SUPPLEMENTARY RESULTS

UBD, *MAS1L* and *ITPR3*

No evidence was found for association of the recently reported *ITPR3* SNP, rs2296336 (ref [23]) in a primary way ($P = 0.91$ in 4,161 cases and 3,485 controls and $P = 0.27$ in the families), nor after conditioning on *HLA-DRB1/HLA-DQB1* ($P = 0.39$ in the 1,912 cases and 1,788 controls, $P = 0.96$ in the families). Recently, the SNPs, rs3131020, rs1233478 and rs389419 located in the UBD and MAS1L gene regions at 29.5 - 29.6 Mb of chromosome 6 have been reported to be associated with T1D [24]. However, in our dataset of 2,369 cases and 1,938 controls, despite these three SNPs being strongly associated prior to conditioning ($P = 2.88\text{x}10^{-11}$, $1.14\text{x}10^{-17}$, $2.57\text{x}10^{-21}$), neither rs3131020 nor rs1233478 show evidence of association after conditioning on *HLA-DRB1/HLA-DQB1* ($P = 0.38$, 0.62). For, rs389419, after conditioning, $P = 0.00091$: when the effects of the *HLA-B* alleles were accounted for, $P = 0.00012$. However, when the effects of *HLA-DRB1*, *HLA-DQB1*, and *HLA-A* were accounted for in the model, rs389419 was not associated with T1D, $P = 0.82$. Examination of the LD between the alleles of *HLA-A* and rs389419, shows that D' >0.8 for most alleles, except HLA-A*33 and HLA-A*68, indicating that UBD and rs389419 is not a primary effect.

Grouping of *HLA-DRB1* and *HLA-DQB1* alleles and genotypes

The large number of *HLA-DQB1* and *HLA-DRB1* alleles results in sparse data, as a number of very rare alleles and/or genotypes, exist exclusively in affected or in unaffected individuals but not both, or only exist in small numbers of affected and unaffected subjects, so the risks are inaccurately modelled. The number of parameters to use to model the effects of the MHC class II loci should also be considered: too many causes a loss of power and poor asymptotic properties of the test statistic, while too few causes residual confounding. A common approach is to group alleles and/or genotypes together by frequency, risk or function. These groupings imply assumptions, which are almost certainly not valid, e.g. that alleles/genotypes confer similar risks if they are rare. Alternatively, rare alleles may be dropped from the analysis. One can also group by function, but the full function of all the different alleles is not yet clear, so this becomes somewhat arbitrary.

Three grouping strategies were considered for the class II loci in order to account for their confounding effects while testing for additional independent T1D loci. One was based on the frequency of the genotypes. Two frequency thresholds were tested, 1% and 5%, such that all genotypes below that frequency threshold were grouped together. The second approach used haplotype risk estimates published by Koeleman *et al.* [33] to categorize class II genotypes into high, neutral and low risk groups. The third approach was based on the *HLA-DRB1* genotype. Non-DR3/DR4 alleles were grouped together (including HLA-DRB1*0403 which was protective in our dataset).

Fifteen loci, including the *TAP2* SNP rs241448, were used to test these grouping strategies. We found that the *P*-value for the test locus, conditional on the class II genotypes, was, at some loci, dependent on the method of grouping of the class II loci adopted *e.g.* the *P*-value for *HLA-B* association varied by nine orders of magnitude between the model grouping genotypes below 0.05 compared to that grouping at 0.01 ($P = 6.20\text{x}10^{-7}$ - $2.14\text{x}10^{-16}$; Supplementary Table 3). Similarly *D6S2444*, ranged from $P = 1\text{x}10^{-4}$ to $7\text{x}10^{-12}$ for the risk-based and frequency-based methods.

SUPPLEMENTARY DISCUSSION

Consistency of the *HLA-A* association

We obtain inconsistent results for *HLA-A* between the case-control set and the families. We do not think this can be attributed to the modelling of the MHC class II effects. Although we do not use the matching of the cases and pseudo-controls when constructing trees in the families, this matching is reintroduced when considering additional loci, so we believe the impact of this is minimal. The major effects at non-class II loci are robust to the model chosen, once a threshold number of groups are reached (Supplementary Table 3). Further, bootstrap analysis showed the tree model generated for the HLA-DQB1/HLA-DRB1 genes was robust (Methods). More likely causes of the discrepancy in *HLA-A* association are ascertainment [31,32], or possible population heterogeneity as the families came from both the UK and USA whereas the cases and controls are British. Hence, the samples will have slightly different genetic backgrounds and different allele frequencies (Supplementary Tables 1; for example the frequency of the highly predisposing DR3/4 genotype in the UK cases is 36% compared to 43% in the ASPs). Additionally, *HLA-A* may have a smaller effect in the ASP families than in cases and controls owing to an epistatic effect of the DR3/4 genotype, for instance. We have reported previously [31] that non-class II gene risk estimates are generally lower in multiplex families than population-based case-control samples or simplex families, possibly owing to epistatic effects of the major MHC class II susceptibility alleles or genotypes. Similarly, a more recent study reported that if a common disease has a susceptibility locus with a large effect, smaller effects of other loci could be masked[32]. Hence, we think the most likely reason for the inconsistent results is power. We were under-powered to find effects of 1.5 in the families (*e.g.* 32% power to detect an effect at $\alpha = 10^{-5}$, for MAF = 0.1 assuming a multiplicative model, compared to 53% power in the larger case-control set). So if the effect was of this magnitude in the families, we may not have found it. We did adjust for geographical regions across Great Britain in the case-control analyses [17,30], ruling out the possibility that the large, independent association of the HLA-A gene in the case-control samples could be a false-positive result owing to population stratification and admixture. Moreover, the *HLA-A* allele frequencies do not vary across Great Britain ($P = 0.52$), and since we have localised T1D susceptibility to *HLA-B*, it is not unexpected that alleles of the functionally-related HLA-A gene are also involved in T1D.

SUPPLEMENTARY METHODS

Genotyping

Genotyping of the HLA-DQB1, HLA-DRB1, HLA-A, HLA-B and HLA-C genes was done using Dynal RELI SSO assays (Invitrogen Ltd, Paisley, UK). When resolution of the HLA-DRB1*04 subtypes was not sufficient we re-genotyped each sample using an appropriate Dynal AllSet SSP assay. Microsatellite markers were genotyped as described previously[5,18]. We genotyped *HLA-A, HLA-B* and *HLA-C* alleles to four-digit resolution according to the HLA gene nomenclature (http://www.anthonynolan.org.uk/HIG/nomen/nomen_index.html). A sequencing-based typing assay was designed (SF, SN, NMW, JMMH, JAT, manuscript in preparation) for the genotyping of the highly polymorphic MICA and MICB genes. Individual SNP genotyping in the families was done using Invader (Third Wave Technologies, Madison, WI) or TaqMan (Perkin Elmer Applied Biosystems, Foster City, CA). An additional, 169 MHC nsSNPs were genotyped as part of a genome-wide nsSNP scan using the GeneChip MegAllele System (Affymetrix, Santa Clara, CA)[30].

As part of the WTCCC project, 2,126 SNPs, were typed between 25 Mb and 35 Mb on chromosome 6p21 with the GeneChip® 500K Mapping Array Set (Affymetrix chip)[17]. The eight

SNPs in the follow-up WTCCC dataset were genotyped by TaqMan (Perkin Elmer Applied Biosystems, Foster City, CA).

Single locus analyses: UK and USA families

All loci conformed to Hardy-Weinberg equilibrium in the unaffected parents, $P > 0.004$. Single locus analyses were carried out by generating sets of cases with matched pseudo-controls (generated from genotypes that could have been transmitted but were not[28]), and testing for association with T1D in a logistic regression framework, conditioning on having at least one affected offspring in every set[28]. Two-digit allele coding, grouping the four-digit subtypes into a two-digit type, were used for the HLA-A, HLA-B and HLA-C genes as this reduced the multiplicity of alleles, hence simplifying the statistical models. However, subtypes of HLA-B*39 have two equally frequent splits (Supplementary Tables 1 and 4) and so were analysed separately. Non-independence of siblings in the ASP families was accounted for by using robust Huber-White sandwich estimators. However, at loci with sparse data, the Wald test is artificially biased towards the alternative, hence no adjustment could be made. Both allelic (alleles coded as continuous variables assuming a multiplicative model, on n – 1 degrees of freedom where n = the number of alleles) and genotype models (which do not assume a specific mode of inheritance on n – 1 degrees of freedom where n = the number of genotypes) were tested and where they were not significantly different, $P > 0.05$, the multiplicative was used. Where necessary, to ensure all parameters in the model were estimable, rare genotypes were grouped together at either 0.05 (five loci) or 0.01 (three loci) minimum frequency, or alleles below 0.005 frequency were grouped (eight loci).

No formal correction for multiple testing was made. However, when considering rejection of the null, we set a threshold of $P < 0.0001$.

Single locus analyses: British cases and controls (non-WTCCC)

All loci conformed to Hardy-Weinberg equilibrium in the controls ($P > 0.003$). Cases were matched to controls, according to 12 broad geographical regions[17,30,34], and analysed within strata by logistic regression. Both genotype and allele models were considered at all loci. The genotypes at, *HLA-DRB1*, *-DQB1* and *–B*, were grouped by frequency at the 0.05 level.

Single locus analyses: WTCCC British cases and controls

All loci conformed to Hardy-Weinberg equilibrium in controls at the level set for the entire WTCCC study ($P < 5 \times 10^{-7}$). Call rate for all SNPs had to be greater than 99%, and minor allele frequency greater than 0.05 in order to be analysed for association with T1D. In total 651 SNPs of the total 2,126 SNPs between 25 Mb and 35 Mb, did not satisfy these criteria and so were excluded from analysis. Cases were matched to controls, according to 12 broad geographical regions[17,30,34], and analysed within strata by logistic regression. Allele models were used for all SNPs.

Power calculations

Our study was extremely well powered to find the effects of the HLA-DQB1 and HLA-DRB1 genes, although our main aim was to test whether any other loci in the MHC had an additional effect. For this hypothesis the power calculations were not straightforward, due to the complexity of the MHC region, with extensive LD and given that we were looking for an effect within the strata of the *HLA-DRB1*/*HLA-DQB1* model. Hence, simulated datasets were generated from sets of cases and pseudo-controls, which had been generated from the ASP families. The affection status was permuted within these sets and the resultant permuted datasets used to test, by conditional logistic regression, the effect of the third locus. Crucially, the grouping from the

recursive partitioning model was maintained. The effect size and variance of the third locus was used to calculate the Wald test to assess significance and subsequently the power of the study. A total of 100,000 replicates were performed. The case-control set was also used to perform power calculations, for the same reasons given above. For a putative causal locus with a minor allele frequency of interest *e.g.* 0.1, the standard error under the null hypothesis, S_0, with OR = 1 was estimated, as was the standard error under the alternative hypothesis, S_1, corresponding to an OR of interest. These estimates were calculated using the groupings of *HLA-DRB1* and *HLA-DQB1* generated by the recursive partitioning method. The power was calculated as the probability that a normal deviate, Z_α, with mean log(OR) and standard error, S_1, exceeds (S_0 x Z_α).

