

## Supplemental Material

### Links to Excel files:

- **CP.xlsx:**

[https://docs.google.com/spreadsheets/d/16\\_OVioCgUZ-EKKLNu1G9H0iOiJpephQ6/edit?usp=drive\\_link&oid=110612840906643856403&rtpof=true&sd=true](https://docs.google.com/spreadsheets/d/16_OVioCgUZ-EKKLNu1G9H0iOiJpephQ6/edit?usp=drive_link&oid=110612840906643856403&rtpof=true&sd=true)

- **AAD.xlsx**

[https://docs.google.com/spreadsheets/d/1-7xyL82Tk87Z1uRsfKhT0JQDjg3epFTm/edit?usp=drive\\_link&oid=110612840906643856403&rtpof=true&sd=true](https://docs.google.com/spreadsheets/d/1-7xyL82Tk87Z1uRsfKhT0JQDjg3epFTm/edit?usp=drive_link&oid=110612840906643856403&rtpof=true&sd=true)

## Supplementary Tables

**Table S1:** Study descriptions

Study	Description
<b>SDRNT1BIO</b>	This is a cohort of people clinically diagnosed with T1D based on AAD, time to insulin, history of ketoacidosis and exclusion of monogenic subtypes of diabetes. Subjects were >16 years at recruitment and comprise one-third of the adult population with T1D in Scotland (1). Random serum C-peptide was measured at the Exeter clinical laboratory (2).
<b>DCCT</b>	Individuals aged 13-39 years with T1D and fasting serum C-peptide $\leq 0.2$ pmol/ml were recruited between 1983 and 1989 in two cohorts. The primary cohort included participants with 1-5 years of diabetes, no pre-existing retinopathy/nephropathy and stimulated C-peptide $\leq 0.5$ pmol/ml. The secondary cohort included participants with 1-15 years of diabetes, pre-existing mild retinopathy and/or nephropathy and stimulated C-peptide $\leq 0.5$ and $\leq 0.2$ pmol/ml for participants with diabetes duration 1-5 and 5-15 years, respectively (3; 4). Stimulated C-peptide measured at baseline was used in current analyses.
<b>CACTI</b>	This is a population-based study of individuals with T1D of duration >10 years at enrolment recruited from Denver, CO, USA, between March 2000 and April 2002 (5). Fasting serum C-peptide was measured during 2014–2016 (6).
<b>WESDR</b>	This study included individuals diagnosed with diabetes <32 years of age and treated with insulin who received primary care in an 11-county area in southern Wisconsin 1979-1980 (7). Random serum C-peptide was measured at years 4 and 10 of follow-up (7). The most recent measurement was used.
<b>EDC</b>	This study is only utilized in the AAD analyses. It included individuals with childhood-onset (<17 years of age) T1D who were diagnosed or seen within 1 year of diagnosis (1950–1980) at the Children's Hospital of Pittsburgh(8).
<b>GS</b>	This is a family-based cohort of 24,000 volunteers across Scotland aged $\geq 18$ years recruited 2006-2011 (9). This cohort was used as the control group and therefore individuals with any record of diabetes in self-report, hospital records or any prescription of insulin or anti-diabetic oral medications were excluded.

SDRNT1BIO: Scottish Diabetes Research Network Type 1 Bioresource; DCCT: Diabetes Control and Complications Trial; CACTI: Coronary Artery Calcification in Type 1 Diabetes; WESDR: Wisconsin Epidemiologic Study of Diabetic Retinopathy; EDC: Pittsburgh Epidemiology of Diabetes Complications study; GS: Generation Scotland

**Table S2:** Subject characteristics

<b>Study</b>	<b>SDRNT1BIO N = 5,349</b>	<b>DCCT N = 1,304</b>	<b>CACTI N = 529</b>	<b>WESDR N = 591</b>	<b>EDC N = 150</b>
<b>Sex (Male)</b>	3021 (56.5%)	695 (53.3%)	235 (44.4)	297 (50.3)	76 (50.7)
<b>Age at diagnosis (Years)</b>	22.9 (14.0)	21.2 (8.1)	13.1 (8.0)	14.5 (7.5)	8.3 (4.1)
<b>Duration (Years)</b>	22.2 (13.5)	5.7 (4.2)	34.1 (9.0)	19.2 (9.0)	43.0 (6.7)
<b>C-peptide</b>					
<b>N with detectable values</b>	1,727	728	83 (15.7%)	68 (11.5%)	-
<b>Subjects with detectable values</b>	4.76 (4.11-5.35) †	0.15 (0.08-0.27) *	58.82 (28.00-278.40) †	0.14 (0.07-0.46) *	-

Values are Mean (SD), N (%) or mean (25-75 percentiles).

