

SUPPLEMENTARY DATA

Meng Zhu, Kuanfeng Xu, Yang Chen, et al. Identification of novel T1D risk loci and their association with age and islet function at diagnosis in autoantibody-positive T1D individuals: based on a two-stage genome-wide association study

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Supplementary Table S1. Characteristics of T1D cases and controls in GWAS and validation stages

Variables	GWAS		Validation Ia		Validation Ib		Validation Ic	
	Case	Control	Case	Control	Case	Control	Case	Control
	(N=1,045)	(N=1,308)	(N=507)	(N=2,443)	(N=494)	(N=841)	(N=550)	(N=490)
Age (mean±SD)	19.91±13.25	42.14±16.27	16.15±13.49	54.47±9.07	23.75±14.68	65.64±6.82	23.15±13.29	33.74±8.60
Sex								
Male	510(48.8)	866(66.21)	245(48.32)	628(25.71)	265(53.64)	600(71.34)	261(47.45)	261(53.27)
Female	535(51.2)	442(33.79)	262(51.68)	1,815(74.29)	229(46.36)	241(28.66)	289(52.55)	229(46.73)
Autoantibody positivity								
ZnT8A	503(48.13)		181(35.70)		140(28.34)		114(20.73)	
GADA	750(71.77)		276(54.55)		446(90.28)		494(89.82)	
IA-2A	506(48.42)		217(42.89)		200(40.49)		229(41.64)	

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Supplementary Table S2. Genetic correlations among children, adolescents, and adults T1D patients

	Subgroup		LDSC			BUHMBOX		
	A	B	rg ^a	P ^a	Number of SNPs	GRS P value ^b	GRS β (95% CI) ^b	BUHMBOX P-value ^b
Age of onset	≤12	12-18	0.99	1.93×10-11	63	1.17×10-91	0.41(0.36-0.46)	1.57×10-2
	>18	12-18	0.88	1.36×10-11	63	5.94×10-50	0.24(0.21-0.28)	1.82×10-12
	>18	≤12	0.84	2.47×10-26	103	4.36×10-45	0.13(1.11-0.15)	3.98×10-28

^a Estimated genetic correlation based on all genotyped SNPs with LD Score regression.

^b Estimated sharing genetic basis of different subgroups with mendelian randomization and BUHMBOX using the independent significant SNPs of Subgroup B (P<1×10-4). Significant GRS P-value indicates evidence of shared genetic structure; significant BUHMBOX P-value indicates evidence of subgroup heterogeneity.

T1D individuals with age of onset ≤12 were regarded as children, 12-18 as adolescents, and >18 as adults.

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Supplementary Table S3. The association results of the selected variants at the discovery stage and the replication stages

Chr.	Position (hg19)	SNP	Allele		Gene	Stage ^a	MAF ^b		OR (95%CI) ^c	P ^c	P _{het}	I ²
			Major	Minor			Cases	Controls				
4	2680515	rs7681728	A/G	<i>FAM193A</i>	discovery	0.39	0.46	0.72(0.63-0.82)	4.98E-07			
					replication Ia	0.43	0.46	0.91(0.80-1.05)	1.95E-01			
					replication Ib	0.43	0.44	0.99(0.84-1.16)	8.51E-01			
					replication Ic	0.35	0.36	0.95(0.8-1.14)	5.74E-01			
					replication I Combined			0.95(0.86-1.03)	2.16E-01	0.784	0.000	
4	58209517	rs987706	C/A	<i>LOC255130</i>	discovery	0.15	0.10	1.57(1.30-1.90)	4.06E-06			
					replication Ia	0.13	0.12	1.04(0.85-1.29)	6.83E-01			
					replication Ib	0.11	0.11	1.01(0.78-1.31)	9.35E-01			
					replication Ic	0.08	0.09	0.95(0.70-1.29)	7.39E-01			
					replication I Combined			1.01(0.88-1.17)	8.60E-01	0.882	0.000	
6	15719924	rs4282401	C/T	<i>DTNBPI,MYLIP</i>	discovery	0.12	0.17	0.65(0.55-0.78)	3.81E-06			
					replication Ia	0.19	0.13	1.51(1.25-1.82)	1.77E-05			
					replication Ib	0.17	0.14	1.25(0.99-1.56)	5.50E-02			
					replication Ic	0.11	0.11	0.94(0.71-1.26)	6.92E-01			
					replication I Combined			1.29(1.13-1.47)	1.08E-04	0.030	0.723	
6	26423560	rs4320356	C/T	<i>BTN3A1</i>	discovery	0.34	0.27	1.40(1.22-1.60)	1.72E-06			
					replication Ia	0.34	0.29	1.29(1.11-1.50)	9.68E-04			
					replication Ib	0.28	0.26	1.13(0.94-1.35)	1.89E-01			
					replication Ic	0.31	0.29	1.10(0.91-1.33)	3.09E-01			
					replication I Combined			1.19(1.08-1.31)	6.74E-04	0.358	0.026	
6	32627833	rs1770	G/A	<i>HLA-DQBI</i>	discovery	0.80	0.47	4.35(3.85-5.00)	8.95E-83			
					replication Ia	0.81	0.47	4.33(3.65-5.15)	2.02E-61			
					replication Ib	0.78	0.41	5.00(4.00-5.88)	5.83E-55			
					replication Ic	0.78	0.45	3.57(2.94-4.35)	9.48E-38			
					replication I Combined			4.22(3.79-4.72)	1.42E-147	0.066	0.632	
9	4314752	rs7038304	A/G	<i>GLIS3, SLC1A1</i>	discovery	0.46	0.52	0.76(0.67-0.86)	9.53E-06			
					replication Ia	0.47	0.50	0.88(0.77-1.01)	7.37E-02			
					replication Ib	0.48	0.46	1.08(0.92-1.27)	3.25E-01			

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					replication Ic	0.45	0.45	0.98(0.82-1.17)	8.34E-01		
					replication I Combined			0.97(0.88-1.06)	4.80E-01	0.158	0.458
9	85806577	rs10867947	C/T	<i>RASEF, FRMD3</i>	discovery	0.47	0.41	1.36(1.20-1.54)	2.40E-06		
					replication Ia	0.47	0.45	1.07(0.93-1.23)	3.55E-01		
					replication Ib	0.49	0.47	1.07(0.92-1.26)	3.89E-01		
					replication Ic	0.51	0.52	0.99(0.83-1.19)	9.34E-01		
					replication I Combined			1.05(0.96-1.15)	2.57E-01	0.851	0.000
10	8102272	rs3802604	T/C	GATA3	discovery	0.42	0.35	1.35(1.18-1.53)	4.78E-06		
					replication Ia	0.45	0.38	1.32(1.14-1.51)	1.34E-04		
					replication Ib	0.41	0.40	1.04(0.88-1.23)	6.39E-01		
					replication Ic	0.39	0.35	1.17(0.98-1.39)	8.00E-02		
					replication I Combined			1.18(1.08-1.30)	2.75E-04	0.080	0.604
10	88662216	rs10887668	A/C	<i>BMPRIA</i>	discovery	0.08	0.05	1.81(1.40-2.34)	5.36E-06		
					replication Ia	0.08	0.07	1.10(0.85-1.42)	4.89E-01		
					replication Ib	0.05	0.07	0.71(0.51-1.00)	5.09E-02		
					replication Ic	0.04	0.03	1.14(0.70-1.84)	6.02E-01		
					replication I Combined			0.96(0.80-1.17)	7.07E-01	0.109	0.548
11	87571991	rs2514249	T/C	<i>TMEM135, RAB38</i>	discovery	0.49	0.44	1.33(1.17-1.50)	9.18E-06		
					replication Ia	0.42	0.46	0.83(0.72-0.96)	9.91E-03		
					replication Ib	0.48	0.46	1.10(0.94-1.30)	2.48E-01		
					replication Ic	0.51	0.53	0.88(0.74-1.06)	1.86E-01		
					replication I Combined			0.98(0.90-1.08)	7.20E-01	0.008	0.794
12	56384804	rs705699	C/T	<i>SUOX</i>	discovery	0.33	0.24	1.56(1.36-1.80)	2.88E-10		
					replication Ia	0.32	0.27	1.25(1.08-1.46)	3.46E-03		
					replication Ib	0.33	0.25	1.44(1.20-1.71)	6.04E-05		
					replication Ic	0.33	0.23	1.68(1.37-2.05)	4.34E-07		
					replication I Combined			1.41(1.27-1.55)	2.02E-11	0.304	0.161
13	44961158	rs9533839	T/C	<i>SERP2</i>	discovery	0.37	0.30	1.37(1.20-1.56)	2.05E-06		
					replication Ia	0.36	0.35	1.00(0.87-1.16)	9.85E-01		
					replication Ib	0.37	0.37	1.00(0.85-1.19)	9.61E-01		
					replication Ic	0.36	0.37	0.97(0.81-1.16)	7.22E-01		
					replication I Combined			0.99(0.90-1.09)	8.78E-01	0.947	0.000

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16	54424148	rs17257468	G/A	<i>IRX3, CRNDE</i>	discovery replication Ia replication Ib replication Ic replication I Combined	0.10 0.07 0.09 0.09 0.95(0.81-1.12)	0.07 0.08 0.09 0.08 5.66E-01	1.71(1.36-2.15) 0.93(0.71-1.21) 0.92(0.70-1.23) 1.03(0.75-1.41) 0.95(0.81-1.12)	5.14E-06 5.80E-01 5.88E-01 8.73E-01 5.66E-01	0.862	0.000
2	79370426	rs1589614	C/T	<i>REGIP, REG3A</i>	discovery replication Ia	0.27 0.31	0.33 0.30	0.73(0.64-0.84) 1.04(0.89-1.21)	6.78E-06 6.48E-01		
3	64505542	rs11713906	T/C	<i>ADAMTS9</i>	discovery replication Ia	0.52 0.49	0.45 0.49	1.35(1.19-1.53) 1.00(0.84-1.19)	2.88E-06 9.92E-01		
17	67408662	rs8071378	C/T	<i>ABCA5,MAP2K6</i>	discovery replication Ia	0.45 0.42	0.39 0.41	1.34(1.18-1.52) 1.07(0.93-1.23)	5.99E-06 3.61E-01		
22	20850440	rs2079099	A/G	<i>KLHL22</i>	discovery replication Ia	0.45 0.49	0.52 0.49	0.73(0.64-0.83) 1.04(0.90-1.19)	1.35E-06 6.12E-01		

^a Replication Ia consist of 507 T1D cases and 2,443 healthy controls recruited from the southeast of China; replication Ib consist of 494 T1D cases and 841 healthy controls recruited from the central of China; replication Ic consist of 550 T1D cases and 490 healthy controls recruited from the south of China; results from different centres were combined with fixed meta-analysis.

^b MAF: Minor allele frequency;

^c OR (95% confidence interval (CI)) and P values were derived from logistic regression analysis with adjustment for sex and the significant eigenvectors (for the discovery and replication II stage) under the assumption of an additive genetic model;

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Supplementary Table S4. Overview of potentially causal variants at the identified loci

Locus	Marker Gene(s)	Variants	Alleles	OR	PP ^a	Variant Type
6p22.2	<i>BTN3A1</i>	rs4320356	A/G	1.40	0.141	ncRNA_exonic
		rs6907924	T/C	1.39	0.118	intergenic
		rs3208733	G/A	1.39	0.110	UTR3
		rs9366657	G/A	1.39	0.104	intergenic
		rs9379874	C/A	1.39	0.104	upstream
		rs3846845	T/G	1.39	0.091	intronic
		rs3846846	G/A	1.39	0.091	intronic
		rs3799379	G/A	1.37	0.040	intronic
		rs12663780	C/T	1.35	0.020	intergenic
		rs2237236	T/C	1.34	0.019	intronic
		rs4712987	G/A	1.35	0.018	intergenic
		rs2273558	G/A	1.37	0.013	intronic
		rs2273193	G/A	0.72	0.010	intronic
		rs4712998	TGAAATTGGTA/T	0.72	0.009	intergenic
		rs7356988	T/C	1.33	0.009	intergenic
10p14	<i>GATA3</i>	rs10905277	G/A	0.74	0.206	UTR5
		rs3802604	G/A	0.74	0.133	intronic
		rs3781094	A/C	0.74	0.116	intronic
		rs2275806	G/A	0.74	0.113	ncRNA_exonic
		rs3802597	A/G	0.75	0.086	intronic
		rs10905284	C/A	0.76	0.064	intronic
		rs3824660	C/T	0.75	0.054	intronic
		rs34610379	TA/T	0.76	0.046	intergenic
		rs386680	C/G	0.78	0.007	intronic
		rs374641	C/T	0.78	0.007	intronic
		rs371668	T/C	0.78	0.007	intronic
		rs10430790	A/T	0.79	0.006	intergenic
		rs477771	A/C	0.78	0.006	intronic
		rs11255520	T/C	0.79	0.006	intergenic
		rs4749572	G/A	0.79	0.006	intergenic
		rs2664903	A/G	0.79	0.006	intergenic
		rs2671299	A/C	0.79	0.006	intergenic
		rs2671300	A/G	0.79	0.006	intergenic
		rs2671301	G/A	0.79	0.006	intergenic
		rs2798846	G/A	0.79	0.006	intergenic
6p21.3	<i>HLA-DQBI</i>	rs9273471	G/A	4.37	0.429	ncRNA_intronic
		rs1770	A/G	4.35	0.346	ncRNA_exonic
		rs4713572	T/C	4.34	0.224	upstream;downstream
12q13.2	<i>SUOX</i>	rs773125	A/G	1.61	0.271	intronic
		rs1081975	C/G	1.60	0.133	intronic
		rs705700	T/C	1.59	0.092	UTR3
		rs10876864	G/A	0.63	0.051	upstream
		rs773114	A/T	1.57	0.039	intronic
		rs1873914	G/C	1.58	0.038	intronic
		rs705702	A/G	1.59	0.033	upstream;downstream
		rs1701704	T/G	1.58	0.030	ncRNA_intronic
		rs705699	G/A	1.56	0.026	intronic
		rs11343216	AT/A	1.58	0.022	intronic
		rs1702877	C/T	1.57	0.022	intronic
		rs34813703	CGTG/C	1.57	0.019	intronic
		rs1689510	G/C	1.57	0.018	intronic
		rs2456973	A/C	1.57	0.018	ncRNA_intronic
		rs773110	C/G	1.57	0.017	intronic
		rs773111	C/A	1.57	0.017	intronic
		rs61937247	A/C	1.57	0.017	intronic
		rs61937249	A/G	1.57	0.017	intronic
		rs61937248	C/T	1.57	0.017	intronic

^a Posterior probability.