Assuming a multiplicative model and a MAF of 0.1, we had 98% power to detect a relative risk of 2.0 at $\alpha = 10^{-5}$ in the 850 ASP families. The power dropped to 60% for a minor allele frequency MAF of 0.05. For an effect of 1.5 we had 32% power at MAF of 0.1. In contrast, in the case-control collection we had 99.9% power to detect an OR=2.0 for an allele with MAF=0.1, at $\alpha = 10^{-5}$ assuming a multiplicative model and for OR=1.5, 53% power. So, we had greater power in the cases and controls than in the families for smaller effect sizes, which reflects the difference in sample size between the case-control set and the families, with the case-control set being almost twice as large.

Testing for age-at-diagnosis effects.

Specific HLA class I alleles were tested for modifying effects on age-at-diagnosis of T1D, separately in the isolated British cases, and the affected offspring from the multiplex families. Regression was used with genotype (or allele) of interest as the outcome variable and age-at-diagnosis as the independent variable. Geography, the twelve sub-regions of Great Britain[17,30,34], was included as a confounder.

Haplotypes

Often *HLA-DRB1*, *HLA-DQA1* and *HLA-DQB1* are analysed as haplotypes as the LD between them is very strong. Pseudo-controls and cases were generated including phase as described by Cordell and Clayton[28]. Phased genotypes were generated using the haplo.stats library in *R* (http://cran-r.project.org) separately in cases and in controls. Here we found no evidence of cis-interactions, when haplotypes were included as splitting criteria in `rpart`, (they were not selected to partition the data) nor when phase information was added into the regression model ($P > 0.05$). Consequently we only used genotypes of the MHC class II loci for the recursive partitioning model.

Combining *P*-values

To generate a combined *P*-value for each of *HLA-B* and *HLA-A*, we carried out Wald tests in the case-control set and separately in the families. The estimates were weighted by the inverse variance and summed, and then divided by the sum of the weights to combine the effects.

SUPPLEMENTARY TABLES

Supplementary Table 1a | The number of families, cases and controls, from the first case-control set, typed at the classical loci (the second case-control set is not included).

Locus	Number of families typed	Number of families typed at *HLA-DRB1* and *HLA-DQB1*	Number controls typed	Number of controls typed at *HLA-DRB1* and *HLA-DQB1*	Number of cases typed	Number of cases typed at *HLA-DRB1* and *HLA-DQB1*
HLA-DQB1	815	N/A	1880	N/A	2036	N/A
HLA-DQA1	252	246	0	0	0	0
HLA-DRB1	809	N/A	1894	N/A	1954	N/A
HLA-A	655	640	1759	1721	1514	1503
HLA-B	754	736	1673	1642	1512	1498
HLA-C	668	649	0	0	0	0

Supplementary Table 1b | *HLA-DQB1* allele frequencies.

HLA-DQB1 allele	UK families, affected offspring, n (%)	UK families, unaffected parents, n (%)	USA families, affected offspring, n (%)	USA families, unaffected parents, n (%)	British cases, n (%)	British controls, n (%)
*02	272 (38.97)	198 (32.78)	561 (35.78)	442 (29.66)	1584 (38.90)	913 (24.28)
*04	10 (1.43)	9 (1.49)	54 (3.44)	44 (2.95)	100 (2.46)	85 (2.26)
*0301	41 (5.87)	68 (11.26)	76 (4.85)	168 (11.28)	244 (5.99)	682 (18.14)
*0302	262 (37.54)	152 (25.17)	607 (38.71)	378 (25.37)	1491 (36.62)	406 (10.80)
*0303	6 (0.86)	20 (3.31)	23 (1.47)	45 (3.02)	61 (1.50)	228 (6.06)
*0304			5 (0.32)	3 (0.20)		
*0305	1 (0.14)	2 (0.33)		1 (0.07)		
*0501	61 (8.74)	70 (11.59)	115 (7.33)	131 (8.79)	388 (9.53)	451 (11.99)
*0502	8 (1.15)	6 (0.99)	34 (2.17)	31 (2.08)	22 (0.54)	18 (0.48)
*0503		3 (0.50)	3 (0.19)	22 (1.48)	6 (0.15)	90 (2.39)
*0504			3 (0.19)	2 (0.13)	1 (0.02)	10 (0.27)
*0601		3 (0.50)	2 (0.13)	6 (0.40)	3 (0.07)	18 (0.48)
*0602	6 (0.86)	28 (4.64)	8 (0.51)	100 (6.71)	12 (0.29)	501 (13.32)
*0603	12 (1.72)	16 (2.65)	19 (1.21)	50 (3.36)	41 (1.01)	197 (5.24)
*0604	17 (2.44)	17 (2.81)	51 (3.25)	53 (3.56)	110 (2.70)	116 (3.09)
*0605			3 (0.19)	2 (0.13)		
*0609	1 (0.14)	5 (0.83)	2 (0.13)	8 (0.54)	9 (0.22)	45 (1.20)
*03[a]				1 (0.07)		
*05[a]	1 (0.14)	4 (0.66)				
*06[a]		3 (0.50)	2 (0.13)	3 (0.20)		

(a) Some individuals carry rare alleles that could not be resolved into 4-digit subtypes, hence 2-digit alleles are reported.

Supplementary Table 1c | *HLA-DRB1* allele frequencies.

HLA-DRB1 allele	UK families, affected offspring, n (%)	UK families, unaffected parents, n (%)	USA families, affected offspring, n (%)	USA families, unaffected parents, n (%)	British cases, n (%)	British controls, n (%)
*01	63 (9.03)	73 (12.05)	115 (7.34)	128 (8.63)	367 (9.39)	446 (11.77)
*03	261 (37.39)	160 (26.40)	510 (32.57)	355 (23.92)	1342 (34.34)	513 (13.54)
*04[a]	3 (0.43)	3 (0.50)	8 (0.51)	4 (0.27)		1 (0.03)
*06				1 (0.07)		
*07	12 (1.72)	52 (8.58)	37 (2.36)	104 (7.01)	165 (4.22)	583 (15.39)
*08	11 (1.58)	10 (1.65)	51 (3.26)	43 (2.90)	100 (2.56)	86 (2.27)
*09	5 (0.72)	5 (0.83)	23 (1.47)	20 (1.35)	45 (1.15)	60 (1.58)
*10	2 (0.29)	1 (0.17)	7 (0.45)	6 (0.40)	5 (0.13)	21 (0.55)
*11	6 (0.86)	18 (2.97)	20 (1.28)	80 (5.39)	42 (1.08)	233 (6.15)
*12		3 (0.50)	4 (0.26)	13 (0.88)	18 (0.46)	63 (1.66)
*13	32 (4.58)	44 (7.26)	83 (5.30)	120 (8.09)	165 (4.22)	377 (9.95)
*14		4 (0.66)	1 (0.06)	22 (1.48)	4 (0.10)	88 (2.32)
*15	6 (0.86)	33 (5.45)	14 (0.89)	109 (7.35)	16 (0.41)	531 (14.02)
*16	7 (1.00)	7 (1.16)	31 (1.98)	28 (1.89)	21 (0.54)	22 (0.58)
*0401[a]	218 (31.23)	136 (22.44)	413 (26.37)	264 (17.79)	1119 (28.63)	423 (11.17)
*0402[a]	6 (0.86)	6 (0.99%)	53 (3.38)	42 (2.83)	46 (1.18)	14 (0.37)
*0403[a]		3 (0.50%)	15 (0.96)	19 (1.28)	25 (0.64)	98 (2.59)
*0404[a]	50 (7.16)	38 (6.27)	131 (8.37)	95 (6.40)	330 (8.44)	215 (5.68)
*0405[a]	16 (2.29)	10 (1.65)	50 (3.19)	31 (2.09)	98 (2.51)	14 (0.37)

(a) Only *0401, *0402, *0403, *0404 and *0405 subtypes of the DRB1*04 type were distinguished. When the subtype could not be resolved we analysed it as DRB1*04.

Supplementary Table 1d | *HLA-B* allele frequencies (two-digit resolution).

HLA-B allele	UK families, affected offspring, n (%)	UK families, unaffected parents, n (%)	USA families, affected offspring, n (%)	USA families, unaffected parents, n (%)	British cases, n (%)	British controls, n (%)
*07	51 (7.46)	55 (9.34)	124 (8.66)	157 (11.67)	249 (8.23)	465 (13.90)
*08	173 (25.29)	114 (19.35)	307 (21.44)	229 (17.03)	788 (26.06)	461 (13.78)
*13	8 (1.17)	13 (2.21)	20 (1.40)	21 (1.56)	43 (1.42)	56 (1.67)
*14	18 (2.63)	21 (3.57)	31 (2.16)	40 (2.97)	54 (1.79)	159 (4.75)
*15	91 (13.30)	59 (10.02)	189 (13.20)	129 (9.59)	388 (12.83)	267 (7.98)
*18	45 (6.58)	29 (4.92)	136 (9.50)	100 (7.43)	202 (6.68)	128 (3.83)
*27	36 (5.26)	31 (5.26)	53 (3.70)	51 (3.79)	113 (3.74)	145 (4.33)
*35	37 (5.41)	41 (6.96)	77 (5.38)	103 (7.66)	130 (4.30)	197 (5.89)
*37		7 (1.19)	10 (0.70)	10 (0.74)	21 (0.69)	51 (1.52)
*38	4 (0.58)	4 (0.68)	17 (1.19)	26 (1.93)	10 (0.33)	26 (0.78)
*39	26 (3.80)	12 (2.04)	81 (5.66)	50 (3.72)	143 (4.73)	79 (2.36)
*40	58 (8.48)	54 (9.17)	115 (8.03)	101 (7.51)	257 (8.50)	232 (6.93)
*41	4 (0.58)	2 (0.34)	18 (1.26)	16 (1.19)	11 (0.36)	23 (0.69)
*42				1 (0.07)		
*44	62 (9.06)	84 (14.26)	131 (9.15)	159 (11.82)	344 (11.38)	567 (16.95)
*45	7 (1.02)	6 (1.02)	8 (0.56)	6 (0.45)	9 (0.30)	26 (0.78)
*46					1 (0.03)	
*47	3 (0.44)	3 (0.51)	2 (0.14)	2 (0.15)	9 (0.30)	8 (0.24)
*49	8 (1.17)	5 (0.85)	22 (1.54)	15 (1.12)	38 (1.26)	34 (1.02)
*50	8 (1.17)	3 (0.51)	16 (1.12)	13 (0.97)	42 (1.39)	35 (1.05)
*51	17 (2.49)	15 (2.55)	40 (2.79)	45 (3.35)	78 (2.58)	109 (3.26)
*52	2 (0.29)	2 (0.34)	4 (0.28)	8 (0.59)	3 (0.10)	20 (0.60)
*53			1 (0.07)	6 (0.45)	3 (0.10)	9 (0.27)
*55	15 (2.19)	8 (1.36)	10 (0.70)	12 (0.89)	37 (1.22)	71 (2.12)
*56	1 (0.15)	2 (0.34)	5 (0.35)	6 (0.45)	14 (0.46)	16 (0.48)
*57	5 (0.73)	16 (2.72)	7 (0.49)	28 (2.08)	26 (0.86)	143 (4.27)
*58	3 (0.44)	2 (0.34)	8 (0.56)	9 (0.67)	11 (0.36)	19 (0.57)
*70	2 (0.29)	1 (0.17)		1 (0.07)		

Supplementary Table 1e | *HLA-B* allele frequencies (four-digit resolution).

