determined the false-negative detection rate for such SNPs.

Genotyping experiment

We studied a case-control collection consisting of 8,379 T1D patients and 10,575 controls from Great Britain. The recruitment of these subjects and sample processing have been described elsewhere (S1). We also studied a family collection including 3,165 type 1 diabetes families with one or two affected offspring (941 from Great Britain and Northern Ireland, 1,129 from Finland, 323 from the USA, 360 from Norway and 412 from Romania). The collection of all DNA samples has been approved by relevant ethical committees and written informed consent has been obtained from all participants.

Genotyping was done using TaqMan. We ordered pre-designed assays for the *IFIH1* SNPs rs35667974 and rs35337543 from Applied Biosystems (Warrington, UK). For other SNPs we ordered Assays-by-design. Genotypes were scored by two researchers independently to minimize error. Genotypes of controls and parents did not deviate from Hardy-Weinberg equilibrium above that expected at random ($P > 0.05$).

Statistical analyses were performed within Stata statistical package (http://www.stata.com), using additional Stata routines (http://www-gene.cimr.cam.ac.uk/clayton/software/). All subjects in the case-control analysis were of the European descent, as we have excluded those of the non-European and unknown descent. Additionally, we performed statistical association tests stratifying for 12 geographical regions of Great Britain. We analyzed cases and controls using logistic regression models (S2). The families were analyzed using the transmission disequilibrium test (S3) and conditional logistic regression (S2). A score test was used to combine tests from family and case-control studies as described previously (S1). We report uncorrected *P*-values. Linkage disequilibrium plot of D' was generated using Haploview 4.1 (S4), while r^2 values were calculated using pwld program in Stata. IFIH1 protein sequence alignment in 44 species was obtained from the UCSC genome browser (http://genome.ucsc.edu/).

Acknowledgements

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Fig. S1. Correlation between allele frequencies in individually genotyped DNA samples and frequency estimates in the sequenced DNA pools

Individual genotypes for 8 SNPs and 20 pooled DNA samples were analyzed. We calculated correlation only if individual genotypes for at least 47 subjects that contributed to the DNA pool of 48 subjects were available, therefore, 54 data points are shown.

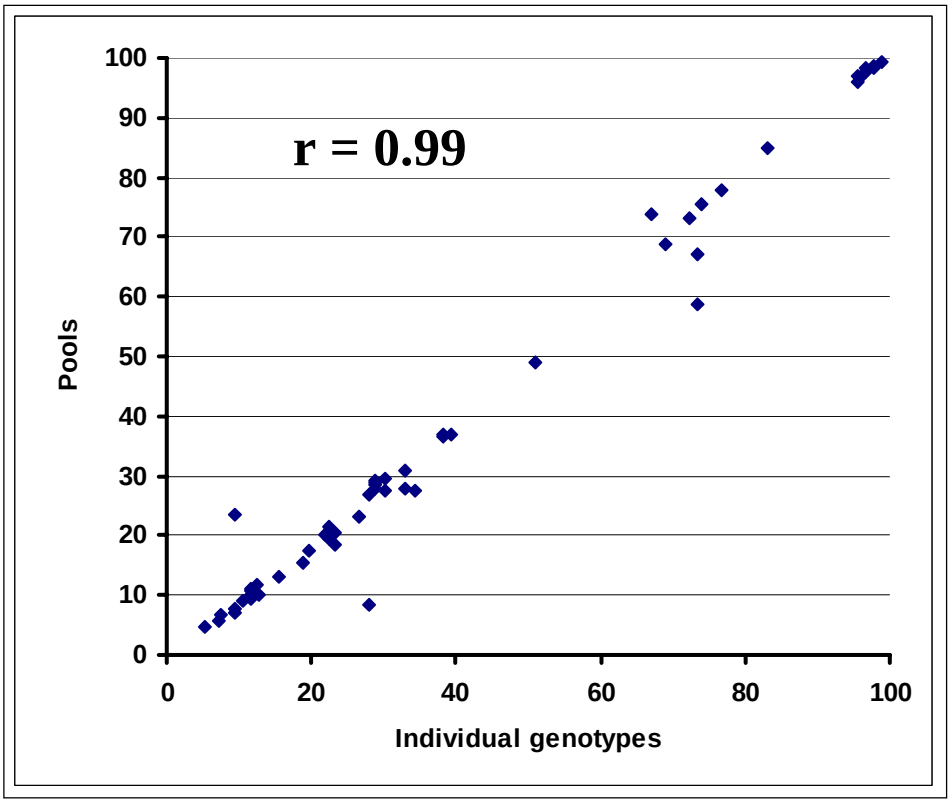

Fig. S2. IFIH1 amino acid alignment in vertebrates

Multiz Alignment of the IFIH1 protein sequence in 44 species showing conserved Isoleucine at position 923 (UCSC genome browser, http://genome.ucsc.edu/). SNP rs35667974/Ile923Val is shown.

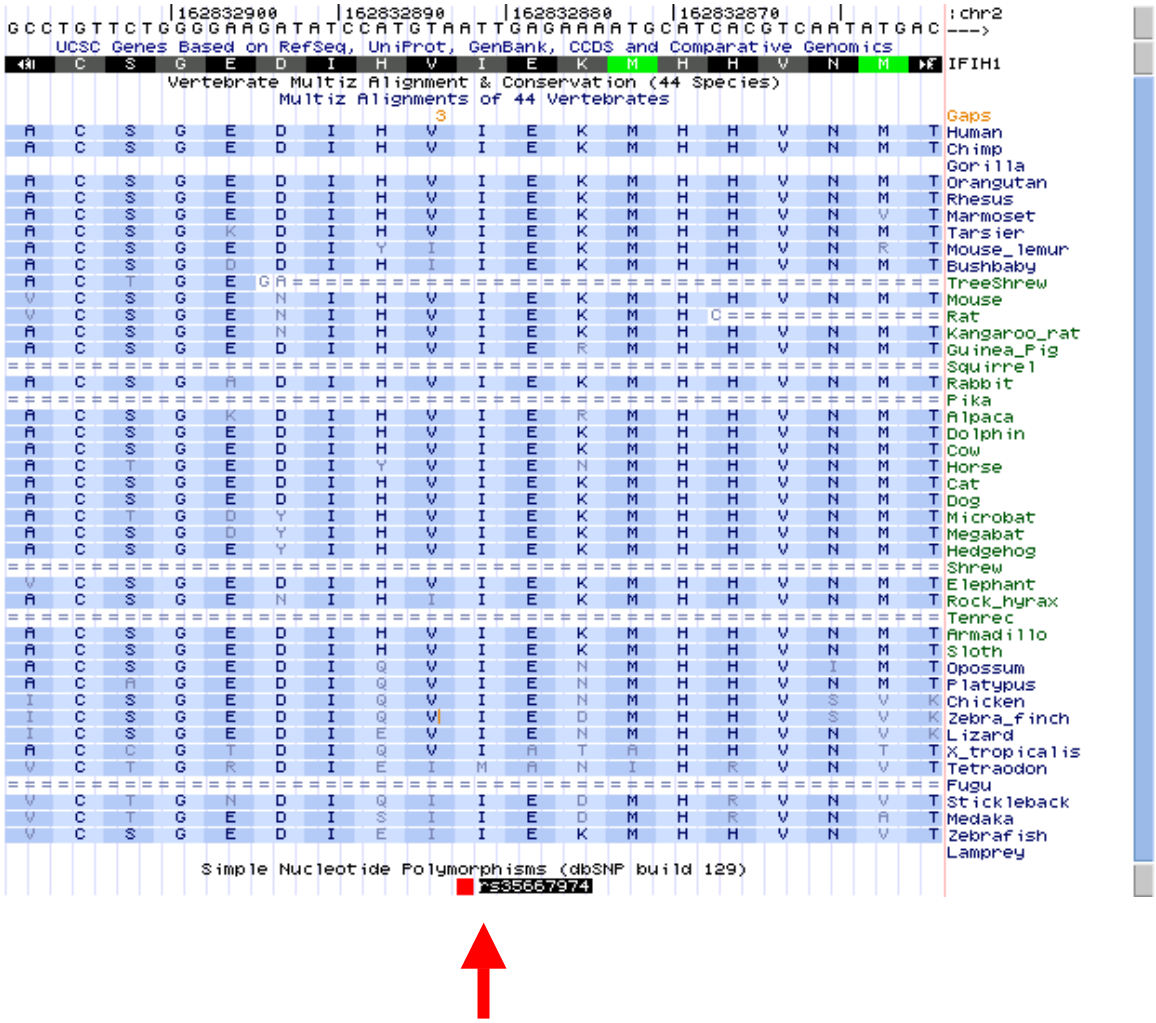

Fig. S3. Schematic presentation of the IFIH1 protein (green), its domains (yellow) and variants (white boxes)

Four rare variants (rs35667974/Ile923Val, rs35337543/IVS8+1, rs35744605/Glu627X, rs35732034/IVS14+1) and a common variant (rs1990760/Thr946Ala) associated with T1D independently of each other are shown above the protein. Other tested polymorphisms are shown below the protein. CARD - caspase recruitment domain.

