SUPPLEMENTARY DATA

Genetic contribution to the divergence in type 1 diabetes risk between children from the general population and children from affected families

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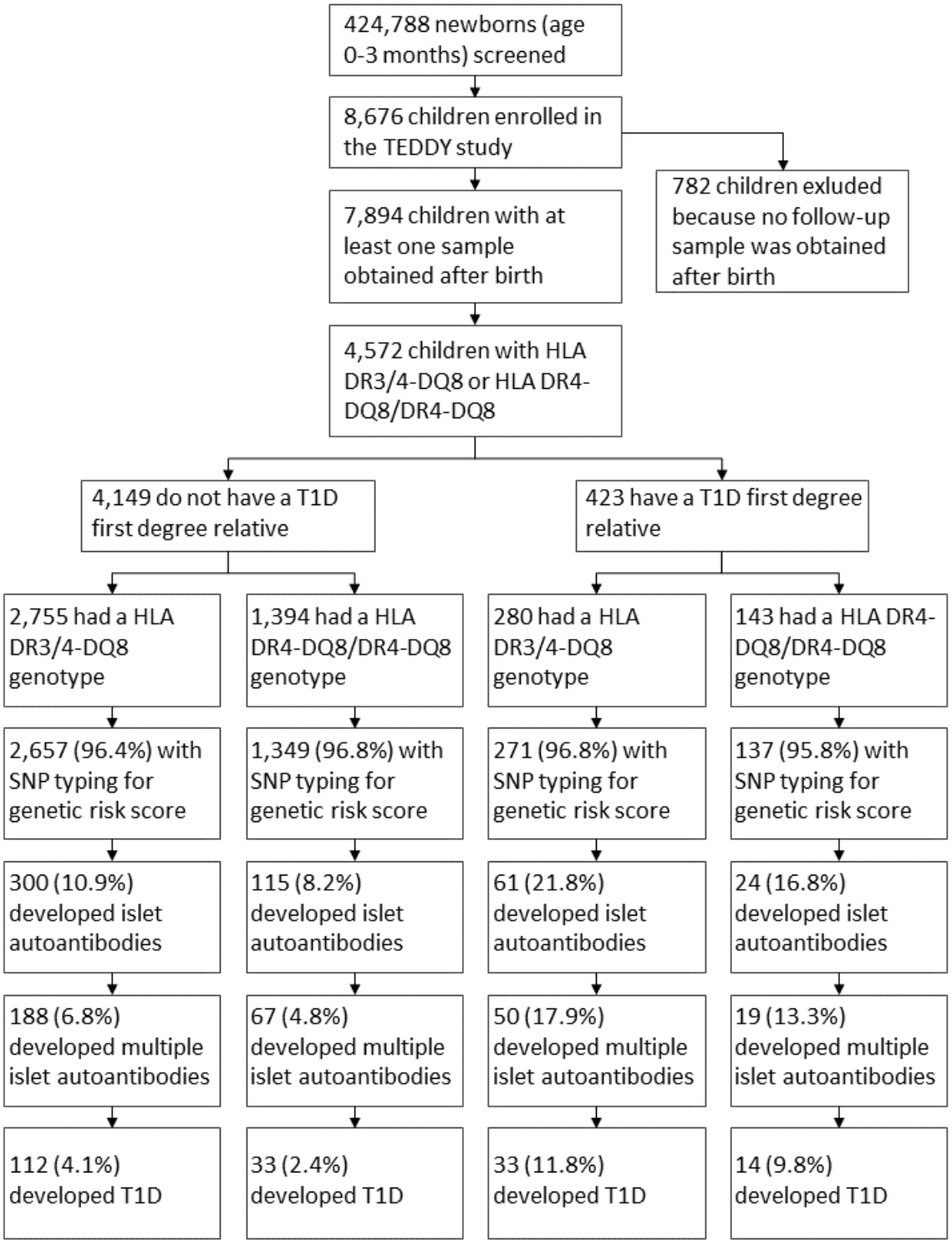
Content