HLA-B allele	Families, affected offspring, n (%)	Families, unaffected parents, n (%)	British case, n (%)	British controls, n (%)
*0702	176 (5.39)	246 (8.09)	238 (7.94)	453 (13.82)
*0704		1 (0.03)		
*0705	3 (0.09)	4 (0.13)		
*0726			1 (0.03)	
*0801	793 (24.29)	581 (19.11)	783 (26.13)	453 (13.82)
*0802		1 (0.03)		
*1302	39 (1.19)	45 (1.48)	43 (1.44)	56 (1.71)
*1401	15 (0.46)	17 (0.56)	12 (0.40)	58 (1.77)
*1402	46 (1.41)	50 (1.64)	41 (1.37)	98 (2.99)
*1501	346 (10.60)	243 (7.99)	347 (11.58)	222 (6.77)
*1503	2 (0.06)	1 (0.03)	3 (0.10)	5 (0.15)
*1504	1 (0.03)			
*1507	2 (0.06)	1 (0.03)	2 (0.07%)	3 (0.09)
*1508	1 (0.03)	1 (0.03)	1 (0.03%)	1 (0.03)
*1509		1 (0.03)	1 (0.03%)	1 (0.03)
*1510	4 (0.12)	2 (0.07)		
*1514				1 (0.03)
*1515	1 (0.03)	3 (0.10)		
*1516	1 (0.03)	2 (0.07)	1 (0.03)	3 (0.09)
*1517	8 (0.25)	6 (0.20)	3 (0.10)	8 (0.24)
*1518	11 (0.34)	9 (0.30)	12 (0.40)	14 (0.43)
*1524	2 (0.06)	2 (0.07)	1 (0.03)	1 (0.03)
*1537	4 (0.12)	1 (0.03)		
*1571		1 (0.03)		
*1801	252 (7.72)	188 (6.18)	200 (6.68)	123 (3.75)
*1802		2 (0.07)		
*1812	3 (0.09)			
*2701		1 (0.03)		2 (0.06)
*2702	1 (0.03)	3 (0.10)	3 (0.10)	2 (0.06)
*2705	60 (1.84)	62 (2.04)	108 (3.60)	140 (4.27)
*2707	1 (0.03)	1 (0.03)		
*2719		1 (0.03)		
*3501	59 (1.81)	73 (2.40)	67 (2.24%)	122 (3.72)
*3502	1 (0.03)	6 (0.20)		7 (0.21)
*3503	8 (0.25)	8 (0.26)	6 (0.20)	17 (0.52)
*3508	9 (0.28)	7 (0.23)	5 (0.17)	5 (0.15)
*3513		1 (0.03)		
*3701	22 (0.67)	29 (0.95)	21 (0.70)	50 (1.53)
*3801	21 (0.64)	27 (0.89)	10 (0.33)	23 (0.70)
*3901	26 (0.80)	24 (0.79)	43 (1.44)	34 (1.04)
*3906	63 (1.93)	40 (1.32)	87 (2.90)	40 (1.22)
*3928				1 (0.03)
*4001	172 (5.27)	155 (5.10)	239 (7.98)	197 (6.01)
*4002	19 (0.5)	27 (0.89)	17 (0.57)	29 (0.88)
*4006	1 (0.03)	2 (0.07)		
*4101	10 (0.31)	14 (0.46)	10 (0.33)	9 (0.27)

*4102	4 (0.12)	8 (0.26)	1 (0.03)	8 (0.24)
*4202		1 (0.03)		1 (0.03)
*4402	169 (5.18)	199 (6.54)	256 (8.54)	367 (11.20)
*4403	60 (1.84)	94 (3.09)	75 (2.50)	165 (5.03)
*4404				4 (0.12)
*4405	2 (0.06)	1 (0.03)	1 (0.03)	1 (0.03)
*4414			1 (0.03)	
*4501	8 (0.25)	8 (0.26)	9 (0.30)	26 (0.79)
*4601			1 (0.03)	
*4701	13 (0.40)	10 (0.33)	9 (0.30)	8 (0.24)
*4801		1 (0.03)		
*4901	42 (1.29)	36 (1.18)	38 (1.27)	33 (1.01)
*5001	40 (1.23)	31 (1.02)	40 (1.34)	34 (1.04)
*5002	3 (0.09)	2 (0.07)		
*5101	55 (1.68)	66 (2.17)	69 (2.30)	89 (2.72)
*5108	2 (0.06)	2 (0.07)	2 (0.07)	
*5201	7 (0.21)	14 (0.46)	2 (0.07)	18 (0.55)
*5301	2 (0.06)	8 (0.26)	1 (0.03)	9 (0.27)
*5501	41 (1.26)	41 (1.35)	37 (1.23)	71 (2.17)
*5601	9 (0.28)	10 (0.33)	14 (0.47)	15 (0.46)
*5701	24 (0.74)	60 (1.97)	26 (0.87)	142 (4.33)
*5702		1 (0.03)		
*5706		2 (0.07)		
*5801	15 (0.46)	16 (0.53)	11 (0.37)	18 (0.55)
*5804	1 (0.03)			
*07 [a]	102 (3.12)	92 (3.03)	8 (0.27)	3 (0.09)
*14 [a]	13 (0.40)	20 (0.66)		
*15 [a]	60 (1.84)	39 (1.28)	14 (0.47)	4 (0.12)
*22 [a]	1 (0.03)			
*27 [a]	64 (1.96)	58 (1.91)		
*35 [a]	79 (2.42)	98 (3.22)	51 (1.70)	38 (1.16)
*38 [a]	6 (0.18)	10 (0.33)		
*39 [a]	52 (1.59)	28 (0.92)	13 (0.43)	
*40 [a]	84 (2.57)	62 (2.04)		1 (0.03)
*41 [a]	13 (0.40)	7 (0.23)		6 (0.18)
*44 [a]	77 (2.36)	90 (2.96)	5 (0.17)	20 (0.61)
*45 [a]	8 (0.25)	7 (0.23)		
*50 [a]			1 (0.03)	
*51 [a]	23 (0.70)	25 (0.82)	4 (0.13)	19 (0.58)
*53 [a]		3 (0.10)	2 (0.07)	
*70 [a]	2 (0.06)	2 (0.07)		
*78 [a]		1 (0.03)		

(a) Individuals that could not be resolved to the four-digit subtypes are reported as two-digit types.

Supplementary Table 1f | *HLA-A* allele frequencies.

HLA-A allele	UK families, affected offspring, n (%)	UK families, unaffected parents, n (%)	USA families, affected offspring, n (%)	USA families, unaffected parents, n (%)	British cases, n (%)	British controls, n (%)
*01	143 (21.97)	123 (22.78)	207 (20.76)	186 (18.06)	648 (21.40)	638 (18.14)
*02	209 (32.10)	180 (33.33)	345 (34.60)	324 (31.46)	1021 (33.72)	1034 (29.39)
*03	95 (14.59)	67 (12.41)	110 (11.03)	125 (12.14)	380 (12.55)	493 (14.01)
*11	32 (4.92)	33 (6.11)	34 (3.41)	46 (4.47)	99 (3.27)	229 (6.51)
*23	5 (0.77)	6 (1.11)	11 (1.10)	14 (1.36)	24 (0.79)	46 (1.31)
*24	62 (9.52)	47 (8.70)	124 (12.44)	107 (10.39)	331 (10.93)	265 (7.53)
*25	7 (1.08)	4 (0.74)	17 (1.71)	21 (2.04)	39 (1.29)	64 (1.82)
*26	13 (2.00)	10 (1.85)	40 (4.01)	37 (3.59)	38 (1.25)	85 (2.42)
*29	15 (2.30)	17 (3.15)	29 (2.91)	35 (3.40)	93 (3.07)	161 (4.58)
*30	20 (3.07)	21 (3.89)	33 (3.31)	27 (2.62)	102 (3.37)	82 (2.33)
*31	21 (3.23)	23 (4.26)	25 (2.51)	23 (2.23)	62 (2.05)	106 (3.01)
*32	8 (1.23)	8 (1.48)	18 (1.81)	28 (2.72)	80 (2.64)	130 (3.70)
*33	6 (0.92)		1 (0.10)	5 (0.49)	23 (0.76)	30 (0.85)
*34				1 (0.10)	3 (0.10)	4 (0.11)
*36				1 (0.10)		
*66		1 (0.19)	3 (0.30)	5 (0.49)	3 (0.10)	12 (0.34)
*68	15 (2.30)			42 (4.08)	78 (2.58)	136 (3.87)
*69				2 (0.19)	1 (0.03)	1 (0.03)
*74				1 (0.10)	3 (0.10)	2 (0.06)

Supplementary Table 1g | *HLA-DPB1* allele frequencies in the T1D families.

HLA-DPB1 allele	Affected offspring, n(%)	Unaffected parents, n (%)
*0101	107 (8.83)	122 (7.43)
*0201	141 (11.63)	192 (11.69)
*0202	34 (2.81)	27 (1.64)
*0301	201 (16.58)	241 (14.68)
*0401	499 (41.17)	699 (42.57)
*0402	64 (5.28)	129 (7.86)
*0404	2 (0.17)	1 (0.06)
*0501	15 (1.24)	23 (1.40)
*0601	37 (3.05)	37 (2.25)
*0801	1 (0.08)	3 (0.18)
*0901	4 (0.33)	10 (0.61)
*1001	20 (1.65)	28 (1.71)
*1101	10 (0.83)	27 (1.64)
*1301	17 (1.40)	27 (1.64)
*1401	14 (1.16)	21 (1.28)
*1501	22 (1.82)	22 (1.34)
*1601	3 (0.25)	3 (0.18)
*1701	3 (0.25)	11 (0.67)
*1901	9 (0.74)	8 (0.49)
*2001	7 (0.58)	7 (0.43)
*2301	0 (0)	2 (0.12)
*3401	0 (0)	1 (0.06)
*5901	2 (0.17)	1 (0.06)

Supplementary Table 1h | Allele frequencies of *HLA-C* in the T1D families.

Allele	UK affected offspring, n(%)	UK unaffected parents, n(%)	USA affected offspring, n(%)	USA unaffected parents, n(%)
*01	18 (2.80)	23 (4.09)	31 (2.48)	32 (2.68)
*02	24 (3.74)	21 (3.74)	54 (4.33)	52 (4.36)
*03	139 (21.65)	105 (18.68)	247 (19.79)	187 (15.69)
*04	37 (5.76)	41 (7.30)	72 (5.77)	108 (9.06)
*05	85 (13.24)	75 (13.35)	159 (12.74)	142 (11.91)
*06	30 (4.67)	45 (8.01)	55 (4.41)	73 (6.12)
*07	249 (38.79)	188 (33.45)	482 (38.62)	437 (36.66)
*08	14 (2.18)	18 (3.20)	20 (1.60)	21 (1.76)
*09	2 (0.31)	1 (0.18)		
*10	1 (0.16)	4 (0.71)		
*12	23 (3.58)	15 (2.67)	59 (4.73)	67 (5.52)
*14	2 (0.31)	2 (0.36)	7 (0.56)	12 (1.01)
*15	11 (1.71)	9 (1.60)	29 (2.32)	24 (2.01)
*16	6 (0.93)	14 (2.49)	19 (1.52)	23 (1.93)
*17	1 (0.16)	1 (0.18)	14 (1.12)	14 (1.17)

Supplementary Table 2a | *P*-values for association tests in the T1D families without and with conditioning on the MHC class II effects.