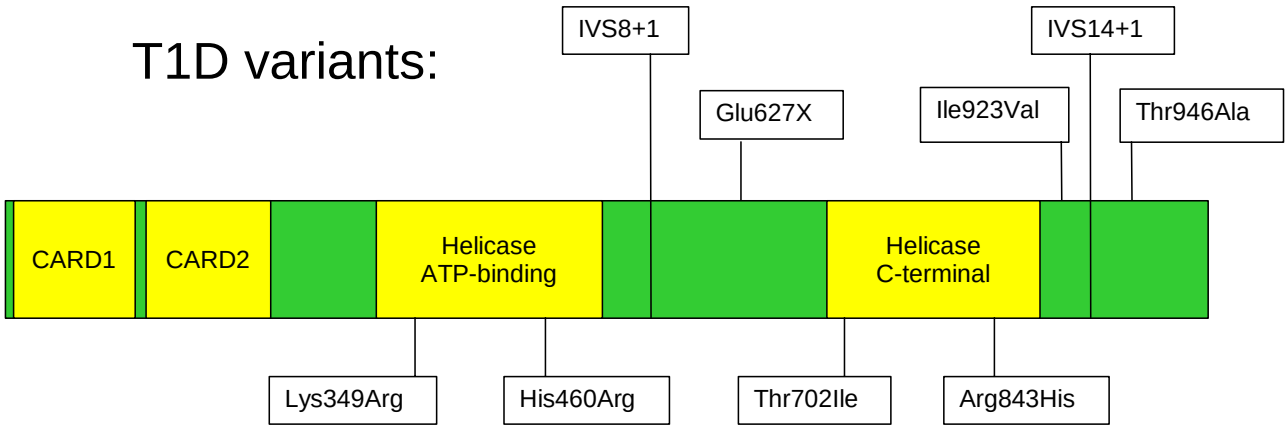

Fig. S4. Linkage disequilibrium in the IFIH1 gene region on chromosome 2, positions 162,690 kb – 163,110 kb

Genes *IFIH1, FAP, GCA* and part of *KCNH7* reside within one linkage disequilibrium block. Linkage disequilibrium plot shows D' calculated for CEU subjects (HapMap data release 23a/phase II on NCBI36 assembly, dbSNP build 126; http://www.hapmap.org/).

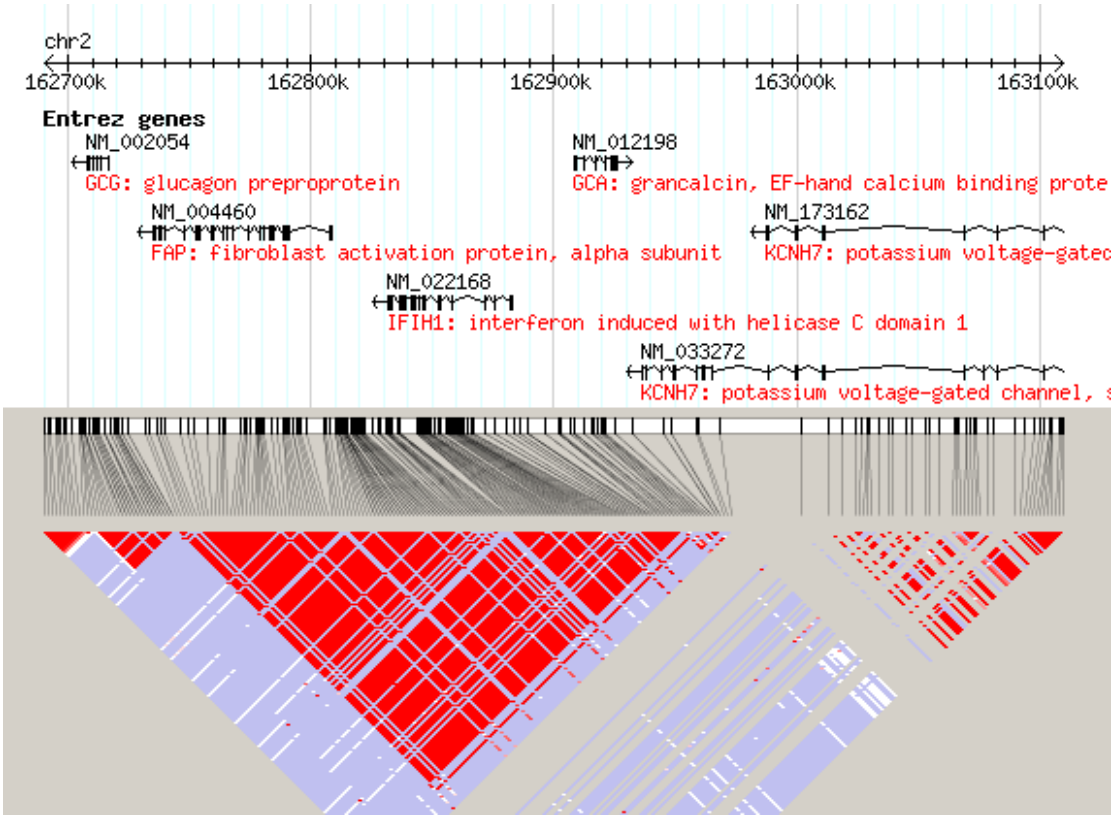

Fig. S5. Statistical power calculations for rare variants

Statistical power to detect association of rare variants at $\alpha = 0.05$ assuming multiplicative model and equal number of cases and controls. Note that samples comprising at least 2,000 cases and 2,000 controls may be needed for >80% power to detect association of rare alleles if they have effects with OR < 2.

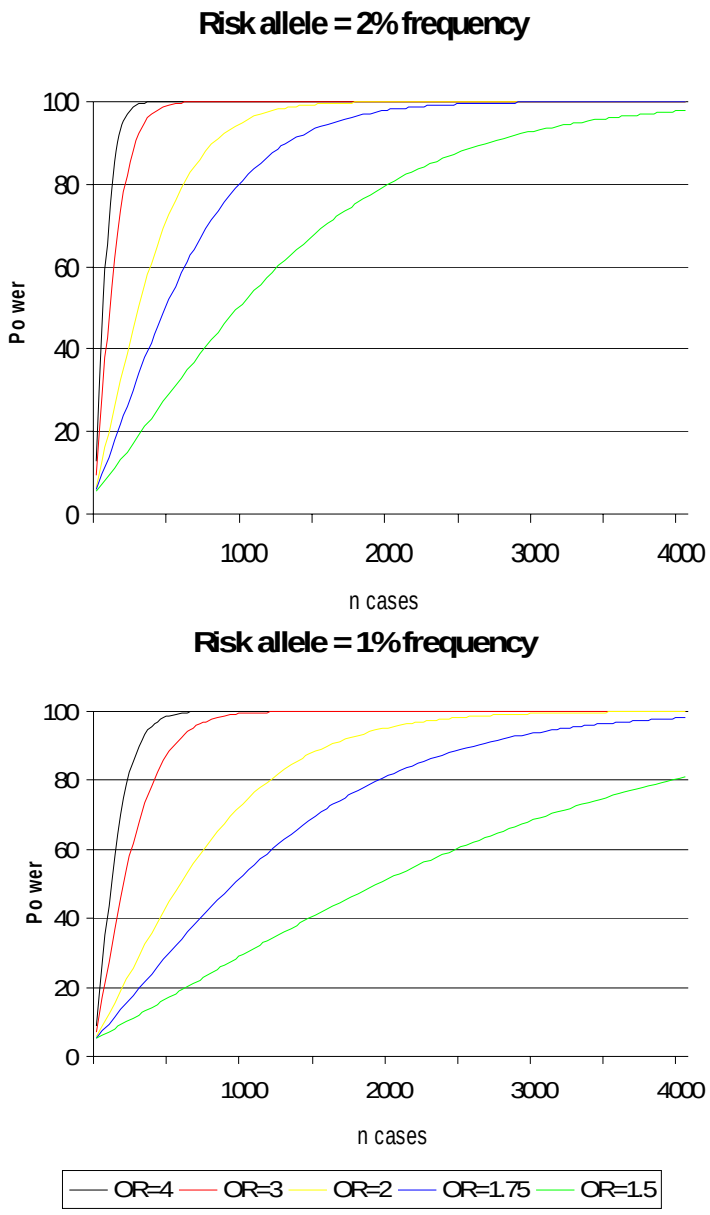

Table S1. Region-specific primers for amplification of 144 target regions in ten genes.

Oligonucleotides used in PCR reaction included region-specific primers with common 5'overhangs.