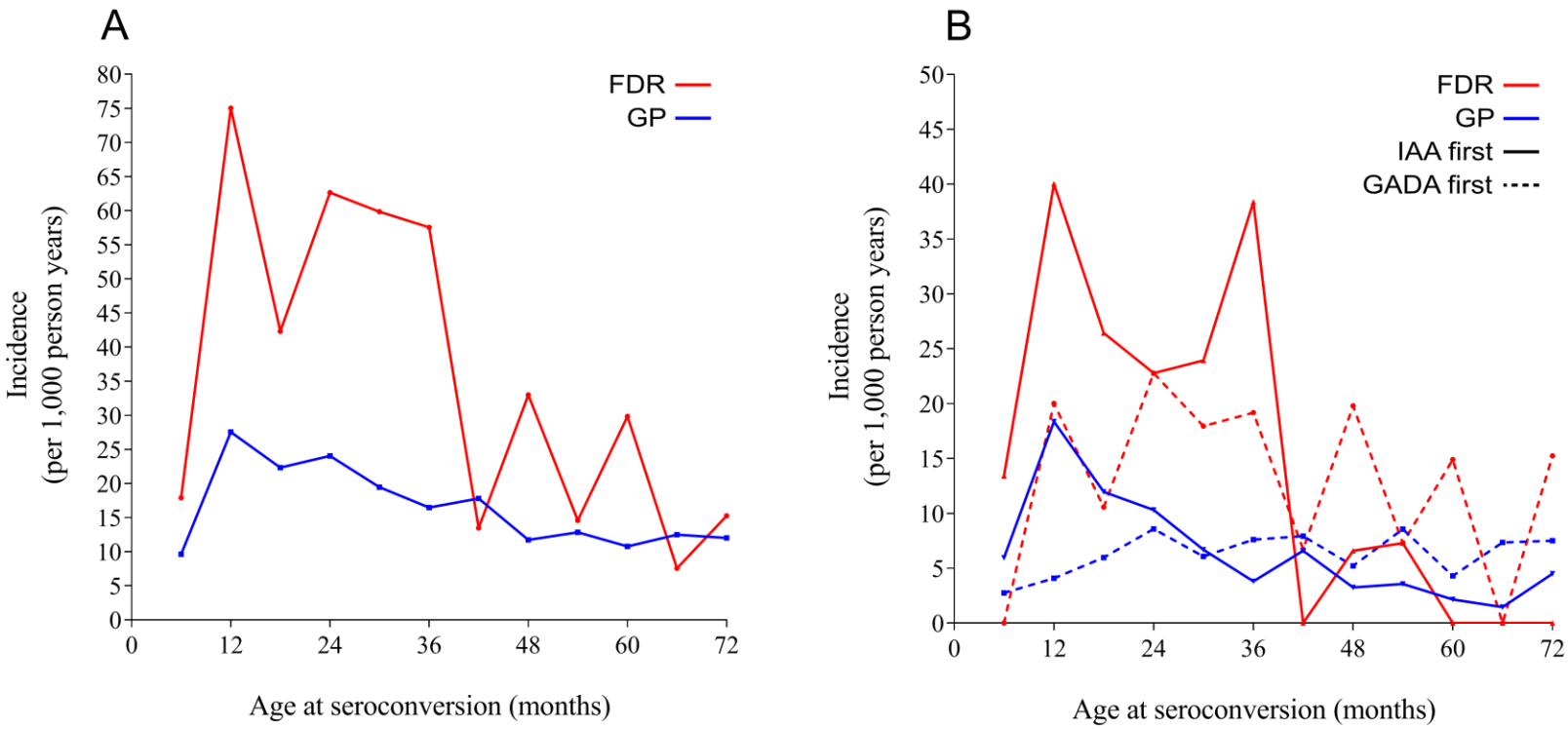
SUPPLEMENTARY DATA

Supplementary Figure 1. Flow chart of study population



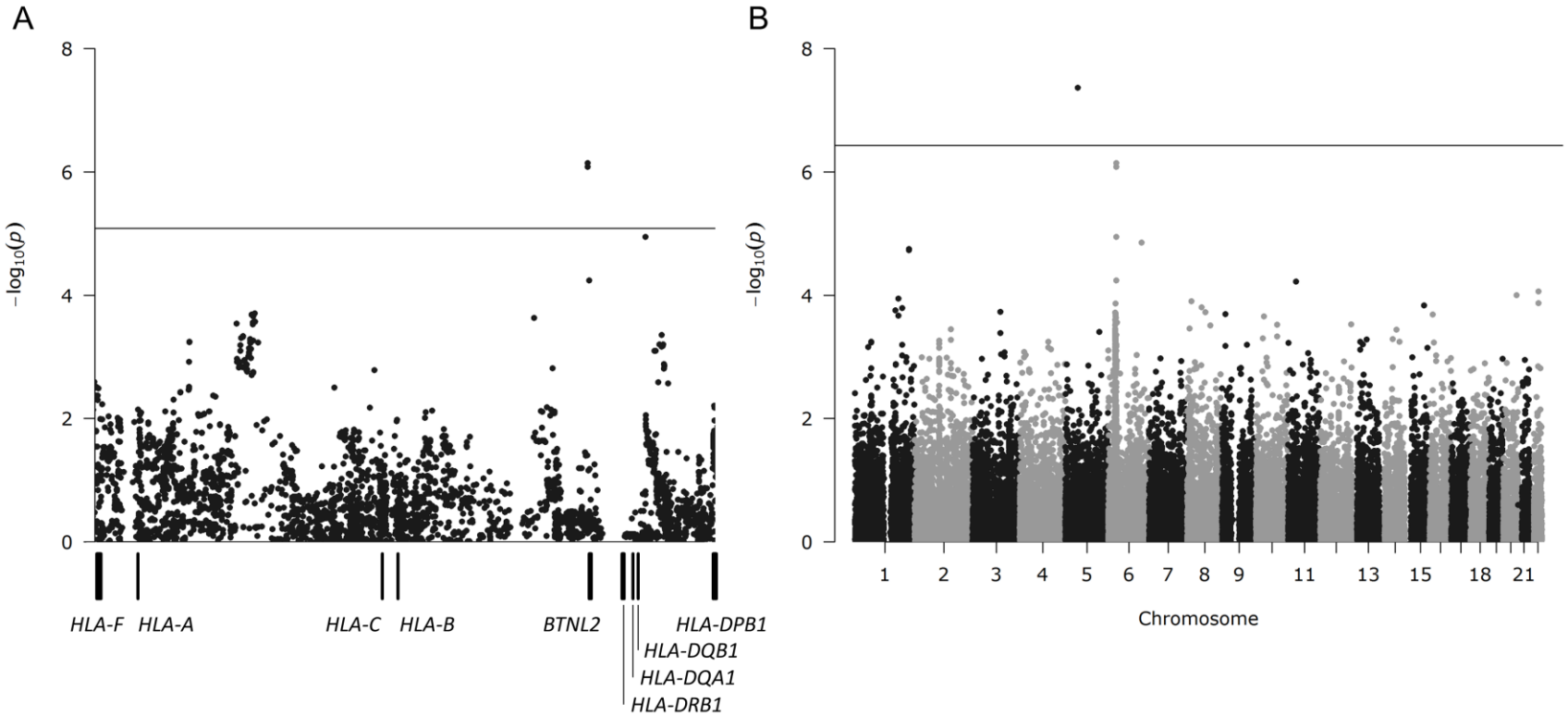
SUPPLEMENTARY DATA

Supplementary Figure 2. (A) Incidence of one or more islet autoantibodies among *DR3/4-DQ8* and *DR4-DQ8/DR4-DQ8* FDR children (red) compared with GP children (blue) by the age of seroconversion. (B) Incidence of first-appearing IAA (solid lines) and first-appearing GADA (broken lines) at seroconversion in *DR3/4-DQ8* and *DR4-DQ8/DR4-DQ8 FDR* children (red) compared with GP children (blue) by the age of seroconversion.



