

SUPPLEMENTARY DATA

Sex effects

An age dependence of sex was found in our collection ($P=0.002$; $OR=1.01[1.004-1.02]$ for males having a higher age-at-diagnosis). This is consistent with observed trends in the literature, that most studies have slightly higher frequency of male adult-onset autoimmune diabetes cases than female (1-3). For instance, sixty percent of UKPDS cases (153 of 255 GADA or ICA positive) were male (average age-at-diagnosis = 48 yr) (4). The Norwegian HUNT2 study, had 68 (54%) males : 58 females (46%) for their LADA subjects and 72 (60%) males: 48 females for their type 1 diabetes diagnosed between 10-50 years. And the Diabetes Incidence in Sweden Study group had 971 type 1 diabetes between 0 and 34 years with 59% of them male.

Body-Mass Index (BMI)

BMI was available for 588 cases and 2,280 controls. Based on the recommendations of the WHO,(5) we determined subjects' height, body weight, hip and waist circumference. Average BMI in cases was 23.5 kg/m^2 and in controls was 25.1 kg/m^2 . The cases had a lower BMI than controls ($P = 1.92 \times 10^{-14}$).

Tagging SNPs

All SNPs were selected as tags based on the linkage disequilibrium (LD) measures in British controls and type 1 diabetes samples. The LD in the German samples may differ to those for the British samples which could account for the inconsistent results obtained in the HLA region between British paediatric-onset type 1 diabetes and adult-onset autoimmune diabetes. Weaker LD between the tagging SNP and the allele of interest could reduce the strength of association. However, in a subset of 434 German cases who had *HLA-DRB1* genotyping, the LD was strong, $r^2=0.76$ between rs660895 and DR4, $r^2=0.94$ between rs2187668 and DR3 and so this explanation for the difference at DR4 is unlikely. Similarly, rs9271366, is in strong LD with *HLA-DRB1*15* ($r^2=0.86$ in the 434 German autoimmune diabetes cases with *HLA-DRB1* genotyping).

Autoantibodies

There have been a number of reports in the literature claiming that the number of autoantibodies, rather than order of appearance of the specific autoantibodies are important for progression to T1D (and also for progression to insulin dependence in LADA) (6; 7). We have not tested this genetically in our autoimmune diabetes cases, as there is no reason to suppose that a single genetic variant would affect all autoantibodies in the same way. Indeed as shown here, they are actually likely to be different and in some instances they are even inversed *e.g.* DR3 is associated with high levels of GADA but with low levels of IA-2A. This inverse association has also been detected in paediatric T1D [JMMH, JAT unpublished] (8).

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Supplementary Table 1. HLA associations in British paediatric-onset type 1 diabetes (diagnosed before age 17 years; JMMH, JAT unpublished). The SNPs rs2187668 and rs660895 were used to tag HLA DR3 and DR4, respectively, and code for the DR3/4/X genotypes. Only samples genotyped at both SNPs were included in the analysis.

SNP or genotype	Cases N(Freq)	Controls N (Freq)	OR [95% CI]	<i>P</i>
rs2187668 (DR3)	5556 (0.33)	2937 (0.14)	6.41 [5.99-6.87]	
rs660895 (DR4)	7144 (0.43)	4389 (0.22)	6.29 [5.89-6.73]	
3/3	682 (0.08)	209 (0.02)	4.42 [3.74-5.23]	
3/4	3,024 (0.37)	601 (0.06)	6.63 [5.96-7.37]	
4/4	982 (0.12)	475 (0.05)	2.72 [2.40-3.08]	
4/X	2,114 (0.26)	2,812 (0.27)	1.00 [ref]	
3/X	1,062 (0.13)	1,874 (0.19)	0.76 [0.69-0.83]	
X/X	317 (0.04)	4,134 (0.41)	0.10 [0.09-0.12]	
				0

Freq – Frequency, N – number of chromosomes, OR- odds ratio, CI – confidence interval

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Supplementary Table 2. Published associations of 19 gene regions in British cases diagnosed at less than 17 years of age. (These are the same regions which were tested in adult-onset autoimmune diabetes, Table 2). Effect sizes are those reported in the listed publication. We also report the P -values for age-at-diagnosis effects (P_{aad}) in childhood-onset type 1 diabetes cases as reported in JC, Cooper, JMMH, JAT unpublished.