Amplicon	Gene	Forward primer	Reverse primer	PCR product, bp
1A01	*CLEC16A*	GCATCCTCCGCTTGTGCTA	CGCTCTCACGCCTCCTAGA	265
1A02	*CLEC16A*	GCTAATGGTCATGGAACTTGG	CAAAGAACAGCAATCATTAGAAACC	231
1A03	*CLEC16A*	ACATGTGGAAGCAAGCCACT	GCCCAACTTCACCCTGCTA	240
1A04	*CLEC16A*	CCTCCAGCATGAGTTAACCTGT	GTGCCCCTCTGGCAATTACT	215
1A05	*CLEC16A*	GCCTGGCTTATGGGCTTAT	TCGTGACAATCGGAGAACTG	251
1A06	*CLEC16A*	AAGTTATTTTTGGTAGCTTGACTTTTT	TCCCCTAACCACCCTGTCTA	225
1A07	*CLEC16A*	GGCTGAGGTGGTCATTTCTC	TTCTTCCCCACTTCTGATGG	257
1A08	*CLEC16A*	GGAAGTCAGTGGGACAGGAC	GTGATAAGGCCTGGGGATTT	259
1A09	*CLEC16A*	CTGATCCAGGAAGCAAGAGG	CACACAGATTAGCAAAATGAGCA	250
1A10	*CLEC16A*	GTTGCCTTCGTTGGACTTTC	GCGTTCATGGGGACACTC	276
1A11	*CLEC16A*	CATCCCAGTCTCCATTTTGG	AGGGACAGAAGAGGCTCTGG	258
1A12	*CLEC16A*	ACCCCATGTGCAGGTTAGAG	CCTTTCTTTGTCCTCCATGC	269
1B01	*CLEC16A*	TTCGGTATGAGGAGGTCAGG	GTGGGGTCTGCTTCCTACAA	245
1B02	*CLEC16A*	TAGCCTCAACGTGGATAGGC	CTTCCCTCCTGTCCTCCTGT	260
1B03	*CLEC16A*	GAATTCGTAGTTTGCCCGACT	TTTATCTGCATAGAACCAGACACC	200
1B04	*CLEC16A*	GATGGCCTCTAAAGCCACAA	AAAAACTCCCTCTGGGATGG	234
1B05	*CLEC16A*	CCCCTTCCTCCTTCCAAGT	GTCTGGGAGTGGTTCTGGAG	248
1B06	*CLEC16A*	TGTGGGGCATCTCACTGAA	AGCAGAGTGGTGTCCCATGT	254
1B07	*CLEC16A*	CAGCTTTGGTGTCTCCATCA	CAGAGCTCCTGGCCATCTT	244
1B08	*CLEC16A*	TGCCTTTTCCTTTGCTTCT	CCACCAAGTGCTCAGAGG	279
1B09	*CLEC16A*	TCCCACATGCTCAGAGTGAA	ACCATGATGAACGAGCTGTG	254
1B10	*CLEC16A*	AGGCCTACTCTTTGCTTCCA	CCCCATATCACTGAGTCACG	243
1B11	*CLEC16A*	CCCCTCGTCAGTGCTCAG	GGAGACCTGCCTGAATTGAC	243
1B12	*CLEC16A*	GGTGTCTCAAGGGCTCAGTG	CGTGTCAGCCGTGTCCTC	245

1C01	*CLEC16A*	CCACCATTTCCCTGCTCT	CACTGGGGTCCCTACCAG	252
1C02	*KCNJ11*	TGCCTTCCTTTTCTCCATTG	GCATGCTTGCTGAAGATGAG	204
1C03	*KCNJ11*	TCATGAAGACTGCCCAAGC	GCCACCAGGAAGATGCTG	256
1C04	*KCNJ11*	ATGCAGGTGGTACGCAAGAC	ATCTCATCGGCCAGGTAGG	278
1C05	*KCNJ11*	GACCTGCACCACCACCAG	AGGCTGTGGTCCTCATCAAG	245
1C06	*KCNJ11*	TTGTGCCCATTGTAGCTGAG	GCCGGGCTACATACCACAT	294
1C07	*SH2B3*	CAAGCCTTGAGTACCCCAAC	ATGTCTGTCCGGTCCTTCAC	241
1C08	*SH2B3*	TACAGCAGACCCAACCCTGT	TGCATCTCTGCTTCTGTGCT	248
1C09	*SH2B3*	ACCTGCCCAGATCCTTAACC	CCCAGGAGAAGCACCTGTTA	258
1C10	*SH2B3*	AGGCCATTGTCTTCTGGGTA	ACCAGGAACACTCCATGAGC	243
1C11	*SH2B3*	CATTTCCTGTCCTGCTACCC	TCCCTCTAGGACCCTGAACTC	247
1C12	*SH2B3*	AGCCCACCATCCTCTCCT	GCCTCTACCCTCTACCCAGTG	256
1D01	*SH2B3*	TCTGTGTCCTGTCAGCACTTG	AAGGCACCAGGTGGAAGAT	247
1D02	*SH2B3*	GCTCAGCCCAGAGGGTCT	ACTTCTGCCTGTGCTCCTCA	256
1D03	*KCNJ11*	CCTGCAGGACGTGTTCA	CCCCCAAAGCCAATAGTC	240
1D04	*PTPN2*	GCTGTGGAGAATTTAAGAGGGATA	TTTTCACTACATCCTGCCTCCT	210
1D05	*PTPN2*	GGCACAGAAGTGGGGTTTAT	CATCGCACTGTCACTCAGG	258
1D06	*PTPN2*	TGAAATGACAGTTGTGGTTTATCA	CATTTCATTTCCAAAAGAAGTCAAG	245
1D07	*PTPN2*	TTAACAAGGCCTTCCTGGAG	TATTGGCCCCAAAATGAAAA	253
1D08	*PTPN2*	GCATGTATATATCTGGTTTGTTTTCAT	TTTCGGGCAAGAAAGGTCT	252
1D09	*PTPN2*	GTCTTAAAGCGTAGAAACCATGA	AAAAATCCATTTTGCAGTAGAAA	240
1D10	*PTPN2*	AACTTCTCCCTTGATTTTCACTTT	TCAATGAGATTAAAATGAGATCGTAA	275
1D11	*PTPN2*	TCCTGGGTTCCAATAACAAG	TGCAGTTATTTGATGCTATGTGT	267
1D12	*PTPN2*	TGTTTTTCATTTCTCTTCCCTACC	AGCCTCATCTTTCAGCCTGT	246
1E01	*PTPN2*	TCCTGCTCTGTGTGCACTTC	AAGCTTGCTGGGCAAAATTA	280
1E02	*PTPN2*	TGCATCTATGTTCGTCTGTGTG	TGCTCTTCATCCCCTGGA	257
1E03	*PTPN22*	GTAAACCACAGCCTTCAGCA	CCCTGAGAGGGTCACATACAG	244
1E04	*PTPN22*	GGAAGATTAATTTTTCTTGGAATCT	GTTGTCAATGCCATGTTCCA	252

1E05	*PTPN22*	ACTTGTTCACTCATGAGCATACACTA	TTTTTGGGTATCTAGAGAAATATGGAA	231
1E06	*PTPN22*	AGCGGAGGACTAGGTGAGAA	AAGATGCCTGAACCCTGAAG	260
1E07	*PTPN22*	TTCTGAGTCTGGGATCCATGT	CCCAAACTGAAAACTATGAAGATG	251
1E08	*PTPN22*	GCTGAATTTGCTTCCAAATGA	TTTTTCAGCTTCCTAAAAAGAAAAAG	271
1E09	*PTPN22*	TGTGTAAGTGTAATGTCTGTTCTCAT	TGTCTTATGCCCAGCCTGA	259
1E10	*PTPN22*	GGTGGTTTTTCAGCCCTTG	TGGCCAGACTCTGACATTTG	255
1E11	*PTPN22*	TGTCCCCAGGTATCTTCTTCC	TGTTTTGAAAAACCAAACAATTAC	259
1E12	*PTPN22*	GATGCCATGGAAGTACAAGACT	TTTTGGATGCCTCACCATTA	241
1F01	*PTPN22*	ATCTGGTCCTGTCGTTCACC	ATAAATCCTGCAACAAATCTGACA	240
1F02	*PTPN22*	CACTGAAAACCAGCCTCTGA	AAAGAAAGCGTAATGATGACACC	240
1F03	*PTPN22*	TGACTAATTGTGTCTGGGAGATG	CTTGATTTAGCAGGGTGCAA	240
1F04	*PTPN22*	CTTCTTCCTTTGACTTTAGGACTTCT	CTGCTGCATTTACAGGTTTAGA	250
1F05	*PTPN22*	TAGTTGGGGAGCCTCTTCAG	TTGAGCCTGCATCTCTACAAAA	250
1F06	*PTPN22*	GGAATCTCAACCACATGATTCT	AAATCAAGAGACATCTTAGAACTGG	243
1F07	*PTPN22*	CATCATGGCCTCCAAGTG	AAATGAAATCTAAAATTCTATGCAAAC	242
1F08	*PTPN22*	AAGAATTTCCTTTGGATTGTTCTAA	CTCAAGGCTCACACATCAGC	246
1F09	*PTPN22*	GAACCGAACTATATTCACTTTCTTCC	GGATTTATTGAATGATGGGTGTT	250
1F10	*PTPN22*	GATGCCATTTCATAATTCAGCA	TCCAATCTTAGGGCTAAATGTCA	248
1F11	*PTPN22*	AAGAGAAAAGGGTGTTGACTTATGA	CATTTTTGTACCTTTCCATTTAGGT	250
1F12	*PTPN22*	GGTATGCAATGGAACATGTTTTT	GGCATGTTTCCCAAAACTCT	190
1G01	*PTPN22*	TGGCAAGATGGAAAAACAACT	AAGGAGGCCTATGGGTGATT	332
1G02	*PTPN22*	TCAACAGTCATCTGAGTCTGTCTT	AACATAAGGACCTATACATGCAACC	249
1G03	*PTPN22*	TTAAAACATCTTTCTTTTCATTCAAC	GGCACTTATTGGCATTTTGC	272
1G04	*IL2RA*	ATCTTCCCATCCCACATCCT	GGACTCCCTCTGGTTCTGTG	260
1G05	*IL2RA*	ACAAAAAGTAGGGCATACCATC	TTTTATTCTGCGGAAACCTCT	241
1G06	*IL2RA*	TGGCCTACAAGGAAGGAAC	GCCCATTTGTGTCTATAGGG	241
1G07	*IL2RA*	CTGGACAGGTGTGCTTCTCA	GCGCTAGCAGGAGTTAGCTG	249