\* pmol/mL

† pmol/L

**Table S3:** C-peptide measurement methods in different studies (10; 11)

Study	Time	Assay	Lower Limit of Detection
SDRNT1BIO	Non-fasting	Roche electrochemiluminescence assay	3 pmol/L
DCCT	After 8-12 hr fasting 90 mins after standard meal*	M-1230 antiserum and other reagents obtained from Novo Industri (Bagsvaerd, Denmark)	0.03 pmol/mL
CACTI	After 12 hr fasting	ALPCO C-peptide ELISA Kit (ALPCO, Salem, NH)	16 pmol/L
WESDR	Non-Fasting	Radioimmunoassay with Heding's M1230 antiserum	0.03 pmol/mL

\* 6 mL of Sustacal/kg of body weight to a maximum of 360 mL (Mead-Johnson, Evansville, Indiana; 1 calorie/mL; 55% carbohydrate, 24% protein, and 21% fat) in a period not exceeding 10 minutes

**Table S4:** Genotyping platforms used in different studies (10; 11)

Study	Genotyping Platform
SDRNT1BIO	Illumina HumanCoreExome
DCCT	Illumina 1M BeadArray
CACTI	Illumina HumanCoreExome
WESDR	Illumina HumanCoreExome
EDC	Illumina HumanCoreExome
Generation Scotland	Illumina OmniExpressExome 8V 1-2A

**Table S5:** C-peptide GWAS and meta-GWAs characteristics

Study	Subjects	SNPs	GC Lambda
SDRNT1BIO	4,828	8,323,557	1.01
DCCT	1,304	8,714,127	1.00
CACTI	529	8,313,150	1.01
WESDR	591	8,212,213	0.99
Meta-GWAS	7,252	8,150,645	1.01

GC: Genomic control

**Table S6:** Association of *DR-DQ* haplotype combinations with C-peptide

	SDRNT1BIO (N = 4,828)				DCCT (N = 1,304)				CACTI (N = 529)				WESDR (N = 591)				Meta-analysis						
HLA Haplotype	N	Beta	SE	P	N	Beta	SE	P	N	Beta	SE	P	N	Beta	SE	P	Freq	Beta	SE	P	Direction*	Het I <sup>2</sup>	Het P
DR3/X	894	0.06	0.13	0.63	221	0.03	0.10	0.73	109	-0.06	0.13	0.63	91	-0.39	0.12	1.28E-03	0.18	-0.08	0.06	0.16	+++	66.90	0.03
DR3/DR3	654	0.08	0.14	0.57	113	0.03	0.11	0.79	35	0.04	0.17	0.81	39	-0.36	0.15	1.40E-02	0.09	-0.04	0.07	0.58	+++	49.20	0.12
DR3/DR4	1333	0.14	0.12	0.27	336	0.11	0.09	0.22	136	-0.09	0.13	0.50	171	-0.24	0.11	2.82E-02	0.27	-0.01	0.05	0.92	+++	62.90	4.43E-02
DR4/X	1092	-0.01	0.12	0.95	360	0.06	0.09	0.51	153	-0.16	0.12	0.20	178	-0.30	0.11	7.03E-03	0.28	-0.08	0.05	0.12	+++	58.30	0.07
DR4/DR4	387	0.15	0.15	0.32	118	-0.09	0.11	0.45	42	0.13	0.16	0.43	46	-0.18	0.14	0.19	0.08	-0.02	0.07	0.74	++	22.50	0.28
DR3/DR15	30	0.85	0.39	3.E-02	3	0.08	0.52	0.87	3	-0.34	0.44	0.44	2	0.62	0.49	0.20	0.01	0.34	0.23	0.13	+++	35.80	0.20
DR4/DR15	40	1.12	0.34	1.E-03	10	0.20	0.29	0.50	4	0.19	0.38	0.61	7	0.47	0.27	0.09	0.01	0.48	0.16	2.00E-03	++++	40.70	0.17
DR15/X	35	1.51	0.36	3.E-05	7	0.23	0.35	0.51	2	-0.23	0.53	0.67	9	1.04	0.24	2.41E-05	0.01	0.84	0.16	3.95E-07	+++	73.40	1.04E-02
DR15/DR15	3	2.05	1.18	0.08	0	NA	NA	NA	1	2.35	0.74	1.57E-03	0	NA	NA	NA	0.00	2.27	0.63	3.02E-04	+?+?	0.00	0.83
X/X	360	Ref			136	Ref			44	Ref			48	Ref			0.08	Ref					

Het: Heterogeneity, Freq = Frequency

\* The order of studies is SDRNT1BIO, DCCT, CACTI and WESDR.