Locus	Position, chr 6	Locus type	Gene	Without conditioning	With conditioning on *HLA-DQB1* and *HLA-DRB1*
D6S1691	24,032,524	Microsatellite		0.0013	0.615
D6S2239	26,181,749	Microsatellite		0.03	0.923
D6S2223	27,765,822	Microsatellite		0.093	0.203
D6S306	28,034,082	Microsatellite		0.055	0.106
D6S2222	28,041,225	Microsatellite		0.41	0.054
D6S258	29,128,778	Microsatellite		0.0098	0.061
D6S1683	29,260,683	Microsatellite		0.155	0.607
HLA-A (two-digit)	30,018,305	Gene	HLA-A	1.3×10^{-6}	0.067
D6S265	30,127,492	Microsatellite		0.689	0.992
rs2844697	31,040,288	SNP	DPCR1	3.41×10^{-15}	0.210
HLA-C (two-digit)	31,344,505	Gene	HLA-C	8.04×10^{-19}	0.286
HLA-B (two-digit)	31,429,628	Gene	HLA-B	3.44×10^{-30}	4.19×10^{-7}
Bw4/Bw6	31,429,628	Epitope	HLA-B	2.43×10^{-18}	6.57×10^{-6}
MIB	31,457,335	Microsatellite		1.2×10^{-5}	0.303
MICA (three-digit)	31,476,505	Gene	MICA	1.82×10^{-10}	0.081
MICA-STR	31,488,134	Microsatellite	MICA	2.4×10^{-6}	0.762
MICB (three-digit)	31,573,871	Gene	MICB	1.96×10^{-15}	0.028
rs2071592	31,623,319	SNP	NFKBIL1	8.2×10^{-4}	0.971
rs3130062	31,633,891	SNP	NFKBIL1	2.1×10^{-4}	0.621
TNFa	31,643,339	Microsatellite		7.41×10^{-13}	0.782
rs2239704	31,648,120	SNP	LTA	2.2×10^{-7}	0.996
rs909253	31,648,292	SNP	LTA	1.7×10^{-3}	0.753
TNFc	31,648,344	Microsatellite		0.187	0.070
rs746868	31,648,408	SNP	LTA	6.65×10^{-8}	0.824
rs2857713	31,648,535	SNP	LTA	0.072	0.279
rs3093543	31,648,736	SNP	LTA	0.313	0.697
rs1041981	31,648,763	SNP	LTA	5.1×10^{-3}	0.441
rs1799964	31,650,287	SNP	TNFA	6.0×10^{-3}	0.556
rs1800630	31,650,455	SNP	TNFA	0.026	0.077
rs1799724	31,650,461	SNP	TNFA	0.204	0.229
rs1800750	31,650,942	SNP	TNFA	1.09×10^{-7}	0.038
rs3091256	31,651,010	SNP	TNFA	4.83×10^{-12}	0.690
rs361525	31,651,080	SNP	TNFA	0.587	0.071
rs1800610	31,651,806	SNP	TNFA	0.144	0.316
TNFe	31,663,889	Microsatellite		0.198	0.497
TNFd	31,664,102	Microsatellite		8.2×10^{-7}	0.608
rs11575842	31,665,205	SNP	NCR3	2.2×10^{-3}	0.755
rs11575836	31,668,681	SNP	NCR3	6.8×10^{-3}	0.672
82-1	31,685,369	Microsatellite		1.4×10^{-6}	0.288
D6S273	31,791,664	Microsatellite		2.8×10^{-7}	0.775

rs1065356	31,794,987	SNP	LY6G6C	0.133	0.675
rs805294	31,796,196	SNP	LY6G6C	$3.47x10^{-13}$	0.517
rs805292	31,797,988	SNP	LY6G6C	0.188	0.961
rs805306	31,800,142	SNP	C6orf25	$2.15x10^{-13}$	0.326
D3A	32,231,288	Microsatellite		$1.68x10^{-14}$	0.093
BTNL2-P393Q	32,470,681	SNP	BTNL2	$9.48x10^{-8}$	0.451
rs28362677	32,470,719	SNP	BTNL2	$2.5x10^{-7}$	0.540
rs28362678	32,470,723	SNP	BTNL2	$7.7x10^{-6}$	0.791
rs2076530	32,471,794	SNP	BTNL2	$5.86x10^{-8}$	0.562
rs2076523	32,478,813	SNP	BTNL2	$4.19x10^{-13}$	0.423
HLA-DRB1	32,654,524	Gene	HLA-DRB1	$2.13x10^{-124}$	NA
HLA-DQA1	32,713,112	Gene	HLA-DQA1	$4.99x10^{-31}$	0.082
HLA-DQB1	32,735,222	Gene	HLA-DQB1	$6.45x10^{-117}$	NA
D6S2444	32,825,065	Microsatellite		$2.90x10^{-24}$	0.007
rs2621330	32,889,502	SNP	HLA-DOB	0.023	0.120
rs7749688	32,889,532	SNP	HLA-DOB	1.4x10-5	0.914
rs2071554	32,892,654	SNP	HLA-DOB	$1.72x10^{-19}$	0.025
rs241448	32,904,663	SNP	TAP2	$6.85x10^{-21}$	$5.29x10^{-5}$
rs241447	32,904,729	SNP	TAP2	$1.62x10^{-21}$	$1.45x10^{-4}$
rs4148876	32,904,771	SNP	TAP2	$1.06x10^{-7}$	0.552
rs2228396	32,905,787	SNP	TAP2	0.183	0.311
rs1057149	32,922,920	SNP	TAP1	0.358	0.913
rs1800453	32,922,953	SNP	TAP1	0.014	0.695
rs17885274	32,924,750	SNP	TAP1	0.92	0.294
rs4148880	32,926,752	SNP	TAP1	0.687	0.282
PPP1R2P1-fs	32,955,287	SNP	PPP1R2P1	0.165	0.952
D6S2445	32,965,120	Microsatellite		$2.49x10^{-11}$	0.019
rs1042337	33,012,959	SNP	HLA-DMB	$4.9x10^{-4}$	0.492
rs2071555	33,013,064	SNP	HLA-DMB	$5.3x10^{-3}$	0.846
rs17214044	33,025,389	SNP	HLA-DMA	$2.5x10^{-3}$	0.041
rs17879829	33,025,390	SNP	HLA-DMA	0.352	0.702
rs6926628	33,025,476	SNP	HLA-DMA	$9.1x10^{-4}$	0.026
rs1063478	33,025,522	SNP	HLA-DMA	$5.5x10^{-7}$	0.012
HLA-DPB1	33,151,681	Gene	HLA-DPB1	$2.5x10^{-3}$	$2.21x10^{-5}$
D6S1560	33,662,673	Microsatellite		0.191	0.878
rs2296336	33,744,638	SNP	ITPR3	0.268	0.959
D6S1629	33,895,781	Microsatellite		0.463	0.779
D6S1568	34,163,523	Microsatellite		0.96	0.555
D6S439	35,260,058	Microsatellite		0.074	0.287
D6S291	36,373,494	Microsatellite		0.062	0.635
D6S1576	36,649,673	Microsatellite		0.013	0.699
D6S1548	37,652,125	Microsatellite		0.222	0.570
D6S1641	39,886,845	Microsatellite		0.328	0.658

NA = Not applicable

Supplementary Table 2b | *P*-values for association tests in the first case-control set without and with conditioning on the MHC class II associations.

Locus	Gene	Position, chr 6	Without conditioning	With conditioning on *HLA-DQB1* and *HLA-DRB1*
rs9461102	CMAH	25,205,277	0.41	0.667
rs7774557	CMAH	25,214,642	0.45	0.682
rs9358856	LRRC16	25,534,747	0.49	0.927
rs1012899	LRRC16	25,713,070	3.8×10^{-5}	0.504
rs11754288	SLC17A4	25,884,928	0.045	0.045
rs1165196	SLC17A1	25,921,129	6.9×10^{-3}	0.101
rs2230653	HIST1H1C	26,164,583	1	0.801
rs1045537	HFE	26,204,727	3.3×10^{-7}	0.482
rs198845	HIST1H1T	26,215,769	0.043	0.844
rs2051542	HIST1H1T	26,216,147	0.16	0.661
rs198844	HIST1H1T	26,216,261	0.62	0.334
rs7745238	BTN2A3	26,531,296	0.32	0.804
rs10946829	BTN2A3	26,534,466	0.10	0.832
rs2893848	BTN2A3	26,538,960	0.41	0.798
rs3736781	BTN1A1	26,613,341	2.7×10^{-5}	0.298
rs2235233	POM121L2	27,387,831	0.11	0.870
rs9357037	ZNF204	27,435,328	0.076	0.779
rs10807020	Q8NAI6	27,464,881	0.014	0.624
rs2076305	Q9UJN8	27,483,590	0.049	5.85×10^{-3}
rs1883216	ZNF184	27,533,164	0.60	0.039
rs200484	HIST1H2BL	27,883,653	1.8×10^{-8}	0.039
rs9380030	OR2B6	28,033,806	1	0.340
rs203877	ZNF165	28,156,603	8.9×10^{-12}	0.830
rs1150674	intergenic	28,242,347	3.3×10^{-5}	0.315
rs1150684	intergenic	28,264,292	0.22	0.726
rs12000	C6orf194	28,335,415	3.7×10^{-3}	0.166
rs1635	C6orf194	28,335,583	0.12	0.050
rs1679709	C6orf194	28,336,321	1.1×10^{-8}	8.53×10^{-3}
rs3800325	PGBD1	28,372,671	4.7×10^{-3}	0.827
rs1997660	PGBD1	28,377,642	1.8×10^{-3}	0.124
rs853684	ZNF323	28,402,529	2.5×10^{-5}	0.446
rs733743	ZKSCAN3	28,435,350	0.65	0.421
rs1361385	ZSCAN12	28,466,299	6.1×10^{-3}	0.724
rs406113	GPX6	28,591,461	0.060	0.547
rs1233627	intergenic	28,859,706	6.3×10^{-4}	0.255
rs209165	intergenic	28,937,465	0.55	0.114
rs2071790	C6orf100	29,019,781	1.0×10^{-9}	0.723
rs6456880	ZNF311	29,071,227	0.33	0.329
rs3131085	intergenic	29,152,680	3.5×10^{-4}	0.013
rs3116856	OR2J2	29,249,828	3.7×10^{-16}	0.719
rs3116817	OR2J4P	29,257,540	6.6×10^{-16}	0.696
rs3116818	OR2J4P	29,257,584	5.8×10^{-7}	0.847