Candidate Gene (region)	SNP	OR [95% CI]	Reference	P_{aad}
<i>PTPN22</i> (1p13.2)	rs2476601 (C>T)	2.05 [1.90-2.20]	(9)	0.073
<i>IFIH1</i> (2q24.2)	rs1990760 (A>G)	0.86 [0.82-0.90]	(9)	0.12
<i>STAT4</i> (2q32.2)	rs7574865 (G>T)	1.10 [1.04-1.15]	(10)	NA
<i>CTLA4</i> (2q33.2)	rs3087243 (G>A)	0.82 [0.78-0.86]	(9)	0.99
<i>IL2</i> (4q27)	rs2069763 (G>T)	1.13 [1.08-1.18]	(9)	4.6×10^{-6}
<i>BACH2</i> (6q15)	rs11755527 (C>G)	1.13 [1.09-1.18]	(9)	0.073
<i>GLIS3</i> (9p24.2)	rs7020673 (G>C)	0.88 [0.83-0.93]	(9)	0.00075
<i>IL2RA</i> (10p15.1)	rs12722495 (A>G)	0.62 [0.57-0.68]	(9)	0.00098
	rs2104286 (A>G)	0.90 [0.84-0.97]	Unpublished	0.0025
<i>RNLS</i> (10q23.31)	rs10509540 (T>C)	0.75 [0.70-0.80]	(11)	2.5×10^{-5}
<i>INS</i> (11p15.5)	rs689 (A>T)	0.42 [0.41-0.46]	(9)	0.0057
<i>ERBB3</i> (12q13.2)	rs2292239 (C>A)	1.31 [1.22-1.41]	(9)	0.78
<i>SH2B3</i> (12q24.12)	rs3184504 (A>G)	1.28 [1.22-1.35]	(9)	0.20
<i>CLEC16A</i> (16p13.13)	rs12708716 (A>G)	0.81 [0.77-0.86]	(9)	0.56
<i>IL27</i> (16p11.2)	rs4788084 (G>A)	0.86 [0.81-0.91]	(11)	0.89
<i>CTRB2</i> (16q23.1)	rs7202877 (T>G)	1.28 [1.21-1.36]	(11)	0.0057
<i>GSDMB</i> (17q12)	rs2290400 (G>A)	0.87 [0.82-0.93]	(11)	0.021
<i>PTPN2</i> (18p11.21)	rs478582 (T>C)	0.83 [0.79-0.88]	(9)	0.17
	rs45450798 (G>C)	1.28 [1.21-1.36]	(9)	0.019
<i>CD226</i> (18q22.2)	rs763361 (C>T)	1.14 [1.07-1.19]	(9)	0.66
<i>UBASH3A</i> (21q22.3)	rs3788013 (C>A)	1.13 [1.08-1.18]	(9)	0.56

OR- odds ratio, CI – confidence interval

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Supplementary Table 3. Age-at-diagnosis effects at T1D-associated SNPs outside of the MHC region, including all 1,384 autoimmune diabetes cases.