1G08	*IL2RA*	TAGCAAGAGGCAACCTGGAC	GGTCTCCATTTCACCTGTGC	277
1G09	*IL2RA*	TCCAGGGATACAGGGCTCTAC	CCAGGGAGATCAAGGGTCTT	249
1G10	*IL2RA*	GGCCCTGACTCCTGTGTTTA	GTCCAGCGTTTGTCTTCTCC	149
1G11	*IL2RA*	CCTGACTTCCTTTAGCCTCGT	CTGTCCATATCTCAGCCTGGT	202
1G12	*IL2RA*	CATGGGGAGGGACCTACTTC	CCTTGGTGATGCCACACTT	243
1H01	*IL2RA*	AGCCTGGCCAACATAGCA	TCACTTGGGCTTCATGACTTC	243
1H02	*IAN4L1*	CCAGCTCCCAAACGTACATC	GAATGGGTTTCTGCCACTGT	202
1H03	*IAN4L1*	GGGGAGGACGTTCATAGCTT	ACTGACTGGGCCCTCAGC	242
1H04	*IAN4L1*	AACACCACCGGCATTGAG	GGCAGAGAGCAGGTAGCAGT	256
1H05	*IAN4L1*	GCCGATACCCAAGAGCTGTA	GCAGTTGTCCGTGTTTGCTA	243
1H06	*IAN4L1*	CAGGCCCTGGATGACTATG	TTCCACTTTGGCCTGGTACT	276
1H07	*IAN4L1*	AGCTCCTGGCTGTGATTGAG	GCAAAAGCATCAAGTGTTTGAC	240
1H08	*IAN4L1*	GAGCTGAGGGAGAACGAGAG	CATGCTCCATAGACCACGAG	249
1H09	*IFIH1*	ACAACAGCACCATCTGCTTG	GCAGGCAGAAAGGTCAGGTA	171
1H10	*IFIH1*	TACATCCAGGTGGAGCCTGT	AGAGTGGGCTGAAGGAGGTT	302
1H11	*IFIH1*	GACTCGGGAATTCGTGGA	TGCTTTGCAAAATCTGCCTA	280
1H12	*IFIH1*	GGTTATTCAGAAGATGTTTGATCTTA	TCACTAGGCAGAATTTGAAGAAT	269
2A01	*IFIH1*	TGTATGGCACTATGATTTGCATT	CCCACATTTTCTCCCTCTGA	283
2A02	*IFIH1*	TGTGCTGTAGAGGTGTGCAGT	TGCTTCCACTATATGGCGTCT	248
2A03	*IFIH1*	GGCCTACGTTCAGTTTCAGG	TCCTTGGCAATGTAAACAGC	240
2A04	*IFIH1*	GGCCTACGTTCAGTTTCAGG	CAATGACACAAATGCCATCA	383
2A05	*IFIH1*	CCTCTTTTCATGCTGGATGC	TTTCAAGGATTTGAGCTGTACTGA	257
2A06	*IFIH1*	TGGATTAAGTGGTGATACCCAAC	AAAGACAATTTAAGCCACGAACA	247
2A07	*IFIH1*	TGTGCTGATATGGAGAAATGAAC	TTCAGCTTTGGCTTGCTTC	246
2A08	*IFIH1*	TTTGATGCAGAAGTTGAAAAACA	AACTGATGATCACAGCACTTGAA	249
2A09	*IFIH1*	CGTTGAATAAAGTGAAAGGGAAA	AGCCTTTGCCATCTTTCTACTG	245
2A10	*IFIH1*	TTGGAGATTCCAGCAGAGGT	TTGGAACTACTTTTGCTTTCCA	464
2A11	*IFIH1*	GGCACAATTTTAGGGGGTTT	ATCATCACCACCCTCATCACT	249

2A12	*IFIH1*	CAATTCGAATGATAGATGCGTA	TGGAGAGCTTATGAGAAGCAGTAA	277
2B01	*IFIH1*	CAAGCTTGTTAACATATCAACTCTAA	GATCATGCCACTGCTCTTCA	430
2B02	*IFIH1*	TTTGATTTACACTGACCAGTTGC	TGGCTATTTCATTGGTGACG	246
2B03	*IFIH1*	TCGCACTGGAAAAATAAATCTG	AACAGGAAAAAGGCTTTGTTTTA	246
2B04	*IFIH1*	AGGATTTGTATCACAACGTACCC	CAAATTCAGAGGTGACCAACAA	241
2B05	*IFIH1*	AAGACCTCCAAATTTCAGGAGA	TTTCTCAATTACATGGATATCTTCC	247
2B06	*IFIH1*	GAATAACCCATCACTAATAACTTTCC	TTGAGAGGCTAAAGGAGAGGAA	246
2B07	*IFIH1*	TCCATGATGATTCTTTCCCTTT	TTGTGCACCATCATTGTTCC	249
2B08	*IFIH1*	GCCAACAGGAATGTTTAATTGC	CAATCAAGTGCTAATCCTCATCAC	255
2B09	*AIRE*	GGGAGCTCCACCCTCTAGTC	AGACGGTCCTGGAACATCAC	387
2B10	*AIRE*	ACCCTACCCCTGGAGAAAAC	CCGGGAAGACTGGAGACC	261
2B11	*AIRE*	GCACTCACCCCCACTGAGA	CACCAGGCCAGCACGTC	250
2B12	*AIRE*	GCCTGCTTCTGGCATAGAGT	GTGGTCCTCCTTCCATCTTG	258
2C01	*AIRE*	GGCCTACACGACTGCCAAG	AGAGCCACTCCCCCAGAG	297
2C02	*AIRE*	CTGGTGCCACAGCCATGT	CCTGAGTGCCCAGGTAAAGG	241
2C03	*AIRE*	GCAGAGACTGGGGAGTTCAG	AGAACCCCTTTCCATCTTGG	357
2C04	*AIRE*	CCCTCTGTGAAAAGACATGGT	CTGCAGGAGACCACAAGGA	386
2C05	*AIRE*	GTTTCAGGGTCCCAGCAGT	CTCCCTCTCCTCCTGTTTCA	358
2C06	*AIRE*	CTCCTCACTTGCGCCTAGA	GTGTGGTTGTGGGCTGTATG	349
2C07	*AIRE*	AGCCCCTCATCCTCTGCT	TCTGCCCTGAGATGTGCTC	214
2C08	*AIRE*	TGGGCTGACCTCTTCTCTTT	AGCAGGGACAGCCTGAGTT	231
2C09	*AIRE*	AACGATGGCCATGATTCTGT	AGTAGGTCACCAGGCAAGGA	385
2C10	*FOXP3*	GGCTCAGGTGGTCGAGTATC	GGAAGAAGAGGAGGCATGG	272
2C11	*FOXP3*	CAAAGCCTCAGACCTGCTG	CCCAGTGCCACAGTAAAGGT	201
2C12	*FOXP3*	CTACCATGTGGGCTTGCAGT	CACAGTTCTCCCACCTGCTC	246
2D01	*FOXP3*	ACCAGGTATGGACGGTGAAT	TCTGTGAAGCCATGGGGTA	277
2D02	*FOXP3*	GGGAGTCAGGGTTTTCGAG	GTGTCAGGGGAGGGGATAG	257
2D03	*FOXP3*	AGGACAGGTCAGTGGACAGG	TATTGGGATGAAGCCTGAGC	271

2D04	*FOXP3*	GGTCACCTGCATGGAATCTT	CTACGGTCTTCCCTGGGAGT	263
2D05	*FOXP3*	GCCAGAAACCAAGTTCACCT	CAGTCTGAGTCTGCCACCAC	261
2D06	*FOXP3*	TTTAAGCCTCTGGGTCACCA	CCCAGAGCCTGTCAGGATTA	250
2D07	*FOXP3*	TGATTCATCCCCACCCTCT	GGAATGGAGGAACCCACTCT	213
2D08	*FOXP3*	TAGCCCCTCTAAACCCCAAG	ATGTGCCTATGAGCCCAGAC	254
2D09	*FOXP3*	GTCTGGGCTCATAGGCACAT	TCCTCCTTTCCTTGATCTTGA	280
2D10	*KCNJ11*	CTCAGAAGTGAGGCCAGCA	GCCTTTCTTGGACACAAAGC	261
2D11	*KCNJ11*	ATCATCCCCGAGGAATACG	GGACATGGTGAAGATGAGCA	216
2D12	*IFIH1*	TCTGTACATTGTGGAGTGGCTAA	TTCAGTAATCCACTGGGAAAGC	240

Table S2. Association analysis of common variants in sequenced pools of DNA from T1D patients and controls