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Supplementary Table S5. Functional annotation of the most probable variants from Bayesian fine-mapping

SNPs	Epigenome ID (EID)	Group	Description	Enhancer	DNase	H3K4me3	H3K4me1	H3K27ac	H3K9ac
rs4320356	E034	Blood & T-cell	Primary T cells from peripheral blood	Y		Y	Y		
	E045	Blood & T-cell	Primary T cells effector/memory enriched from peripheral blood			Y			
	E044	Blood & T-cell	Primary T regulatory cells from peripheral blood				Y		
	E041	Blood & T-cell	Primary T helper cells PMA-I stimulated					Y	
	E042	Blood & T-cell	Primary T helper 17 cells PMA-I stimulated			Y			
	E040	Blood & T-cell	Primary T helper memory cells from peripheral blood 1			Y			Y
	E037	Blood & T-cell	Primary T helper memory cells from peripheral blood 2					Y	
	E038	Blood & T-cell	Primary T helper naive cells from peripheral blood			Y			
	E047	Blood & T-cell	Primary T CD8+ naive cells from peripheral blood						
	E026	Mesench	Bone Marrow Derived Cultured Mesenchymal Stem Cells	Y		Y	Y		Y
	E049	Mesench	Mesenchymal Stem Cell Derived Chondrocyte Cultured Cells			Y	Y		Y
	E025	Mesench	Adipose Derived Mesenchymal Stem Cell Cultured Cells	Y		Y	Y		Y
	E023	Mesench	Mesenchymal Stem Cell Derived Adipocyte Cultured Cells			Y	Y		Y
	E093	Thymus	Fetal Thymus			Y	Y		
rs10905277	E062	Blood & T-cell	Primary mononuclear cells from peripheral blood		Y	Y		Y	Y
	E034	Blood & T-cell	Primary T cells from peripheral blood		Y	Y	Y	Y	
	E045	Blood & T-cell	Primary T cells effector/memory enriched from peripheral blood			Y	Y	Y	
	E033	Blood & T-cell	Primary T cells from cord blood			Y	Y		
	E044	Blood & T-cell	Primary T regulatory cells from peripheral blood			Y			Y
	E043	Blood & T-cell	Primary T helper cells from peripheral blood			Y	Y	Y	
	E039	Blood & T-cell	Primary T helper naive cells from peripheral blood			Y	Y	Y	
	E041	Blood & T-cell	Primary T helper cells PMA-I stimulated			Y	Y		Y
	E042	Blood & T-cell	Primary T helper 17 cells PMA-I stimulated			Y	Y	Y	
	E040	Blood & T-cell	Primary T helper memory cells from peripheral blood 1			Y	Y		Y
	E037	Blood & T-cell	Primary T helper memory cells from peripheral blood 2			Y			Y
	E048	Blood & T-cell	Primary T CD8+ memory cells from peripheral blood			Y			Y
	E038	Blood & T-cell	Primary T helper naive cells from peripheral blood			Y		Y	Y
	E047	Blood & T-cell	Primary T CD8+ naive cells from peripheral blood			Y	Y	Y	Y
	E029	HSC & B-cell	Primary monocytes from peripheral blood			Y	Y		
	E112	Thymus	Thymus			Y	Y	Y	
rs9273471	E093	Thymus	Fetal Thymus		Y	Y	Y	Y	
	E031	HSC & B-cell	Primary B cells from cord blood	Y			Y		
	E032	HSC & B-cell	Primary B cells from peripheral blood	Y		Y	Y	Y	
	E046	HSC & B-cell	Primary Natural Killer cells from peripheral blood	Y			Y		
	E093	Thymus	Fetal Thymus	Y			Y	Y	
rs773125	E116	ENCODE2012	GM12878 Lymphoblastoid Cells	Y		Y	Y	Y	Y
	E092	Digestive	Fetal Stomach	Y				Y	

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E085	Digestive	Fetal Intestine Small	Y			Y	Y
E084	Digestive	Fetal Intestine Large	Y			Y	Y
E109	Digestive	Small Intestine				Y	Y
E106	Digestive	Sigmoid Colon				Y	
E075	Digestive	Colonic Mucosa			Y	Y	Y
E101	Digestive	Rectal Mucosa Donor 29			Y	Y	Y
E102	Digestive	Rectal Mucosa Donor 31	Y		Y	Y	Y
E110	Digestive	Stomach Mucosa	Y			Y	
E077	Digestive	Duodenum Mucosa	Y			Y	
E079	Digestive	Esophagus				Y	
E094	Digestive	Gastric					
E087	Other	Pancreatic Islets					Y
E066	Other	Liver	Y			Y	Y
E098	Other	Pancreas				Y	

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Supplementary Table S6. eQTL overlapping of the most probable variants from Bayesian fine-mapping

Locus	Marker Gene(s)	Variants	Alleles	OR	PP ^a	eQTLs ^b
6p22.2	<i>BTN3A1</i>	rs4320356	A/G	1.40	0.141	<i>BTN3A1</i> in Brain Cortex, Adrenal Gland, Artery Coronary, Brain Cortex, Esophagus Mucosa, Esophagus Muscularis, Lung, Stomach, Testis, Thyroid (GTEx), and whole blood (2,116 samples)
10p14	<i>GATA3</i>	rs10905277	G/A	0.74	0.206	<i>GATA3</i> in whole blood (2,116 samples), <i>GATA3</i> sQTL in whole blood (5,257 samples)
6p21.3	<i>HLA-DQBI, HLA-DRB6</i>	rs9273471	G/A	4.37	0.429	<i>HLA-DQBI</i> in Brain Cortex, <i>HLA-DRB6</i> in Adipose Subcutaneous, <i>HLA-DRB6</i> in Adipose Visceral Omentum, <i>HLA-DRB6</i> in Esophagus Gastroesophageal Junction (GTEx); <i>HLA-DQA2</i> in monocyte (105 Japanese)
12q13.2	<i>SUOX</i>	rs773125	A/G	1.61	0.271	<i>SUOX</i> in Adipose Visceral Omentum, Brain Cortex, Brain Putamen basal ganglia, Breast Mammary Tissue, Esophagus Mucosa, Lung, Nerve Tibial, Ovary, Pancreas, Prostate, Small Intestine Terminal Ileum, Spleen, Stomach, and Thyroid (GTEx), and <i>SUOX</i> in NK cell (105 Japanese)

^a Posterior probability.^b Only variant in high LD ($r^2 > 0.8$) with the top QTL for a given gene was considered as a QTL overlapping. The eQTL results were derived from GTEx (<https://gtexportal.org/>), PMID: 28553958, PMID: 27918533, or PMID: 25685889.

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Supplementary Table S7. eQTL associations in pancreas

SNP	Gene Symbol	P-Value	Tissues	Ethnicity	Source ^a
rs4320356	BTN3A1	2.60E-05	Pancreas	Europeans	GTEx
rs9273471	HLA-DQB1	8.20E-27	Pancreas	Europeans	GTEx
rs9273471	HLA-DRB6	4.80E-14	Pancreas	Europeans	GTEx
rs9273471	HLA-DQA2	8.70E-14	Pancreas	Europeans	GTEx
rs705699	SUOX	2.00E-20	Pancreas	Europeans	GTEx

^a eQTL results were derived from GTEx (<https://gtexportal.org/>)

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Supplementary Table S8. The association results of the identified four variants in WTCCC

Chr.	Position (hg19)	SNP	Allele		Gene	MAF		OR (95%CI) ^a	<i>P</i> ^a
			Major	Minor		Caes	Controls		
6	26423560	rs4320356	C/T		<i>BTN3A1</i>	0.46	0.43	1.15(1.08-1.22)	6.43E-06
6	32627833	rs1770	G/A		<i>HLA-DQBI</i>	0.74	0.59	4.55(4.17-5.00)	3.25E-302
10	8102272	rs3802604	T/C		<i>GATA3</i>	0.38	0.35	1.11(1.05-1.18)	5.05E-04
12	56384804	rs705699	C/T		<i>SUOX</i>	0.47	0.41	1.27(1.20-1.35)	3.24E-15

^a Adjusting for sex and the significant eigenvectors (eigenvector 1, 3 and 4).

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Supplementary Table S9. Summary of the reported associations with T1D risk in previous studies

Region	Chr.	SNP	Position (hg19)	Sources ^a	Info	Gene	Alleles		MAF ^b		OR(95% CI) ^c	P ^c	MAF in 1000 Genome				Most significant associations in Europeans ^d			
							Major/ Minor	Cases	Controls				AFR	AMR	ASN	EUR	OR	P	Risk Allele	Study
1	1q32.1	rs3024505	206939904	G	1	<i>IL10</i>	G/A	0.03	0.04	0.78(0.56-1.09)	1.45E-01	0.04	0.1	0.02	0.17	1.19	1.90E-09	C	9,12	
1	1q32.1	rs3024493	206943968	I	0.994	<i>IL10</i>	C/A	0.03	0.04	0.78(0.56-1.09)	1.48E-01	0.02	0.1	0.02	0.17	1.22	2.01E-08	C	10	
1	1q32.1	rs6691977	200814959	I	1	<i>CAMSAP2</i>	C/T	0.4	0.42	0.96(0.84-1.08)	4.72E-01	0.4	0.32	0.48	0.24	1.13	4.30E-08	C	12	
2	2q11.2	rs9653442	100825367	I	0.982	<i>AFF3</i>	T/C	0.41	0.37	1.19(1.05-1.36)	7.01E-03	0.25	0.38	0.41	0.46	1.21	6.23E-05	G	7	
3	2q13	rs4849135	111615079	G	1	<i>MAPT</i>	G/T	0.26	0.29	0.85(0.74-0.97)	1.75E-02	0.45	0.22	0.28	0.27	1.12	4.35E-08	G	12	
4	2q24.2	rs1990760	163124051	G	1	<i>IFIH1</i>	C/T	0.22	0.19	1.22(1.05-1.42)	9.69E-03	0.11	0.45	0.22	0.39	1.17	5.84E-17	T	9-10, 12	
4	2q24.2	rs2111485	163110536	G	1	<i>IFIH1</i>	A/G	0.21	0.18	1.21(1.03-1.42)	1.97E-02	0.15	0.44	0.19	0.4	1.18	3.81E-18	G	12	
5	2q33.2	rs3087243	204738919	G	1	<i>CTLA4</i>	G/A	0.15	0.18	0.83(0.71-0.98)	2.38E-02	0.18	0.4	0.24	0.45	1.19	7.40E-21	G	7, 9, 12	
5	2q33.2	rs11571316	204731089	I	0.998	<i>CTLA4</i>	G/A	0.15	0.18	0.84(0.71-0.99)	3.39E-02	0.18	0.38	0.24	0.43	1.22	2.44E-15	G	10	
6	2p23.3	rs478222	25301755	I	0.989	<i>EFR3B</i>	T/A	0.48	0.49	0.98(0.86-1.1)	6.88E-01	0.07	0.49	0.48	0.45	1.15	3.50E-09	A	10	
7	4q27	rs4505848	123132492	I	0.999	<i>ADAD1, IL21, IL2</i>	A/G	0.49	0.47	1.05(0.93-1.19)	3.91E-01	0.1	0.42	0.47	0.35	1.13	3.77E-10	G	9, 12	
7	4q27	rs6827756	123184411	I	0.999	<i>ADAD1, IL21, IL2</i>	T/C	0.4	0.42	0.96(0.85-1.08)	4.81E-01	0.32	0.46	0.4	0.38	1.14	5.40E-12	T	10, 12	
7	4q27	rs17388568	123329362	G	1	<i>ADAD1, IL21, IL2</i>	G/A	0.13	0.12	1(0.83-1.2)	9.69E-01	0.03	0.17	0.13	0.3	1.13	1.06E-09	A	7-8, 10	
8	4q32.3	rs2611215	166574267	I	1	<i>RP11-340B18.1</i>	G/A	0.39	0.38	1.03(0.91-1.17)	6.49E-01	0.15	0.11	0.35	0.15	1.18	1.80E-11	T	12	
9	5p13.2	rs11954020	35883251	I	0.994	<i>IL7R</i>	C/G	0.23	0.24	0.97(0.84-1.12)	6.73E-01	0.35	0.38	0.19	0.42	1.11	4.40E-08	G	12	
10	6p21.32	rs9272346	32604372	I	0.946	<i>HLA-DQA1</i>	A/G	0.15	0.38	0.32(0.28-0.36)	3.65E-62	0.42	0.34	0.46	0.45	5.56	5.47E-134	A	8	
10	6p21.32	rs9268645	32408527	I	0.999	<i>HLA-DRA</i>	G/C	0.25	0.36	0.59(0.51-0.67)	7.36E-16	0.3	0.41	0.46	0.37	-	1.00E-100	-	9	
11	6q15	rs597325	91002494	G	1	<i>BACH2</i>	A/G	0.53	0.47	1.26(1.1-1.43)	4.83E-04	0.05	0.33	0.46	0.41	1.14	1.13E-11	G	10, 12	
11	6q15	rs11755527	90958231	I	0.999	<i>BACH2</i>	C/G	0.45	0.41	1.17(1.03-1.33)	1.28E-02	0.2	0.42	0.4	0.45	-	5.40E-08	-	9	
12	6q22.32	rs1538171	126752884	I	0.973	<i>CENPW</i>	G/C	0.01	0.02	0.85(0.51-1.43)	5.48E-01	0.17	0.37	0.01	0.46	1.12	7.40E-10	G	12	
13	6q27	rs924043	170379025	I	0.983	<i>RP11-302L19.1</i>	T/C	0.38	0.38	0.97(0.85-1.1)	6.11E-01	0.42	0.28	0.38	0.14	1.19	8.06E-09	C	10	
14	6q22.32	rs9375435	126661858	G	1	<i>CENPW</i>	T/C	0.01	0.01	0.89(0.54-1.47)	6.39E-01	0.19	0.36	0.01	0.46	1.12	1.97E-09	T	10, 12	
14	6q22.32	rs9388489	126698719	G	1	<i>CENPW</i>	G/A	0.01	0.01	0.91(0.54-1.54)	7.26E-01	0.17	0.37	0.01	0.45	1.17	4.20E-13	G	9, 12	
15	6q25.3	rs1738074	159465977	G	1	<i>TAGAP</i>	T/C	0.41	0.4	0.99(0.87-1.13)	8.97E-01	0.32	0.48	0.37	0.45	-	6.00E-03	-	9	