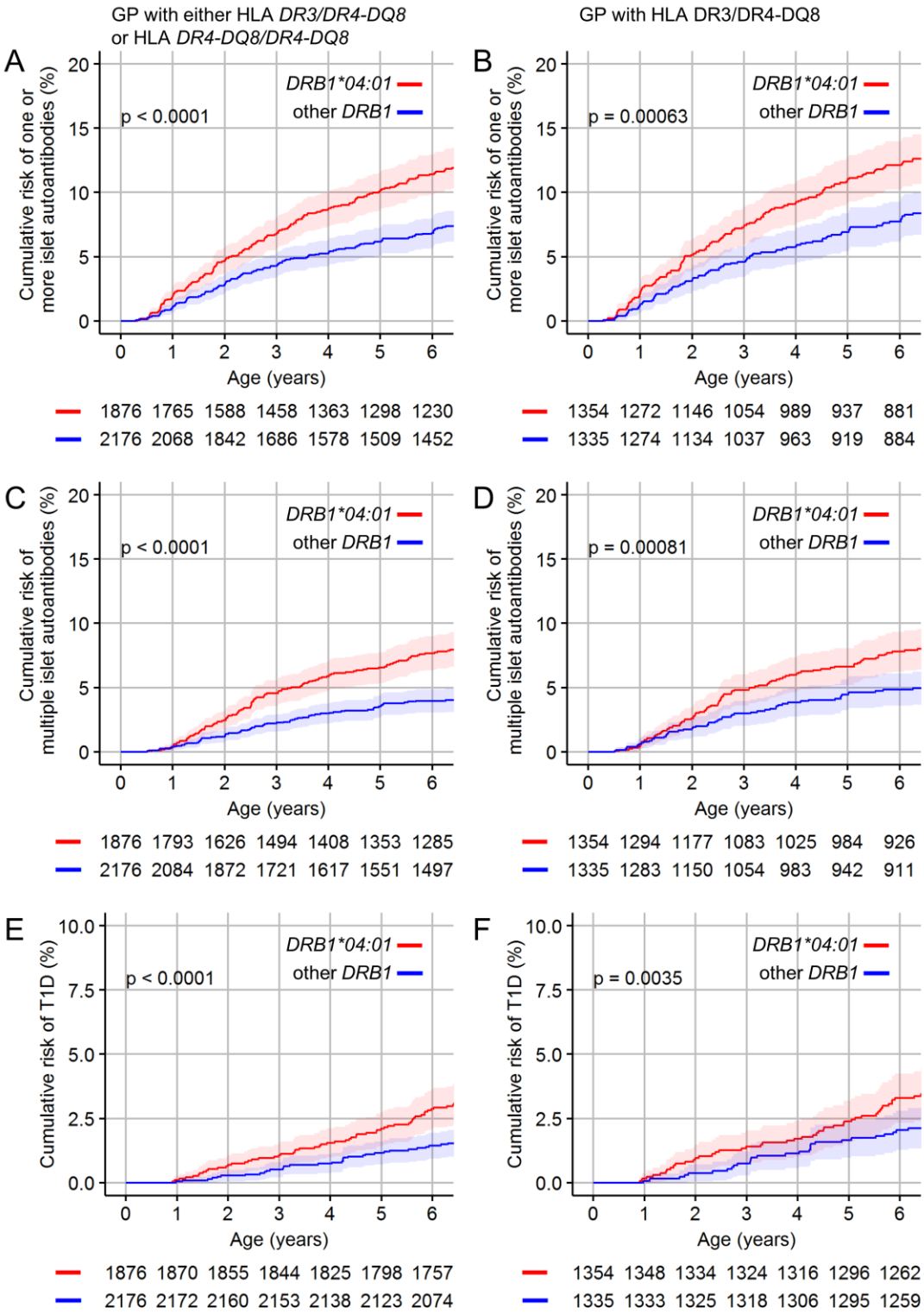
SUPPLEMENTARY DATA

Supplementary Figure 3. Manhattan plot of allele enrichment in FDR children. SNPs were analyzed across the HLA region on chromosome 6 (A) and across all Immunochip data (B).
P-values were calculated using χ^2 tests. The thresholds for *P*-values after Bonferroni correction (8.2×10^{-6} and 4.5×10^{-7}) are indicated using sold lines.



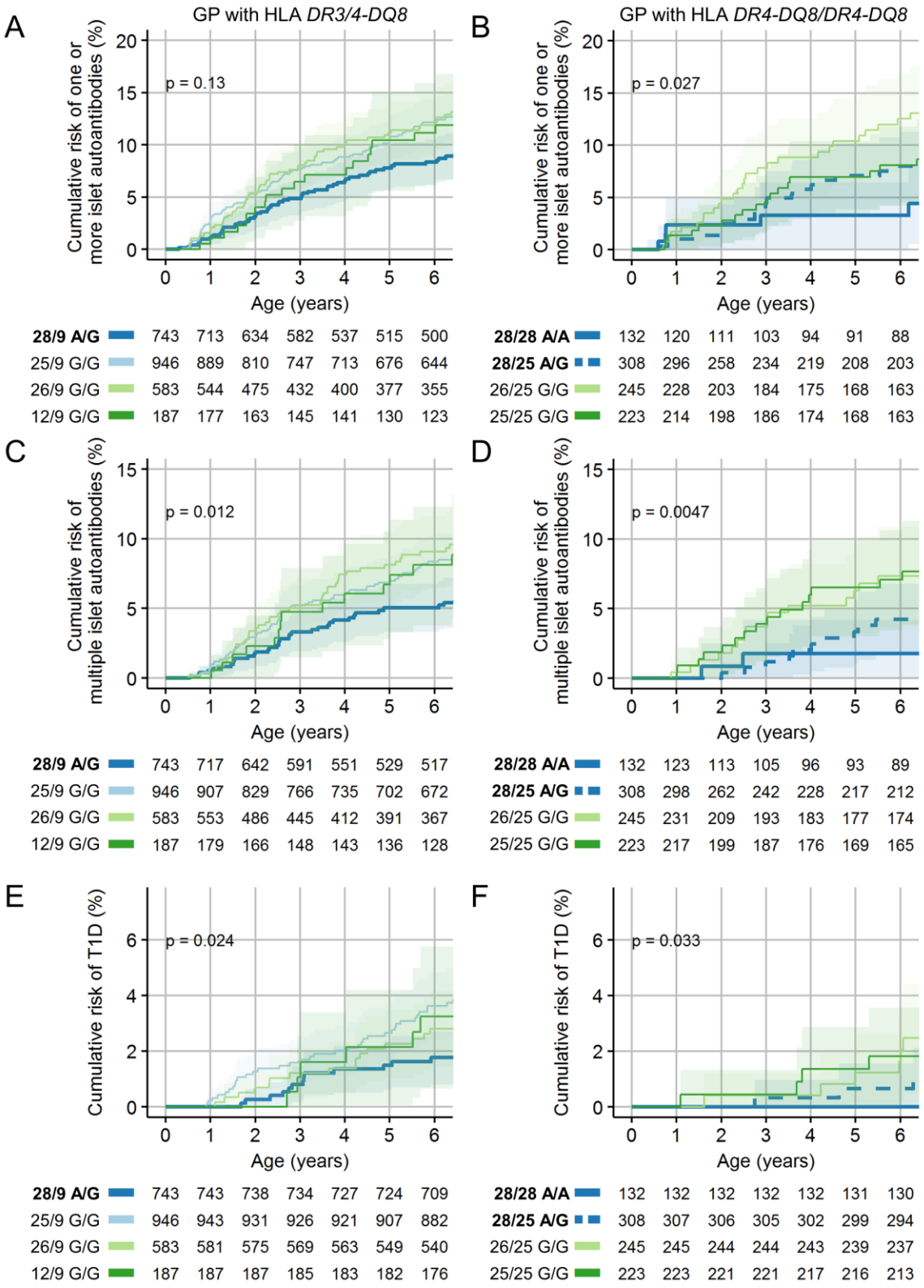
SUPPLEMENTARY DATA

Supplementary Figure 4. Risk of developing one or more islet autoantibodies (A, B), multiple islet autoantibodies (C, D) and diabetes (E, F) in GP children with HLA *DR3/DRB1*04:01-DQ8* or *DRB1*04:01-DQ8/DRB1*04:xx-DQ8*, where **04:xx* was any allele other than *DRB1*04:04* or *DRB1*04:07* (red) vs children without *DRB1*04:01* (blue). The risks are also shown separately for GP children with HLA *DR3/DR4*04:01-DQ8* (B, D, F). *P*-values were calculated using log-rank tests.