Gene	rs#	Major allele	Minor allele	T1D				Controls				*P*-value, χ^2 test
				reads with minor allele, n	total reads, n	minor allele, %	estimated chromosomes with minor allele, n	reads with minor allele, n	total reads, n	minor allele, %	estimated chromosomes with minor allele, n	
SH2B3	rs3184504	T	c	19,777	47,620	41.5	399 / 960	22,868	43,163	53.0	509 / 960	0.00000050
PTPN22	rs2476601	C	t	4,496	30,364	14.8	142 / 960	2,531	30,042	8.4	81 / 960	0.000013
IFIH1	rs1990760	A	g	8,055	25,955	31.0	298 / 960	11,606	30,326	38.3	367 / 960	0.00086
CLEC16A	rs2302557	G	c	4,135	8,353	49.5	475 / 960	3,108	7,134	43.6	418 / 960	0.0091
IL2RA	rs28360490	T	g	4,828	59,233	8.2	78 / 960	7,269	62,449	11.6	112 / 960	0.010
CLEC16A	rs2286973	G	a	6,466	18,427	35.1	337 / 960	6,084	14,990	40.6	390 / 960	0.013
IL2RA	rs28360489	G	a	4,892	58,370	8.4	80 / 960	7,268	62,133	11.7	112 / 960	0.016
IL2RA	rs7076103	G	a	2,811	19,005	14.8	142 / 960	3,230	17,225	18.8	180 / 960	0.020
KCNJ11	rs5215	A	g	5,136	14,603	35.2	338 / 960	3,871	12,464	31.1	298 / 960	0.056
AIRE	rs1800521	T	c	3,967	10,740	36.9	355 / 960	2,757	8,408	32.8	315 / 960	0.057
PTPN22	rs3761935	A	c	3,518	19,264	18.3	175 / 960	6,655	31,167	21.4	205 / 960	0.089
AIRE	rs1133779	T	c	1,255	2,809	44.7	429 / 960	979	2,389	41.0	393 / 960	0.097
KCNJ11	rs5218	C	t	4,790	16,534	29.0	278 / 960	5,005	15,642	32.0	307 / 960	0.15
IFIH1	rs11441874	T	a	1,390	19,769	7.0	67 / 960	1,447	26,350	5.5	53 / 960	0.16
CLEC16A	rs8052325	A	g	5,649	69,044	8.2	79 / 960	6,595	66,437	9.9	95 / 960	0.18
PTPN22	rs1217418	C	t	13,809	29,699	46.5	446 / 960	16,700	38,298	43.6	419 / 960	0.20
KCNJ11	rs1800467	C	g	539	20,174	2.7	26 / 960	581	15,923	3.6	35 / 960	0.22
KCNJ11	rs5219	G	a	14,332	37,331	38.4	369 / 960	13,310	37,209	35.8	343 / 960	0.23
IAN4L1	rs759011	C	t	8,445	31,823	26.5	255 / 960	8,317	28,798	28.9	277 / 960	0.25

AIRE	rs1800525	G	a	672	10,794	6.2	60 / 960	613	8,141	7.5	72 / 960	0.26
AIRE	rs878081	C	t	5,195	27,323	19.0	183 / 960	5,090	24,254	21.0	201 / 960	0.28
IAN4L1	rs1046355	C	t	5,117	19,682	26.0	250 / 960	5,417	19,258	28.1	270 / 960	0.29
AIRE	rs1800520	C	g	1,076	14,438	7.5	72 / 960	871	13,788	6.3	61 / 960	0.33
PTPN22	rs1217419	C	a	12,122	25,470	47.6	457 / 960	10,793	23,765	45.4	436 / 960	0.34
IL2RA	rs11256369	G	c	12,321	49,266	25.0	240 / 960	11,285	48,636	23.2	223 / 960	0.35
AIRE	rs1055311	C	t	1,866	6,925	26.9	259 / 960	1,612	5,600	28.8	276 / 960	0.37
CLEC16A	rs16957839	C	t	4,219	45,947	9.2	88 / 960	4,371	42,648	10.2	98 / 960	0.43
CLEC16A	rs2302558	C	t	2,218	23,383	9.5	91 / 960	2,744	26,745	10.3	98 / 960	0.57
IFIH1	rs3747517	G	a	12,013	47,867	25.1	241 / 960	12,522	47,796	26.2	252 / 960	0.58
IL2RA	rs12358961	A	t	16,836	49,011	34.4	330 / 960	16,294	48,334	33.7	324 / 960	0.77
IAN4L1	rs9657881	G	a	1,010	18,910	5.3	51 / 960	977	19,369	5.0	48 / 960	0.77
IAN4L1	rs4725936	T	c	12,886	52,009	24.8	238 / 960	14,360	56,703	25.3	243 / 960	0.78
AIRE	rs41277544	G	a	1,208	26,472	4.6	44 / 960	1,121	24,038	4.7	45 / 960	0.92

Table S3. Association analysis of rare variants in sequenced pools of DNA from T1D patients and controls

Gene	Location	rs# or ss# (for new SNPs)	Major allele	Minor allele	T1D				Controls				*P*-value, exact test
					reads with minor allele, n	total reads, n	minor allele, %	estimated chromosomes with minor allele, n	reads with minor allele, n	total reads, n	minor allele, %	estimated chromosomes with minor allele, n	
IFIH1	intron 4	rs35502110	C	t	474	39,047	1.2	12 / 960	506	33,156	1.5	15 / 960	0.70
IFIH1	exon 7, H460R	rs10930046	A	g	403	43,256	0.9	9 / 960	310	43,781	0.7	7 / 960	0.80
IFIH1	exon 14, I923V	rs35667974	A	g	261	36,095	0.7	7 / 960	906	37,475	2.4	23 / 960	0.0049
IFIH1	intron 14,+1splice	rs35732034	G	a	221	34,941	0.6	6 / 960	455	37,386	1.2	12 / 960	0.24
IFIH1	exon 7, sSNP	rs12479043	G	c	161	35,462	0.5	4 / 960	83	33,280	0.2	2 / 960	0.69
IFIH1	intron 8,+1splice	rs35337543	G	c	35	9,719	0.4	3 / 960	221	8,808	2.5	24 / 960	0.000044
IFIH1	exon 10, E627X	rs35744605	G	t	84	29,557	0.3	3 / 960	169	29,844	0.6	5 / 960	0.73
IFIH1	exon 5, K349R	ss107794691	A	g	37	14,332	0.3	2 / 960	58	14,309	0.4	4 / 960	0.69
IFIH1	exon 1, sSNP	ss119336615	G	a	57	23,188	0.2	2 / 960	1	20,541	0.0	0 / 960	0.50
IFIH1	intron 3	ss107794692	A	t	66	30,460	0.2	2 / 960	66	28,675	0.2	2 / 960	1.00
IFIH1	intron 4	ss119336620	C	g	48	39,161	0.1	1 / 960	0	33,227	0.0	0 / 960	1.00
IFIH1	intron 4	ss119336619	C	g	45	38,774	0.1	1 / 960	40	39,650	0.1	1 / 960	1.00
IFIH1	exon 11, T702I	ss107794690	C	t	22	21,083	0.1	1 / 960	77	20,056	0.4	4 / 960	0.37
IFIH1	intron 5	ss119336622	G	a	33	35,210	0.1	1 / 960	29	35,799	0.1	1 / 960	1.00
IFIH1	intron 3	ss119336618	C	t	28	30,575	0.1	1 / 960	5	28,684	0.0	0 / 960	1.00
IFIH1	exon 7, sSNP	ss119336624	C	t	28	42,289	0.1	1 / 960	3	43,784	0.0	0 / 960	1.00
IFIH1	intron 12	ss119336629	T	c	15	23,643	0.1	1 / 960	1	21,166	0.0	0 / 960	1.00
IFIH1	intron 12	ss119336630	T	a	29	47,745	0.1	1 / 960	0	48,069	0.0	0 / 960	1.00
IFIH1	intron 11	ss119336627	T	c	18	31,712	0.1	1 / 960	0	35,470	0.0	0 / 960	1.00