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16	7p15.2	rs7804356	26891665	I	0.998	<i>SKAP2</i>	T/C	0.11	0.1	1.17(0.96-1.43)	1.28E-01	0.15	0.2	0.11	0.22	1.14	5.30E-09	T	9
17	7p12.2	rs62447205	50465830	I	0.997	<i>IKZF1</i>	A/G	0.16	0.14	1.13(0.95-1.35)	1.65E-01	0.23	0.22	0.13	0.31	1.12	2.50E-08	A	12
18	9p24.2	rs6476839	4290823	I	0.997	<i>GLIS3</i>	A/T	0.44	0.4	1.2(1.06-1.36)	4.76E-03	0.47	0.48	0.42	0.44	1.12	1.00E-09	T	12
18	9p24.2	rs7020673	4291747	I	0.997	<i>GLIS3</i>	C/G	0.49	0.45	1.19(1.05-1.35)	6.13E-03	0.14	0.43	0.48	0.46	1.14	5.40E-12	C	9
18	9p24.2	rs10758593	4292083	I	0.998	<i>GLIS3</i>	G/A	0.44	0.4	1.18(1.04-1.34)	8.33E-03	0.49	0.47	0.42	0.44	1.12	1.42E-09	A	10, 12
19	10q23.31	rs12416116	90035654	I	0.988	<i>RNLS</i>	C/A	0.24	0.26	0.85(0.74-0.98)	2.72E-02	0.35	0.24	0.23	0.29	1.18	3.90E-15	C	12
19	10q23.31	rs10509540	90023033	G	1	<i>RNLS</i>	T/C	0.23	0.25	0.87(0.75-1)	5.36E-02	0.2	0.23	0.23	0.27	1.33	1.30E-28	T	9, 10
20	10p15.1	rs10795791	6108340	I	0.987	<i>IL2RA,RBM17</i>	G/A	0.4	0.42	0.9(0.8-1.02)	1.10E-01	0.28	0.49	0.44	0.42	1.21	2.59E-23	G	12
20	10p15.1	rs12251307	6123495	G	1	<i>IL2RA,RBM17</i>	C/T	0.23	0.21	1.12(0.96-1.3)	1.40E-01	0.34	0.14	0.22	0.1	1.33	3.73E-05	C	7, 9
20	10p15.1	rs7090530	6110875	G	1	<i>IL2RA,RBM17</i>	A/C	0.27	0.28	0.9(0.79-1.04)	1.51E-01	0.43	0.4	0.3	0.42	1.22	2.93E-15	A	10
20	10p15.1	rs11258747	6472891	G	1	<i>PRKCQ</i>	G/T	0.04	0.03	1.16(0.84-1.61)	3.73E-01	0.11	0.12	0.03	0.22	-	1.20E-07	-	9
21	10p11.22	rs722988	33426147	G	1	<i>NRP1</i>	C/T	0.2	0.21	0.94(0.81-1.1)	4.51E-01	0.49	0.44	0.26	0.37	1.11	4.88E-08	G	11
22	10p15.1	rs2104286	6099045	G	1	<i>IL2RA,RBM17</i>	T/C	0.13	0.13	0.98(0.82-1.17)	8.13E-01	0.03	0.13	0.12	0.22	1.24	5.98E-23	T	8, 12
23	11p15.5	rs689	2182224	I	0.956	<i>INS</i>	T/A	0.02	0.04	0.41(0.29-0.59)	1.34E-06	0.21	0.29	0.05	0.28	2.38	1.00E-100	T	12
23	11p15.5	rs72853903	2198665	I	0.987	<i>INS</i>	C/T	0.02	0.04	0.56(0.39-0.81)	1.87E-03	0.05	0.28	0.04	0.32	1.32	5.29E-40	C	12
23	11p15.5	rs7111341	2213166	G	1	<i>INS</i>	C/T	0.06	0.08	0.7(0.55-0.89)	4.36E-03	0.42	0.23	0.08	0.28	1.58	3.14E-88	C	9, 12
23	11p15.5	rs7928968	2050299	I	0.92	<i>INS</i>	A/T	0.21	0.23	0.87(0.75-1.01)	7.21E-02	0.28	0.23	0.24	0.25	1.25	2.78E-14	T	10
24	11q13.1	rs694739	64097233	I	0.992	<i>BAD</i>	A/G	0.14	0.16	0.92(0.77-1.1)	3.78E-01	0.04	0.36	0.17	0.4	1.05	2.37E-07	T	11
25	12q13.2	rs705704	56435412	G	1	<i>ERBB3,DGKA,IKZF4</i>	G/A	0.31	0.22	1.57(1.37-1.81)	1.78E-10	0.1	0.25	0.25	0.33	1.35	4.31E-31	A	10
25	12q13.2	rs705705	56435504	G	1	<i>ERBB3,DGKA,IKZF4</i>	G/C	0.31	0.22	1.57(1.37-1.81)	2.03E-10	0.11	0.25	0.26	0.33	1.25	4.40E-32	C	12
25	12q13.2	rs11171739	56470625	G	1	<i>ERBB3,DGKA,IKZF4</i>	T/C	0.32	0.23	1.54(1.34-1.76)	7.15E-10	0.19	0.35	0.27	0.42	1.22	1.99E-25	C	9, 12
25	12q13.2	rs2292239	56482180	G	1	<i>ERBB3,DGKA,IKZF4</i>	G/T	0.3	0.22	1.49(1.3-1.72)	1.83E-08	0.45	0.27	0.27	0.34	1.3	6.46E-19	A	7, 9
25	12q13.2	rs11171710	56368078	G	1	<i>ERBB3,DGKA,IKZF4</i>	A/G	0.51	0.45	1.22(1.08-1.38)	1.32E-03	0.1	0.41	0.49	0.47	-	7.23E-22	-	11
26	12q13.13	rs11170466	53585859	G	1	<i>ITGB7</i>	C/T	0.2	0.18	1.08(0.92-1.26)	3.49E-01	0.05	0.06	0.17	0.07	1.19	7.86E-09	T	11
27	12p13.31	rs10492166	9885999	I	0.988	<i>CD69</i>	G/A	0.38	0.38	0.99(0.88-1.13)	9.35E-01	0.45	0.49	0.35	0.5	1.15	6.00E-09	G	10
27	12p13.31	rs4763879	9910164	G	1	<i>CD69</i>	G/A	0.47	0.47	1(0.88-1.14)	9.69E-01	0.08	0.35	0.39	0.36	1.09	1.90E-11	A	9
28	13q32.3	rs9585056	100081766	G	1	<i>GPR183</i>	T/C	0.07	0.07	0.98(0.77-1.24)	8.44E-01	0.43	0.29	0.06	0.25	1.12	3.30E-08	C	12

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29	14q32.2	rs4900384	98498951	I	0.964	RP11-61O1.1	G/A	0.32	0.36	0.81(0.7-0.92)	1.79E-03	0.42	0.39	0.36	0.28	1.09	3.70E-09	G	9
29	14q32.2	rs1456988	98488007	G	1	RP11-61O1.1	G/T	0.45	0.49	0.83(0.73-0.94)	4.05E-03	0.43	0.37	0.49	0.29	1.12	2.86E-08	G	12
30	14q32.2	rs941576	101306045	I	0.986	<i>DLK1</i>	A/G	0.26	0.28	0.91(0.79-1.05)	1.90E-01	0.45	0.48	0.34	0.4	1.1	9.33E-05	A	10
30	14q32.2	rs56994090	101306447	I	0.983	<i>DLK1</i>	T/C	0.26	0.28	0.92(0.8-1.06)	2.40E-01	0.44	0.49	0.33	0.38	1.14	1.13E-11	T	12
31	14q24.1	rs1465788	69263599	I	0.998	ZFP36L1	C/T	0.23	0.27	0.8(0.7-0.92)	2.27E-03	0.31	0.35	0.22	0.3	1.16	1.80E-12	G	9
32	14q24.1	rs911263	68753593	I	0.992	<i>RAD51B</i>	T/C	0.12	0.12	1.01(0.83-1.22)	9.52E-01	0.17	0.29	0.11	0.33	1.12	4.93E-06	T	12
33	15q14	rs72727394	38847022	G	1	<i>BACH2</i>	C/T	0.13	0.12	1.13(0.93-1.36)	2.20E-01	0.08	0.22	0.11	0.19	1.15	3.60E-10	T	12
34	15q25.1	rs3825932	79235446	I	0.983	<i>CTSH</i>	T/C	0.1	0.09	1.09(0.88-1.35)	4.07E-01	0.21	0.46	0.09	0.36	-	7.70E-08	-	9
34	15q25.1	rs34593439	79234957	I	0.986	<i>CTSH</i>	G/A	0.04	0.04	0.91(0.66-1.24)	5.41E-01	0.08	0.06	0.07	0.11	1.28	9.02E-14	G	12
34	15q25.1	rs12148472	79231478	I	0.998	<i>CTSH</i>	T/C	0.04	0.04	0.91(0.67-1.24)	5.62E-01	0.15	0.09	0.07	0.13	1.2	2.37E-06	T	10
35	16p13.13	rs193778	11351211	I	0.893	CLEC16A,DEXI	A/G	0	0.01	0.34(0.16-0.69)	3.23E-03	0.14	0.15	0	0.25	1.14	4.40E-10	G	12
35	16p13.13	rs12708716	11179873	I	0.994	CLEC16A,DEXI	A/G	0.22	0.25	0.83(0.72-0.96)	1.16E-02	0.45	0.33	0.19	0.36	1.21	3.39E-21	A	7-9, 12
35	16p13.13	rs12927355	11194771	I	0.998	CLEC16A,DEXI	C/T	0.19	0.22	0.83(0.71-0.96)	1.32E-02	0.24	0.27	0.16	0.33	1.25	1.91E-16	C	10
36	16p11.2	rs151234	28505660	I	0.693	<i>IL27</i>	G/C	0.02	0.01	1.72(0.93-3.18)	8.45E-02	0.06	0.1	0.01	0.13	1.19	4.80E-11	C	12
36	16p11.2	rs9924471	28591530	G	1	<i>IL27</i>	G/A	0.15	0.18	0.87(0.74-1.03)	1.08E-01	0.16	0.21	0.18	0.13	1.24	1.21E-11	A	10
36	16p11.2	rs4788084	28539848	I	0.996	<i>IL27</i>	C/T	0.24	0.26	0.9(0.78-1.04)	1.59E-01	0.22	0.4	0.26	0.36	1.16	2.60E-13	G	9, 12
37	16q23.1	rs8056814	75252327	I	0.997	<i>CTRBI</i>	G/A	0.19	0.2	0.94(0.8-1.1)	4.39E-01	0.35	0.1	0.22	0.08	1.32	3.03E-19	A	10, 12
37	16q23.1	rs7202877	75247245	G	1	<i>CTRBI</i>	T/G	0.2	0.21	0.97(0.83-1.13)	6.54E-01	0.16	0.09	0.22	0.1	1.28	3.10E-15	G	9
38	17q21.2	rs7221109	38770286	G	1	SMARCE1	C/T	0.2	0.23	0.85(0.73-0.98)	2.87E-02	0.18	0.36	0.25	0.39	1.05	1.30E-09	C	9
39	17q12	rs2290400	38066240	I	0.994	<i>ORMDL3,GSDMB</i>	T/C	0.3	0.27	1.07(0.93-1.23)	3.18E-01	0.49	0.42	0.33	0.48	1.15	5.50E-13	A	9, 12
39	17q12	rs12453507	38053207	I	0.988	<i>ORMDL3,GSDMB</i>	C/G	0.3	0.27	1.06(0.93-1.22)	3.95E-01	0.38	0.43	0.34	0.48	1.11	1.05E-08	G	12
40	18q22.2	rs763361	67531642	G	1	<i>CD226</i>	C/T	0.36	0.36	1.06(0.93-1.21)	3.78E-01	0.26	0.45	0.37	0.49	1.12	8.03E-11	T	9, 12
40	18q22.2	rs1615504	67526644	I	1	<i>CD226</i>	C/T	0.37	0.36	1.06(0.93-1.21)	3.86E-01	0.25	0.45	0.37	0.49	1.13	1.79E-11	T	12
41	18p11.21	rs1893217	12809340	G	1	<i>PTPN2</i>	A/G	0.18	0.17	1.07(0.91-1.25)	4.23E-01	0.05	0.07	0.16	0.16	1.2	1.63E-08	G	9-10
41	18p11.21	rs2542151	12779947	I	0.98	<i>PTPN2</i>	T/G	0.18	0.17	1.06(0.9-1.25)	4.93E-01	0.17	0.13	0.16	0.15	1.21	4.75E-15	G	7,8, 12
42	19q13.32	rs402072	47219122	I	0.995	<i>PRKD2</i>	T/C	0.14	0.14	0.94(0.79-1.12)	5.20E-01	0.06	0.11	0.12	0.17	1.15	4.72E-08	T	12
42	19q13.32	rs425105	47208481	I	0.571	<i>PRKD2</i>	T/C	0.18	0.18	0.93(0.80-1.10)	3.83E-01	0.13	0.12	0.16	0.18	1.16	2.70E-11	A	9
43	20p13	rs6043409	1616206	G	1	<i>SIRPG</i>	G/A	0.17	0.18	0.89(0.76-1.04)	1.48E-01	0.16	0.26	0.16	0.33	1.13	2.98E-10	G	12

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43	20p13	rs2281808	1610551	I	0.991	<i>SIRPG</i>	C/T	0.17	0.18	0.91(0.77-1.07)	2.41E-01	0.26	0.27	0.15	0.33	1.11	1.20E-11	C	9
44	21q22.3	rs11203202	43825357	I	0.999	<i>UBASH3A</i>	C/G	0.2	0.22	0.9(0.77-1.05)	1.68E-01	0.17	0.22	0.17	0.31	1.16	1.24E-15	G	12
44	21q22.3	rs11203203	43836186	G	1	<i>UBASH3A</i>	G/A	0.05	0.04	1.17(0.86-1.58)	3.24E-01	0.12	0.26	0.03	0.35	1.16	2.91E-15	A	9-10, 12
45	22q12.2	rs5753037	30581722	I	0.99	<i>HORMAD2,RP3-43804.4</i>	T/C	0.41	0.45	0.83(0.73-0.94)	3.74E-03	0.14	0.27	0.44	0.41	1.1	2.60E-16	T	9, 12
45	22q12.2	rs4820830	30531091	I	1	<i>HORMAD2,RP3-43804.4</i>	C/T	0.41	0.45	0.85(0.75-0.97)	1.31E-02	0.15	0.27	0.44	0.4	1.14	1.20E-12	C	12
46	22q12.3	rs229533	37587111	I	0.999	<i>RAC2,C1QTNF6</i>	C/A	0.21	0.25	0.86(0.75-1.00)	4.29E-02	0.34	0.47	0.26	0.41	1.11	1.80E-08	C	12
47	Xq28	rs2664170	153945602	I	0.994	GAB3	A/G	0.19	0.19	0.99(0.87-1.12)	3.64E-01	0.48	0.36	0.21	0.27	1.16	7.80E-09	G	9
48	1p13.2	rs6679677	114303808	NA	NA	<i>PHTF1 PTPN22</i>	C/A	NA	NA	NA	NA	0	0.04	0	0.1	1.89	1.10E-122	A	7-8, 12
48	1p13.2	rs2476601	114377568	NA	NA	<i>PHTF1 PTPN22</i>	G/A	NA	NA	NA	NA	0	0.04	0	0.1	1.89	1.10E-122	A	9-10, 12
49	2q24.2	rs35667974	163124637	NA	NA	<i>IFIH1</i>	T/C	NA	NA	NA	NA	0	0	0	0.01	1.75	1.01E-11	T	12
50	3p21.31	rs113010081	46457412	NA	NA	<i>CCR5</i>	T/C	NA	NA	NA	NA	0.01	0.05	0	0.11	1.18	4.60E-08	T	12
51	4p15.2	rs10517086	26085511	NA	NA	<i>RP11-324H7.1</i>	G/A	NA	NA	NA	NA	0.32	0.25	0.01	0.29	1.09	4.60E-10	A	9
52	6q15	rs72928038	90976768	NA	NA	<i>BACH2</i>	G/A	NA	NA	NA	NA	0.02	0.13	0	0.18	1.2	6.38E-14	A	12
53	6q23.3	rs6920220	138006504	NA	NA	<i>TNFAIP3</i>	G/A	NA	NA	NA	NA	0.12	0.1	0	0.17	1.12	7.26E-06	A	12-13
54	7p12.1	rs4948088	51027194	NA	NA	<i>COBL</i>	C/A	NA	NA	NA	NA	0.03	0.06	0	0.03	1.3	4.40E-08	C	9
55	10p15.1	rs61839660	6094697	NA	NA	<i>IL2RA RBM17</i>	C/T	NA	NA	NA	NA	0	0.05	0	0.08	1.6	2.84E-39	C	12
56	10p15.1	rs41295121	6129643	NA	NA	<i>IL2RA RBM17</i>	C/T	NA	NA	NA	NA	0	0	0.01	0.01	2.04	4.90E-08	C	12
57	12q24.13	rs3184504	111884608	NA	NA	<i>SH2B3 NAA25</i>	C/T	NA	NA	NA	NA	0.03	0.3	0.01	0.47	1.27	1.77E-21	T	9-10
57	12q24.13	rs653178	112007756	NA	NA	<i>SH2B3 NAA25</i>	T/C	NA	NA	NA	NA	0.03	0.3	0.01	0.47	1.3	1.56E-44	C	12
57	12q24.13	rs17696736	112486818	NA	NA	<i>SH2B3 NAA25</i>	A/G	NA	NA	NA	NA	0.02	0.26	0.01	0.44	1.24	3.62E-29	G	7-8, 12
58	15q14	rs12908309	38928677	NA	NA	<i>RASGRP1</i>	G/A	NA	NA	NA	NA	0.27	0.15	0	0.21	1.18	4.31E-08	G	10
59	17q21.31	rs1052553	44073889	NA	NA	<i>MAPT</i>	A/G	NA	NA	NA	NA	0.03	0.19	0	0.23	1.12	8.20E-08	A	12
60	19p13.2	rs34536443	10463118	NA	NA	<i>TYK2</i>	C/G	NA	NA	NA	NA	0	0.02	0	0.03	1.49	4.39E-15	G	12
60	19p13.2	rs12720356	10469975	NA	NA	<i>TYK2</i>	A/C	NA	NA	NA	NA	0.01	0.05	0	0.1	1.22	3.70E-07	A	12
61	19q13.33	rs516246	49206172	NA	NA	<i>FUT2</i>	C/T	NA	NA	NA	NA	0.49	0.38	0.01	0.43	1.15	5.22E-14	T	12
61	19q13.33	rs602662	49206985	NA	NA	<i>FUT2</i>	G/A	NA	NA	NA	NA	0.49	0.4	0.01	0.46	1.12	4.23E-05	A	10

a Sources: G, genotyped; I, imputed;