rs3117328	LOC651503	29,338,556	$6.3x10^{-5}$	0.088
rs3130827	LOC651503	29,338,662	$2.8x10^{-6}$	0.162
rs9257694	OR5U1	29,382,465	$1.6x10^{-7}$	0.147
rs9257770	OR11A1	29,431,817	1	0.019
rs3749971	OR12D3	29,450,754	$4.4x10^{-5}$	0.030
rs3128853	O12D2	29,472,766	$9.6x10^{-6}$	0.700
rs2073154	O12D2	29,472,794	$2.1x10^{-11}$	0.528
rs2073151	O12D2	29,472,930	$1.8x10^{-11}$	0.473
rs2074469	OR10C1	29,515,949	0.036	0.199
rs2074468	OR10C1	29,516,249	$1.4x10^{-4}$	0.358
rs2074466	OR10C1	29,516,292	$2.5x10^{-4}$	0.582
rs3131020	intergenic	29,583,881	$2.9x10^{-11}$	0.38
rs1233478	intergenic	29,585,800	$1.14x10^{-17}$	0.62
rs389419	OR2I1	29,629,424	$2.57x10^{-21}$	0.001
rs2076487	UBD	29,631,838	0.98	0.201
rs2076486	UBD	29,631,851	0.88	0.213
rs2076484	UBD	29,631,982	0.78	0.515
rs740884	GABR1	29,682,610	0.61	0.410
rs2535241	ZFP57	29,748,764	1	0.093
rs1611209	LOC554223	29,867,902	$3.7x10^{-3}$	$2.70x10^{-3}$
rs1610645	LOC554223	29,867,975	0.042	0.013
rs885937	LOC554223	29,877,042	0.032	0.029
HLA-A (two-digit)	HLA-A	30,018,305	$1.6x10^{-14}$	$1.67x10^{-10}$
rs6904029	HCG9	30,051,046	$8.4x10^{-8}$	0.135
rs3765604	HLA-G	30,084,003	$2.8x10^{-3}$	0.774
rs356969	HLA-J	30,085,124	$2.7x10^{-6}$	0.678
rs10484549	C6orf12	30,134,269	$1.3x10^{-5}$	0.168
rs7770557	ZNRD1	30,137,088	$1.1x10^{-4}$	0.942
rs2074479	RNF39	30,148,988	0.018	0.233
rs2023472	TRIM31	30,183,843	$2.9x10^{-4}$	0.726
rs3734838	TRIM31	30,188,210	$6.8x10^{-5}$	0.143
rs757262	TRIM40	30,222,934	0.50	0.842
rs757259	TRIM40	30,223,521	0.011	0.772
rs12212092	TRIM10	30,236,421	$4.4x10^{-8}$	0.601
rs929156	TRIM15	30,247,678	$4.6x10^{-3}$	0.421
rs2023477	LOC441140	30,337,442	0.38	0.729
rs2516690/rs6986	RPP21	30,421,319	$2.4x10^{-3}$	0.818
rs978009	intergenic	30,490,558	$2.8x10^{-4}$	0.183
rs2105960	RANP1	30,561,768	0.48	0.761
rs9262138	DHX16	30,735,846	$6.6x10^{-3}$	0.270
rs3130645	MDC1	30,780,321	0.014	0.039
rs9262152	MDC1	30,788,895	$1.9x10^{-9}$	0.873
rs2517560	MDC1	30,788,947	1	0.014
rs886424	C6orf214	30,889,981	$4.3x10^{-8}$	0.591
rs2894046	C6orf214	30,890,084	$5.8x10^{-4}$	0.845
rs886423	C6orf214	30,890,184	$2.6x10^{-28}$	0.479
rs2394412	C6orf214	30,890,214	$1.1x10^{-3}$	0.935

rs9295924	C6orf214	30,890,340	$2.0x10^{-7}$	0.576
rs1264303	GTF2H4	30,990,492	$4.3x10^{-3}$	0.176
rs2074506	GTF2H4	30,998,462	0.031	0.060
rs4678	GTF2H4	31,001,920	$7.7x10^{-20}$	0.212
rs3131787	SFTPG	31,007,503	$2.8x10^{-3}$	0.633
rs3131784	SFTPG	31,011,927	0.46	0.639
rs3132580	DPCR1	31,028,103	$1.6x10^{-30}$	0.318
rs2240804	DPCR1	31,028,869	0.36	0.182
rs2844697	intergenic	31,040,288	$8.71x10^{-51}$	0.094
rs3095150	intergenic	31,040,511	$1.5x10^{-22}$	0.652
rs2532924	intergenic	31,040,661	$7.1x10^{-13}$	0.519
rs3095089	intergenic	31,041,773	$4.2x10^{-5}$	0.370
rs2254847	intergenic	31,041,827	$5.5x10^{-11}$	0.881
rs3131933	intergenic	31,041,843	$1.0x10^{-9}$	0.085
rs1634730	C6orf205	31,062,224	0.25	0.968
rs3094672	intergenic	31,101,356	$9.9x10^{-30}$	0.144
rs2523898	intergenic	31,101,512	0.028	0.041
rs4713420	intergenic	31,101,546	$1.1x10^{-18}$	0.532
rs2233974	C6orf15	31,187,995	$3.7x10^{-37}$	0.520
rs3815087	PSORS1C1	31,201,566	0.025	0.237
rs130067	CCHCR1	31,226,490	0.043	0.237
rs130076	CCHCR1	31,230,461	$6.5x10^{-13}$	0.029
rs9263871	HCG27	31,278,507	$1.8x10^{-7}$	0.528
HLA-B (two-digit)	HLA-B	31,429,628	$3.59x10^{-42}$	$1.74x10^{-7}$
rs2308655	HLA-B	31,430,282	$7.3x10^{-14}$	$8.72x10^{-3}$
rs1051488	HLA-B	31,430,890	$3.3x10^{-8}$	0.309
rs3130639	intergenic	31,595,299	$1.2x10^{-15}$	0.161
rs2516489	intergenic	31,596,017	$1.1x10^{-5}$	0.325
rs1800750	TNFA/LTA	31,650,942	$6.3x10^{-16}$	$1.08x10^{-3}$
rs2736182	AIF1	31,691,291	1	0.186
rs9267522	BAT2	31,711,749	$3.55x10^{-100}$	0.777
rs3132453	BAT2	31,712,023	1	0.363
rs805295	LY6G6D	31,783,276	$8.0x10^{-4}$	0.346
rs2242653	LY6G6D	31,783,744	0.018	0.757
rs3749952	LY6G6D	31,791,136	1	0.166
rs1802127	MSH5	31,837,904	1	0.416
rs707936	G7C	31,841,629	$1.9x10^{-5}$	0.137
rs2227956	HSPA1L	31,886,251	$2.34x10^{-114}$	0.518
rs644827	SLC44A4	31,946,420	$1.2x10^{-3}$	0.607
rs2242665	SLC44A4	31,947,288	$8.4x10^{-4}$	0.555
rs2075798	SLC44A4	31,954,720	0.032	0.499
rs7887	EHMT2	31,972,526	0.91	0.076
rs9332739	C2	32,011,783	$2.0x10^{-9}$	0.526
rs4151651	CFB	32,023,593	$5.3x10^{-3}$	$5.35x10^{-3}$
rs438999	SKIV2L	32,036,285	$1.8x10^{-22}$	0.852
rs437179	SKIV2L	32,036,993	0.14	0.482
rs2269429	TNXB/CREBL1	32,137,161	$8.5x10^{-3}$	0.226

rs185819	TNXB/CREBL1	32,158,045	$6.5x10^{-9}$	0.317
rs1150752	TNXB/CREBL1	32,172,704	$1.08x10^{-72}$	0.506
rs2070600	AGER	32,259,421	4.4x10-3	0.207
rs7775397	C6orf10	32,369,230	$8.40x10^{-85}$	0.381
rs3749966	C6orf10	32,369,485	$8.0x10^{-22}$	0.067
rs560505	C6orf10	32,369,749	$4.8x10^{-27}$	0.735
rs1003878	C6orf10	32,407,800	$1.1x10^{-36}$	0.322
rs1265754	C6orf10	32,411,670	$1.26x10^{-60}$	0.042
rs1033500	C6orf10	32,415,360	$3.7x10^{-27}$	0.976
rs9268368	C6orf10	32,441,933	$6.2x10^{-22}$	0.627
rs9268384	C6orf10	32,444,564	$9.3x10^{-27}$	0.976
rs3129941	C6orf10	32,445,664	$6.10x10^{-192}$	0.548
rs2076530	BTNL2	32,471,794	$2.8x10^{-20}$	0.330
rs2076523	BTNL2	32,478,813	$9.94x10^{-43}$	0.129
HLA-DRB1	HLA-DRB1	32,654,524	$3.99x10^{-300}$	N/A
HLA-DQB1	HLA-DQB1	32,735,222	$<10^{-300}$	N/A
rs1573649	HLA-DQB2	32,839,236	$2.92x10^{-54}$	0.604
rs2621330	HLA-DOB	32,889,502	$9.1x10^{-9}$	0.051
rs2070121	HLA-DOB	32,889,532	$1.7x10^{-7}$	0.087
rs2071554	HLA-DOB	32,892,654	$3.55x10^{-70}$	0.158
rs241448	TAP2	32,904,663	$3.0x10^{-26}$	0.074
rs241447	TAP2	32,904,729	$1.1x10^{-5}$	0.215
rs1800453/rs1135216	TAP1	32,922,953	0.11	0.671
rs4148880/rs1057141	TAP1	32,926,752	0.099	0.901
rs9276814/rs17587	PSMB9	32,933,068	$4.2x10^{-3}$	0.749
rs1042337	HLA-DMB	33,012,959	$2.2x10^{-4}$	0.033
rs2071555	HLA-DMB	33,013,064	1	0.647
rs1063478	HLA-DMA	33,025,522	$1.7x10^{-6}$	0.421
rs2308935/rs1126769	HLA-DPA1	33,144,413	0.033	0.053
rs2281390	HLA-DPA2	33,167,647	$1.0x10^{-11}$	$2.50x10^{-3}$
rs3128917	HLA-DPA2	33,167,974	$4.6x10^{-12}$	0.906
rs2281388	HLA-DPA2	33,168,096	1	0.268
rs7764491	HLA-DPA2	33,168,818	0.014	0.323
rs3117035	HLA-DPB2	33,194,227	0.56	0.126
rs466384/rs14398	WDR46	33,362,643	0.93	0.723
rs3130257	WDR46	33,364,449	$2.4x10^{-4}$	0.916
rs2071888	TAPBP	33,380,833	$1.0x10^{-10}$	0.018
rs3130100	ZBTB22	33,391,744	$4.0x10^{-9}$	0.024
rs3130267	MYL8P	33,414,772	$4.1x10^{-10}$	$4.60x10^{-3}$
rs211449	LYPLA2	33,441,894	$6.4x10^{-3}$	0.143
rs2296336	ITPR3	33,744,638	0.91	0.386
rs2281820	MLN	33,876,875	0.88	0.405
rs1150781	C6orf1	34,322,300	0.66	0.983
rs15922	TAF11	34,958,804	0.46	0.150

Supplementary Table 3a | Assessing the association of the alleles of the test locus using conventional grouping strategies for the confounding effects of the class II loci. P_r: *P* value for addition of the test locus to class II genotypes grouped according to risk estimates published by Koeleman *et al.* [33] (categorised as high/medium/low/unclassified) in a white ethnic group of European descent. P_{34x}: *P* value for addition of the test locus to *HLA-DRB1* genotypes classified as HLA-DRB1*03, *04, *X where X is any non-HLA-DRB1*03 or 04 allele but includes HLA-DRB1*0403. P_1: *P* value for addition of the test locus to class II genotypes where genotypes below 0.01 frequency are grouped together. P_5: *P* value for addition of the test locus to class II genotypes where genotypes below 0.05 frequency are grouped together.