IFIH1	exon 2, N160D	ss119336617	A	g	0	27,046	0.0	0 / 960	40	24,529	0.2	2 / 960	0.50
IFIH1	exon 16, sSNP	ss119336633	C	t	16	33,439	0.0	0 / 960	35	36,251	0.1	1 / 960	1.00
IFIH1	exon 13, R820H	ss119336631	G	a	10	48,168	0.0	0 / 960	34	48,145	0.1	1 / 960	1.00
IFIH1	exon 12, sSNP	ss119336628	C	t	3	24,346	0.0	0 / 960	23	21,332	0.1	1 / 960	1.00
IFIH1	exon 16, V988L	ss119336634	G	t	4	33,792	0.0	0 / 960	45	36,255	0.1	1 / 960	1.00
IFIH1	intron 14	ss119336632	A	g	2	35,269	0.0	0 / 960	40	37,416	0.1	1 / 960	1.00
IFIH1	exon 6, E428G	ss119336623	A	g	1	19,220	0.0	0 / 960	35	26,514	0.1	1 / 960	1.00
IFIH1	exon 1, R149G	ss119336616	A	g	1	23,102	0.0	0 / 960	22	20,558	0.1	1 / 960	1.00
IFIH1	exon 10, R595H	ss119336626	G	a	1	27,125	0.0	0 / 960	29	29,774	0.1	1 / 960	1.00
IFIH1	intron 7	ss119336625	T	c	1	35,400	0.0	0 / 960	33	33,057	0.1	1 / 960	1.00
AIRE	exon 12, R471C	ss107794714	C	t	499	30,860	1.6	16 / 960	500	23,119	2.2	21 / 960	0.51
AIRE	intron 5	rs41277546	C	t	343	26,698	1.3	12 / 960	532	24,489	2.2	21 / 960	0.16
AIRE	intron 10	ss107794713	C	t	137	13,747	1.0	10 / 960	150	11,830	1.3	12 / 960	0.83
AIRE	3'UTR	ss107794717	C	g	48	5,536	0.9	8 / 960	46	4,499	1.0	10 / 960	0.81
AIRE	intron 4	ss107794708	G	t	56	6,652	0.8	8 / 960	73	7,132	1.0	10 / 960	0.81
AIRE	intron 13	ss107794716	C	t	262	37,459	0.7	7 / 960	39	32,013	0.1	1 / 960	0.070
AIRE	exon 11, T441M	ss107794712	C	t	57	14,711	0.4	4 / 960	34	11,847	0.3	3 / 960	1.00
AIRE	exon 10, sSNP	ss107794711	G	a	32	10,902	0.3	3 / 960	11	8,382	0.1	1 / 960	0.62
AIRE	exon 12, sSNP	ss107794715	C	t	90	31,258	0.3	3 / 960	67	23,211	0.3	3 / 960	1.00
AIRE	exon 10, sSNP	ss119336604	C	g	23	10,780	0.2	2 / 960	0	8,383	0.0	0 / 960	0.50
AIRE	intron 6	ss107794710	G	a	30	14,368	0.2	2 / 960	21	13,798	0.2	1 / 960	1.00
AIRE	exon 3, sSNP	ss119336600	G	a	20	10,160	0.2	2 / 960	3	8,037	0.0	0 / 960	0.50
AIRE	exon 8, I309M	ss119336602	C	g	21	20,841	0.1	1 / 960	0	17,253	0.0	0 / 960	1.00
AIRE	exon 12, sSNP	rs7281600	G	a	29	31,073	0.1	1 / 960	11	23,098	0.0	0 / 960	1.00
AIRE	intron 12	ss119336606	G	a	9	31,175	0.0	0 / 960	40	23,242	0.2	2 / 960	0.50

AIRE	exon 4, sSNP	ss107794707	C	t	1	6,721	0.0	0 / 960	26	7,138	0.4	3 / 960	0.25
AIRE	exon 5, V199I	ss119336601	G	a	3	27,267	0.0	0 / 960	67	24,541	0.3	3 / 960	0.25
AIRE	exon 8, R328W	ss119336603	C	t	1	20,124	0.0	0 / 960	21	17,221	0.1	1 / 960	1.00
CLEC16A	3'UTR	rs11647285	G	a	942	44,026	2.1	21 / 960	811	31,847	2.5	24 / 960	0.76
CLEC16A	intron 11	ss107794687	C	t	431	40,186	1.1	10 / 960	808	32,947	2.5	24 / 960	0.023
CLEC16A	exon 24, S991N	ss107794725	G	a	213	33,615	0.6	6 / 960	112	25,129	0.4	4 / 960	0.75
CLEC16A	intron 23	ss107794688	C	t	168	33,712	0.5	5 / 960	450	25,138	1.8	17 / 960	0.016
CLEC16A	exon 24, A1042T	ss107794727	G	a	187	45,728	0.4	4 / 960	34	32,146	0.1	1 / 960	0.37
CLEC16A	exon 15, Y604I	ss107794721	T	a	201	70,829	0.3	3 / 960	11	66,309	0.0	0 / 960	0.25
CLEC16A	exon 24, V977M	ss107794724	G	a	90	33,833	0.3	3 / 960	54	25,129	0.2	2 / 960	1.00
CLEC16A	exon 22, S901N	ss107794723	G	a	119	47,294	0.3	2 / 960	101	39,194	0.3	2 / 960	1.00
CLEC16A	3'UTR	ss107794728	G	a	106	44,959	0.2	2 / 960	158	32,088	0.5	5 / 960	0.45
CLEC16A	5UTR	ss107794719	G	t	29	12,665	0.2	2 / 960	34	10,159	0.3	3 / 960	1.00
CLEC16A	5UTR	ss107794718	G	a	24	12,679	0.2	2 / 960	30	10,217	0.3	3 / 960	1.00
CLEC16A	exon 17, R674W	ss119336668	C	t	35	20,409	0.2	2 / 960	4	17,557	0.0	0 / 960	0.50
CLEC16A	intron 13	ss119336661	C	t	24	14,088	0.2	2 / 960	2	10,881	0.0	0 / 960	0.50
CLEC16A	exon 3, sSNP	ss119336650	C	a	77	46,226	0.2	2 / 960	23	42,674	0.1	1 / 960	1.00
CLEC16A	exon 10, E424K	ss119336659	G	a	62	40,283	0.2	1 / 960	2	42,074	0.0	0 / 960	1.00
CLEC16A	intron 23	ss107794726	C	a	41	33,845	0.1	1 / 960	122	25,129	0.5	5 / 960	0.22
CLEC16A	exon 22, sSNP	ss107794722	G	a	54	47,310	0.1	1 / 960	49	39,196	0.1	1 / 960	1.00
CLEC16A	exon 24, sSNP	ss107794729	G	a	51	45,887	0.1	1 / 960	95	32,143	0.3	3 / 960	0.62
CLEC16A	exon 5, A179V	ss107794720	C	t	43	39,135	0.1	1 / 960	42	38,202	0.1	1 / 960	1.00
CLEC16A	intron 22	ss119336672	C	t	42	28,170	0.1	1 / 960	8	21,715	0.0	0 / 960	1.00
CLEC16A	exon 24, V983M	ss119336674	G	a	47	33,828	0.1	1 / 960	2	25,133	0.0	0 / 960	1.00
CLEC16A	intron 22	ss119336673	A	g	30	28,430	0.1	1 / 960	0	21,747	0.0	0 / 960	1.00

CLEC16A	intron 7	ss119336652	C	t	45	46,388	0.1	1 / 960	9	40,432	0.0	0 / 960	1.00
CLEC16A	exon 24, A1041T	ss119336677	G	a	44	45,889	0.1	1 / 960	4	32,160	0.0	0 / 960	1.00
CLEC16A	exon 24, sSNP	ss119336676	C	t	40	45,672	0.1	1 / 960	5	32,143	0.0	0 / 960	1.00
CLEC16A	intron 8	ss119336654	G	a	29	36,218	0.1	1 / 960	71	32,401	0.2	2 / 960	1.00
CLEC16A	exon 10, sSNP	ss119336658	C	g	31	40,149	0.1	1 / 960	0	42,071	0.0	0 / 960	1.00
CLEC16A	exon 24, A986G	ss119336675	C	g	26	33,773	0.1	1 / 960	0	25,131	0.0	0 / 960	1.00
CLEC16A	exon 8, R314W	ss119336653	C	t	27	39,783	0.1	1 / 960	10	32,417	0.0	0 / 960	1.00
CLEC16A	exon 10, R383Q	ss119336657	G	a	26	40,240	0.1	1 / 960	13	42,077	0.0	0 / 960	1.00
CLEC16A	exon 15, H607N	ss119336665	C	a	40	71,134	0.1	1 / 960	1	66,488	0.0	0 / 960	1.00
CLEC16A	exon 20, A813T	ss119336669	G	a	15	42,764	0.0	0 / 960	33	34,674	0.1	1 / 960	1.00
CLEC16A	exon 22, V893M	ss119336670	G	a	11	47,179	0.0	0 / 960	43	39,188	0.1	1 / 960	1.00
CLEC16A	exon 15, sSNP	ss119336664	G	a	7	70,611	0.0	0 / 960	85	66,484	0.1	1 / 960	1.00
CLEC16A	exon 17, sSNP	ss119336667	G	a	2	20,703	0.0	0 / 960	23	17,755	0.1	1 / 960	1.00
CLEC16A	exon 2, sSNP	ss119336649	C	t	4	47,760	0.0	0 / 960	40	45,903	0.1	1 / 960	1.00
CLEC16A	exon 11, T484M	ss119336660	C	t	3	40,382	0.0	0 / 960	86	32,891	0.3	3 / 960	0.25
CLEC16A	intron 14	ss119336662	C	t	3	67,334	0.0	0 / 960	79	66,482	0.1	1 / 960	1.00
CLEC16A	intron 9	ss119336656	G	c	1	35,604	0.0	0 / 960	52	38,194	0.1	1 / 960	1.00
CLEC16A	exon 24, sSNP	ss119336678	C	t	1	45,808	0.0	0 / 960	23	32,134	0.1	1 / 960	1.00
CLEC16A	intron 14	ss119336663	A	g	1	67,478	0.0	0 / 960	44	66,466	0.1	1 / 960	1.00
CLEC16A	intron 15	ss119336666	T	g	0	37,993	0.0	0 / 960	81	38,979	0.2	2 / 960	0.50
CLEC16A	exon 4, H168R	ss119336651	A	g	0	24,105	0.0	0 / 960	36	26,862	0.1	1 / 960	1.00
CLEC16A	exon 9, Y355H	ss119336655	T	c	0	35,923	0.0	0 / 960	31	38,183	0.1	1 / 960	1.00
CLEC16A	exon 22, P937R	ss119336671	C	g	0	47,010	0.0	0 / 960	22	39,208	0.1	1 / 960	1.00
FOXP3	exon 6, sSNP	rs2232367	C	t	866	27,194	3.2	31 / 960	551	20,086	2.7	26 / 960	0.59
FOXP3	intron 10	ss107794731	G	a	86	48,070	0.2	2 / 960	145	40,773	0.4	3 / 960	1.00