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b MAF: Minor allele frequency;

c OR (95% confidence interval (CI)) and P values were derived from logistic regression analysis with adjustment for sex and the significant eigenvectors under the assumption of an additive genetic model;

d The associations were derived from seven published GWAS studies of T1D, and the most significant associations were extracted. The seven studies were showed as follows:

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Supplementary Table S10. Identification of five independent susceptibility loci in the MHC region

SUPPLEMENTARY DATA

HLA Loci	Step ^a	Variants	Info	MAF ^b		Unadjusted			Adjusted		Adjusted for
				Cases	Controls	OR (95%CI) ^c	P ^c	OR (95%CI) ^d	P ^d		
	Step 1	rs1770		0.80	0.47	4.35(3.85-5.00)	8.95×10⁻⁸³	-	-	-	
		HLA-DRB1 amino acid position 74		-	-	-	3.84×10⁻⁷⁴	-	6.38×10⁻²⁴		
		Arg	0.887	0.22	0.06	4.93(3.95-6.14)	1.38×10^{-45}	2.74(-2.17-3.47)	4.29×10^{-17}		
	Step 2	Ala	0.912	0.32	0.48	0.51(0.44-0.57)	3.32×10^{-25}	1.42(-1.18-1.71)	1.91×10^{-4}		rs1770
		Leu	0.908	0.02	0.08	0.29(0.21-0.41)	9.90×10^{-13}	0.67(-0.46-0.97)	0.034		
		Glu	0.89	0.35	0.3	1.34(1.17-1.52)	1.07×10^{-5}	0.68(-0.58-0.79)	1.07×10^{-6}		
		Gln	0.988	0.09	0.09	0.87(0.7-1.09)	0.222	0.49(-0.39-0.63)	7.43×10^{-9}		
HLA-DRB1/DQA1/DQB1		HLA-DRB1 amino acid position 11		-	-	-	7.26×10⁻⁴⁵	-	8.47×10⁻¹²		
		Pro	0.992	0.04	0.14	0.24(0.18-0.31)	1.14×10^{-26}	0.49(0.36-0.67)	5.99×10^{-6}		
	Step3	Asp	0.961	0.3	0.18	1.85(1.61-2.14)	1.78×10^{-17}	1.93(1.45-2.58)	8.50×10^{-6}		rs1770 and HLA-DRB1 position 74
		Val	0.928	0.21	0.15	1.44(1.23-1.69)	6.96×10^{-6}	0.75(0.59-0.95)	0.019		
		Ser	0.959	0.35	0.42	0.78(0.68-0.88)	1.08×10^{-4}	1.1(0.85-1.42)	0.459		
		Gly	0.999	0.09	0.09	0.87(0.7-1.09)	0.222	-	-		
		Leu	0.885	0.02	0.01	1.35(0.81-2.25)	0.243	3.16(1.81-5.52)	4.93×10^{-5}		
		HLA-A amino acid position 9		-	-	-	5.70×10⁻⁷	-	2.47×10⁻¹¹		
HLA-A	Step4	Ser	0.961	0.35	0.27	1.46(1.27-1.67)	7.63×10^{-8}	1.64(1.38-1.95)	1.66×10^{-8}		All four digital alleles in HLA-DRB1/DQA1/DQB1
		Tyr	0.990	0.25	0.30	0.79(0.68-0.9)	7.36×10^{-4}	0.88(0.74-1.04)	0.141		
		Phe	0.990	0.27	0.30	0.87(0.76-1.00)	0.051	0.95(0.81-1.12)	0.567		
		Thr	0.961	0.13	0.13	0.99(0.82-1.19)	0.898	0.46(0.35-0.61)	4.40×10^{-8}		
		HLA-C amino acid position 275		-	-	-	1.70×10⁻¹¹		9.78×10⁻¹²		
HLA-C	Step5	Lys	0.995	0.04	0.08	0.48(0.36-0.63)	1.65×10^{-7}	0.5(0.36-0.71)	6.92×10^{-5}		All four digital alleles in HLA-DRB1/DQA1/DQB1 and HLA-A position 9
		Gly	0.988	0.14	0.09	1.64(1.34-2.00)	1.29×10^{-6}	2.2(1.71-2.83)	9.55×10^{-10}		
		Glu	0.999	0.82	0.83	0.95(0.81-1.12)	0.595	0.76(0.63-0.94)	0.011		

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^a Stepwise conditional analysis: the analysis were clasified into two major parts (variants within HLA-DRB1/DQA1/DQB1 and variants outside of HLA-DRB1/DQA1/DQB1); in the first step, sex and PCAs were adjusted; the variants with the lowest P were included in the next step until no variants were significant ($P<5.0\times10^{-8}$); to identify variants outside of HLA-DRB1/DQA1/DQB1, we adjusted all four digital alleles in HLA-DRB1/DQA1/DQB1 refer to Nat Genet. 2015 Aug;47(8):898-905; ^b MAF: Minor allele frequency; ^c Derived from logistic regression analysis with adjustment for sex and the significant eigenvectors under the assumption of an additive genetic model; ^d Additionally conditioned on the most significant variant in HLA-DRB1-DQA1-DQB1 region or the whole four digital alleles in HLA-DRB1-DQA1-DQB1.

SUPPLEMENTARY DATA

Supplementary Table S11. Summary of linkage disequilibrium values for our identified independent loci and those reported in Gaussians (r^2/D')

	HLA-DQB1 amino acid position 57					HLA-DRB1 amino acid position 13				
	AA_DQB1_57_A	AA_DQB1_57_D	AA_DQB1_57_S	AA_DQB1_57_V	AA_DRB1_13_F	AA_DRB1_13_G	AA_DRB1_13_H	AA_DRB1_13_R	AA_DRB1_13_S	AA_DRB1_13_Y
rs1770	0.26(1.00)	0.07(0.42)	0.05(1.00)	0.10(1.00)	0.13(0.78)	0.23(0.91)	0.09(0.83)	0.17(1.00)	<0.01(0.06)	0.06(1.00)
HLA-DRB1 amino acid position 74										
AA_DRB1_74_R	0.35(1.00)	0.23(1.00)	<0.01(1.00)	0.01(1.00)	0.05(1.00)	0.03(1.00)	0.03(1.00)	0.02(1.00)	0.46(1.00)	0.01(1.00)
AA_DRB1_74_A	0.16(0.76)	0.04(0.31)	0.01(0.39)	0.09(1.00)	0.15(0.78)	0.04(0.41)	0.06(0.44)	0.16(1.00)	0.01(0.19)	0.07(1.00)
AA_DRB1_74_L	0.02(0.97)	0.03(0.86)	<0.01(0.03)	<0.01(1.00)	0.02(1.00)	0.33(1.00)	0.01(1.00)	0.01(0.97)	0.02(1.00)	0.01(1.00)
AA_DRB1_74_E	0.03(0.41)	0.06(0.47)	<0.01(0.01)	0.03(1.00)	0.56(0.87)	0.08(1.00)	<0.01(0.12)	0.05(1.00)	0.06(0.63)	0.05(1.00)
AA_DRB1_74_Q	0.17(0.84)	0.11(0.82)	<0.01(0.74)	<0.01(1.00)	0.04(1.00)	0.02(1.00)	0.01(0.85)	0.01(1.00)	0.03(1.00)	1.00(1.00)
HLA-DRB1 amino acid position 11										
AA_DRB1_11_P	0.04(1.00)	0.02(0.48)	0.09(0.56)	<0.01(0.34)	0.04(1.00)	0.02(0.98)	0.02(1.00)	1.00(1.00)	0.03(1.00)	0.01(1.00)
AA_DRB1_11_D	0.11(0.93)	0.17(0.95)	0.01(1.00)	0.02(1.00)	0.88(1.00)	0.05(1.00)	0.06(1.00)	0.03(1.00)	0.10(1.00)	0.03(1.00)
AA_DRB1_11_V	0.05(0.31)	0.03(0.30)	0.01(1.00)	<0.01(0.07)	0.04(1.00)	0.04(1.00)	0.94(1.00)	0.02(1.00)	0.07(1.00)	0.02(0.95)
AA_DRB1_11_S	<0.01(0.08)	0.01(0.11)	<0.01(0.07)	0.01(0.26)	0.22(1.00)	0.27(1.00)	0.13(1.00)	0.07(1.00)	0.50(1.00)	0.06(1.00)
AA_DRB1_11_G	0.17(0.84)	0.11(0.82)	<0.01(0.74)	0.01(1.00)	0.04(1.00)	0.02(1.00)	0.01(0.85)	0.01(1.00)	0.03(1.00)	1.00(1.00)
AA_DRB1_11_L	0.01(1.00)	0.02(0.96)	<0.01(1.00)	0.24(0.98)	0.05(1.00)	<0.01(1.00)	<0.01(1.00)	<0.01(1.00)	<0.01(1.00)	<0.01(0.87)
HLA-A amino acid position 9										
AA_A_9_S	0.02(0.14)	0.01(0.10)	<0.01(0.06)	0.01(0.47)	<0.01(0.06)	0.01(0.32)	<0.01(0.09)	<0.01(0.26)	0.01(0.24)	0.08(0.59)
AA_A_9_Y	0.01(0.30)	0.02(0.26)	<0.01(0.14)	<0.01(0.43)	<0.01(0.01)	0.02(0.20)	<0.01(0.06)	<0.01(0.04)	0.01(0.25)	0.02(0.62)
AA_A_9_F	0.02(0.35)	0.02(0.27)	<0.01(0.01)	<0.01(0.04)	0.01(0.10)	<0.01(0.06)	<0.01(0.06)	<0.01(0.11)	0.10(0.29)	0.01(0.51)
AA_A_9_T	0.03(0.30)	0.06(0.50)	<0.01(0.69)	0.04(0.30)	0.01(0.51)	0.01(0.61)	0.01(0.70)	<0.01(0.28)	0.15(0.56)	<0.01(0.51)
HLA-C amino acid position 275										
AA_C_275_K	0.01(0.19)	<0.01(0.21)	<0.01(0.07)	<0.01(0.40)	<0.01(0.40)	<0.01(0.13)	0.02(0.26)	<0.01(<0.01)	<0.01(0.22)	<0.01(0.27)
AA_C_275_G	0.02(0.57)	0.02(0.54)	<0.01(0.12)	<0.01(0.57)	0.02(0.24)	0.01(0.10)	<0.01(0.41)	<0.01(0.13)	0.01(0.58)	0.01(1.00)
AA_C_275_E	<0.01(0.22)	0.01(0.22)	<0.01(0.06)	<0.01(0.46)	0.01(0.10)	<0.01(0.07)	<0.01(0.04)	<0.01(0.07)	0.01(0.41)	0.01(0.65)

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Supplementary Table S11. Summary of linkage disequilibrium values for our identified independent loci and those reported in Gaussians (r^2/D') (continue)

	HLA-DRB1 amino acid position 71				HLA-A amino acid position 62				HLA_B_39	HLA_DPB1_0402
	AA_DRB1_71_A	AA_DRB1_71_E	AA_DRB1_71_K	AA_DRB1_71_R	AA_A_62_E	AA_A_62_G	AA_A_62_Q	AA_A_62_R		
rs1770	0.15(1.00)	0.05(0.83)	0.08(0.88)	0.01(0.10)	<0.01(0.10)	<0.01(0.04)	<0.01(0.07)	<0.01(0.19)	<0.01(0.23)	<0.01(0.04)
HLA-DRB1 amino acid position 74										
AA_DRB1_74_R	0.01(1.00)	0.01(1.00)	0.84(1.00)	0.38(1.00)	<0.01(0.06)	0.01(0.44)	0.02(0.58)	0.14(0.40)	<0.01(1.00)	<0.01(0.85)
AA_DRB1_74_A	0.14(1.00)	0.07(1.00)	0.06(0.69)	0.02(0.21)	<0.01(0.01)	<0.01(0.03)	<0.01(0.07)	<0.01(0.17)	<0.01(0.24)	<0.01(0.04)
AA_DRB1_74_L	<0.01(0.87)	<0.01(0.69)	0.01(1.00)	0.02(1.00)	<0.01(0.22)	0.01(0.25)	<0.01(0.07)	<0.01(0.63)	0.03(0.30)	<0.01(0.01)
AA_DRB1_74_E	0.04(1.00)	0.02(1.00)	0.08(1.00)	0.18(1.00)	<0.01(0.08)	0.02(0.13)	0.01(0.17)	0.02(0.51)	<0.01(0.02)	<0.01(0.11)
AA_DRB1_74_Q	<0.01(1.00)	<0.01(1.00)	0.02(1.00)	0.04(1.00)	0.01(0.49)	0.02(0.67)	0.07(0.55)	<0.01(0.40)	<0.01(1.00)	<0.01(0.10)
HLA-DRB1 amino acid position 11										
AA_DRB1_11_P	0.87(1.00)	<0.01(1.00)	0.02(1.00)	0.20(0.84)	<0.01(0.20)	<0.01(0.11)	<0.01(0.04)	<0.01(0.46)	<0.01(<0.01)	<0.01(0.14)
AA_DRB1_11_D	0.03(1.00)	0.01(1.00)	0.05(1.00)	0.12(1.00)	<0.01(0.05)	0.02(0.17)	0.01(0.26)	0.01(0.49)	<0.01(0.01)	<0.01(0.04)
AA_DRB1_11_V	0.02(1.00)	<0.01(0.26)	<0.01(0.01)	0.01(0.41)	0.01(0.10)	<0.01(0.14)	<0.01(0.03)	0.01(0.45)	<0.01(0.04)	<0.01(0.03)
AA_DRB1_11_S	0.06(1.00)	0.05(0.84)	0.16(0.76)	0.10(0.40)	<0.01(0.11)	<0.01(0.11)	0.01(0.16)	0.07(0.51)	<0.01(0.12)	<0.01(0.40)
AA_DRB1_11_G	0.01(1.00)	<0.01(1.00)	0.02(1.00)	0.04(1.00)	0.01(0.49)	0.02(0.67)	0.07(0.55)	<0.01(0.40)	<0.01(1.00)	<0.01(0.09)
AA_DRB1_11_L	<0.01(1.00)	<0.01(1.00)	<0.01(1.00)	0.01(1.00)	<0.01(0.05)	<0.01(0.26)	<0.01(0.21)	<0.01(0.58)	<0.01(1.00)	<0.01(0.09)
HLA-A amino acid position 9										
AA_A_9_S	<0.01(0.30)	<0.01(0.36)	<0.01(0.22)	0.01(0.27)	0.68(1.00)	0.19(1.00)	0.01(0.19)	0.08(1.00)	<0.01(0.15)	<0.01(0.10)
AA_A_9_Y	<0.01(0.03)	0.01(0.65)	0.01(0.34)	0.01(0.27)	0.12(1.00)	0.02(0.32)	0.17(0.45)	<0.01(0.03)	<0.01(0.29)	<0.01(0.03)
AA_A_9_F	<0.01(0.11)	<0.01(0.32)	<0.01(0.29)	<0.01(0.11)	0.12(1.00)	0.56(0.78)	0.06(0.54)	0.07(1.00)	<0.01(<0.01)	<0.01(0.20)
AA_A_9_T	<0.01(0.17)	0.06(0.45)	0.10(0.33)	0.13(0.57)	0.04(1.00)	0.06(1.00)	0.02(0.47)	0.52(0.77)	<0.01(1.00)	<0.01(0.26)
HLA-C amino acid position 275										
AA_C_275_K	<0.01(<0.01)	<0.01(0.17)	<0.01(0.51)	<0.01(0.29)	0.01(0.21)	<0.01(0.21)	<0.01(0.06)	<0.01(0.47)	<0.01(1.00)	<0.01(<0.01)
AA_C_275_G	<0.01(0.11)	<0.01(0.33)	0.01(0.75)	0.01(0.54)	<0.01(0.03)	<0.01(0.10)	<0.01(0.04)	0.01(0.64)	<0.01(1.00)	<0.01(0.22)
AA_C_275_E	<0.01(0.05)	<0.01(0.28)	0.01(0.63)	0.01(0.42)	0.01(0.10)	<0.01(0.03)	<0.01(0.05)	0.01(0.54)	<0.01(1.00)	<0.01(0.10)

