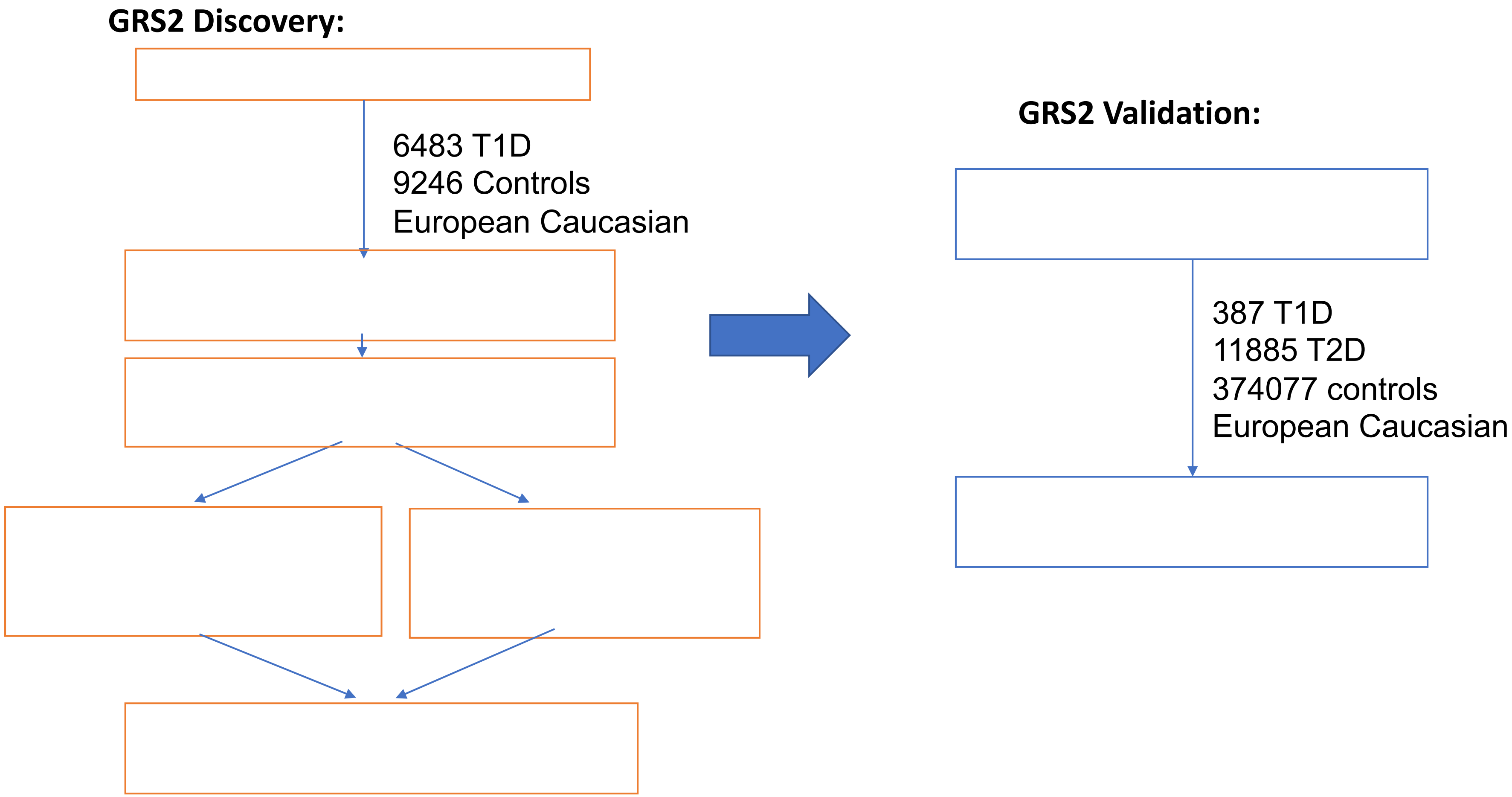


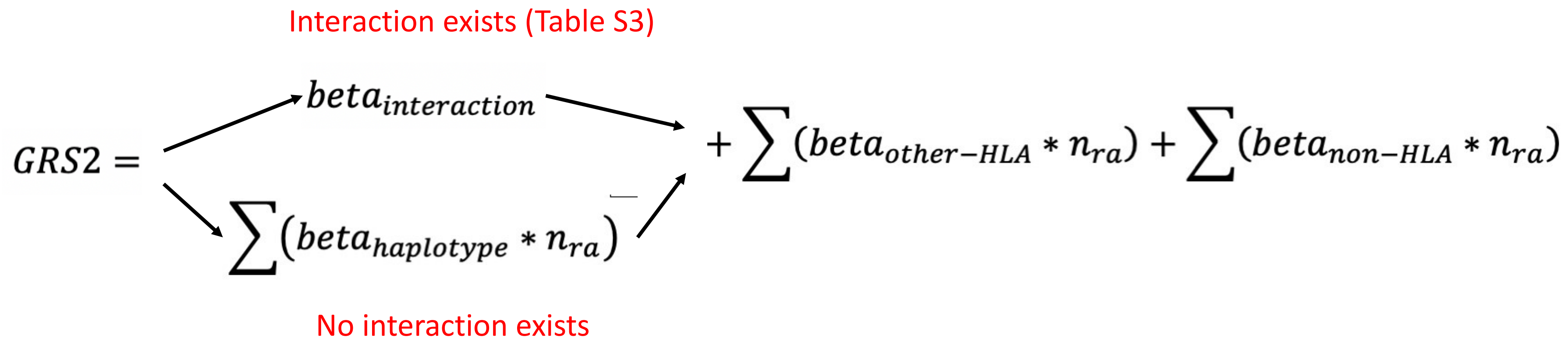
GRS2 Discovery:

6483 T1D
9246 Controls
European Caucasian

GRS2 Validation:

387 T1D
11885 T2D
374077 controls
European Caucasian

Figure S1- Flow chart showing Construction of overall Genetic Risk score**.**



Interaction exists (Table S3)

$$beta_{interaction}$$

$$GRS2 = \quad + \sum(beta_{other-HLA} * n_{ra}) + \sum(beta_{non-HLA} * n_{ra})$$

$$\sum(beta_{haplotype} * n_{ra})$$

No interaction exists

n_{ra} : number of risk alleles at variant

$beta_{haplotype}$: beta(s) from Table S1

$beta_{interaction}$: beta from Table S3

$beta_{other-HLA}$: beta(s) from Table S4

$beta_{non-HLA}$: beta(s) from Table S5

...where $beta = \log(Odds\ Ratio)$ for each variant.

Figure S2 – Algorithm to generate full T1D-GRS2 score from variants. For haplotypes with an interaction the beta is taken from Table S3, without an interaction it is scored independently for each haplotype of the pair (from table S1). The sum of scores from the remaining variants is then added.