**Table S7:** Association of *DR-DQ* haplotype combinations with risk of type 1 diabetes

	Generation Scotland		SDRNT1BIO				
HLA Haplotype	N	Frequency	N	Frequency	Beta	SE	P
<i>DR3/X</i>	1225	0.16	922	0.19	1.53	0.09	2.E-70
<i>DR3/DR3</i>	207	0.03	645	0.13	3.25	0.13	2.E-129
<i>DR3/DR4</i>	430	0.06	1341	0.27	2.92	0.09	1.E-216
<i>DR4/X</i>	1298	0.17	1133	0.23	1.36	0.07	2.E-77
<i>DR4/DR4</i>	209	0.03	391	0.08	2.11	0.11	9.E-85
<i>DR3/DR15</i>	392	0.05	34	0.01	-0.48	0.2	2.E-02
<i>DR4/DR15</i>	432	0.06	43	0.01	-0.66	0.18	2.E-04
<i>DR15/X</i>	1221	0.16	54	0.01	-1.42	0.15	4.E-20
<i>DR15/DR15</i>	220	0.03	5	0.00	-1.97	0.46	2.E-05
<i>X/X</i>	1840	0.25	390	0.08	Ref	Ref	Ref
<b>Total</b>	7474	1.00	4958	1.00	-	-	-

**Table S8:** Association of non-HLA type 1 diabetes risk loci with C-peptide and AAD

CHR	BP	SNP	T1D						CP						AOD					
			A1	A2	OR	P	Gene	Study	A1	A2	Freq	BETA	SE	P	A1	A2	Freq	BETA	SE	P
1	63,643,100	rs2269241	T	C	1.11	4.67E-12	PGM1	R	T	C	0.22	0.04	0.02	9.86E-02	T	C	0.22	-0.01	0.02	7.26E-01
1	92,358,141	rs34090353	G	C	1.08	1.10E-08	RPAP2	R	C	G	0.62	0.01	0.02	6.63E-01	C	G	0.63	0.02	0.02	2.44E-01
1	113,834,946	rs2476601	G	A	1.89	0	PTPN22	O	A	G	0.18	0.04	0.03	1.09E-01	A	G	0.18	0.03	0.03	2.47E-01
1	119,895,261	rs2641348	A	G	1.11	1.61E-08	NOTCH2	R	A	G	0.12	-0.01	0.03	6.89E-01	A	G	0.12	0.02	0.03	4.53E-01
1	154,465,420	rs2229238	T	C	0.90	1.38E-12	IL6R	R	T	C	0.20	0.05	0.03	4.31E-02	T	C	0.20	0.00	0.03	9.36E-01
1	172,746,562	rs78037977	A	G	0.88	2.41E-09	FASLG	R	A	G	0.11	-0.03	0.03	3.68E-01	A	G	0.12	0.08	0.03	1.29E-02
1	192,570,207	rs2816313	G	A	1.09	4.57E-09	RGS1	R	A	G	0.72	0.00	0.02	8.97E-01	A	G	0.72	0.10	0.02	1.53E-05
1	200,845,831	rs6691977	T	C	1.13	4.30E-08		O	T	C	0.21	0.05	0.02	4.00E-02	T	C	0.21	-0.07	0.02	4.71E-03
1	206,766,559	rs3024505	G	A	0.86	6.40E-08	IL10	O	A	G	0.86	-0.03	0.03	2.58E-01	A	G	0.87	-0.04	0.03	1.35E-01