FOXP3	exon 12, R397W	rs28935477	C	t	42	26,035	0.2	2 / 960	30	16,416	0.2	2 / 960	1.00
FOXP3	intron 10	ss119336609	G	a	70	48,282	0.1	1 / 960	46	40,789	0.1	1 / 960	1.00
FOXP3	intron 6	ss119336607	G	a	31	27,349	0.1	1 / 960	1	20,098	0.0	0 / 960	1.00
FOXP3	intron 10	ss119336610	C	g	35	33,853	0.1	1 / 960	1	29,747	0.0	0 / 960	1.00
FOXP3	exon 9, V292I	ss119336608	G	a	1	31,600	0.0	0 / 960	73	20,794	0.4	3 / 960	0.25
IAN4L1	exon 3, sSNP	ss107794735	G	a	221	9,049	2.4	23 / 960	202	7,092	2.8	27 / 960	0.67
IAN4L1	exon 3, I148V	ss107794733	A	g	141	50,098	0.3	3 / 960	180	48,334	0.4	4 / 960	1.00
IAN4L1	exon 3, L204P	ss107794734	T	c	21	15,645	0.1	1 / 960	36	13,669	0.3	3 / 960	0.62
IAN4L1	intron 2	ss119336612	C	t	61	54,848	0.1	1 / 960	4	58,345	0.0	0 / 960	1.00
IAN4L1	intron 2	ss119336611	C	t	52	54,984	0.1	1 / 960	5	58,328	0.0	0 / 960	1.00
IAN4L1	exon 3, sSNP	ss119336614	C	a	1	20,915	0.0	0 / 960	20	19,314	0.1	1 / 960	1.00
IAN4L1	exon 3, F87L	ss119336613	T	g	0	33,252	0.0	0 / 960	30	29,142	0.1	1 / 960	1.00
IL2RA	exon 2, sSNP	rs2228150	G	a	1160	47,841	2.4	23 / 960	1308	45,384	2.9	28 / 960	0.57
IL2RA	exon 4, sSNP	rs2228149	C	t	1331	56,771	2.3	23 / 960	1301	50,188	2.6	25 / 960	0.88
IL2RA	intron 4	rs11256360	C	t	1191	54,781	2.2	21 / 960	1322	49,959	2.6	25 / 960	0.65
IL2RA	intron 3	rs942200	G	a	778	39,232	2.0	19 / 960	983	36,239	2.7	26 / 960	0.37
IL2RA	5'UTR	ss107794686	G	t	77	22,356	0.3	3 / 960	0	19,584	0.0	0 / 960	0.25
IL2RA	intron 7	ss107794695	A	g	47	19,338	0.2	2 / 960	50	17,365	0.3	3 / 960	1.00
IL2RA	intron 6	ss119336644	C	g	83	45,462	0.2	2 / 960	0	39,793	0.0	0 / 960	0.50
IL2RA	exon 3, T91M	ss107794693	C	t	93	54,034	0.2	2 / 960	81	49,553	0.2	2 / 960	1.00
IL2RA	exon 3, S111N	rs56054476	G	a	72	54,096	0.1	1 / 960	63	49,549	0.1	1 / 960	1.00
IL2RA	exon 2, sSNP	ss119336637	C	t	62	51,073	0.1	1 / 960	2	45,663	0.0	0 / 960	1.00
IL2RA	intron 5	ss119336643	T	a	48	59,712	0.1	1 / 960	65	62,716	0.1	1 / 960	1.00
IL2RA	exon 7, sSNP	ss119336646	G	a	37	46,820	0.1	1 / 960	5	39,797	0.0	0 / 960	1.00
IL2RA	intron 2	ss119336639	A	t	35	50,885	0.1	1 / 960	0	45,656	0.0	0 / 960	1.00

IL2RA	intron 7	ss119336647	G	a	4	19,241	0.0	0 / 960	26	17,499	0.1	1 / 960	1.00
IL2RA	intron 4	ss119336642	C	t	5	55,777	0.0	0 / 960	45	50,115	0.1	1 / 960	1.00
IL2RA	exon 1, M15I	ss119336636	G	a	2	23,259	0.0	0 / 960	22	19,587	0.1	1 / 960	1.00
IL2RA	intron 2	ss119336638	G	a	3	51,141	0.0	0 / 960	133	45,650	0.3	3 / 960	0.25
IL2RA	intron 6	ss119336645	C	t	2	46,979	0.0	0 / 960	30	39,799	0.1	1 / 960	1.00
IL2RA	exon 3, V116A	ss119336641	T	c	2	53,732	0.0	0 / 960	67	49,543	0.1	1 / 960	1.00
IL2RA	5'UTR	ss119336635	C	g	0	22,513	0.0	0 / 960	30	19,589	0.2	1 / 960	1.00
KCNJ11	exon , sSNP	rs8175351	G	a	156	8,671	1.8	17 / 960	116	5,137	2.3	22 / 960	0.52
KCNJ11	exon , sSNP	rs5216	C	g	354	20,199	1.8	17 / 960	236	15,950	1.5	14 / 960	0.72
KCNJ11	exon , S385C	rs41282930	C	g	29	8,663	0.3	3 / 960	33	5,138	0.6	6 / 960	0.51
KCNJ11	exon 1, sSNP	ss119336648	C	t	23	17,326	0.1	1 / 960	3	16,339	0.0	0 / 960	1.00
PTPN2	intron 3	ss107794699	T	c	37	32,684	0.1	1 / 960	140	32,191	0.4	4 / 960	0.37
PTPN2	exon 9, G401C	ss119336682	G	t	25	29,897	0.1	1 / 960	0	24,537	0.0	0 / 960	1.00
PTPN2	intron 4	ss119336680	G	a	22	31,994	0.1	1 / 960	1	27,793	0.0	0 / 960	1.00
PTPN2	exon 3, S82G	ss119336684	A	g	23	34,228	0.1	1 / 960	31	32,199	0.1	1 / 960	1.00
PTPN2	3'UTR	ss119336683	T	c	1	41,335	0.0	0 / 960	39	37,203	0.1	1 / 960	1.00
PTPN2	exon 5, sSNP	ss119336681	A	g	0	21,836	0.0	0 / 960	24	22,016	0.1	1 / 960	1.00
PTPN2	exon 2, sSNP	ss119336679	T	c	0	40,076	0.0	0 / 960	42	42,187	0.1	1 / 960	1.00
PTPN22	exon 10, R263Q	rs33996649	G	a	517	34,506	1.5	14 / 960	744	41,689	1.8	17 / 960	0.72
PTPN22	intron 17	rs34209542	T	c	270	19,001	1.4	14 / 960	610	31,218	2.0	19 / 960	0.48
PTPN22	intron 20	rs34639107	T	a	311	31,289	1.0	10 / 960	267	35,866	0.7	7 / 960	0.63
PTPN22	exon 18, K750N,	ss107794704	G	c	96	23,006	0.4	4 / 960	55	30,137	0.2	2 / 960	0.69
PTPN22	intron 2	ss107794700	A	g	92	27,317	0.3	3 / 960	71	27,158	0.3	3 / 960	1.00
PTPN22	exon 13, H370N	ss107794702	C	a	79	35,655	0.2	2 / 960	91	34,995	0.3	2 / 960	1.00
PTPN22	exon 18, R748G	ss119336709	A	g	30	23,086	0.1	1 / 960	0	30,142	0.0	0 / 960	1.00

PTPN22	exon 14, P622R	ss119336706	C	g	39	30,416	0.1	1 / 960	0	30,023	0.0	0 / 960	1.00
PTPN22	exon 10, R266W	ss107794701	C	t	37	34,122	0.1	1 / 960	77	41,656	0.2	2 / 960	1.00
PTPN22	intron 2	ss119336687	G	c	28	27,321	0.1	1 / 960	0	27,175	0.0	0 / 960	1.00
PTPN22	intron 12	ss119336699	T	a	44	43,851	0.1	1 / 960	0	46,481	0.0	0 / 960	1.00
PTPN22	exon 13, sSNP	ss119336704	C	t	34	34,025	0.1	1 / 960	1	37,000	0.0	0 / 960	1.00
PTPN22	exon 13, Q456E	ss107794703	C	g	46	46,035	0.1	1 / 960	113	39,778	0.3	3 / 960	0.62
PTPN22	exon 8, S201F	ss119336693	C	t	33	38,841	0.1	1 / 960	4	36,915	0.0	0 / 960	1.00
PTPN22	exon 13, sSNP	ss119336702	T	c	37	44,688	0.1	1 / 960	52	39,805	0.1	1 / 960	1.00
PTPN22	exon 18, sSNP	ss119336708	A	g	18	23,298	0.1	1 / 960	0	30,137	0.0	0 / 960	1.00
PTPN22	exon 1, sSNP	ss119336685	C	t	26	36,361	0.1	1 / 960	1	29,375	0.0	0 / 960	1.00
PTPN22	intron 9	ss119336695	C	t	25	37,403	0.1	1 / 960	1	33,773	0.0	0 / 960	1.00
PTPN22	exon 3, V71A	ss119336688	T	c	18	27,266	0.1	1 / 960	1	27,176	0.0	0 / 960	1.00
PTPN22	exon 13, S576C	ss119336705	C	g	21	34,054	0.1	1 / 960	0	37,011	0.0	0 / 960	1.00
PTPN22	intron 2	ss119336686	T	c	16	27,321	0.1	1 / 960	1	27,154	0.0	0 / 960	1.00
PTPN22	intron 5	ss119336690	A	g	9	21,938	0.0	0 / 960	45	23,580	0.2	2 / 960	0.50
PTPN22	intron 6	ss119336691	G	a	4	26,361	0.0	0 / 960	35	23,731	0.1	1 / 960	1.00
PTPN22	exon 15, I650M	ss119336707	T	g	2	42,936	0.0	0 / 960	47	49,106	0.1	1 / 960	1.00
PTPN22	intron 12	ss119336698	G	c	2	44,389	0.0	0 / 960	38	46,476	0.1	1 / 960	1.00
PTPN22	intron 8	ss119336694	A	g	1	37,931	0.0	0 / 960	41	36,916	0.1	1 / 960	1.00
PTPN22	exon 13, sSNP	ss119336700	G	a	1	43,200	0.0	0 / 960	45	41,549	0.1	1 / 960	1.00
PTPN22	exon 13, Y528C	ss119336703	A	g	0	41,180	0.0	0 / 960	86	39,031	0.2	2 / 960	0.50
PTPN22	intron 10	ss119336696	T	g	0	34,345	0.0	0 / 960	72	41,669	0.2	2 / 960	0.50
PTPN22	intron 3	ss119336689	A	c	0	30,596	0.0	0 / 960	38	38,660	0.1	1 / 960	1.00
PTPN22	intron 10	ss119336697	G	c	0	34,324	0.0	0 / 960	39	41,662	0.1	1 / 960	1.00
PTPN22	intron 7	ss119336692	T	g	0	36,547	0.0	0 / 960	32	37,816	0.1	1 / 960	1.00