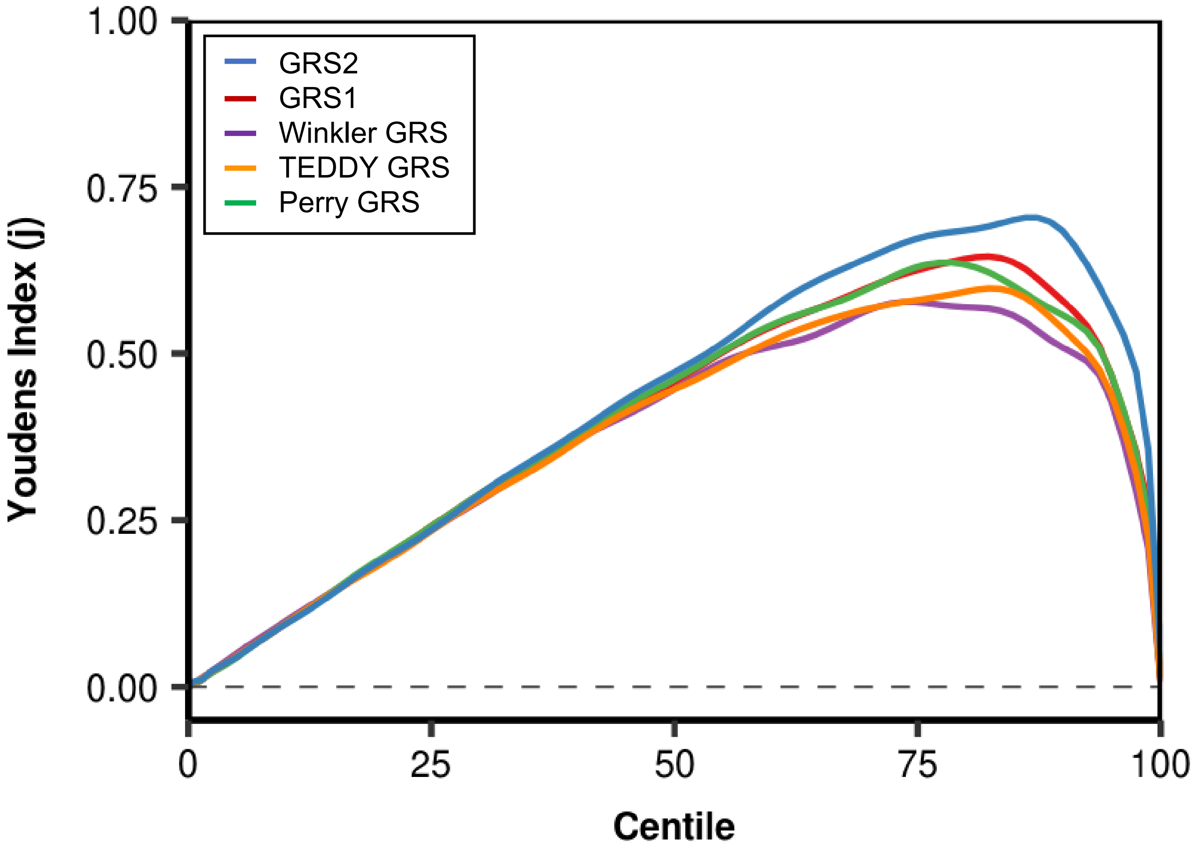


Figure S3 - Youden's Index statistic (j = sensitivity + specificity - 1) versus centile of UK BioBank T1D cases to demonstrate comparative performance of different genetic risk scores and illustrate the level and centile position of each Genetic Risk Score’s maximum discrimination.