1	212,796,238	rs11120029	G	T	1.10	1.82E-08	TATDN3	R	T	G	0.84	-0.04	0.03	1.84E-01	T	G	0.84	-0.01	0.03	7.48E-01
2	12,512,805	rs10169963	C	T	1.07	2.78E-08	AC096559.1	R	T	C	0.58	-0.02	0.02	4.05E-01	T	C	0.58	0.01	0.02	5.47E-01
2	100,147,438	rs12712067	G	T	0.93	4.12E-09	AFF3	R	T	G	0.65	-0.03	0.02	1.59E-01	T	G	0.66	-0.02	0.02	3.91E-01
2	100,147,625	rs13415583	T	G	0.90	1.10E-07	AFF3	O	T	G	0.35	0.03	0.02	1.49E-01	T	G	0.34	0.02	0.02	4.36E-01
2	110,857,502	rs4849135	G	T	0.89	4.40E-08		O	T	G	0.28	-0.03	0.02	1.79E-01	T	G	0.28	0.00	0.02	8.86E-01
2	162,254,026	rs2111485	G	A	0.85	3.80E-18	IFIH1	O	A	G	0.36	-0.01	0.02	6.83E-01	A	G	0.36	-0.02	0.02	4.02E-01
2	162,268,127	rs35667974	T	C	0.59	9.30E-09	IFIH1	O	NA	NA	NA	NA	NA	NA	T	C	0.01	0.08	0.10	4.14E-01
2	162,280,432	rs72871627	A	G	0.61	2.40E-06	IFIH1	O	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2	191,105,394	rs7582694	C	G	0.92	2.83E-09	STAT4	R	C	G	0.24	0.01	0.02	5.60E-01	C	G	0.24	0.03	0.02	1.87E-01
2	203,874,196	rs3087243	G	A	0.84	7.40E-21	CTLA4	O	A	G	0.62	0.00	0.02	9.17E-01	A	G	0.62	-0.06	0.02	6.58E-03
2	241,468,331	rs10933559	A	G	1.11	2.39E-11	FARP2	R	A	G	0.22	0.02	0.02	5.13E-01	A	G	0.22	0.00	0.02	9.23E-01
3	46,415,921	rs113010081	T	C	0.85	4.60E-08	CCR5	O	T	C	0.12	0.04	0.03	2.71E-01	T	C	0.12	0.06	0.03	7.67E-02
4	973,543	rs113881148	C	A	1.08	5.72E-09	TMEM175	R	A	C	0.64	0.02	0.02	3.33E-01	A	C	0.64	0.01	0.02	5.10E-01
4	38,602,849	rs337637	G	A	0.92	2.57E-10	KLF3	R	A	G	0.65	-0.01	0.02	7.28E-01	A	G	0.64	-0.03	0.02	2.28E-01
4	122,322,441	rs75793288	C	G	1.15	5.60E-13	IL2, IL21	O	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4	165,653,115	rs2611215	G	A	1.18	1.80E-11		O	A	G	0.18	0.02	0.03	3.49E-01	A	G	0.18	0.02	0.03	5.48E-01
5	35,883,149	rs11954020	C	G	1.11	4.40E-08	IL7R	O	C	G	0.41	0.01	0.02	7.56E-01	C	G	0.41	-0.01	0.02	6.65E-01