PTPN22	exon 13, I444L	ss119336701	A	t	0	45,881	0.0	0 / 960	21	39,801	0.1	1 / 960	1.00
SH2B3	exon 6, E400K	ss107794706	G	a	91	22,702	0.4	4 / 960	12	20,262	0.1	1 / 960	0.37
SH2B3	exon 8, N537D	ss119336716	A	g	34	23,588	0.1	1 / 960	0	16,442	0.0	0 / 960	1.00
SH2B3	exon 8, L476F	ss119336715	C	t	32	25,029	0.1	1 / 960	4	19,587	0.0	0 / 960	1.00
SH2B3	intron 5	ss119336711	T	c	31	35,146	0.1	1 / 960	34	30,675	0.1	1 / 960	1.00
SH2B3	exon 8, R566W	ss107794689	C	t	9	23,704	0.0	0 / 960	51	16,433	0.3	3 / 960	0.25
SH2B3	exon 7, sSNP	ss119336714	C	t	8	33,433	0.0	0 / 960	29	25,318	0.1	1 / 960	1.00
SH2B3	intron 5	ss119336712	C	t	4	33,908	0.0	0 / 960	36	30,673	0.1	1 / 960	1.00
SH2B3	exon 7, A453T	ss119336713	G	a	3	33,446	0.0	0 / 960	24	25,314	0.1	1 / 960	1.00
SH2B3	exon 5, sSNP	ss119336710	C	t	3	36,726	0.0	0 / 960	24	30,659	0.1	1 / 960	1.00

Table S4. Association analysis of the two rare intronic *CLEC16A* SNPs in T1D patients and controls from Great Britain

SNP	Allele [a]		Case – control study								
	1>2		11	(%)	12	(%)	22	(%)	MAF,%	OR (95% CI) [b]	*P*-value [c]
ss107794687	C>T	T1D	6,291	95.7	279	4.2	6	0.09	2.2	1.01	0.89
Intron 11		Controls	6,299	95.7	280	4.3	4	0.06	2.2	(0.86-1.19)	
ss107794688	C>T	T1D	7,248	96.6	253	3.4	2	0.03	1.7	0.88	0.13
Intron 23		Controls	7,034	96.2	273	3.7	6	0.08	2.0	(0.74-1.04)	

a – Major allele is coded 1, minor allele is coded 2

b – Odds ratios (OR) for minor (rarer) alleles are shown

c – two-tailed *P*-value were calculated using logistic regression

Table S5. Association analysis of the *IFIH1* polymorphisms in T1D patients and controls and in families comprising one or more offspring with T1D and their parents

	Allele [a]		Case – control study							Family study			Combined
	1>2		11	(%)	12 (%)	22 (%)	MAF,%	OR (95% CI) [b]	*P*-value [c]	T/NT	RR (95% CI) [b]	*P*-value [d]	*P*-value [e]
Rare polymorphisms													
rs35667974/Ile923Val	A>G	T1D	7,853	(97.8)	172 (2.1)	3 (0.04)	1.1	0.51	1.3×10^{-14}	67/	0.60	5.9×10^{-4}	2.1×10^{-16}
Exon 14		Controls	9,166	(95.7)	404 (4.2)	4 (0.04)	2.2	(0.43-0.61)		111	(0.45-0.82)		
rs35337543/IVS8+1	G>C	T1D	7,945	(98.0)	163 (2.0)	0 (0.0)	1.0	0.68	1.1×10^{-4}	51/	0.85	0.20	1.4×10^{-4}
Intron 8, splice site		Controls	9,330	(97.1)	280 (2.9)	0 (0.0)	1.5	(0.56-0.83)		60	(0.59-1.23)		
rs35744605/Glu627X	G>T	T1D	8,109	(99.1)	76 (0.9)	0 (0.0)	0.46	0.69	9.0×10^{-3}	17/	0.55	2.8×10^{-2}	1.3×10^{-3}
Exon10		Controls	9,621	(98.7)	131 (1.3)	0 (0.0)	0.67	(0.52-0.91)		31	(0.30-0.99)		
rs35732034/IVS14+1	G>A	T1D	8,047	(98.6)	109 (1.3)	2 (0.03)	0.69	0.74	1.2×10^{-2}	35/	0.63	2.1×10^{-2}	1.1×10^{-3}
Intron 14, splice site		Controls	9,552	(98.1)	180 (1.9)	1 (0.01)	0.93	(0.59-0.94)		56	(0.41-0.95)		
ss107794690/Thr702Ile	C>T	T1D	8,064	(99.4)	46 (0.6)	1 (0.01)	0.30	0.89	0.52	not	tested		
Exon 11		Controls	9,655	(99.3)	65 (0.7)	0 (0.0)	0.33	(0.61-1.28)					
ss107794691/Lys349Arg	A>G	T1D	8,081	(99.5)	42 (0.5)	0 (0.0)	0.26	1.23	0.35	not	tested		
Exon 5		Controls	9,674	(99.6)	41 (0.4)	0 (0.0)	0.21	(0.80-1.89)					
rs10930046/His460Arg	A>G	T1D	8,159	(97.6)	195 (2.3)	2 (0.02)	1.2	1.20	0.062	not	tested		
Exon 7		Controls	10,302	(98.0)	206 (2.0)	1 (0.01)	1.0	(0.99-1.46)					
Common polymorphisms													
rs3747517/Arg843His	G>A	T1D	4,720	(56.3)	3,120 (37.2)	539 (6.4)	25.1	0.87	7.1×10^{-10}	not	tested		
Exon 13		Controls	5,519	(52.2)	4,216 (39.9)	840 (7.9)	27.9	(0.83-0.91)					
rs1990760/Thr946Ala	A>G	T1D	3,280	(42.3)	3,502 (45.1)	977 (12.6)	35.2	0.86	2.3×10^{-14}	1,219/	0.87	2.6×10^{-4}	9.5×10^{-17}
Exon 15		Controls	3,789	(37.2)	4,813 (47.3)	1,573 (15.5)	39.1	(0.81-0.88)		1,395	(0.81-0.94)		

a – Major allele is coded 1, minor allele is coded 2

b – Odds ratios (OR) and relative risks (RR) for minor (rarer) alleles are shown

c – two-tailed *P*-values were calculated using logistic regression

d – one-tailed *P*-values were calculated using transmission disequilibrium test with robust variance estimates

e – combined *P*-values for the case-control and family data were calculated using a score test as described previously (*26*)

95% CI – 95% confidence interval, MAF – minor allele frequency, T/NT- number of alleles transmitted and non-transmitted to the affected offspring

Table S6. Testing independence of T1D association of the four rare *IFIH1* variants and the common rs1990760/Thr946Ala SNP

Logistic regression analyses in the case-control dataset and conditional logistic regression analyses in the affected families were done to test whether T1D association of the four rare *IFIH1* variants is independent of the common rs1990760/Thr946Ala SNP. Note that adding each of the four rare variants significantly improves the model of T1D association for the rs1990760/Thr946Ala polymorphism in all tests, apart from the rs35337543/IVS8+1 in the families. The most likely reason for no effect of rs35337543/IVS8+1 in the families is lack of statistical power: for example, this variant was not polymorphic in 1,129 Finnish families that substantially contributed to our family dataset.

SNP	Frequency (UK), %	*P* (case-control)	*P* (families)
rs35667974/Ile923Val	2.2	4.1×10^{-9}	0.0063
rs35337543/IVS8+1	1.5	0.00019	0.82
rs35744605/Glu627X	0.67	0.0031	0.0068
rs35732034/IVS14+1	0.93	0.0072	0.0090
rs1990760/Thr946Ala	39.1	-	-

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