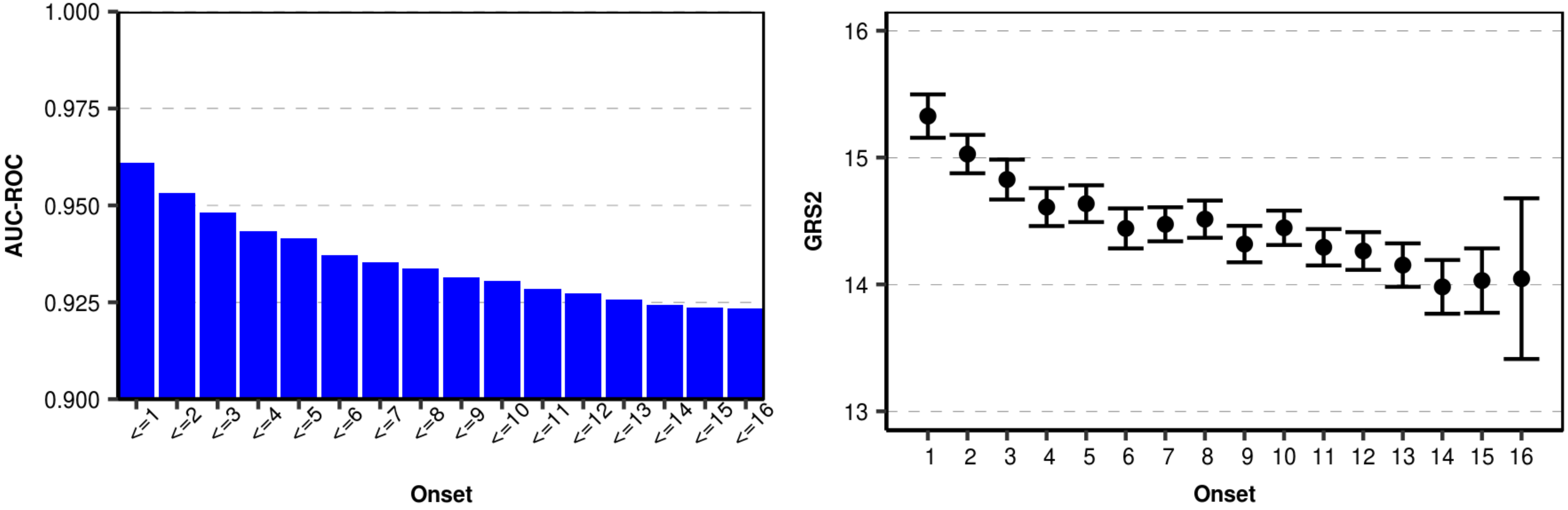


Figure S4 - AUC ROC by onset age in the T1DGC dataset with truncated axis to emphasize improved discrimination of T1D at youngest age.

Table S1

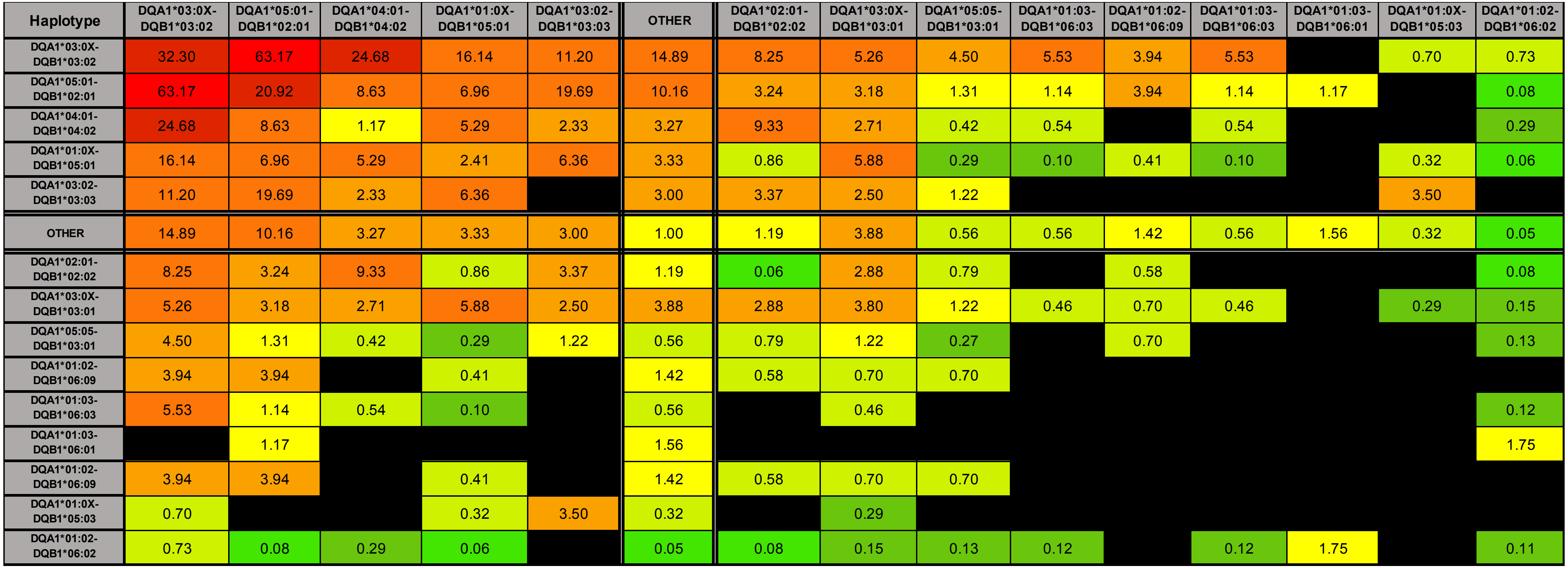
DQA1	DQB1	Freq*	Marker**	r^2	Odds Ratio	Beta
03:0X	03:02	0.154	rs9275490	0.987	7.99	2.08
01:02	06:02	0.1437	rs17843689	0.968	4.02	1.39
05:01	02:01	0.1314	rs9273369	0.998	3.54	1.26
02:01	02:02	0.1108	rs17211699	0.985	1.62	0.48
05:05	03:01	0.1106	rs9469200	0.975	0.97	-0.03
01:0X	05:01	0.1088	rs10947332	0.994	0.63	-0.46
03:0X	03:01	0.0648	rs1281935	0.882	0.53	-0.63
01:03	06:03	0.0567	rs62406889	0.968	0.52	-0.65
02:01	03:03	0.0366	rs28746898	0.955	0.47	-0.76
04:01	04:02	0.0227	rs12527228	0.956	0.41	-0.89
01:0X	05:03	0.0208	rs1794265	0.990	0.27	-1.31
03:02	03:03	0.0079	rs9405117	0.956	0.24	-1.43
01:02	06:09	0.0071	rs16822632	0.954	0.11	-2.21
01:03	06:01	0.0066	rs117806464	0.986	0.09	-2.41