SUPPLEMENTARY DATA

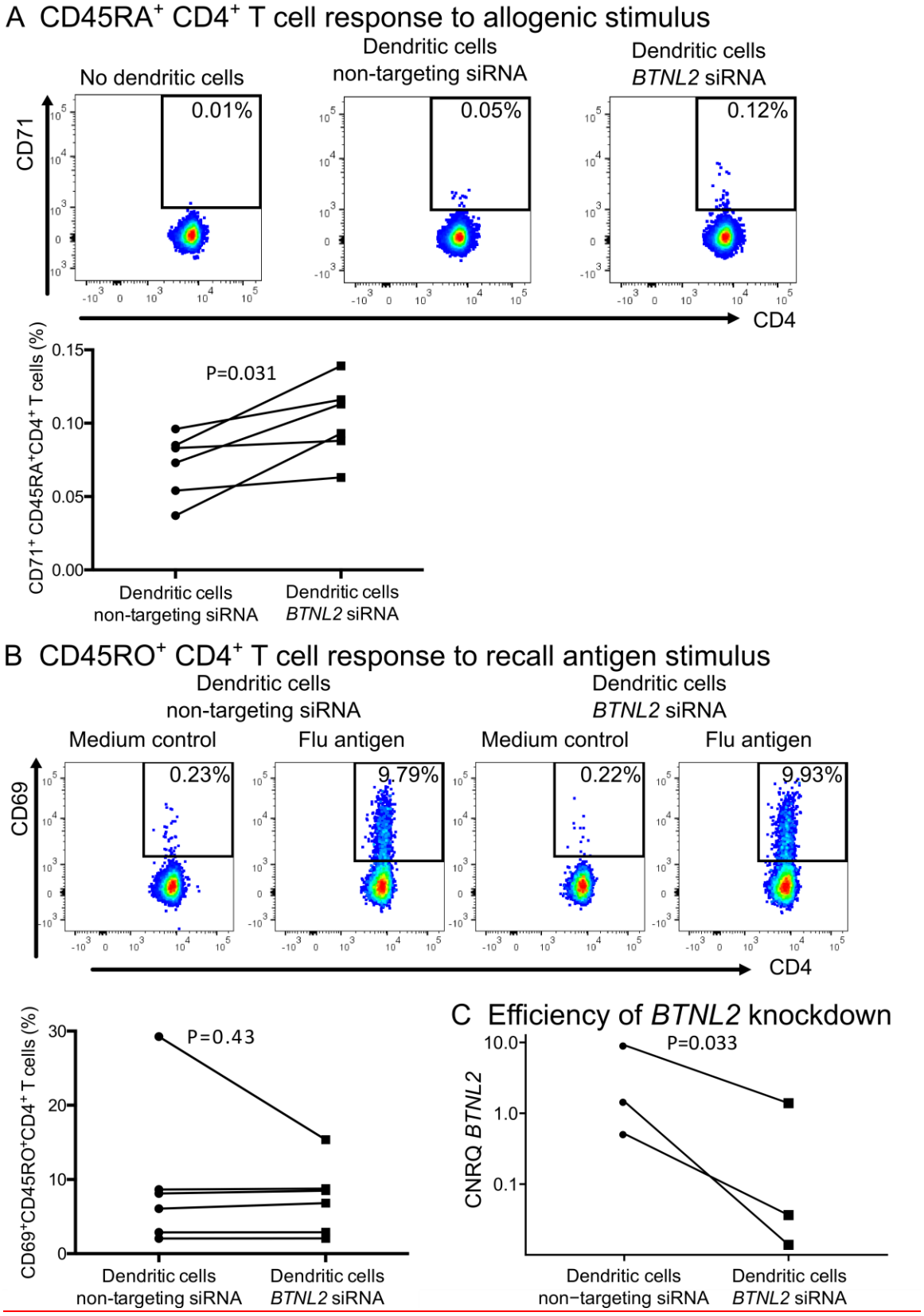
Supplementary Figure 5. Kaplan–Meier curves for the risk of one or more islet autoantibodies (A, B), multiple islet autoantibodies (C, D), and diabetes (E, F) in GP children stratified into children with the *HLA DR3/DR4-DQ8* (A, C, E) or *HLA DR4-DQ8/DR4-DQ8* (B, D, F) genotypes and according to *BTNL2* haplotypes. For both HLA genotypes, the 4 major *BTNL2* genotypes are shown. The genotypes that include haplotype 28, which is the only *BTNL2* haplotype that has the SNP rs3763305 A allele, are indicated as thick blue lines. Shaded areas represent the 95% CI. Numbers represent children at risk. P-values were calculated using log-rank tests.



SUPPLEMENTARY DATA

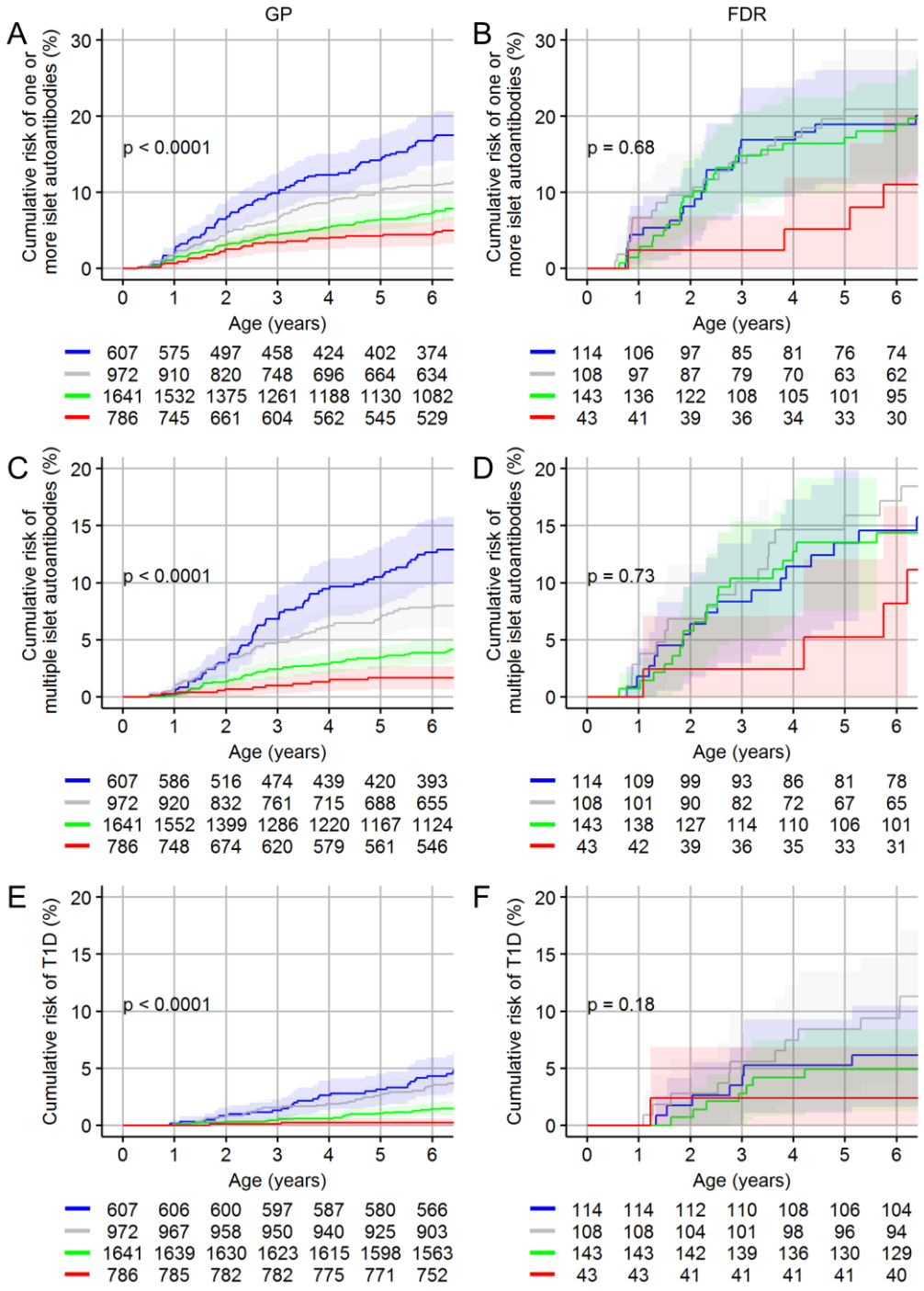
Supplementary Figure 6. Effect of BTNL2 knockdown in monocyte-derived dendritic cells on $CD4^+$ T cell activation. A. Activation of isolated $CD4^+$ $CD25^-$ T cells by allogeneic monocyte-derived dendritic cells transfected with non-targeting siRNA or BTNL2 targeting siRNA in mixed lymphocyte cultures. CD71 expression, previously reported as a marker of allo-reactive T cell activation, was used to measure the activation of the $CD4^+$ T cells. Dendritic cells were transfected as previously described (1). The upper panels are exemplary FACS plots for 42 hour cultures of $CD4^+$ T cells only and in the presence of allo-reactive transfected dendritic cells. The lower graph indicates the mean frequency $CD71^+$ $CD45RA^+$ $CD4^+$ T cells at the end of the 42 hour culture (4 replicates) after subtraction of the mean frequency of $CD71^+$ $CD45RA^+$ $CD4^+$ T cells in quadruplicate cultures without dendritic cells. Each of three dendritic cell samples was tested against two different allogeneic $CD4^+$ T cell preparation yielding 6 data sets. Activation was increased when $CD4^+$ T cells were activated with dendritic cells transfected with *BTNL2*-targeting siRNA as compared to non-targeting siRNA (p=0.031, Wilcoxon matched pair sign test). B. Activation of isolated $CD4^+$ $CD25^-$ T cells by autologous monocyte-derived dendritic cells transfected with non-targeting siRNA or *BTNL2*-targeting siRNA in the presence of flu or tetanus toxoid antigen. CD69 expression was used to measure the activation of the $CD4^+$ T cells. The upper panels are exemplary FACS plots for 42 hour cultures of $CD4^+$ T cells plus dendritic cells in the presence and absence of flu antigen. The lower graph indicates the mean frequency $CD69^+$ $CD4^+$ T cells at the end of the 42 hour culture (triplicates) after subtraction of the mean frequency of $CD69^+$ $CD4^+$ T cells in triplicates cultures without antigen. Each of three dendritic cell samples was tested against flu and tetanus toxoid yielding 6 data sets. Activation was not different when $CD4^+$ T cells were activated with dendritic cells transfected with BTNL2-targeting siRNA as compared to non-targeting siRNA (p=0.43, Wilcoxon matched pair sign test). C. Efficiency of knockdown with BTNL2 vs non-targeting siRNA in dendritic cells used for A and B. 200ng of RNA from siRNA transfected cells was subjected to cDNA synthesis using a mix of oligo-dT-primer and random primer with the iScript cDNA synthesis Kit (Bio-Rad) followed by pre-amplification with gene specific primers and the SsoAdvanced PreAmp Supermix (Bio-Rad). qbase+-software (Biogazelle) was used for analysis of qPCR experiments. BTNL2 expression was normalized to reference genes TELO2 and TRMT61A and the Calibrated Normalized Relative Quantities (CNRQ) relative to the treatment with non-targeting siRNA is shown (p=0.033).