			T1D						CP						AOD					
CHR	BP	SNP	A1	A2	OR	P	Gene	Study	A1	A2	Freq	BETA	SE	P	A1	A2	Freq	BETA	SE	P
5	40,521,603	rs1876142	G	T	0.91	2.18E-14	PTGER4	R	T	G	0.63	0.00	0.02	9.31E-01	T	G	0.64	-0.01	0.02	5.55E-01
5	56,146,422	rs10213692	T	C	0.91	2.85E-09	ANKRD55/IL6ST	R	T	C	0.23	0.01	0.02	7.55E-01	T	C	0.23	0.02	0.02	5.24E-01
6	424,915	rs9405661	C	A	1.08	2.26E-09	IRF4	R	A	C	0.53	0.01	0.02	6.44E-01	A	C	0.54	-0.02	0.02	4.41E-01
6	90,267,049	rs72928038	G	A	1.20	6.40E-14	BACH2	O	A	G	0.80	0.03	0.03	2.20E-01	A	G	0.80	-0.01	0.03	6.04E-01
6	126,431,738	rs1538171	C	G	1.12	7.40E-10		O	C	G	0.48	0.00	0.02	9.08E-01	C	G	0.48	-0.01	0.02	5.36E-01
6	137,682,468	rs12665429	T	C	0.91	1.36E-13	TNFAIP3	R	T	C	0.36	-0.03	0.02	1.16E-01	T	C	0.37	0.02	0.02	4.00E-01
6	159,049,210	rs212408	G	T	1.11	1.42E-15	TAGAP	R	T	G	0.65	-0.03	0.02	2.40E-01	T	G	0.65	-0.01	0.02	6.36E-01
7	20,557,306	rs17143056	A	G	0.91	2.44E-08	ABCB5	O	A	G	0.18	0.03	0.03	3.37E-01	A	G	0.18	0.02	0.03	3.92E-01
7	28,102,567	rs10245867	G	T	0.93	3.15E-08	JAZF1	R	T	G	0.68	-0.03	0.02	2.34E-01	T	G	0.69	-0.02	0.02	3.08E-01
7	50,398,132	rs62447205	A	G	0.89	2.50E-08	IKZF1	O	A	G	0.26	-0.02	0.02	3.49E-01	A	G	0.26	0.07	0.02	2.71E-03
7	50,961,290	rs10277986	A	T	0.76	1.40E-07		O	A	T	0.96	-0.13	0.08	8.79E-02	A	T	0.96	0.12	0.06	6.55E-02
8	11,877,675	rs2250903	G	T	0.91	1.35E-10	CTSB	R	T	G	0.73	-0.01	0.02	6.95E-01	T	G	0.73	-0.01	0.02	7.26E-01
9	4,290,823	rs6476839	A	T	1.12	1.00E-09	GLIS3	O	A	T	0.42	-0.02	0.02	3.71E-01	A	T	0.41	-0.06	0.02	1.87E-03
9	99,823,263	rs1405209	T	C	1.08	3.45E-08	NR4A3	R	T	C	0.38	-0.03	0.02	1.93E-01	T	C	0.37	0.01	0.02	4.81E-01
10	6,052,734	rs61839660	C	T	0.62	2.80E-39	IL2RA	O	T	C	0.93	0.10	0.04	1.73E-02	T	C	0.93	-0.19	0.04	2.00E-06
10	6,066,377	rs10795791	A	G	1.16	5.60E-11	IL2RA	O	A	G	0.45	0.00	0.02	9.49E-01	A	G	0.45	0.01	0.02	4.58E-01
10	6,087,680	rs41295121	C	T	0.49	4.90E-08	IL2RA	O	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
10	33,137,219	rs722988	T	C	1.11	3.21E-15	NRP1	R	T	C	0.39	0.02	0.02	3.31E-01	T	C	0.39	-0.02	0.02	4.48E-01
10	88,275,897	rs12416116	C	A	0.85	3.90E-15		O	A	C	0.74	0.01	0.02	6.91E-01	A	C	0.75	-0.04	0.02	1.10E-01
11	2,160,994	rs689	T	A	0.42	0	INS	O	A	T	0.16	-0.14	0.03	6.34E-07	A	T	0.16	-0.08	0.03	4.03E-03
11	2,177,435	rs72853903	C	T	0.85	6.20E-10	INS	O	T	C	0.75	-0.05	0.02	2.58E-02	T	C	0.76	-0.06	0.02	1.90E-02
11	35,267,496	rs11033048	C	T	1.09	1.53E-10	SLC1A2	R	T	C	0.59	0.00	0.02	9.37E-01	T	C	0.59	-0.03	0.02	1.43E-01
11	60,961,822	rs79538630	G	T	1.21	1.14E-09	CD5/CD6	R	T	G	0.96	-0.03	0.05	5.26E-01	T	G	0.96	0.07	0.05	1.92E-01
11	61,828,092	rs968567	C	T	0.90	8.42E-09	FADS2	R	T	C	0.83	0.00	0.03	8.78E-01	T	C	0.83	-0.02	0.03	4.82E-01
11	64,367,826	rs645078	A	C	0.93	3.34E-09	CCDC88B	R	A	C	0.36	0.02	0.02	4.58E-01	A	C	0.36	0.00	0.02	9.08E-01
11	128,734,337	rs605093	G	T	1.08	4.25E-09	FLI1	R	T	G	0.52	0.02	0.02	2.77E-01	T	G	0.53	-0.01	0.02	5.63E-01
12	8,942,630	rs1805731	T	C	1.07	4.16E-08	M6PR	R	T	C	0.40	0.02	0.02	2.77E-01	T	C	0.39	-0.05	0.02	1.11E-02
12	9,753,255	rs917911	A	C	1.10	1.90E-07	CD69	O	A	C	0.38	0.01	0.02	6.95E-01	A	C	0.38	-0.04	0.02	4.14E-02