Candidate Gene (region)	SNP	P_{cont}	P_{cat}
<i>PTPN22</i> (1p13.2)	rs2476601 (C>T)	0.22	0.31
<i>IFIH1</i> (2q24.2)	rs1990760 (A>G)	0.071	0.36
<i>STAT4</i> (2q32.2)	rs7574865 (G>T)	0.81	0.94
<i>CTLA4</i> (2q33.2)	rs3087243 (G>A)	0.46	0.22
<i>IL2</i> (4q27)	rs2069763 (G>T)	0.93	0.026*
<i>BACH2</i> (6q15)	rs11755527 (C>G)	0.017	0.13
<i>GLIS3</i> (9p24.2)	rs7020673 (G>C)	0.47	0.58
† <i>IL2RA</i> (10p15.1)	rs12722495 (A>G)	0.027	0.23
	rs2104286 (A>G)	0.053	0.0037
<i>RNLS</i> (10q23.31)	rs10509540 (T>C)	0.43	0.033
<i>INS</i> (11p15.5)	rs689 (A>T)	0.13*	0.029*
<i>ERBB3</i> (12q13.2)	rs2292239 (C>A)	0.34	0.025
<i>SH2B3</i> (12q24.12)	rs3184504 (A>G)	0.36	0.20*
<i>CLEC16A</i> (16p13.13)	rs12708716 (A>G)	0.049	0.021
<i>IL27</i> (16p11.2)	rs4788084 (G>A)	0.023*	0.018*
<i>CTRB2</i> (16q23.1)	rs7202877 (T>G)	0.90	0.0050
<i>GSDMB</i> (17q12)	rs2290400 (G>A)	0.55	0.27
‡ <i>PTPN2</i> (18p11.21)	rs478582 (T>C)	0.0057	0.22
	rs45450798 (G>C)	0.25	0.068
<i>CD226</i> (18q22.2)	rs763361 (C>T)	0.96	0.65
<i>UBASH3A</i> (21q22.3)	rs3788013 (C>A)	0.73	0.86

P_{cont} is the P -value for the test of age-at-diagnosis as a continuous trait and P_{cat} is the P -value for the test of age-at-diagnosis categorised into quartiles (Methods).

* Uses genotype effects model

† The average age-at-diagnosis of cases carrying the G/G genotype at the *IL2RA* SNP, rs2104286 (which confers protection from type 1 diabetes) was 35.4 years, compared to 34.1 years for cases with the A/G genotype and 32.6 years for cases with the A/A genotype.

‡ The average age-at-diagnosis of cases carrying the protective C/C genotype at the *PTPN2* SNP, rs478582 was 34.9 years, compared to 33.6 years for cases carrying the C/G genotype, and just 31.6 years for the cases with the common G/G genotype.

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Supplementary Table 4. Distribution of phenotypes in autoimmune diabetes cases overall and for each autoantibody sub-group.

Phenotype	All cases	GADA		IA-2A	
		Positives	Negatives	Positives	Negatives
N (%)	1,384	1,147 (83)	233 (17)	476 (51)	457 (49)
Age-at-diagnosis (yr)					
Mean (SD)	33.3 (15.7)	34.7 (15.3)	26.4 (15.9)	34.8 (17.0)	35.4 (15.9)
Median	31	33	23	31	34
Age (yr)					
Mean (SD)	36.0 (15.7)	36.7 (15.4)	32.7 (16.8)	37.3 (16.4)	41.1 (15.0)
Median	34	35	30	35	41
Duration (yr)					
Mean (SD)	3.0 (8.4)	2.2 (7.1)	7.0 (12.4)	2.7 (7.2)	5.8 (11.7)
Median	0	0	0	0	0
Year of recruitment (yr)					
Mean (SD)	2004 (4.6)	2004 (4.3)	2003 (5.2)	2007 (2.3)	2007 (2.4)
Median	2005	2005	2005	2008	2008
Year of birth (yr)					
Mean (SD)	1968 (14.8)	1968 (14.8)	1970 (14.6)	1970 (16.1)	1966 (14.6)
Median	1969	1969	1972	1972	1966
Sex					
Male N (%)	757 (55)	613 (54)	142 (62)	246 (52)	255 (56)
Female N (%)	619 (45)	529 (46)	88 (38)	224 (48)	200 (44)