*Frequency of HLA haplotype in European American population (Klitz et al Tissue Antigens 2003)

**Minor allele corresponds to presence of haplotype

Table S1 - Fourteen HLA haplotypes or alleles included in the T1D GRS2. Also displayed is odds ratios for DR-DQ alleles (adjusted for included haplotype combination odds ratios)

Table S2



Haplotype	DQA1*03:0X-DQB1*03:02	DQA1*05:01-DQB1*02:01	DQA1*04:01-DQB1*04:02	DQA1*01:0X-DQB1*05:01	DQA1*03:02-DQB1*03:03	OTHER	DQA1*02:01-DQB1*02:02	DQA1*03:0X-DQB1*03:01	DQA1*05:05-DQB1*03:01	DQA1*01:03-DQB1*06:03	DQA1*01:02-DQB1*06:09	DQA1*01:03-DQB1*06:03	DQA1*01:03-DQB1*06:01	DQA1*01:0X-DQB1*05:03	DQA1*01:02-DQB1*06:02
DQA1*03:0X-DQB1*03:02	32.30	63.17	24.68	16.14	11.20	14.89	8.25	5.26	4.50	5.53	3.94	5.53		0.70	0.73
DQA1*05:01-DQB1*02:01	63.17	20.92	8.63	6.96	19.69	10.16	3.24	3.18	1.31	1.14	3.94	1.14	1.17		0.08
DQA1*04:01-DQB1*04:02	24.68	8.63	1.17	5.29	2.33	3.27	9.33	2.71	0.42	0.54		0.54			0.29
DQA1*01:0X-DQB1*05:01	16.14	6.96	5.29	2.41	6.36	3.33	0.86	5.88	0.29	0.10	0.41	0.10		0.32	0.06
DQA1*03:02-DQB1*03:03	11.20	19.69	2.33	6.36		3.00	3.37	2.50	1.22					3.50	
OTHER	14.89	10.16	3.27	3.33	3.00	1.00	1.19	3.88	0.56	0.56	1.42	0.56	1.56	0.32	0.05
DQA1*02:01-DQB1*02:02	8.25	3.24	9.33	0.86	3.37	1.19	0.06	2.88	0.79		0.58				0.08
DQA1*03:0X-DQB1*03:01	5.26	3.18	2.71	5.88	2.50	3.88	2.88	3.80	1.22	0.46	0.70	0.46		0.29	0.15
DQA1*05:05-DQB1*03:01	4.50	1.31	0.42	0.29	1.22	0.56	0.79	1.22	0.27		0.70				0.13
DQA1*01:02-DQB1*06:09	3.94	3.94		0.41		1.42	0.58	0.70	0.70						
DQA1*01:03-DQB1*06:03	5.53	1.14	0.54	0.10		0.56		0.46							0.12
DQA1*01:03-DQB1*06:01		1.17				1.56									1.75
DQA1*01:02-DQB1*06:09	3.94	3.94		0.41		1.42	0.58	0.70	0.70						
DQA1*01:0X-DQB1*05:03	0.70			0.32	3.50	0.32		0.29							
DQA1*01:02-DQB1*06:02	0.73	0.08	0.29	0.06		0.05	0.08	0.15	0.13	0.12		0.12	1.75		0.11

Table S2- Heat map of T1D odds ratios of DR-DQ haplotype combinations. Odds ratios are shown whenever there were ≥50 cases (derived from 4,600 total cases). X=any other haplotype not specifically noted.