			T1D						CP						AOD					
CHR	BP	SNP	A1	A2	OR	P	Gene	Study	A1	A2	Freq	BETA	SE	P	A1	A2	Freq	BETA	SE	P
12	53,077,434	rs7313065	C	A	1.10	3.28E-09	ITGB7	R	A	C	0.83	0.03	0.03	2.31E-01	A	C	0.83	-0.01	0.03	6.97E-01
12	56,041,720	rs705705	G	C	1.25	4.40E-32	IKZF4	O	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
12	111,569,952	rs653178	T	C	1.30	1.60E-44	SH2B3	O	T	C	0.56	-0.02	0.02	2.54E-01	T	C	0.56	-0.02	0.02	2.93E-01
13	42,343,795	rs74537115	C	T	1.11	5.41E-09	AKAP11	R	T	C	0.84	0.03	0.03	3.18E-01	T	C	0.84	0.01	0.03	6.10E-01
13	99,429,512	rs9585056	T	C	1.12	3.30E-08	GPR183	O	T	C	0.73	0.05	0.02	1.73E-02	T	C	0.73	0.01	0.02	5.73E-01
14	68,286,876	rs911263	C	T	1.08	1.69E-08	RAD51B	R	T	C	0.73	0.01	0.02	8.22E-01	T	C	0.74	0.04	0.02	1.10E-01
14	98,021,670	rs1456988	T	G	1.12	2.90E-08		O	T	G	0.70	-0.02	0.02	3.13E-01	T	G	0.71	0.02	0.02	3.21E-01
14	100,840,110	rs56994090	T	C	0.88	1.10E-11		O	T	C	0.39	-0.03	0.02	1.69E-01	T	C	0.38	-0.02	0.02	4.58E-01
15	38,554,821	rs72727394	C	T	1.15	3.60E-10	RASGRP1	O	T	C	0.78	0.00	0.02	8.42E-01	T	C	0.79	0.06	0.02	8.36E-03
15	78,942,615	rs34593439	G	A	0.78	9.00E-14	CTSH	O	A	G	0.92	0.01	0.04	7.89E-01	A	G	0.92	-0.20	0.04	2.14E-07
16	11,100,914	rs12927355	C	T	0.82	3.00E-22	DEXI	O	T	C	0.72	-0.06	0.02	1.34E-02	T	C	0.72	0.00	0.02	9.41E-01
16	11,257,354	rs193778	A	G	1.14	4.40E-10	DEXI	O	A	G	0.28	-0.05	0.02	1.88E-02	A	G	0.28	0.02	0.02	2.92E-01
16	20,331,769	rs4238595	T	C	0.91	2.43E-11	UMOD	R	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
16	28,494,339	rs151234	G	C	1.19	4.80E-11	IL27	O	C	G	0.85	0.07	0.03	1.77E-02	C	G	0.85	0.02	0.03	6.06E-01
16	75,218,429	rs8056814	G	A	1.32	3.00E-19	BCAR1	O	A	G	0.90	-0.03	0.03	4.37E-01	A	G	0.90	0.05	0.03	1.91E-01
17	39,896,954	rs12453507	G	C	0.90	1.00E-08	IKZF3,ORMDL3, GSDMB	O	C	G	0.48	0.00	0.02	8.44E-01	C	G	0.48	-0.04	0.02	7.56E-02
17	40,618,898	rs757411	T	C	0.90	1.10E-07	CCR7	O	T	C	0.62	0.02	0.02	2.53E-01	T	C	0.62	-0.02	0.02	4.66E-01
17	45,996,523	rs1052553	A	G	0.88	1.65E-15	MAPT	R	A	G	0.22	0.02	0.02	3.77E-01	A	G	0.21	0.03	0.03	3.10E-01
17	47,956,725	rs2597169	A	G	1.08	3.35E-09	PRR15L	R	A	G	0.36	0.04	0.02	5.07E-02	A	G	0.36	-0.01	0.02	7.97E-01
18	12,809,341	rs1893217	A	G	1.21	1.20E-15	PTPN2	O	A	G	0.20	-0.02	0.03	5.36E-01	A	G	0.20	0.01	0.03	7.24E-01
18	12,830,539	rs12971201	G	A	0.89	2.10E-06	PTPN2	O	A	G	0.63	-0.02	0.02	3.21E-01	A	G	0.64	-0.03	0.02	1.26E-01
18	69,859,408	rs1615504	C	T	1.13	1.80E-11	CD226	O	T	C	0.49	-0.02	0.02	3.96E-01	T	C	0.49	-0.01	0.02	6.82E-01
19	10,352,442	rs34536443	G	C	0.67	4.40E-15	TYK2	O	C	G	0.96	0.00	0.06	9.75E-01	C	G	0.97	-0.03	0.06	6.29E-01
19	10,359,299	rs12720356	A	C	0.82	3.70E-07	TYK2	O	A	C	0.08	0.00	0.04	9.26E-01	A	C	0.08	0.03	0.04	4.60E-01
19	46,715,865	rs402072	T	C	0.87	4.70E-08		O	T	C	0.14	-0.07	0.03	2.76E-02	T	C	0.14	0.06	0.03	3.33E-02
19	48,702,915	rs516246	T	C	0.87	5.20E-14	FUT2	O	T	C	0.53	0.01	0.02	6.97E-01	T	C	0.55	0.00	0.02	8.45E-01
20	1,635,560	rs6043409	G	A	0.88	3.00E-10		O	A	G	0.31	0.02	0.02	3.51E-01	A	G	0.32	-0.01	0.02	6.14E-01
21	42,405,248	rs11203202	C	G	1.16	1.20E-15	UBASH3A	O	C	G	0.37	-0.01	0.02	6.53E-01	C	G	0.37	0.00	0.02	9.62E-01