SUPPLEMENTARY DATA

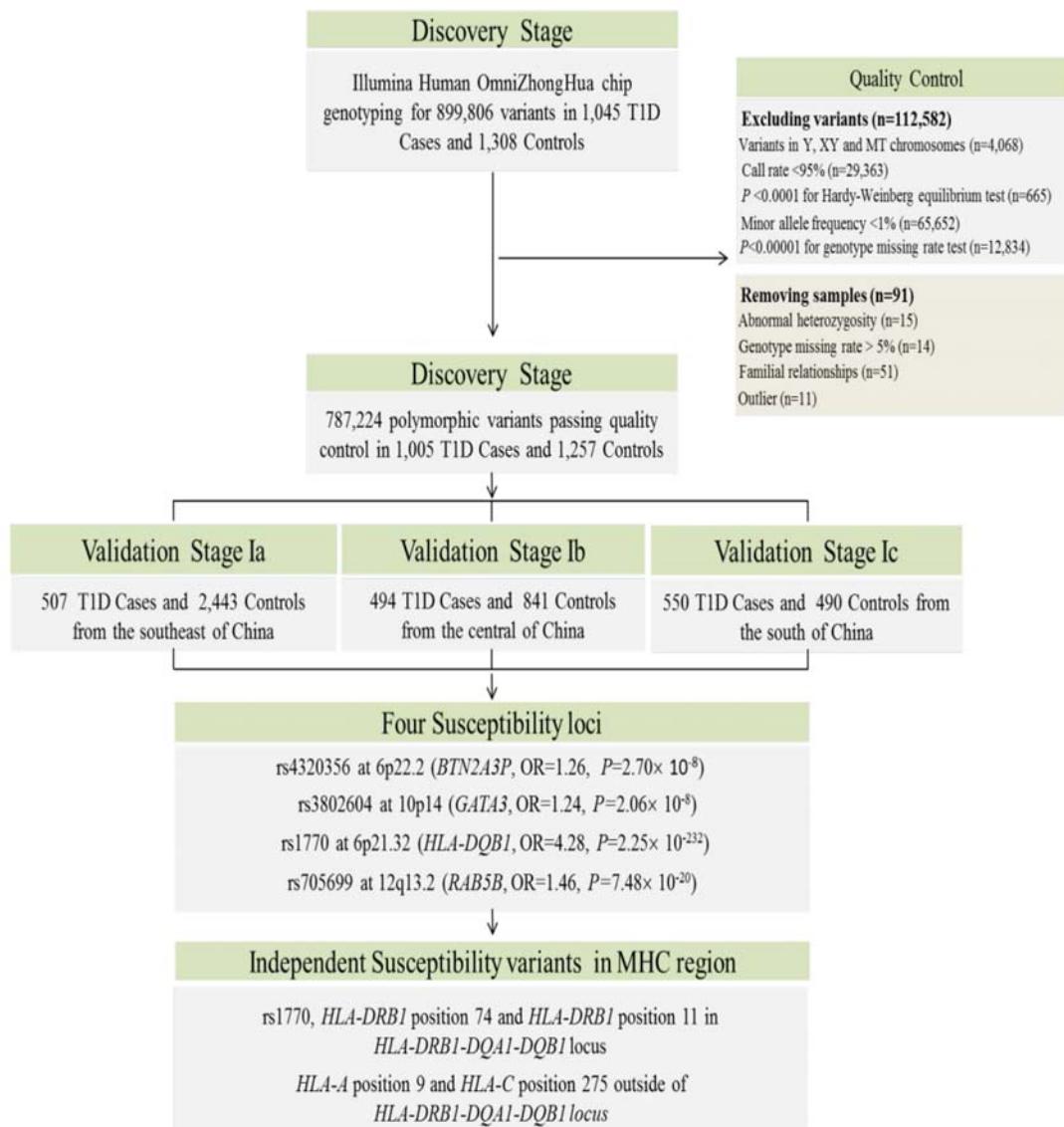
Supplementary Table S12. Effect sizes of the identified variants in T1D patients with age of onset ≤ 17 and > 17

SNP	Age of Onset ≤ 17 ^a		Age of Onset > 17 ^a		Meta		
	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P _{het}	I ²
rs1770	6.87(5.51-8.57)	8.23E-66	3.29(2.76-3.92)	1.02E-40	4.37(3.81-5.01)	2.86E-07	0.96
AA_DRB1_74_32659926_R	7.05(5.42-9.18)	4.60E-48	3.55(2.75-4.56)	9.89E-23	4.93(4.11-5.92)	2.17E-04	0.93
AA_DRB1_74_32659926_L	6.51(3.59-11.82)	7.39E-10	2.36(1.61-3.45)	1.11E-05	3.17(2.30-4.37)	4.90E-03	0.87
AA_DRB1_74_32659926_Q	1.44(1.08-1.92)	1.26E-02	1.09(0.84-1.41)	5.18E-01	1.23(1.02-1.50)	1.54E-01	0.51
AA_DRB1_74_32659926_E	1.42(1.21-1.67)	2.27E-05	1.27(1.08-1.49)	3.17E-03	1.34(1.20-1.50)	3.31E-01	0.00
AA_DRB1_11_32660115_P	6.61(4.33-10.11)	2.47E-18	3.17(2.33-4.31)	1.72E-13	4.08(3.18-5.24)	5.91E-03	0.87
AA_DRB1_11_32660115_V	1.64(1.35-1.99)	6.20E-07	1.29(1.05-1.57)	1.43E-02	1.46(1.27-1.68)	8.89E-02	0.65
AA_DRB1_11_32660115_D	1.98(1.66-2.37)	6.59E-14	1.82(1.53-2.16)	8.28E-12	1.90(1.67-2.14)	4.88E-01	0.00
AA_DRB1_11_32660115_L	1.42(0.77-2.59)	2.58E-01	1.30(0.70-2.43)	4.09E-01	1.36(0.88-2.10)	8.47E-01	0.00
AA_C_275_31345841_G	1.29(1.00-1.66)	5.17E-02	1.94(1.54-2.45)	2.44E-08	1.61(1.36-1.91)	2.00E-02	0.82
AA_C_275_31345841_K	2.37(1.63-3.46)	6.24E-06	1.89(1.35-2.65)	2.37E-04	2.09(1.63-2.69)	3.74E-01	0.00
AA_A_9_30018537_F	1.09(0.92-1.30)	2.93E-01	1.2(1.01-1.42)	3.43E-02	1.15(1.02-1.29)	4.48E-01	0.00
AA_A_9_30018537_S	1.48(1.25-1.76)	4.86E-06	1.41(1.19-1.67)	5.96E-05	1.45(1.28-1.63)	6.74E-01	0.00
AA_A_9_30018537_T	1.02(0.81-1.28)	8.96E-01	1.04(0.83-1.31)	7.27E-01	1.03(0.87-1.21)	8.76E-01	0.00
rs3802604	1.50(1.28-1.76)	5.11E-07	1.21(1.04-1.42)	1.62E-02	1.35(1.21-1.51)	6.17E-02	0.71
rs705699	1.71(1.44-2.03)	1.10E-09	1.47(1.24-1.75)	9.43E-06	1.59(1.40-1.79)	2.28E-01	0.31
rs4320356	1.51(1.27-1.78)	2.01E-06	1.33(1.12-1.57)	1.14E-03	1.42(1.26-1.60)	3.01E-01	0.06

^a OR_{add} (95% confidence interval (CI)) and P values were derived from logistic regression analysis with adjustment for sex and the significant eigenvectors under the assumption of an additive genetic model;

SUPPLEMENTARY DATA

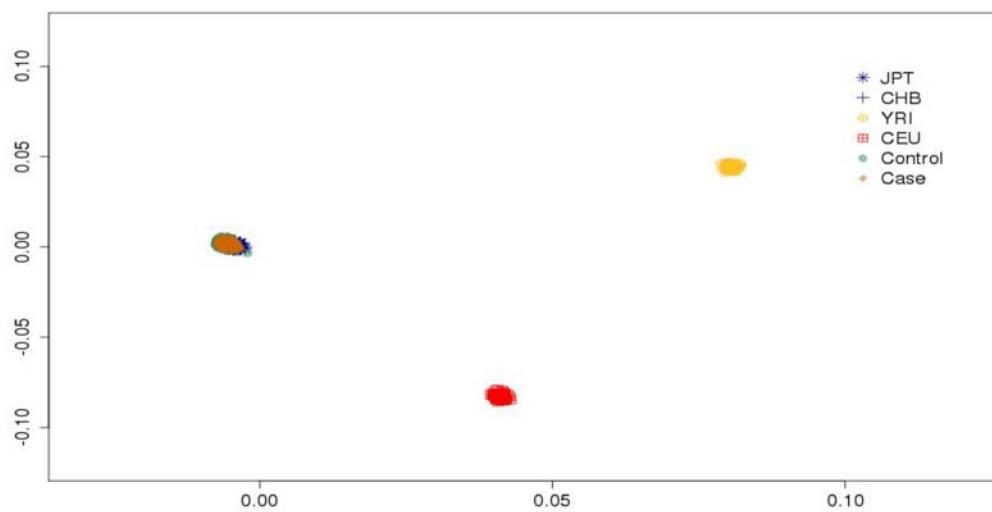
Supplementary Figure S1. Summary of the study design and work flow.



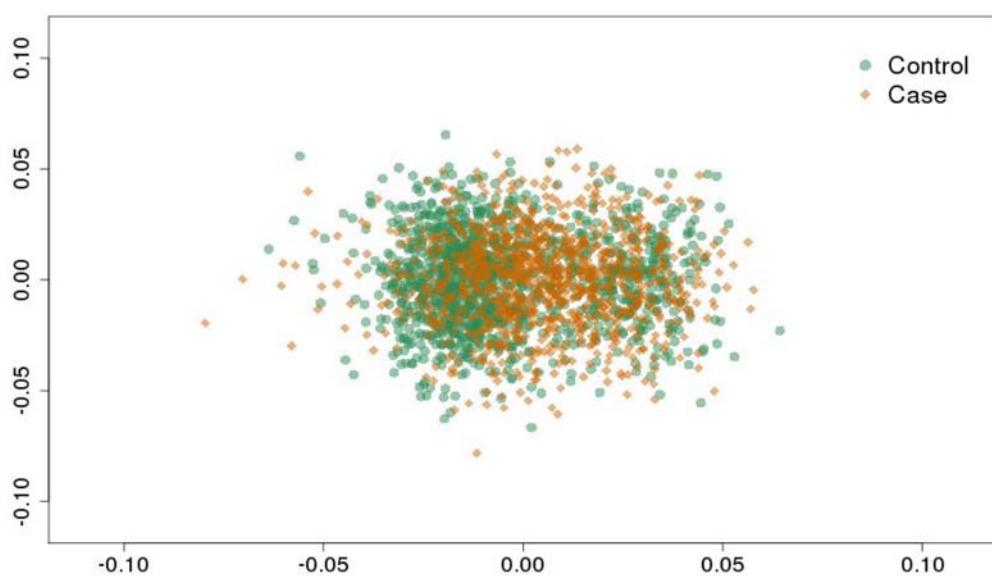
SUPPLEMENTARY DATA

Supplementary Figure S2. Principal component analysis. The first two principal components for each individual were plotted: A) the relatedness between the studied 1,005 cases and 1,257 controls, together with European (CEU), African (YRI), Chinese (CHB), and Japanese (JPT) data from the HapMap project was analyzed to determine ethnicity; and B) the population structures between the cases and the controls.