Table S3

Haplotype 1		Haplotype 2		Interaction		
DQA1	**DQB1**	**DQA1**	**DQB1**	**P value***	**Odds Ratio**	**Beta**
05:01	02:01	03:0X	03:02	7.6E-23	37.80	3.63
03:0X	03:01	01:0X	05:01	9.4E-23	22.99	3.14
03:0X	03:02	03:0X	03:02	1.9E-20	10.06	2.31
03:0X	03:01	03:0X	03:02	7.6E-19	8.70	2.16
05:01	02:01	03:0X	03:01	8.1E-16	2.96	1.08
03:0X	03:01	02:01	02:02	1.2E-10	2.90	1.06
04:01	04:02	02:01	02:02	2.9E-09	1.84	0.61
05:01	02:01	01:0X	05:01	5.7E-08	1.19	0.17
05:01	02:01	02:01	02:02	1.7E-07	1.19	0.17
05:01	02:01	05:01	02:01	2.9E-07	1.06	0.05
01:02	06:02	01:02	06:02	5.9E-07	0.79	-0.24
05:01	02:01	05:05	03:01	1.4E-06	0.60	-0.51
05:01	02:01	01:03	06:03	1.7E-06	0.52	-0.65
03:0X	03:02	01:03	06:03	2.9E-06	0.50	-0.69
03:0X	03:01	03:0X	03:01	4.5E-06	0.42	-0.87
03:02	03:03	03:0X	03:02	6.3E-05	0.32	-1.15
03:0X	03:01	05:05	03:01	1.6E-04	0.23	-1.47
05:01	02:01	01:02	06:02	2.6E-04	0.14	-1.94

Table S3- Eighteen GRS2 terms used to account for the interactions shown in Table S2 in sufficiently common DR-DQ haplotype combinations. *Shown are logistic regression P-values of multiplacative interaction terms.

Table S4

Locus	SNP	Odds Ratio	Beta	Allele	MAF*
B*3906	rs540653847	5.94	1.78	GC	0.006
XL9 Regulatory	rs9271346	5.43	1.69	T	0.183
BTNL2 Regulatory	rs116522341	3.45	1.24	C	0.025
Intergenic DRB1-DQA1	rs1281934	2.46	0.90	G	0.067
DPB1*1501	rs2567287	2.31	0.84	A	0.009
Intergenic BTNL2-DRA1	rs75658393	2.26	0.81	T	0.018
A*2402	rs72848653	2.17	0.78	T	0.078
A*2902	rs144530872	2.10	0.74	A	0.042
Intergenic DRA1-DRB1	rs9269173	1.95	0.67	A	0.021
A*0205	rs9500974	1.88	0.63	T	0.009
C*0602	rs12189871	1.57	0.45	T	0.091
A*0201	rs12153924	1.56	0.44	A	0.275
B*1801	rs371250843	1.47	0.39	T	0.037
A*0301	rs9259118	1.36	0.31	T	0.142
DPB1*0301	rs559242105	1.27	0.24	CTA	0.117
DPB1*0101	rs17214657	0.82	-0.19	C	0.064
DPB1*0501	rs9378176	0.61	-0.49	G	0.023
B*4403	rs2524277	0.55	-0.60	A	0.060
DPB1*0402	rs6934289	0.51	-0.68	C	0.109
B*4501	rs16899379	0.44	-0.83	A	0.006
B*5701	rs149663102	0.39	-0.94	T	0.039

Table S4-Twenty-one non-DR-DQ loci within the HLA region used in the T1D GRS.