			T1D						CP						AOD					
CHR	BP	SNP	A1	A2	OR	P	Gene	Study	A1	A2	Freq	BETA	SE	P	A1	A2	Freq	BETA	SE	P
21	44,201,934	rs6518350	A	G	0.88	9.60E-08	ICOSLG	O	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
21	44,204,668	rs56178904	C	T	0.90	6.48E-11	ICOSLG	R	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
22	30,135,102	rs4820830	T	C	1.14	1.20E-12		O	T	C	0.59	-0.01	0.02	6.50E-01	T	C	0.59	-0.03	0.02	1.22E-01
22	37,191,071	rs229533	A	C	1.11	1.80E-08	C1QTNF6, RAC2	O	A	C	0.45	0.02	0.02	3.63E-01	A	C	0.45	-0.03	0.02	1.88E-01

R: Robertson et al (12), O: Onengut-Gumuscu (13); A1: Non-effect allele; A2: Effect allele

**Table S9:** AAD GWAS and meta-GWAs characteristics

<b>Study</b>	<b>Subjects</b>	<b>SNPs</b>	<b>GC Lambda</b>
SDRNT1BIO	5,349	8,330,960	1.02
DCCT	1,304	8,714,127	1.00
CACTI	529	8,313,150	1.00
WESDR	591	8,212,212	1.01
EDC	150	8,162,100	1.01
Meta-GWAS	7,923	8,154,710	1.02

GC: Genomic control

**Table S10:** Association of *DR-DQ* haplotype combinations with AAD

	SDRNT1BIO (N = 5342)				DCCT (N = 1304)				CACTI (N = 529)				WESDR (N = 591)				EDC (N = 150)				Meta-Analysis							
HLA Haplotype	N	Beta	SE	P	N	Beta	SE	P	N	Beta	SE	P	N	Beta	SE	P	N	Beta	SE	P	Freq	Beta	SE	P	Direction*	Het I <sup>2</sup>	Het P	
DR3/X	988	-0.38	0.09	1.E-05	221	-0.10	0.10	0.34	109	0.08	0.20	0.68	91	-0.30	0.18	0.10	33	-0.25	0.24	0.31	0.18	-0.23	0.06	6.96E-05	---+	43.10	0.13	
DR3/DR3	678	-0.35	0.09	1.E-04	113	-0.13	0.12	0.30	35	-0.29	0.26	0.27	39	-0.23	0.22	0.30	7	0.26	0.36	0.47	0.10	-0.25	0.07	1.14E-04	----+	6.40	0.37	
DR3/DR4	1412	-0.78	0.08	8.E-22	336	-0.33	0.10	5.47E-04	136	-0.08	0.20	0.68	171	-0.49	0.17	3.12E-03	47	-0.10	0.23	0.68	0.27	-0.52	0.05	7.68E-22	-----	82.10	1.69E-04	
DR4/X	1207	-0.44	0.08	1.E-07	360	-0.18	0.10	0.06	153	-0.10	0.20	0.62	178	-0.10	0.17	0.57	41	-0.16	0.23	0.49	0.26	-0.29	0.05	1.67E-07	-----	44.40	0.13	
DR4/DR4	419	-0.35	0.10	5.E-04	118	-0.23	0.12	0.06	42	0.07	0.25	0.77	46	-0.08	0.21	0.71	4	-0.12	0.44	0.79	0.08	-0.25	0.07	3.43E-04	---+	0.00	0.49	
DR3/DR15	41	0.23	0.24	0.35	3	0.94	0.56	0.09	3	0.00	0.68	1.00	2	1.43	0.74	0.05	0	NA	NA	NA	0.01	0.39	0.20	0.05	++0+?	19.20	0.29	
DR4/DR15	58	0.29	0.21	0.17	10	0.10	0.31	0.74	4	-0.21	0.60	0.72	7	-0.27	0.41	0.51	1	0.10	0.82	0.91	0.01	0.13	0.15	0.40	++++	0.00	0.76	
DR15/X	81	0.80	0.18	1.E-05	7	0.04	0.37	0.91	2	-2.27	0.83	6.16E-03	9	0.46	0.37	0.22	0	NA	NA	NA	0.01	0.53	0.15	2.56E-04	+++?	80.50	1.49E-03	
DR15/DR15	9	0.14	0.50	0.79	0	NA	NA	NA	1	0.86	1.15	0.46	0	NA	NA	NA	0	NA	NA	NA	0.00	0.25	0.46	0.58	+?+??	0.00	0.57	
X/X	449	Ref			136	Ref			44	Ref			48	Ref			17	Ref			0.08	Ref						

Het: Heterogeneity, Freq = Frequency

\* The order of studies is SDRNT1BIO, DCCT, CACTI, WESDR and EDC.