A

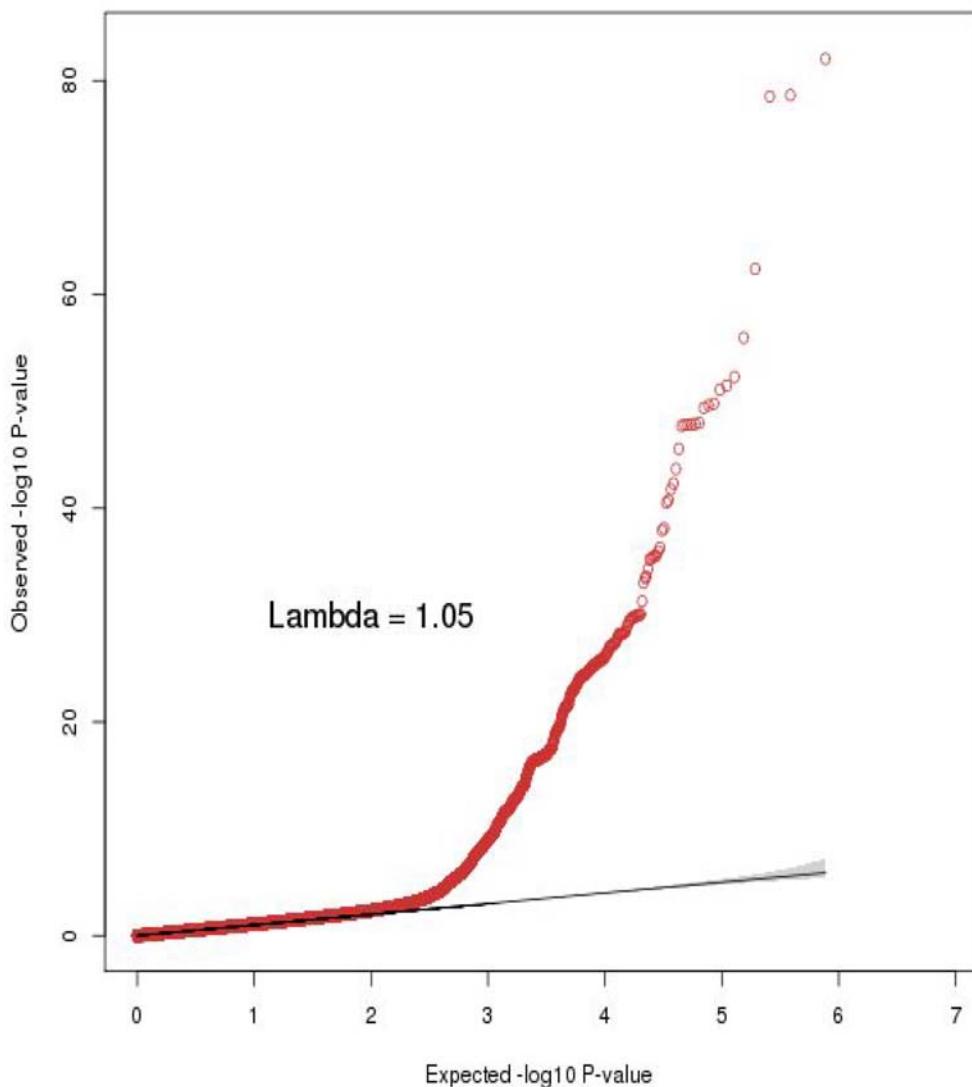


B



SUPPLEMENTARY DATA

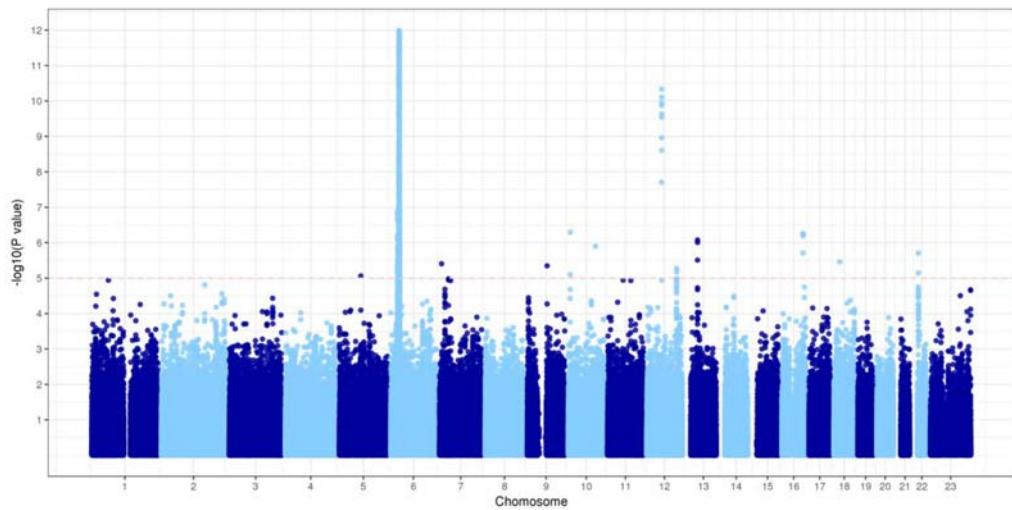
Supplementary Figure S3. Quantile-quantile plot and genomic inflation factor lambda for associations with T1D risk. Observed P values are plotted as a function of theoretical P values. Gray areas indicate 90% confidence intervals from a null distribution of P values.



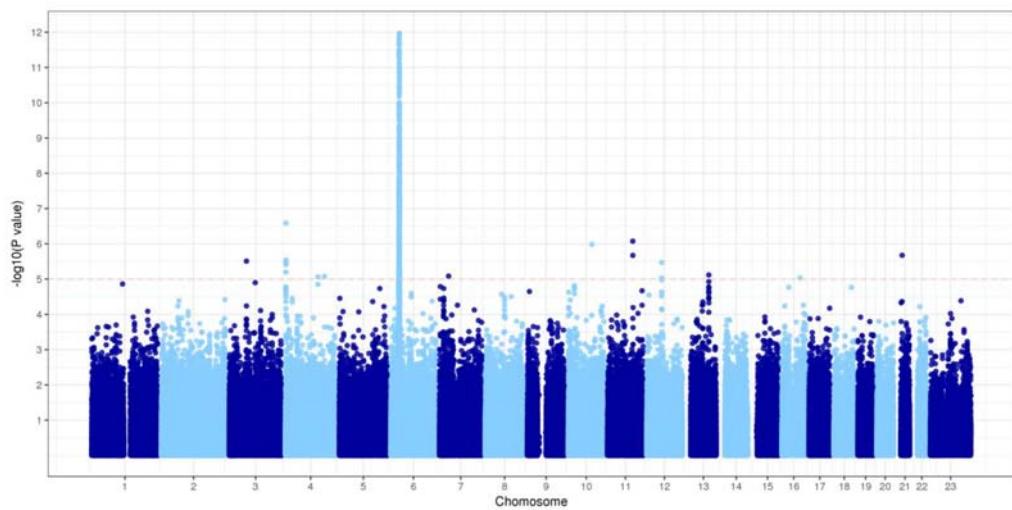
SUPPLEMENTARY DATA

Supplementary Figure S4. Manhattan plot for the associations between genetic variants and T1D risk in early-onset T1D cases (A) and late-onset T1D cases. The associations (-log₁₀ (*P*) values, Y-axis) are plotted against genomic position (X-axis by chromosome and the chromosomal position of NCBI build 37). The purple horizontal line corresponds to a *P*-value of 1.0×10⁻⁵.

A



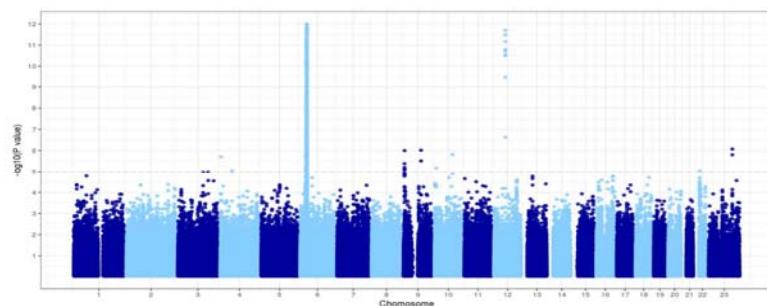
B



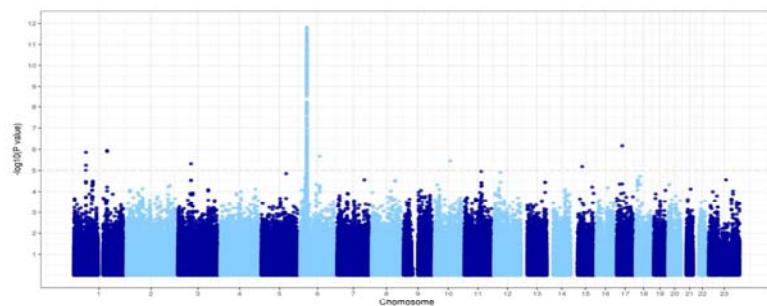
SUPPLEMENTARY DATA

Supplementary Figure S5. Manhattan plot for the associations between genetic variants and T1D risk in GADA+ T1D cases (A), GADA- T1D cases (B), IA-2A+ T1D cases (C), IA-2A- T1D cases (D), ZnT8A + T1D cases (E), ZnT8A- T1D cases (F), Multi antibodies positive T1D cases (G), and Single antibody positive T1D cases (H). The associations ($-\log_{10}(P)$ values, Y-axis) are plotted against genomic position (X-axis by chromosome and the chromosomal position of NCBI build 37). The purple horizontal line corresponds to a P -value of 1.0×10^{-5} .