SUPPLEMENTARY DATA



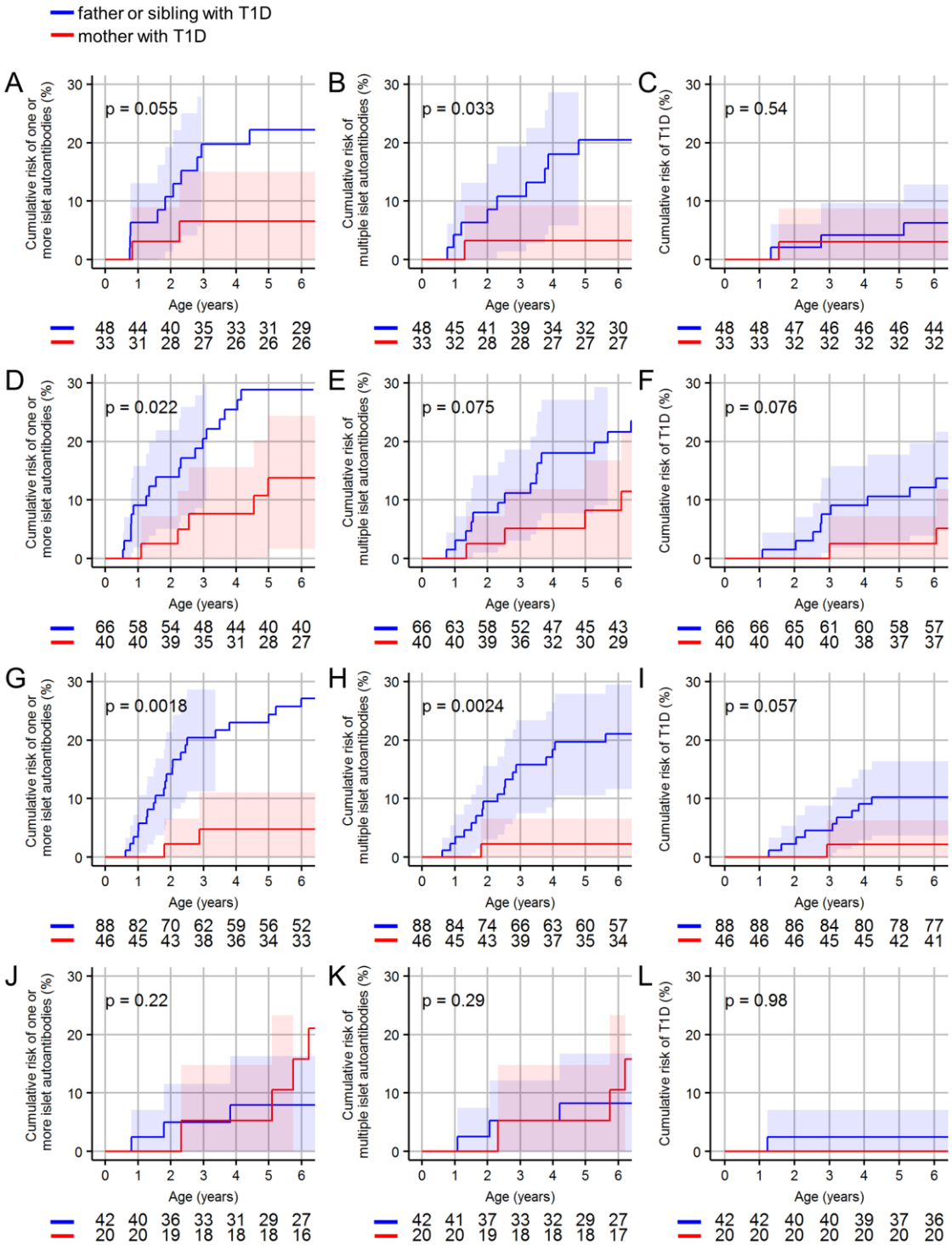
SUPPLEMENTARY DATA

Supplementary Figure 7. Risk of developing islet autoantibodies and diabetes in FDR children (B, D, F) and in GP children (A, B, C) according to genetic susceptibility strata based on *BTNL2* SNP rs3763305 and genetic risk score (GRS). Risks are shown for the development of one or more islet autoantibodies (A, B), multiple islet autoantibodies (C, D), and diabetes (E, F). All of the children had the *DR3/DR4-DQ8* or *DR4-DQ8/DR4-DQ8* genotype. Genetic susceptibility strata were defined as follows: 1. rs3763305 GG AND GRS in the upper quartile (red); 2. rs3763305 GG AND GRS in the second quartile, OR rs3763305 GA or AA AND GRS in the upper quartile (grey); 3. rs3763305 GG AND GRS in the lower 50th centile OR rs3763305 GA or AA AND GRS in the second quartile (green); and 4. rs3763305 GA or AA AND GRS in the lower 50th centile (blue). *P*-values were calculated across all strata using log-rank tests.



SUPPLEMENTARY DATA

Supplementary Figure 8. Risk of developing one or more islet autoantibodies (A, D, G, J), multiple islet autoantibodies (B, E, H, K) and diabetes (C, F, I, L) in children with a mother with T1D (red) compared with children with a father or sibling with T1D (blue). Children have been stratified by genetic risk score and HLA *DRB1*04* subtype into four risk strata from highest genetic susceptibility (A, B, C), to the lowest genetic susceptibility (J, K, L). *P*-values were calculated using log-rank tests.



SUPPLEMENTARY DATA

Supplementary Table 1. Genotype frequencies for SNPs used in the genetic risk score in FDR children and in GP children

		Genotype frequency [%] *						
		FDR children			GP children			
SNP	Gene	PP	SP	SS	PP	SP	SS	*P*-value
rs6897932	*IL7R*	11.8	34.5	53.7	7.7	41.0	51.3	0.0020
rs1004446	*INS*	9.0	44.7	46.3	14.4	45.6	40.0	0.0025
rs3825932	*CTSH*	10.9	40.0	49.2	13.9	44.1	42.1	0.014
rs3024505	*IL10*	2.4	20.9	76.8	2.2	27.0	70.8	0.025
rs3184504	*SH2B3*	27.4	46.8	25.8	30.9	48.8	20.3	0.027
rs2292239	*ERBB3*	42.8	44.0	13.2	46.4	44.1	9.6	0.043
rs1990760	*IFIH1*	13.5	50.1	36.3	18.3	47.4	34.3	0.053
rs10517086	*Unknown*	46.8	46.6	6.6	51.4	40.7	7.9	0.058
rs229541	*IL2B*	29.8	49.4	20.8	34.5	48.3	17.2	0.064
rs7804356	*SCAP2*	3.3	34.0	62.6	5.7	35.2	59.1	0.079
rs2069763	*IL2*	35.5	51.1	13.5	39.4	45.5	15.1	0.088
rs3757247	*BACH2*	28.9	48.6	22.5	33.2	47.7	19.1	0.10
rs4948088	*COBL*	0.2	5.9	93.9	0.3	8.8	90.9	0.12
rs7020673	*GLIS3*	21.7	47.3	31.0	24.4	49.0	26.5	0.12
rs2476601	*PTPN22*	76.1	22.5	1.4	80.3	18.6	1.1	0.12
rs2816316	*RGS1*	5.0	29.6	65.5	3.3	30.4	66.3	0.20
rs9388489	*C6ORF*	26.7	51.8	21.5	29.7	47.6	22.7	0.25
rs425105	*PRKD2*	1.4	28.6	70.0	2.7	27.1	70.2	0.26