Test locus	Number of families typed at all three loci	P_r	P_{34x}	P_1	P_5
HLA-B	736	3.95×10^{-11}	7.68×10^{-10}	6.20×10^{-7}	2.14×10^{-16}
rs241448	660	2.95×10^{-9}	0.1101	1.69×10^{-4}	3.15×10^{-6}
rs241447	667	1.35×10^{-8}	0.2640	3.05×10^{-4}	5.23×10^{-6}
HLA-DPB1	395	9.14×10^{-7}	5.13×10^{-5}	1.25×10^{-7}	2.51×10^{-7}
HLA-Bw4/6	742	2.13×10^{-6}	1.53×10^{-7}	2.47×10^{-5}	5.14×10^{-6}
HLA-C	649	3.78×10^{-5}	0.2731	0.1163	1.84×10^{-5}
D6S2444	306	1.22×10^{-4}	2.74×10^{-10}	0.0056	6.58×10^{-12}
rs2071554	678	2.68×10^{-4}	2.07×10^{-8}	0.1150	7.69×10^{-10}
MICB	532	3.60×10^{-4}	0.0123	1.90×10^{-4}	2.31×10^{-5}
rs1800750	697	0.0029	0.0126	0.0223	8.29×10^{-4}
MICA	528	0.0029	0.0031	0.0358	1.25×10^{-4}
rs2844697	711	0.0029	0.0039	0.5343	3.25×10^{-4}
HLA-A	640	0.0075	1.30×10^{-4}	0.0055	4.09×10^{-5}
D6S258	298	0.0125	0.0027	1.68×10^{-8}	4.79×10^{-8}
rs4148876	652	0.0329	0.1196	0.9218	6.27×10^{-4}
rs2076523	597	0.1525	0.6133	0.1214	1.01×10^{-4}

Comparison of these frequency and risk grouping strategies in our families (Supplementary Results) revealed that the *P*-value for the test locus, conditional on the class II genotypes, was, at some loci, dependent on the method of grouping of the class II loci adopted *e.g.* the *P*-value for *HLA-B* association varied by nine orders of magnitude between the model grouping genotypes below 0.05 compared to that grouping at 0.01 ($P = 6.20\times10^{-7}$ - 2.14×10^{-16}). Similarly *D6S2444*, ranged from $P = 1\times10^{-4}$ to 7×10^{-12} for the risk-based and frequency-based methods.

Supplementary Table 3b | Assessing the effects of different number of terminal leaf nodes of the tree model of the MHC class II loci in the family dataset. *P* values are given for the association of the test locus with disease, having accounted for *HLA-DRB1* and *HLA-DQB1* genotype associations using a model that partitions them into 22 groups (P_{22}) 18 groups (P_{18}) 16 groups (P_{16}) and 12 groups (P_{12}).

Test locus	Number of families typed at all 3 loci	P_{22}	P_{18}	P_{16}	P_{12}
HLA-B	736	3.32×10^{-7}	4.69×10^{-7}	4.19×10^{-7}	1.15×10^{-6}
rs241448	660	1.48×10^{-4}	5.12×10^{-5}	5.28×10^{-5}	5.32×10^{-5}
rs241447	667	5.15×10^{-4}	1.54×10^{-4}	1.45×10^{-4}	1.74×10^{-4}
HLA-DPB1	395	3.41×10^{-5}	2.41×10^{-5}	2.21×10^{-5}	1.25×10^{-5}
HLA-Bw4/6	742	8.66×10^{-6}	8.08×10^{-6}	6.57×10^{-6}	1.61×10^{-6}
HLA-C	649	0.4018	0.2882	0.2858	0.5042
D6S2444	306	4.57×10^{-4}	0.00133	0.0073	3.14×10^{-4}
rs2071554	678	0.0303	0.0166	0.0245	0.0142
MICB	532	0.0328	0.0246	0.0276	0.0319
rs1800750	697	0.0337	0.0382	0.0378	0.0306
MICA	528	0.1020	0.0932	0.0810	5.28×10^{-4}
rs2844697	711	0.1821	0.2157	0.2101	0.1383
HLA-A	640	0.0875	0.0644	0.0675	0.0660
D6S258	298	0.0509	0.0597	0.0611	0.0270
rs4148876	652	0.6278	0.5548	0.5522	0.2207
rs2076523	597	0.2832	0.4221	0.4226	0.1870

Supplementary Table 4a | Allele frequencies, odds ratios with 95% confidence intervals for *HLA-A* in the second case-control set of 1,051 cases and 1,125 controls. Allele HLA-A*02 is used as reference as it was the most common. *HLA-A* was associated independently of *HLA-DRB1* and *HLA-DQB1* in the second case-control set, $P = 1.77 \times 10^{-5}$.

HLA-A allele	British cases, n(%)	British controls n(%)	OR [95% CI] without conditioning on *HLA-DRB1/HLA-DQB1*	OR [95% CI] conditioning on *HLA-DRB1/HLA-DQB1*
*24	241 (11.48%)	185 (8.22%)	1.19 [0.93-1.51]	1.42 [0.96-2.09][a]
*30	69 (3.29%)	53 (2.36%)	1.23 [0.82-1.84]	1.38 [0.74-2.57]
*29	64 (3.05%)	76 (3.38%)	0.86 [0.59-1.26]	1.23 [0.68-2.24]
*03	269 (12.81%)	326 (14.49%)	0.78 [0.63-0.97]	1.13 [0.80-1.58]
*25	28 (1.33%)	42 (1.87%)	0.60 [0.35-1.03]	1.04 [0.43-2.55]
*74	1 (0.05%)	1 (0.04%)	1.22 [0.06-19.55]	1.02 [0.01-110.7]
*02	651 (31.00%)	644 (28.62%)	1.00 [reference]	1.00 [reference]
*68	63 (3.00%)	61 (2.71%)	0.90 [0.61-1.35]	0.99 [0.50-1.95]
*31	46 (2.19%)	56 (2.49%)	0.82 [0.52-1.27]	0.94 [0.47-1.91]
*26	27 (1.29%)	55 (2.44%)	0.40 [0.24-0.67]	0.86 [0.40-1.85]
*66	3 (0.14%)	7 (0.31%)	0.29 [0.07-1.23]	0.80 [0.15-4.41]
*23	18 (0.86%)	42 (1.87%)	0.47 [0.26-0.85]	0.71 [0.29-1.74]
*01	468 (22.29%)	454 (20.18%)	1.01 [0.84-1.21]	0.56 [0.42-0.75]
*11	93 (4.43%)	147 (6.53%)	0.61 [0.45-0.83]	0.52 [0.32-0.84]
*32	46 (2.19%)	85 (3.78%)	0.52 [0.35-0.78]	0.37 [0.21-0.67]
*33	13 (0.62%)	14 (0.62%)	0.74 [0.33-1.65]	0.24 [0.08-0.74]

(a) Note that although HLA-A*24 is not significantly different to HLA-A*02, it is more strongly associated with T1D than HLA-A*01, *11, *32 and *33.

Supplementary Table 4b | T1D association of the *HLA-A* alleles conditioned on the MHC class II genes and *HLA-B* in the families and the first case-control set.

HLA-A allele	Allele frequency, n (%)		Families, RR [95% CI]	Case-control set, OR [95% CI]	
	Cases	Controls	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1, HLA-DRB1* and *HLA-B*
*24	331 (10.9)	265 (7.5)	1.20[0.89-1.61]	1.66[1.22-2.24]	1.54[1.11-2.16]
*03	380 (12.6)	493 (14.0)	0.84[0.65-1.10]	1.16[0.88-1.52]	1.17[0.87-1.58]
*02	1,021 (33.7)	1,034 (29.4)	1.00 [reference]	1.00 [reference]	1.00 [reference]
*30	102 (3.4)	82 (2.3)	1.03[0.62-1.71]	1.28[0.78-2.10]	0.89[0.50-1.57]
*29	93 (3.1)	161 (4.6)	0.79[0.52-1.19]	0.83[0.54-1.28]	0.85[0.53-1.35]
*68	78 (2.6)	136 (3.9)	0.81[0.52-1.27]	0.82[0.52-1.30]	0.84[0.52-1.36]
*32	80 (2.6)	130 (3.7)	0.50[0.30-0.84]	0.64[0.40-1.01]	0.64[0.39-1.04]
*33	23 (0.76)	30 (0.85)	0.93[0.40-2.13]	0.58[0.25-1.39]	0.63[0.25-1.60]
*26	38 (1.3)	85 (2.4)	0.86[0.50-1.50]	0.49[0.27-0.88]	0.63[0.34-1.16]
*25	39 (1.3)	64 (1.8)	0.55[0.31-0.95]	0.87[0.46-1.67]	0.62[0.31-1.23]
*01	648 (21.4)	638 (18.1)	0.86[0.69-1.07]	0.67[0.53-0.84]	0.58[0.43-0.79]
*23	24 (0.8)	46 (1.3)	0.77[0.40-1.50]	0.57[0.26-1.26]	0.51[0.22-1.17]
*11	99 (3.3)	229 (6.5)	0.77[0.52-1.15]	0.44[0.29-0.66]	0.47[0.30-0.73]
*31	62 (2.1)	106 (3.0)	0.76[0.49-1.20]	0.36[0.22-0.59]	0.41[0.24-0.69]

Relative risks, RR; odds ratios, OR; confidence interval, CI

Alleles are ordered by risk in the case-control set (once *HLA-DQB1*, *HLA-DRB1* and *HLA-B* have been accounted for). The most common allele, HLA-A*02, gives the tightest 95% CIs so is used as reference. Results are given for the families (736) and the first case-control set (1,451 T1D patients and 1,628 controls) that were successfully typed at all four classical loci). Allele frequencies in the families are shown in Supplementary Table 1.

Supplementary Table 5a | Association of the *HLA-B* alleles with T1D. HLA-B*08 is used as reference.

HLA-B allele	Allele frequency, n (%)		Families, RR [95% CI]	Case-control set, OR [95% CI]	
	Cases	Controls	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1, HLA-DRB1* and *HLA-A*
*49	38 (1.3)	34 (1.0)	1.07[0.58-1.98]	3.23 [1.39-7.53]	2.40 [0.97-5.94]
*50	42 (1.4)	35 (1.1)	1.73[0.83-3.59]	2.31 [1.10-4.85]	1.66 [0.76-3.60]
*39	143 (4.7)	79 (2.4)	2.82[1.80-4.41]	2.53 [1.57-4.07]	1.55 [0.92-2.62]
*18	202 (6.7)	128 (3.8)	1.41[1.00-1.98]	1.92 [1.27-2.90]	1.57 [0.96-2.58]
*13	43 (1.4)	56 (1.7)	0.93[0.69-1.20]	2.03 [1.03-4.03]	1.51 [0.72-3.20]
*41	11 (0.36)	23 (0.69)	0.49[0.22-1.07]	1.52 [0.49-4.72]	1.02 [0.27-3.82]
*08	788 (26.1)	461 (13.8)	1.00[reference]	1.00 [reference]	1.00 [reference]
*55	37 (1.2)	71 (2.1)	0.58[0.32-1.06]	1.35 [0.68-2.67]	0.96 [0.46-2.01]
*07	249 (8.2)	465 (13.9)	0.91[0.69-1.20]	1.32 [0.94-1.84]	0.89 [0.60-1.33]
*44	344 (11.4)	567 (17.0)	0.79[0.60-1.04]	1.05 [0.79-1.39]	0.81 [0.57-1.15]
*51	78 (2.6)	109 (3.3)	0.76[0.49-1.20]	0.98 [0.57-1.68]	0.75 [0.41-1.36]
*53	3 (0.10)	9 (0.27)	0.38[0.06-2.58]	1.26 [0.17-9.14]	0.72 [0.09-5.75]
*15	388 (12.8)	267 (8.0)	0.98[0.75-1.30]	1.03 [0.76-1.39]	0.70 [0.49-1.01]
*35	130 (4.3)	197 (5.9)	0.79[0.56-1.12]	0.86 [0.58-1.28]	0.69 [0.44-1.08]
*40	257 (8.5)	232 (6.9)	0.93[0.70-1.24]	0.91 [0.66-1.25]	0.68 [0.46-1.01]
*52	3 (0.10)	20 (0.60)	0.14[0.01-1.61]	0.73 [0.11-4.95]	0.68 [0.09-5.10]
*45	9 (0.30)	26 (0.78)	1.92[0.66-5.59]	0.68 [0.24-1.97]	0.59 [0.19-1.83]
*37	21 (0.69)	51 (1.5)	0.82[0.36-1.88]	0.70 [0.30-1.64]	0.57 [0.23-1.43]
*14	54 (1.8)	159 (4.8)	0.92[0.61-1.41]	0.70 [0.42-1.16]	0.54 [0.30-0.96]
*47	9 (0.30)	8 (0.24)	0.86[0.46-1.61]	0.87 [0.16-4.70]	0.54 [0.09-3.08]
*56	14 (0.46)	16 (0.48)	1.14[0.28-4.60]	0.70 [0.23-2.08]	0.47 [0.15-1.53]
*58	11 (0.36)	19 (0.57)	1.36[0.48-3.83]	0.55 [0.19-1.57]	0.46 [0.15-1.43]
*57	26 (0.86)	143 (4.3)	0.60[0.30-1.20]	0.53 [0.27-1.04]	0.42 [0.21-0.86]
*27	113 (3.7)	145 (4.3)	0.81[0.56-1.17]	0.55 [0.36-0.82]	0.41 [0.26-0.66]
*38	10 (0.33)	26 (0.78)	0.33[0.14-0.77]	0.51 [0.14-1.77]	0.36 [0.10-1.39]