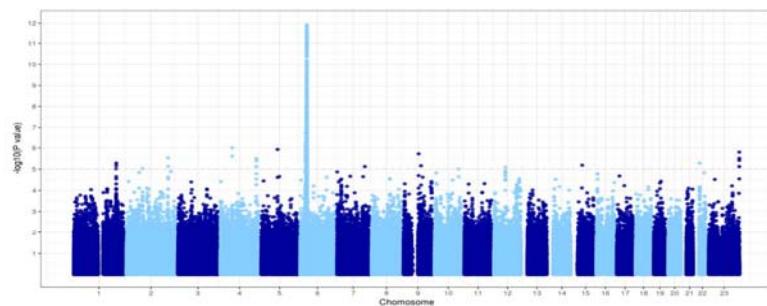
A. GADA+ T1D



B. GADA- T1D

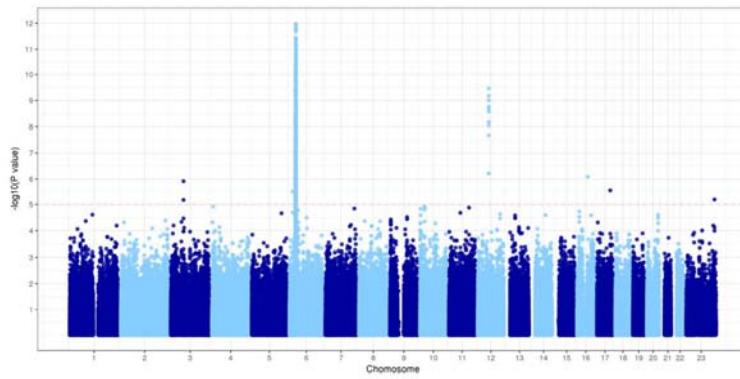


C. IA-2A+ T1D

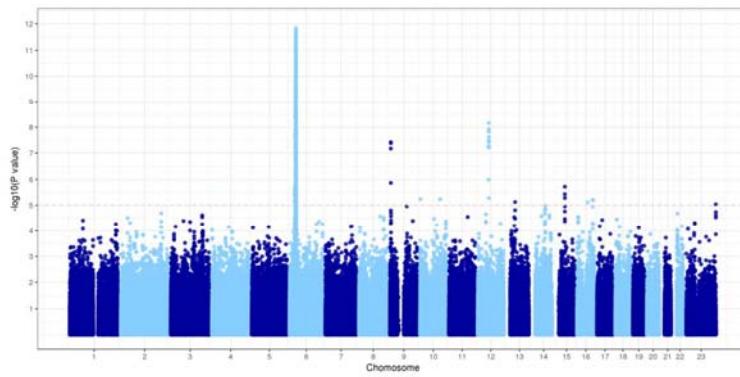


SUPPLEMENTARY DATA

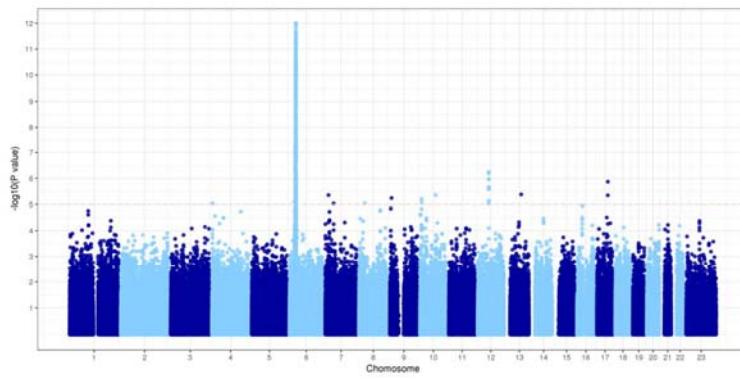
D. IA-2A- T1D



E. ZnT8A + T1D

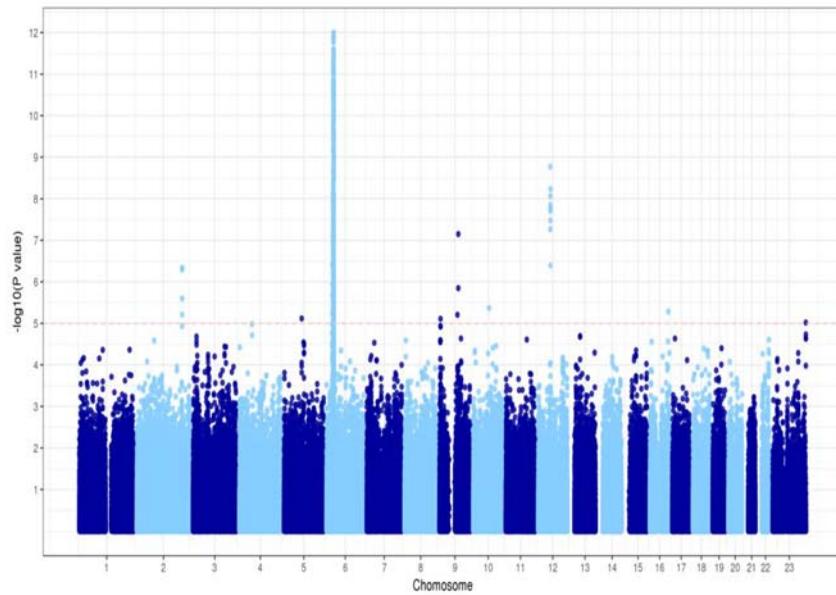


F. ZnT8A- T1D

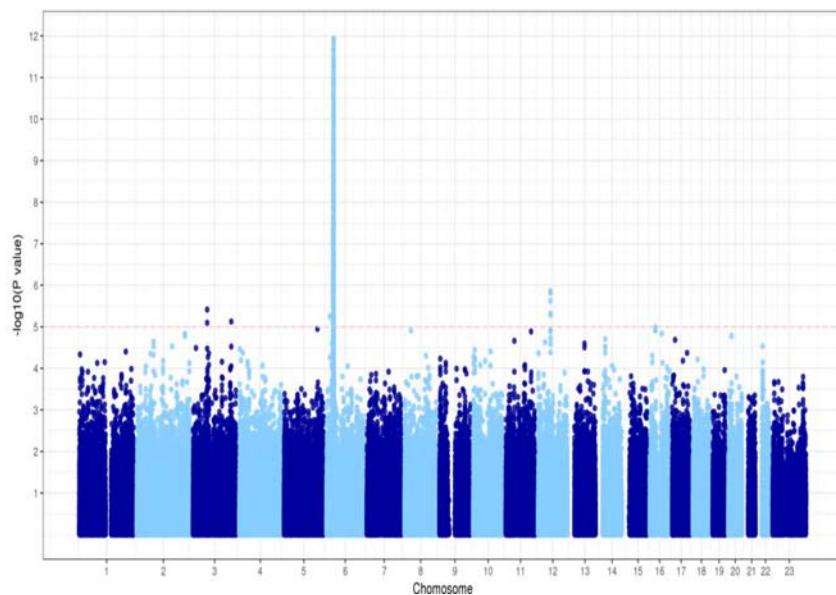


SUPPLEMENTARY DATA

G. Multi antibodies positive T1D

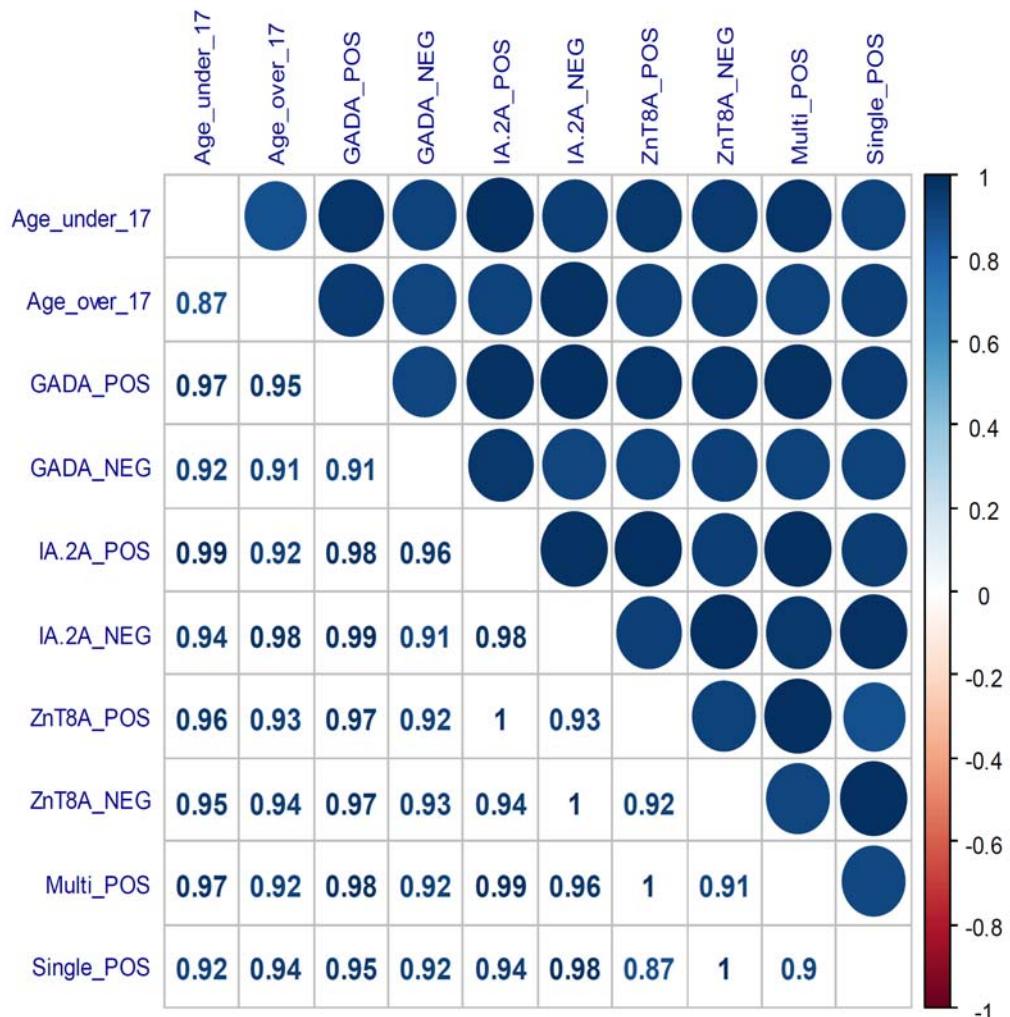


H. Single antibody positive T1D



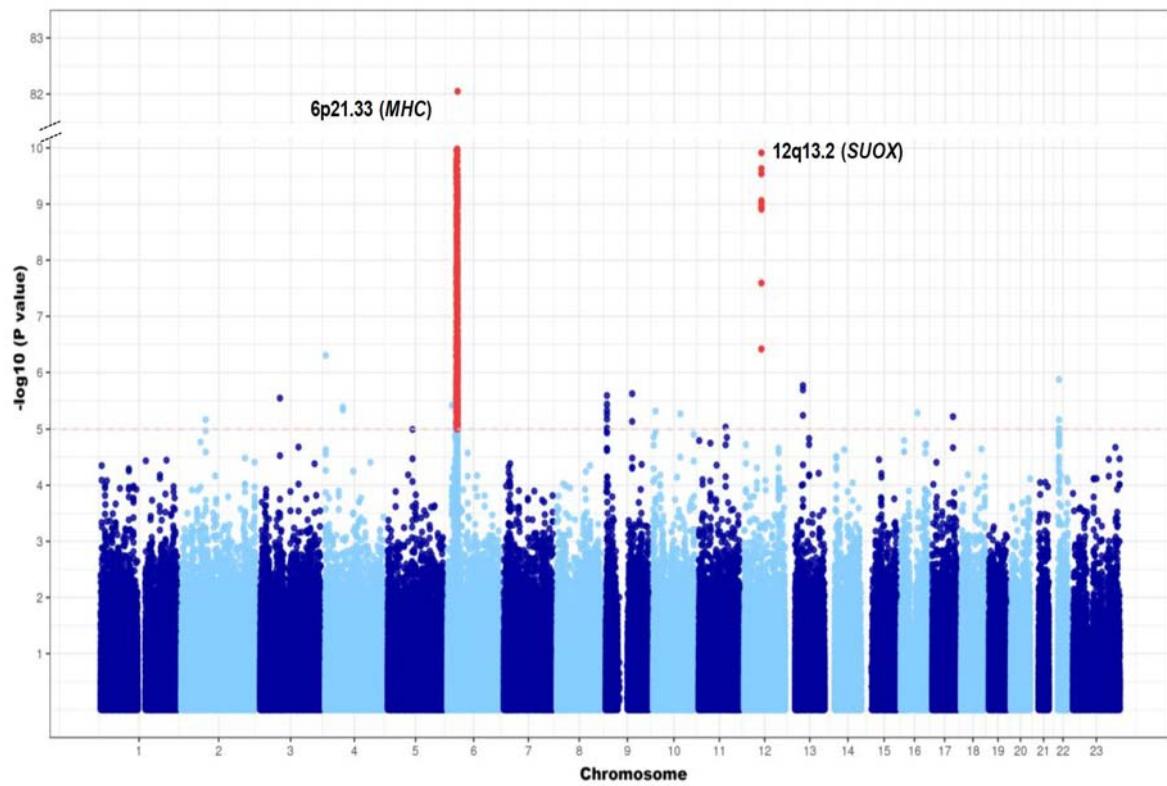
SUPPLEMENTARY DATA

Supplementary Figure S6. Genetic correlations among different subgroups of T1D. Blue, positive genetic correlation; red, negative genetic correlation. The lower matrix corresponds to correlation coefficient.



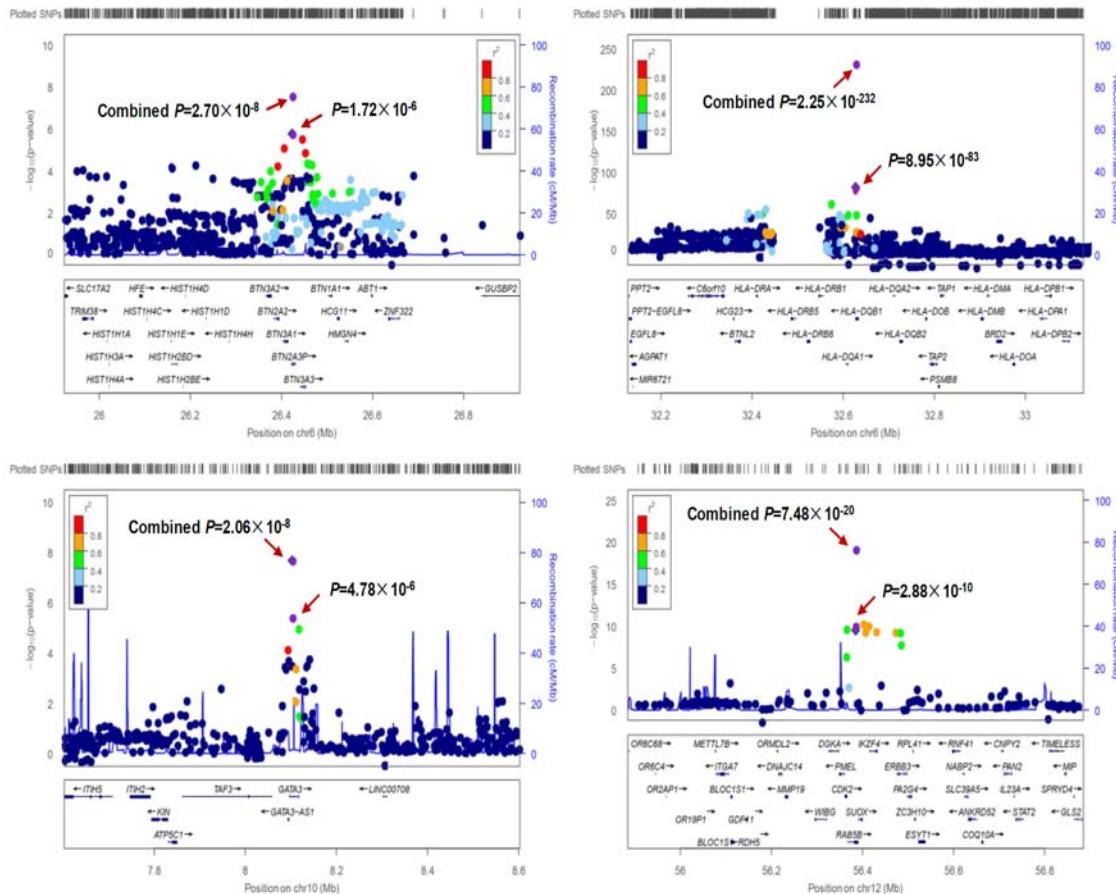
SUPPLEMENTARY DATA

Supplementary Figure S7. Manhattan plot for the associations between genetic variants and T1D risk. The associations (-log₁₀ (P) values, Y-axis) are plotted against genomic position (X-axis by chromosome and the chromosomal position of NCBI build 37). The purple horizontal line corresponds to a P-value of 1.0×10^{-5} .



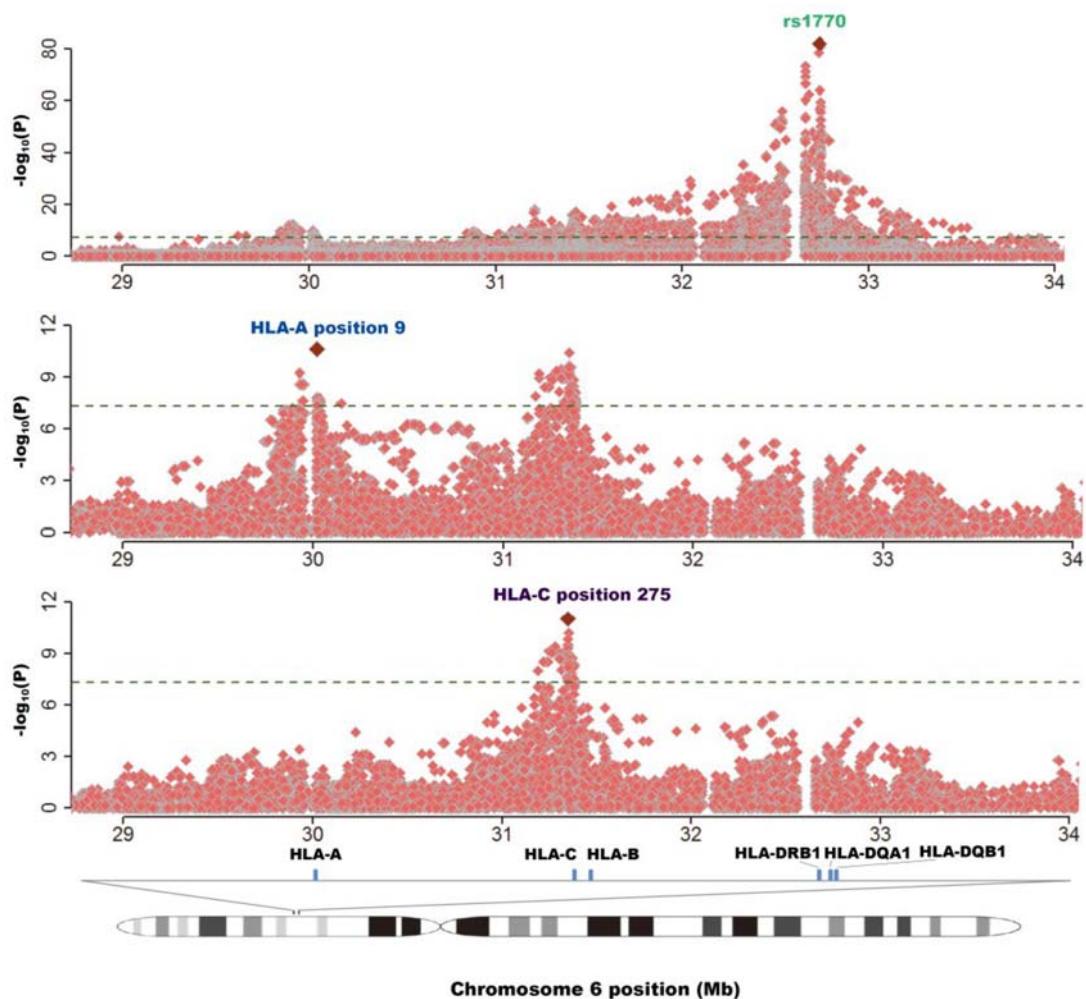
SUPPLEMENTARY DATA

Supplementary Figure S8. Regional association plots with lead variants showed using purple circles at 6p22.2 (A), 6p21.32 (B), 10p14 (C), and 12q13.2 (D). Associations of individual variants are plotted as $-\log_{10} P$ against chromosomal position. The right y-axis shows the recombination rate estimated from the 1,000 Genomes Project ASN data.