Table S5

Gene*	SNP	Odds Ratio	Beta	Allele	Source
INS	rs3842753	2.29	0.83	G	Internal
PTPN22	rs2476601	1.89	0.64	A	Onengut
CTSH	rs2289702	1.32	0.28	C	Internal
ATXN2	rs653178	1.30	0.26	C	Onengut
COBL	rs4948088	1.30	0.26	C	Winkler
IL27	rs9924471	1.24	0.22	A	Poicot
ERBB3	rs4759229	1.24	0.22	A	Internal
PTPN2	rs1893217	1.21	0.19	G	Onengut
BACH2	rs72928038	1.20	0.18	A	Onengut
RNLS	rs60888743	1.20	0.18	A	Internal
ITGB7	rs11170466	1.19	0.17	T	Poicot
UBASH3A	rs9981624	1.19	0.17	C	Interal
CENPW	rs9388489	1.17	0.16	A	Onengut
HORMAD2	rs5763779	1.16	0.15	A	Internal
PRKD2	rs425105	1.16	0.15	T	Onengut
RASGRP1	rs72727394	1.15	0.14	T	Onengut
ADAD1	rs17388568	1.13	0.12	A	Poicot
CD226	rs1615504	1.13	0.12	T	Onengut
COBL	rs6476839	1.12	0.11	T	Onengut
IRF7	rs9585056	1.12	0.11	C	Onengut
C1QTNF6	rs229541	1.11	0.10	A	Poicot
SIRPG	rs2281808	1.11	0.10	C	Steck
TAGAP	rs1738074	0.92	-0.08	T	Poicot
MEG3	rs56994090	0.88	-0.13	C	Onengut
CLEC1	rs10492166	0.87	-0.14	A	Poicot
PTPN22	rs3024505	0.86	-0.15	A	Onengut
IFIH1	rs2111485	0.85	-0.16	A	Onengut
CTLA4	rs3087243	0.84	-0.17	A	Onengut
CLEC16A	rs12708716	0.83	-0.19	G	Poicot
TYK2	rs144309607	0.67	-0.40	T	Onengut
IL2RA	rs61839660	0.62	-0.48	T	Onengut
IL2RA	rs41295121	0.49	-0.71	T	Onengut

Table S5- Thirty-two SNPs marking 31 non-HLA loci used in the GRS2. Genes identified are candidate genes either theorized or directly implicated.

Table S6

UKB centile	T1D GRS1		TEDDY GRS		Winkler GRS		Perry GRS		T1D GRS2	
	Value	J*	Value	J*	Value	J*	Value	J*	Value	J*
5	9.76	0.046	8.75	0.048	6.52	0.050	9.53	0.045	6.49	0.047
10	10.42	0.094	9.16	0.095	6.92	0.099	10.30	0.095	7.21	0.092
15	10.93	0.144	9.44	0.145	7.19	0.143	10.85	0.145	7.70	0.142
20	11.49	0.193	9.66	0.185	7.42	0.185	11.36	0.195	8.12	0.190
25	12.02	0.242	9.87	0.236	7.63	0.234	11.83	0.242	8.51	0.237
30	12.41	0.289	10.06	0.284	7.82	0.278	12.23	0.288	8.88	0.287
35	12.70	0.335	10.24	0.318	8	0.329	12.55	0.332	9.25	0.337
40	12.95	0.378	10.41	0.367	8.17	0.369	12.83	0.378	9.62	0.382
45	13.18	0.413	10.59	0.410	8.35	0.404	13.08	0.419	9.98	0.430
50	13.40	0.462	10.77	0.444	8.53	0.449	13.32	0.464	10.34	0.472
55	13.63	0.502	10.96	0.480	8.72	0.490	13.56	0.502	10.69	0.517
60	13.87	0.542	11.15	0.518	8.91	0.513	13.80	0.541	11.03	0.567
65	14.13	0.572	11.36	0.548	9.12	0.531	14.05	0.568	11.38	0.612
70	14.40	0.598	11.58	0.570	9.34	0.571	14.32	0.598	11.72	0.641
75	14.68	0.625	11.82	0.578	**9.58**	**0.577**	14.60	0.631	12.07	0.673
80	**14.98**	**0.645**	**12.08**	**0.595**	9.85	0.568	**14.92**	**0.638**	12.45	0.684
85	15.30	0.629	12.39	0.589	10.16	0.572	15.27	0.600	**12.88**	**0.698**
90	15.70	0.576	12.79	0.529	10.56	0.510	15.68	0.549	13.41	0.684
95	16.34	0.472	13.41	0.437	11.2	0.424	16.31	0.464	14.19	0.563
AUC-ROC**	0.893 (0.877-0.908)		0.874 (0.856-0.891)		0.868 (0.851 - 0.885)		0.891 (0.8752 - 0.9061)		0.921 (0.907-0.935)	

Table S6- Case control discrimination of recently published type 1 diabetes genetic risk scores comparing by GRS value and corresponding Youden's index value referenced against interval centiles of T1D cases in UK Biobank.

*Youdens index (specificity + sensitivity - 1)
**(95% Confidence intervals)