Supplementary Table 5b | Mean age of T1D patients at diagnosis (years). Both HLA-B*39 ($P = 0.0021$ for 1,497 British cases and $P = 0.0022$ for one affected offspring selected at random from each of 733 families) and HLA-A*24 ($P = 0.01$ for 1,927 British cases and $P = 0.0016$ for one affected offspring selected at random from 637 families) were found to be associated with a younger age-at-diagnosis of T1D.

HLA-B or *HLA-A* genotype	Families, one affected child per family	Case-control set, patients
HLA-B*39/39	2.4	6.0
HLA-B*39/X	8.2	6.4
HLA-B*X/X	10.9	7.4
HLA-A*24/24	4.9	6.9
HLA-A*24/Y	9.6	6.6
HLA-A*Y/Y	11.5	7.5

X – any *HLA-B* allele other than HLA-B*39; Y – any *HLA-A* allele other than HLA A*24

Supplementary Table 5c | Frequency distribution and ORs of HLA-B*39 and HLA-A*24, by age-at-diagnosis of T1D, from up to 1,927 cases and up to 733 families, using just one affected offspring chosen at random. Age is categorised into centiles (25th/50th/75th/100th), which corresponds to 0-4 yr / 4-7 yr / 7-10 yr / 10+ yr in the isolated cases and 0-5 yr / 5-10 yr / 10-14 yr / 14+ yr in the affected offspring. Note that the distributions have not been corrected for class II effects.

All British Cases *			Families **		
Centile year groups	Frequency of HLA-B*39, n(%)	Frequency of HLA-A*24, n(%)	Centile year groups	Frequency of HLA-B*39, n(%)	Frequency of HLA-A*24, n(%)
0-4 yrs	57 (6.5%)	105 (11.9%)	0-5 yrs	25 (6.7%)	47 (13.8%)
4-7 yrs	47 (4.0%)	100 (13.6%)	5-10 yrs	19 (4.4%)	44 (14.3%)
7-10 yrs	37 (4.1%)	63 (9.57%)	10-14 yrs	10 (3.0%)	26 (8.3%)
10+ yrs	2 (2.4%)	63 (8.36%)	14+ yrs	8 (2.3%)	27 (8.5%)

Supplementary Table 5d | Association of the HLA-B*39 allele subtypes in T1D.

	Allele Frequency n(%)		Families, RR (95% CI)	Case-control set, OR (95% CI)	
HLA-B allele	Cases	Controls	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1, HLA-DRB1* and *HLA-A*
*44	344 (11.38)	567 (16.95)	1.00 [reference]	1.00 [reference]	1.00 [reference]
*3901	43 (1.44)	34 (1.04)	2.34 [0.86-6.37]	1.95 [0.94-4.07]	2.06 [0.97-4.37]
*3906	87 (2.90)	40 (1.22)	5.62 [2.13-14.84]	2.71 [1.47-4.99]	1.83 [0.97-3.45]

We tested the four-digit subtypes of HLA-B*39 as they are split into approximately equally frequent subtypes (Supplementary Table 1). The two most common subtypes of HLA-B39 are given. Although allele HLA-B*3906 conferred somewhat higher RR than HLA-B*3901 in the families, their 95% CIs overlapped, indicating the need for even larger datasets in future analyses. However, it is likely that both subtypes of HLA-B*39 contribute to HLA-B*39 susceptibility.

Supplementary Table 6a | The top 20 most associated SNPs from the WTCCC scan without conditioning on the MHC class II loci. As expected, all 20 SNPs were located in the MHC class II region.

Locus	Position	*P* value
rs9273363	32734250	4.29×10^{-298}
rs9270986	32682038	1.22×10^{-151}
rs3135377	32493377	2.52×10^{-144}
rs9272346	32712350	3.06×10^{-138}
rs9272723	32717405	1.79×10^{-133}
rs3916765	32793528	2.84×10^{-131}
rs9275523	32782972	9.30×10^{-131}
rs9275418	32778222	1.69×10^{-127}
rs3132959	32406920	7.36×10^{-125}
rs3129932	32444105	1.10×10^{-124}
rs910049	32423705	2.22×10^{-121}
rs3129768	32703061	7.28×10^{-110}
rs3129934	32444165	9.21×10^{-110}
rs3129900	32413957	5.34×10^{-109}
rs9469220	32766288	2.79×10^{-101}
rs3131294	32288124	6.05×10^{-90}
rs9268230	32395545	1.09×10^{-89}
rs9275134	32758590	9.49×10^{-86}
rs2856688	32762618	1.70×10^{-85}
rs6936863	32792007	2.00×10^{-83}

Supplementary Table 6b | Association analysis of the eight most associated SNPs from the WTCCC scan after conditioning on the MHC class II loci in both the original study (1,281 cases and 860 controls) and the follow-up study of 2,484 cases and 2,019 controls.

* SNP	HLA Class region	Physical position / bp	Unconditioned *P* in original case-control set	*P* conditioned on *HLA-DRB1* and *HLA-DQB1* in 1,281 cases, 860 controls	*P* conditioned on *HLA-DRB1* and *HLA-DQB1* 2,484 cases, 2,019 controls	*P* conditioned on *HLA-DRB1, HLA-DQB1, HLA-B* in 2,484 cases, 2,019 controls
rs3130531	I	31314595	0.0056	6.74×10^{-7}	5.08×10^{-7}	0.1590
†rs7770592	I	29503726	0.1328	3.82×10^{-6}	1.38×10^{-4}	2.24×10^{-4}
rs2240063	I	31222724	0.0029	1.50×10^{-5}	4.28×10^{-4}	0.7885
rs9268541	II	32492505	7.96×10^{-10}	2.16×10^{-5}	4.18×10^{-5}	0.0029
rs9263702	I	31202174	8.66×10^{-10}	2.47×10^{-5}	1.61×10^{-5}	0.2351
†rs1233367	I	29730199	0.6062	5.44×10^{-5}	3.73×10^{-4}	0.0011
†rs9268831	II	32535726	2.81×10^{-26}	9.68×10^{-5}	6.95×10^{-8}	5.44×10^{-6}

* rs9272346 failed assay design

† These loci were also tested for association independent to *HLA-DRB1*, *HLA-DQB1* and *HLA-A*. rs9268831 was found to have an independent T1D association ($P = 4.39\times10^{-6}$) whereas rs1233367 and rs7770592 did not ($P = 0.1021$ and 0.0106 respectively).

Supplementary Table 6c | Association of HLA-B alleles in the follow-up to the WTCCC study comprising up to 2,484 cases and 2,019 controls. *HLA-B* was associated with T1D after *HLA-DRB1* and *HLA-DQB1* were accounted for in the model, $P = 3.80 \times 10^{-17}$.

HLA-B allele	Allele frequency, n (%)		Case-control set, OR [95% CI]	
	Cases	Controls	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1, HLA-DRB1* and *HLA-A*
*49	61 (1.22)	65 (1.16)	1.56 [0.84-2.89]	1.93 [0.98-3.77]
*50	63 (1.26)	54 (0.96)	1.88 [1.05-3.36]	2.01 [1.09-3.70]
*18	341 (6.84)	197 (3.52)	1.92 [1.39-2.67]	2.07 [1.43-3.00]
*39	229 (4.60)	113 (2.02)	2.84 [1.96-4.14]	2.57 [1.71-3.85]
*13	78 (1.57)	95 (1.70)	1.88 [1.16-3.07]	2.19 [1.28-3.74]
*41	21 (0.42)	33 (0.59)	1.39 [0.61-3.17]	1.08 [0.43-2.67]
*08	1314 (26.37)	776 (13.87)	0.94 [0.76-1.16]	1.20 [0.92-1.58]
*55	60 (1.20)	113 (2.02)	1.07 [0.63-1.82]	1.02 [0.58-1.79]
*07	391 (7.85)	837 (14.96)	0.93 [0.72-1.19]	0.81 [0.61-1.07]
*44	603 (12.10)	971 (17.36)	1.00 [reference]	1.00 [reference]
*51	128 (2.57)	188 (3.36)	0.97 [0.65-1.44]	0.98 [0.64-1.49]
*15	610 (12.24)	421 (7.52)	0.96 [0.74-1.22]	0.87 [0.67-1.14]
*35	219 (4.40)	351 (6.23)	0.77 [0.57-1.03]	0.77 [0.55-1.06]
*40	403 (8.09)	373 (6.67)	0.96 [0.74-1.25]	0.96 [0.72-1.28]
*45	15 (0.30)	41 (0.73)	0.47 [0.19-1.15]	0.49 [0.20-1.23]
*37	32 (0.64)	91 (1.63)	0.55 [0.29-1.05]	0.64 [0.31-1.30]
*14	83 (1.67)	247 (4.41)	0.59 [0.40-0.88]	0.65 [0.42-0.99]
*57	44 (0.88)	229 (4.09)	0.40 [0.24-0.67]	0.44 [0.25-0.75]
*27	185 (3.71)	237 (4.24)	0.62 [0.45-0.87]	0.61 [0.43-0.87]
*38	24 (0.48)	49 (0.88)	1.15 [0.50-2.63]	0.86 [0.34-2.17]