SUPPLEMENTARY DATA

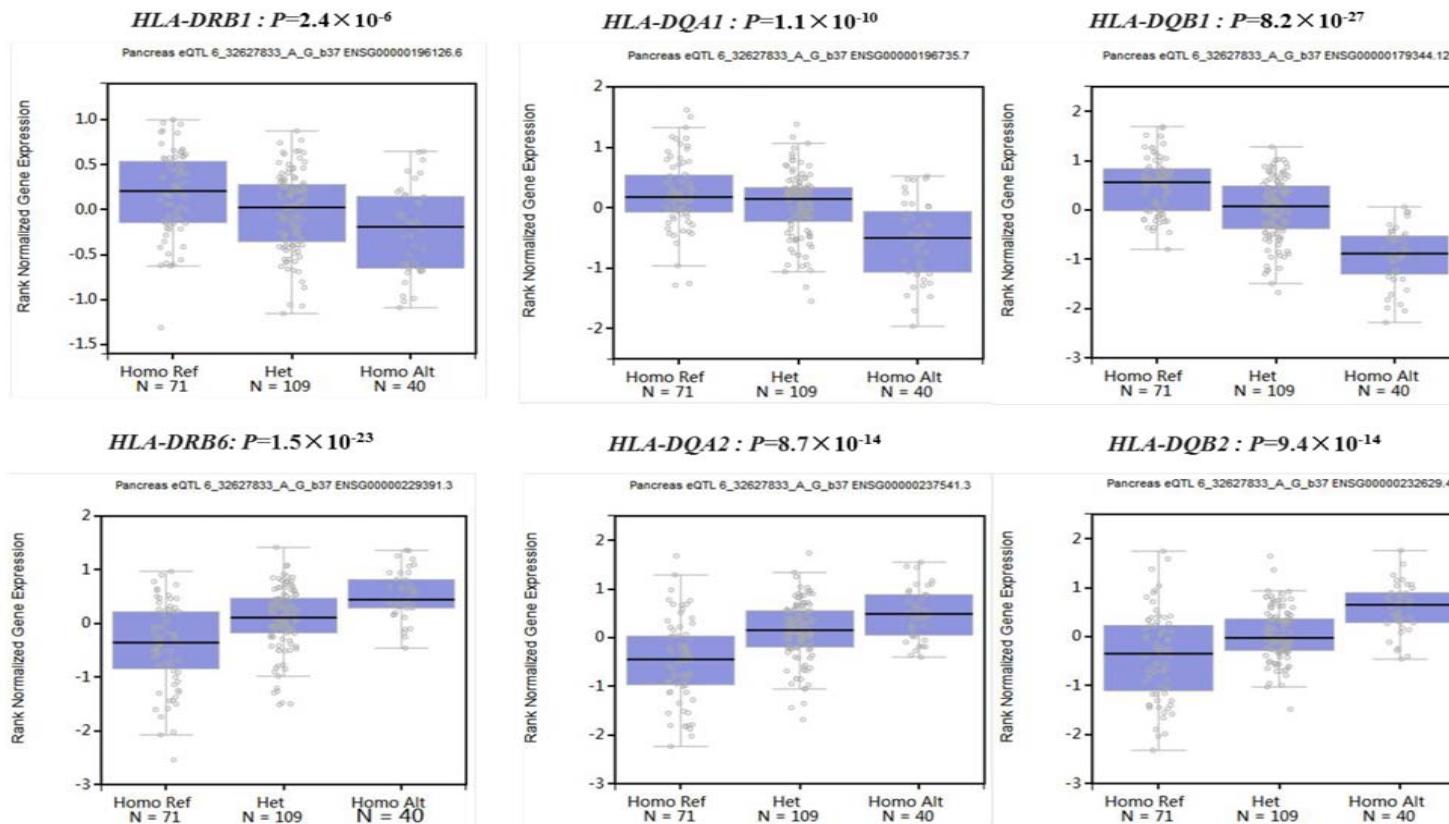
Supplementary Figure S9. Independent HLA loci associated with T1D risk across the MHC region. HLA variants, including SNPs, classical alleles and amino acid polymorphisms, were tested for T1D risk using the imputed genotype. In each panel, the green line marks the genome-wide significance level $P=5.0\times10^{-8}$, and the diamonds represent $-\log_{10}(P\text{-values})$ for the variants. The strongest associations were located at the *HLA-DRB1-DQA1-DQB1* locus, led by rs1770 (OR=0.23; $P=8.95\times10^{-83}$). After adjusting for all four-digit alleles of *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB1*, the strongest independent signal was amino acid site 9 of HLA-A ($P=2.47\times10^{-11}$). Further adjusting for amino acid position 9 of HLA-A, the next signal was observed at position 275 of *HLA-C* ($P=9.78\times10^{-12}$).



SUPPLEMENTARY DATA

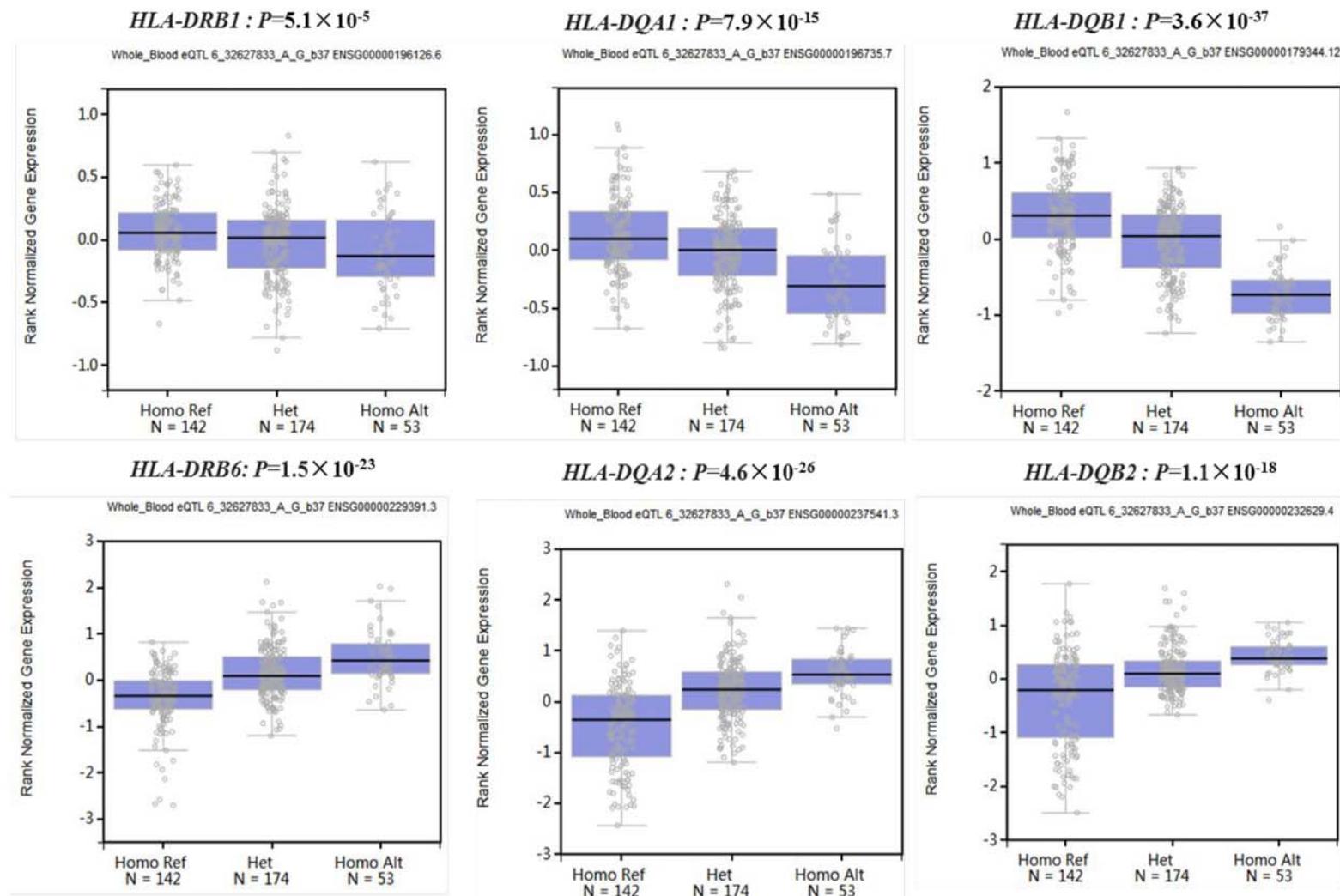
Supplementary Figure S10. The eQTLs of rs1770 and *HLA-DRB-DQA-DQB* gene family based on GTEx. (A) eQTLs in pancreas; (B) eQTLs in whole blood.

A: Pancreas



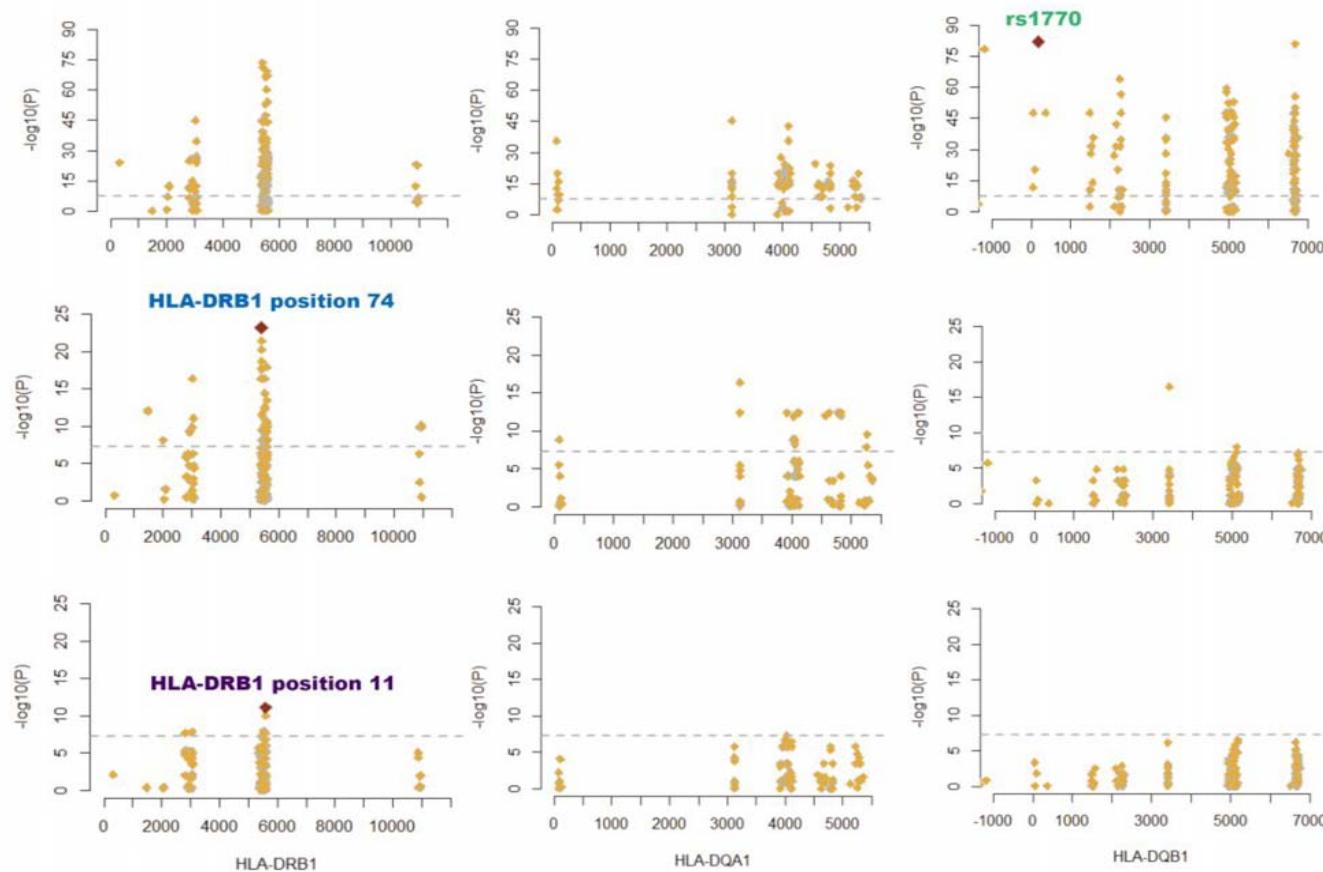
SUPPLEMENTARY DATA

B: Whole Blood



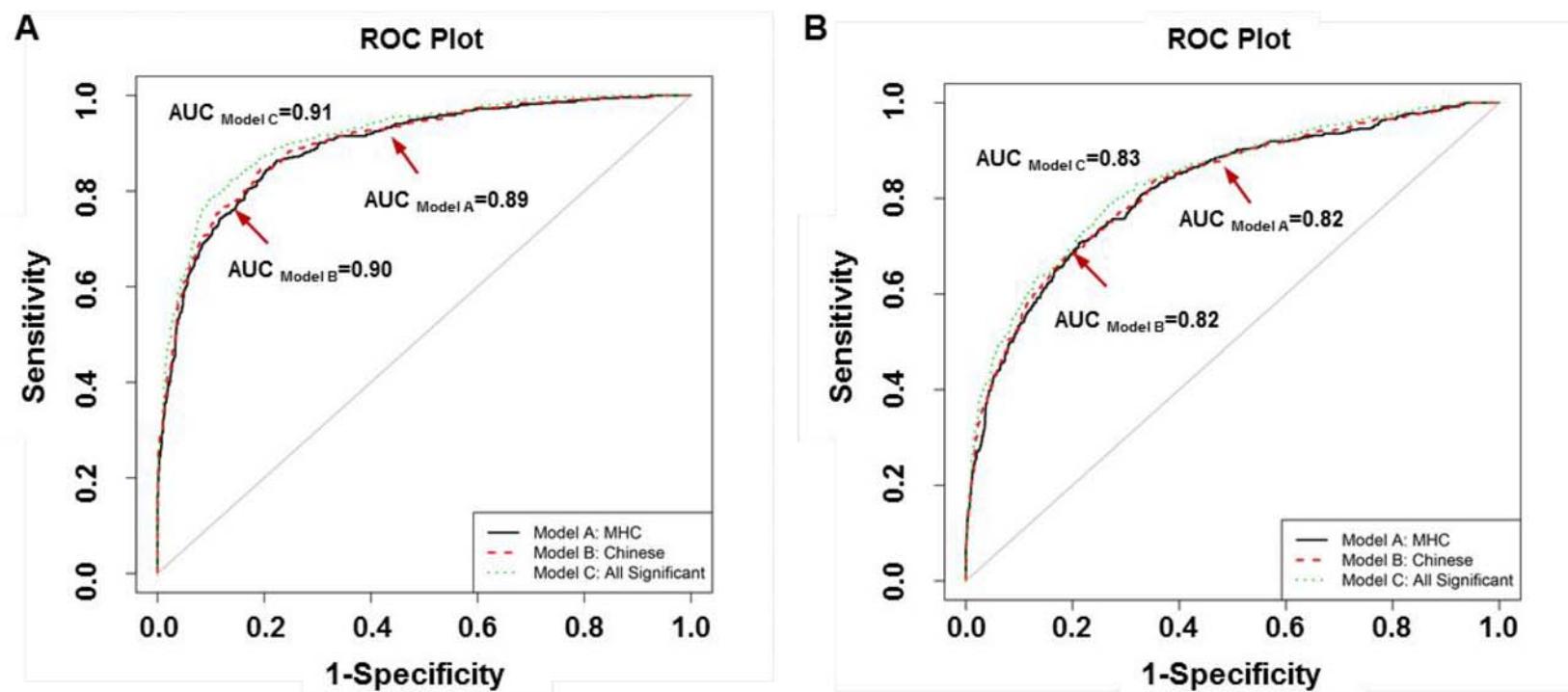
SUPPLEMENTARY DATA

Supplementary Figure S11. Independent associated loci in *HLA-DRB1-DQA1-DQB1* locus. In each panel, the dots mark HLA variants along the gene (x-axis) and their association $-\log_{10}(P\text{-values})$ (y-axis). The horizontal dashed lines mark $P=5\times 10^{-8}$. The most strongly associated variant in each signal is highlighted with purple, rs1770. After this site, the next independently associated signal was HLA-DR β 1 at position 74 ($P=6.38\times 10^{-24}$), followed by position 11 of HLA-DR β 1 ($P=8.47\times 10^{-12}$).



SUPPLEMENTARY DATA

Supplementary Figure S12. Significantly higher prediction value in early-onset T1D patients based on the identified eight variants. ROC curve prediction using the five independent variants of MHC region (Model A), all eight identified variants in Chinese population (Model B), and further included the validated variants from Caucasian population (Model C) in early-onset (A) and late-onset (B) T1D patients.



SUPPLEMENTARY DATA

Supplementary Figure S13. Manhattan plot for the associations between genetic variants and T1D age at diagnosis.