rs45450798	*PTPN2*	66.7	29.3	4.0	69.6	27.5	2.9	0.26
rs5753037	*Unknown*	42.8	43.3	13.9	40.6	47.2	12.2	0.27
rs3087243	*CTLA4*	14.7	47.8	37.6	17.5	47.0	35.5	0.31
rs2395029	*HLA_B_5701*	0.0	1.2	98.8	0.0	2.2	97.7	0.32
rs17574546	*Unknown*	61.6	33.4	5.0	64.3	31.8	3.9	0.41
rs2281808	*SIRPG*	9.7	46.0	44.3	11.8	44.5	43.7	0.43
rs1465788	*ZFP36L1*	7.1	44.4	48.5	7.9	41.2	50.9	0.43
rs3788013	*UBASH3A*	35.9	50.1	13.9	35.0	48.6	16.4	0.44
rs4788084	*IL27*	17.5	47.8	34.8	19.4	48.3	32.3	0.50
rs763361	*CD226*	26.0	48.7	25.3	27.1	49.8	23.0	0.57
rs6920220	*TNFAIP3*	64.5	30.5	5.0	63.6	32.0	4.4	0.73
rs1738074	*TAGAP*	19.9	46.3	33.8	18.6	48.0	33.4	0.76
rs12708716	*CLEC16A*	12.6	42.2	45.3	12.2	44.0	43.8	0.76
rs7221109	*unknown*	13.9	44.2	41.8	13.6	45.9	40.4	0.79
rs2664170	*GAB3*	56.5	22.7	20.8	57.6	21.4	20.9	0.83
rs4763879	*CD69*	37.7	49.1	13.3	38.9	47.7	13.4	0.86
rs947474	*PRKCQ*	3.5	30.5	66.0	3.2	30.1	66.8	0.89
rs5979785	*TLR8*	17.5	18.4	64.1	18.2	18.5	63.3	0.92
rs7202877	*unknown*	79.7	19.1	1.2	79.1	19.5	1.3	0.95
rs1264813	*HLA_A_24*	82.7	16.6	0.7	82.3	17.0	0.7	0.98

rs10509540	*C10orf59*	7.1	38.3	54.6	7.3	38.3	54.4	0.98
rs12722495	*IL2R*	0.7	16.5	82.7	0.7	16.6	82.7	1.00

* P refers to the protective allele and S refers to the susceptible allele

SUPPLEMENTARY DATA

Supplementary Table 2. Cox proportional hazards models for the development of islet autoantibodies and diabetes in FDR children compared with GP children in TEDDY children with the HLA *DR3/4-DQ8* genotype

Variable	One or more islet autoantibodies				Multiple islet autoantibodies				Diabetes			
	Model 1 *		Model 2 *		Model 1 *		Model 2 *		Model 1 *		Model 2 *	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
First-degree relative	2.24 (1.67–3.01)	<0.0001	1.95 (1.45–2.63)	<0.0001	2.92 (2.09–4.07)	<0.0001	2.47 (1.76–3.46)	<0.0001	3.48 (2.30–5.28)	<0.0001	2.86 (1.88–4.36)	<0.0001
*DRB1*0401/x* †			1.26 (0.95–1.68)	0.11			1.24 (0.88–1.74)	0.22			1.17 (0.76–1.79)	0.47
Genetic risk score ‡			1.50 (1.33–1.68)	<0.0001			1.63 (1.41–1.88)	<0.0001			1.56 (1.29–1.87)	<0.0001
BTNL2 rs3763305 GG §			1.09 (0.79–1.51)	0.60			1.43 (0.95–2.17)	0.090			1.92 (1.11–3.35)	0.021
ITGA1 rs7735139 GG §			1.26 (0.88–1.82)	0.20			1.14 (0.73–1.80)	0.56			1.25 (0.72–2.18)	0.43

* Model 1 and 2 are adjusted for sex, country (reference: US) and HLA genotype; † reference: *DRB1* without 0401 or 0401/0404 and 0401/0407; ‡ per unit increase; § reference: GA/AA genotype

SUPPLEMENTARY DATA

Supplementary Table 3. Genotype frequencies of *BTNL2* SNP rs3765503 in validation cohort

	BTNL2 rs3765503 genotype			
	GG	AG	AA	*P*-value*
Control	487 (71%)	200 (29%)	0 (0%)	<0.0001
Diabetes	3496 (81%)	842 (19%)	0 (0%)	

* *P*-value was calculated using Fisher's exact test.