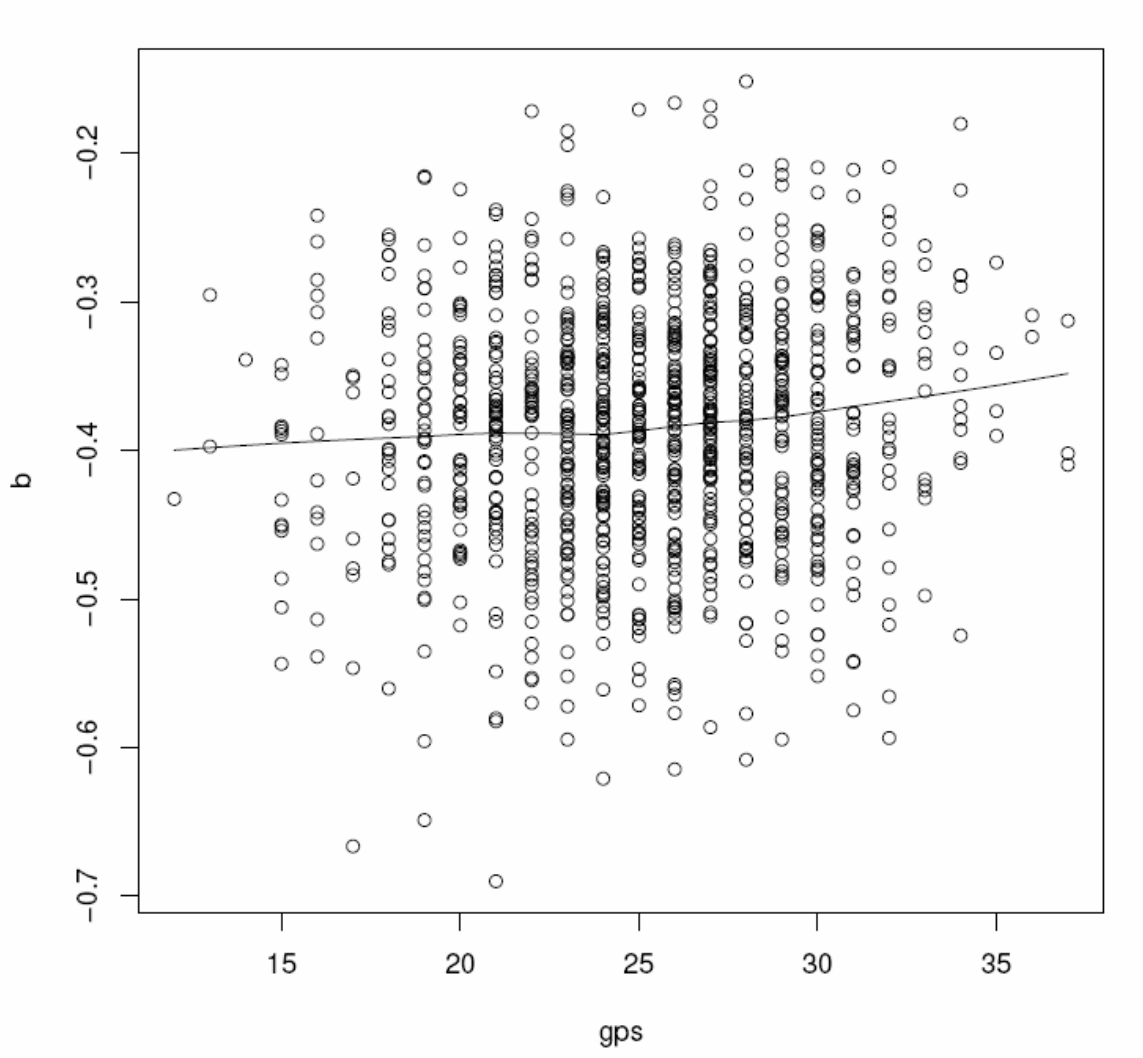
Supplementary Table 6d | Association of *HLA-A* alleles in the follow-up to the WTCCC study comprising up to 2,484 cases and 2,019 controls. *HLA-A* was associated with T1D after HLA-DRB1 and HLA-DQB1 were accounted for in the model, $P = 4.59 \times 10^{-15}$.

HLA-A allele	Allele frequency, n (%)		Case-control set, OR [95% CI]	
	Cases	Controls	Conditioning on *HLA-DQB1* and *HLA-DRB1*	Conditioning on *HLA-DQB1, HLA-DRB1* and *HLA-B*
*24	599 (11.15)	458 (7.83)	1.54 [1.23-1.93]	1.44 [1.12-1.86]
*03	673 (12.53)	828 (14.16)	1.11 [0.91-1.36]	1.22 [0.97-1.52]
*02	1752 (32.61)	1702 (29.11)	1.00 [reference]	1.00 [reference]
*30	173 (3.22)	137 (2.34)	1.32 [0.92-1.90]	0.80 [0.51-1.23]
*29	168 (3.13)	244 (4.17)	0.93 [0.67-1.28]	1.00 [0.70-1.44]
*68	149 (2.77)	203 (3.47)	0.86 [0.61-1.23]	0.91 [0.62-1.33]
*32	127 (2.36)	218 (3.73)	0.56 [0.40-0.79]	0.63 [0.44-0.92]
*33	37 (0.69)	45 (0.77)	0.47 [0.24-0.90]	0.59 [0.29-1.23]
*26	70 (1.30)	141 (2.41)	0.67 [0.43-1.06]	0.79 [0.49-1.29]
*25	70 (1.30)	106 (1.81)	0.98 [0.59-1.61]	0.67 [0.39-1.16]
*01	1180 (21.97)	1104 (18.88)	0.68 [0.57-0.80]	0.62 [0.49-0.78]
*23	44 (0.82)	89 (1.52)	0.70 [0.39-1.24]	0.72 [0.38-1.35]
*11	201 (3.74)	378 (6.47)	0.53 [0.40-0.71]	0.60 [0.43-0.82]
*31	114 (2.12)	164 (2.81)	0.49 [0.33-0.71]	0.52 [0.34-0.80]

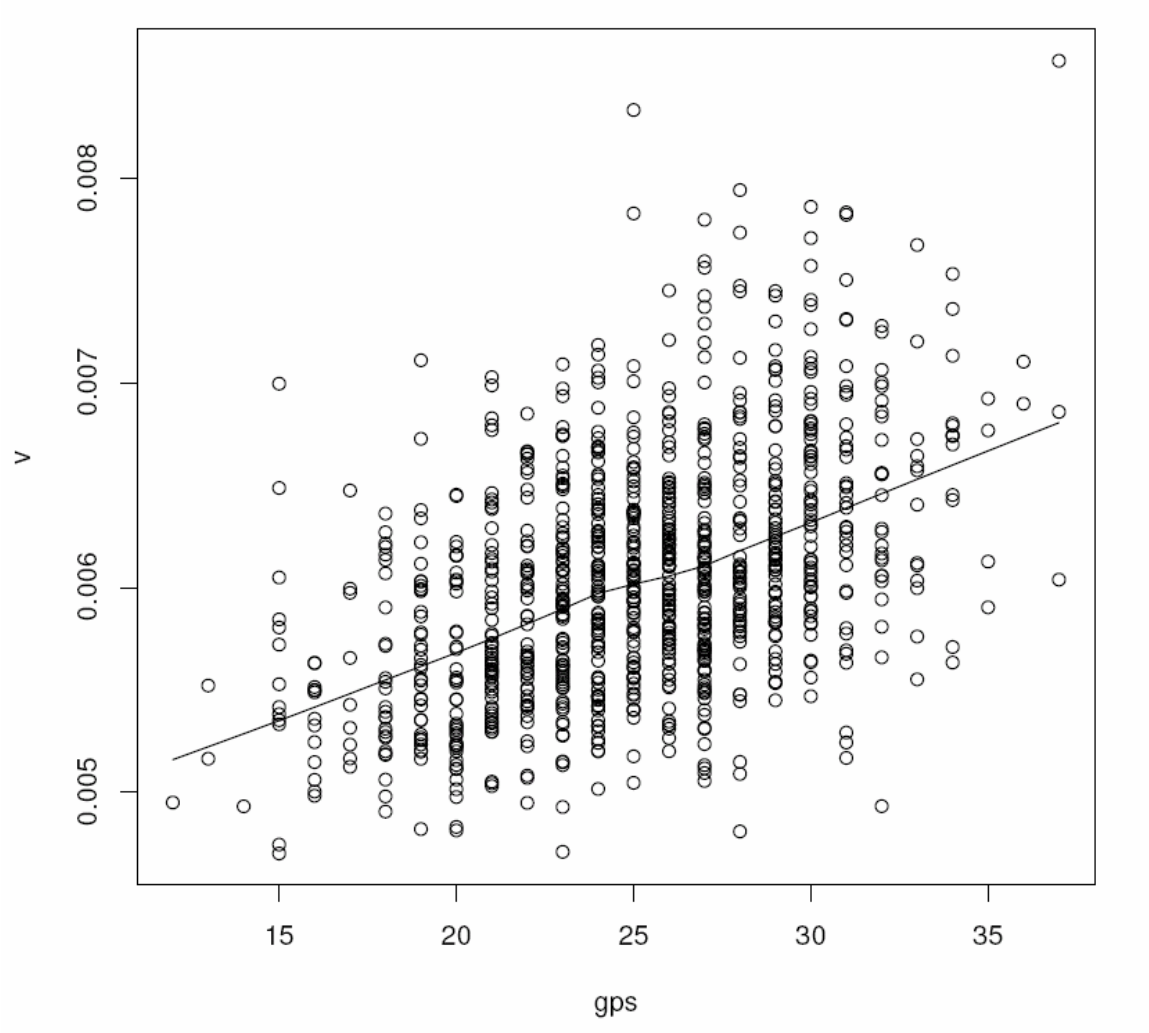
Supplementary Table 7 | Relative risks and odds ratios for the different groups in the tree models used for the families and the first case-control set. In both cases a reasonably common and neutral group is used as reference. Groups marked in bold are relatively neutral.

Group	Families RR [95% CI]	Case-control set OR [95% CI]
1	8.13 [3.24-20.42]	
2	6.01 [1.99-18.12]	6.15 [4.26-8.90]
3	4.99 [3.53-7.07]	
4	4.04 [1.39-11.71]	
5	3.61 [2.44-5.34]	
6	1.91 [0.69-5.28]	
7	1.86 [1.30-2.64]	1.74 [1.15-2.62]
8	1.25 [0.80-1.94]	1.11 [0.53-2.32]
9	**1.00 [reference]**	**1.00 [reference]**
10	0.55 [0.37-0.81]	0.52 [0.24-1.15]
11	0.53 [0.33-0.86]	0.35 [0.22-0.55]
12	0.45 [0.06-3.58]	0.23 [0.14-0.39]
13	0.27 [0.17-0.43]	0.21 [0.11-0.41]
14	0.09 [0.04-0.18]	0.07 [0.01-0.63]
15	0.03 [0.02-0.06]	0.09 [0.05-0.15]
16		0.03 [0.02-0.04]

Supplementary Figure 1a | Bootstrap analysis of β against group size. 1,000 bootstrap samples were generated and the association of *HLA-DRA* SNP, rs9268831, assessed (Methods). We show the plot of the bootstrap logit coefficient, β against the number of terminal groups in the model of the class II effects with lowess smoother[21]. A general trend of a reduction in effect size (increase in β) with increasing group size is observed. However this increase is small, hence there is only a small dependence of β on group number. b = β, gps = groups



Supplementary Figure 1b | Bootstrap analysis of var(β) against group size (Methods). We show the plot of the bootstrap var(β) from the *HLA-DRA* SNP, rs9268831, bootstrap samples, against the number of terminal groups in the model of the class II effects with lowess smoother[21] . Note the variance increases with increasing numbers of groups. v = var(β), gps = groups



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