The validation cohort consists of 5,025 Caucasian subjects with European decent and HLA *DR3/4-DQ8* genotype according to the algorithm defined by Barker et al. (2), which is based on the tag SNPs rs7454108 and rs2040410. Samples were genotyped on the Illumina Immunochip array and imputed to the TOPMed Reference Panel. rs3763305 was directly genotyped on the Immunochip. rs2040410, and rs7454108 were imputed with high confidence (R2>0.99). Principal components were generated by calculating PC axes in unrelated controls using a set of 83,458 LD-pruned variants and projecting the remaining samples onto this PC space. A set of 33,249 European ancestry unrelated case-control subjects were identified for analysis by comparing PCs to 1000 Genomes Phase 3 subjects (3). We ensured samples were unrelated (less than second degree relationship) using KING version 2.13 (http://people.virginia.edu/~wc9c/KING/). 5,025 of these samples have the HLA *DR3/4-DQ8* genotype.

SUPPLEMENTARY DATA

Supplementary Table 4. Haplotypes of 34 SNPs in *BTNL2* and their frequencies in HLA *DR3/4-DQ8* and *DR4-DQ8/DR4-DQ8*. SNPs in bold are those that were identified as enriched within FDR children. Haplotype ID 'X' indicates that they are not among the 30 most frequent haplotypes.

frequency [%] in																																				
DR3/4-DQ8	*DR4-DQ8/ DR4-DQ8*	Haplotype ID	rs3817969	rs3129953	rs28362678	rs2076530	rs9268480	rs2076529	rs9268481	rs3129954	rs3129955	rs4248166	rs2294884	rs2294883	rs2294882	rs2294881	rs2294880	rs9268482	rs2294878	rs3817966	**rs3817964**	rs3817963	rs3817962	**rs3763305**	rs2076525	rs2076523	rs2076522	rs3793127	rs10947260	rs10947261	rs10947262	rs3806155	rs3806156	rs3806157	rs2395158	rs3763307
42.82	0.26	9	G	A	G	A	G	A	A	G	G	A	A	T	A	A	A	A	C	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	G	T
18.12	18.70	25	G	G	G	G	A	G	G	G	G	A	A	T	A	A	G	T	A	G	A	G	A	G	G	G	G	A	A	C	G	A	A	C	A	A
15.14	14.62	28	G	G	G	G	A	G	G	G	G	A	A	T	A	A	G	T	A	G	**T**	G	A	**A**	G	G	G	A	A	C	G	T	A	C	A	A
12.48	12.29	26	G	G	G	G	A	G	G	G	G	A	A	T	A	A	G	T	A	G	A	G	A	G	G	G	G	A	A	C	G	T	A	C	A	A
9.86	3.56	12	G	G	G	A	G	A	A	A	A	A	A	T	A	A	A	A	C	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	A	T
0.60	0.09	27	G	G	G	G	A	G	G	G	G	A	A	T	A	A	G	T	A	G	A	G	A	G	G	G	G	G	A	C	G	T	A	C	A	A
0.31	0.27	16	G	G	G	A	G	A	A	G	G	A	A	T	A	A	A	A	C	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	A	T
0.26	0.07	5	A	G	A	G	G	G	A	G	G	G	C	A	G	G	A	A	A	A	A	A	C	G	A	G	C	G	G	A	A	T	A	C	A	T
0.15	0.10	21	G	G	G	A	G	A	A	G	G	G	C	A	G	G	A	A	A	A	A	A	C	G	A	G	C	G	G	A	A	T	A	C	A	T
0.09	0.03	4	A	G	A	G	G	G	A	G	G	G	C	A	G	G	A	A	A	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	A	T
0.05	0.03	23	G	G	G	G	A	G	G	G	G	A	A	T	A	A	A	T	A	G	A	G	A	G	G	G	G	A	A	C	G	T	A	C	A	A
0.00	0.07	3	A	G	A	G	G	G	A	G	G	A	A	A	G	G	G	A	C	G	A	G	C	G	A	G	C	G	A	A	A	T	A	A	A	T
0.03	0.00	8	G	A	G	A	G	A	A	G	G	A	A	T	A	A	A	A	C	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	A	T
0.03	0.00	13	G	G	G	A	G	A	A	A	A	A	A	T	G	G	A	A	A	A	A	A	C	G	A	G	C	G	G	A	A	T	A	C	A	T
0.02	0.00	17	G	G	G	A	G	A	A	G	G	A	A	T	A	A	A	A	C	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	G	T
0.00	0.00	1	A	A	A	G	G	G	A	G	G	G	C	A	G	G	A	A	A	A	A	A	C	G	A	G	C	G	G	A	A	T	A	C	A	T
0.02	0.00	6	A	G	G	G	G	G	A	G	G	G	A	A	G	G	G	A	C	G	A	A	A	G	A	G	C	G	G	C	A	T	A	A	A	T
0.00	0.02	10	G	A	G	A	G	A	A	G	G	A	A	T	G	G	A	A	A	A	**T**	A	C	**A**	A	G	C	G	G	A	A	T	A	C	A	T
0.02	0.00	11	G	A	G	G	A	G	G	G	G	A	A	T	A	A	G	T	A	G	**T**	G	A	**A**	G	G	G	A	A	C	G	T	A	C	A	A
0.00	0.00	14	G	G	G	A	G	A	A	A	G	A	A	T	A	A	A	A	C	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	G	T
0.00	0.00	15	G	G	G	A	G	A	A	G	A	A	A	T	A	A	A	A	C	A	A	A	C	G	A	A	C	G	A	C	G	T	C	A	A	T
0.00	0.02	24	G	G	G	G	A	G	G	G	G	A	A	T	A	A	G	T	A	G	A	G	A	G	G	G	G	A	A	C	A	T	A	C	A	A
0.00	0.00	x	G	A	G	A	G	A	A	G	G	A	A	T	G	G	A	A	A	A	A	A	C	G	A	G	C	G	G	A	A	T	A	C	A	T
0.00	0.00	x	G	G	G	A	G	A	A	G	G	G	C	A	G	G	A	A	A	A	**T**	A	C	**A**	A	G	C	A	G	A	A	T	A	C	A	T

SUPPLEMENTARY DATA

Supplementary Table 5. Relationship between *BTNL2* SNP rs3765503 genotypes and HLA *DR3* and *DRB1*04* subtypes in children with the HLA *DR3/DR4-DQ8* genotype

HLA *DR* genotype	*BTNL2* rs3763305 genotype			Allele frequency (%)	
	AA	GA	GG	A	G
DR3/DR3	2 (0.1%)	9 (0.6%)	1608 (99.3%)	0.4	99.6
*DR3/DRB1*04:01*	0 (0.0%)	15 (1.0%)	1496 (99.0%)	0.5	99.5
*DR3/DRB1*04:02*	0 (0.0%)	2 (1.2%)	165 (98.8%)	0.6	99.4
*DR3/DRB1*04:04*	1 (0.1%)	837 (78.1%)	233 (21.8%)	39.2	60.8
*DR3/DRB1*04:05*	0 (0.0%)	0 (0.0%)	134 (100.0%)	0.0	100.0
*DR3/DRB1*04:06*	0 (0.0%)	1 (100.0%)	0 (0.0%)	50.0	50.0
*DR3/DRB1*04:07*	0 (0.0%)	33 (68.8%)	15 (31.2%)	34.4	65.6
*DR3/DRB1*04:08*	0 (0.0%)	1 (4.8%)	20 (95.2%)	2.4	97.6
*DR3/DRB1*04:10*	0 (0.0%)	0 (0.0%)	1 (100.0%)	0.0	100.0

Supplementary Table 6. Association of the *BTNL2* rs3763305 genotype with HLA *DRB1*04* subtype alleles in children with the HLA *DR3/DR4-DQ8* genotype from the Bavarian diabetes registry DiMelli

	BTNL2 rs3763305 genotype		
*DRB1*04* subtype	AA	AG	GG
*DR3/DRB1*04:01*	0 (0.0%)	0 (0.0%)	89 (100.0%)
*DR3/DRB1*04:02*	0 (0.0%)	0 (0.0%)	21 (100.0%)
*DR3/DRB1*04:04*	0 (0.0%)	18 (75.0%)	6 (25.0%)
*DR3/DRB1*04:05*	0 (0.0%)	0 (0.0%)	7 (100.0%)

Supplementary Table 7. Cox proportional hazards models for developing one or more islet autoantibodies, multiple islet autoantibodies and diabetes according to *BTNL2* rs3763305 in children with the HLA *DR3/DRB1*0404-DQ8* or HLA *DRB1*0404-DQ8/DRB1*0404-DQ8* genotypes adjusted for the HLA *DR3/DR4-DQ8* genotype

	One or more islet autoantibodies		Multiple islet autoantibodies		Diabetes	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
HLA *DR3/DR4-DQ8* *	1.48 (0.81–2.70)	0.20	1.64 (0.70–3.82)	0.25	1.26 (0.44–3.59)	0.66
BTNL2 rs3763305 GG †	1.13 (0.74–1.74)	0.57	1.49 (0.88–2.54)	0.14	2.38 (1.25–4.55)	0.0086

* Reference: *DR4-DQ8/DR4-DQ8*; † reference: GA/AA genotype

SUPPLEMENTARY DATA

Supplementary Table 8. Cumulative risk of developing islet autoantibodies or diabetes by 6 years old in children stratified by genetic risk score and HLA *DRB1*04* subtype

Risk strata	One or more islet autoantibodies		Multiple islet autoantibodies		Diabetes	
	GP children	FDR children	GP children	FDR children	GP children	FDR children
1: High-risk *DR4* * AND 1st quartile GRS	17.4%	16.7%	12.7%	14.3%	4.1%	4.8%
	(13.6–21.2%)	(7.9–24.6%)	(9.3–16.0%)	(6.1–21.9%)	(2.2–5.9%)	(0.1–9.2%)
2: High-risk *DR4* AND 2nd quartile GRS OR	11.9%	23.4%	9.0%	17.0%	4.1%	9.1%
low-risk *DR4* * AND 1st quartile GRS	(9.6–14.1%)	(14.7–31.2%)	(7.0–10.9%)	(9.3–24.1%)	(2.8–5.3%)	(3.5–14.3%)
3: High-risk *DR4* AND GRS <50th centile	8.2%	19.3%	4.5%	14.8%	1.5%	7.1%
OR low-risk *DR4* AND 2nd quartile GRS	(6.7–9.7%)	(12.2–25.9%)	(3.3–5.7%)	(8.4–20.7%)	(0.9–2.2%)	(2.8–11.2%)
4: Low-risk *DR4* AND GRS <50th centile	4.3%	11.1%	1.6%	9.2%	0.5%	1.6%
	(2.9–5.5%)	(2.3–19.1%)	(0.8–2.4%)	(1.2–16.6%)	(0.1–0.9%)	(0.0–4.8%)
P-value †	<0.0001	0.45	<0.0001	0.60	<0.0001	0.18

* High-risk *DR4* was defined as *DR3/DRB1*0401* or *DRB1*0401-DQ8/DR4* without 0404 or 0407, and low risk were all other genotypes; † *P*-values were calculated as log-rank tests per column over the four strata. GRS, genetic risk score

SUPPLEMENTARY DATA

Supplementary Table 9. Hazard ratios (HRs) and 95% CIs for developing one or more islet autoantibodies, multiple islet autoantibodies and diabetes in FDR children (FDR mother vs FDR father vs FDR sibling vs FDR multiplex), adjusted for sex, genetic factors (reference: *DR4-DQ8/DR4-DQ8*), and country (reference US)

	One or more islet autoantibodies		Multiple islet autoantibodies		Diabetes	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
FDR multiplex	1.94 (0.62–6.12)	0.26	3.37 (1.06–10.66)	0.039	5.90 (1.84–18.94)	0.0029
FDR mother	0.85 (0.50–1.44)	0.54	0.97 (0.52–1.79)	0.91	1.39 (0.67–2.87)	0.38
FDR father	2.37 (1.71–3.28)	<0.0001	2.89 (2.00–4.17)	<0.0001	3.06 (1.89–4.94)	<0.0001
FDR sibling	2.68 (1.70–4.22)	<0.0001	3.41 (2.07–5.62)	<0.0001	5.15 (2.94–9.03)	<0.0001
*DRB1*04:01/x* *	1.44 (1.11–1.86)	0.0057	1.49 (1.09–2.04)	0.012	1.40 (0.94–2.07)	0.096
Genetic risk score †	1.49 (1.35–1.65)	<0.0001	1.68 (1.48–1.90)	<0.0001	1.68 (1.43–1.98)	<0.0001
BTNL2 rs3763305 GG ‡	1.02 (0.77–1.36)	0.88	1.34 (0.93–1.94)	0.12	1.74 (1.07–2.84)	0.026
ITGA1 rs7735139 "GG" ‡	1.25 (0.91–1.73)	0.17	1.14 (0.76–1.72)	0.52	1.21 (0.72–2.03)	0.47

* Reference: *DRB1* without 0401 or 0401/0404 and 0401/0407; † per unit increase; ‡ reference: GA/AA genotype

SUPPLEMENTARY DATA

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Nature 2015;526:68