**Table S11:** Summary of the locus-specific genotypic scores computed for *CTSH* and their association with AAD

Trait Type	Trait Name	CHR	Start	End	Type	Tissue	QTLs N	Strongest QTL P*	Effect	P	FDR <0.05
Methylation	cg17270013	15	78,185,519	79,036,756	cis	Blood	482	0	-0.096	4.61E-06	TRUE
Methylation	cg07448499	15	78,185,519	79,036,756	cis	Blood	449	0	-0.084	5.62E-05	TRUE
Methylation	cg17922215	15	78,388,660	79,012,268	cis	Blood	368	0	-0.082	9.20E-05	TRUE
Methylation	cg20059407	15	78,796,769	78,965,955	cis	Blood	340	2.40E-169	-0.074	3.99E-04	TRUE
Methylation	cg25744700	15	77,955,110	79,019,093	cis	Blood	605	0	-0.071	6.89E-04	TRUE
Methylation	cg08500346	15	78,672,020	78,966,343	cis	Blood	203	0	0.026	2.18E-01	FALSE
Transcript	Expression(eQTLGen)	15	77,974,313	79,068,033	cis	Whole blood and PBMC	1128	0	-0.075	2.93E-04	TRUE
Transcript	Expression(eQTLGen)	3	128,578,726	128,604,581	trans	Whole blood and PBMC	3	2.50E-08	-0.016	4.39E-01	FALSE
Transcript	Expression(eQTLGen)	2	43,494,369	43,494,369	trans	Whole blood and PBMC	1	6.75E-08	0.016	4.51E-01	FALSE
Protein	Pro-cathepsin H Levels	6	31,483,699	33,225,090	trans	Blood plasma	1251	9.88E-11	-2.007	4.44E-05	TRUE
Protein	Pro-cathepsin H Levels	15	67,936,125	88,137,453	cis	Blood plasma	8408	0	-0.068	6.41E-03	TRUE
Protein	Pro-cathepsin H Levels	9	133,257,521	133,279,427	trans	Blood plasma	7	1.81E-09	-0.926	1.17E-01	FALSE
Protein	Pro-cathepsin H Levels	10	17,745,424	18,057,165	trans	Blood plasma	38	1.12E-18	0.417	2.38E-01	FALSE
Protein	Pro-cathepsin H Levels	3	186,664,498	186,738,246	trans	Blood plasma	98	3.11E-14	-0.503	2.69E-01	FALSE
Protein	Pro-cathepsin H Levels	15	88,860,173	89,081,990	trans	Blood plasma	16	1.27E-08	-0.403	2.81E-01	FALSE
Protein	Pro-cathepsin H Levels	19	3,487,496	3,492,245	trans	Blood plasma	2	2.28E-10	-0.786	4.18E-01	FALSE
Protein	Pro-cathepsin H Levels	14	92,766,577	92,905,767	trans	Blood plasma	129	9.26E-11	-0.496	4.53E-01	FALSE
Protein	Pro-cathepsin H Levels	15	66,152,081	66,971,753	trans	Blood plasma	87	7.71E-08	-0.268	5.19E-01	FALSE
Protein	Pro-cathepsin H Levels	19	18,082,539	18,230,100	trans	Blood plasma	141	6.56E-11	0.211	6.42E-01	FALSE
Protein	Pro-cathepsin H Levels	3	58,306,852	58,521,123	trans	Blood plasma	164	2.04E-10	0.238	6.84E-01	FALSE

\* values <2E-308 are truncated to 0.

**Table S12:** Summary of SNPs instruments for Pro-cathepsin H selected from Ferkingstad et al, 2021 (14)

SNP	CHR	BP(HG38)	Effect Allele	Other Allele	Effect allele frequency	Effect	SE	P
rs112348856	15	78,835,181	A	G	0.37	-0.357	0.009	2.23E-308
rs62013198	15	78,931,980	A	T	0.11	0.699	0.018	2.23E-308
rs565840574	10	17,806,399	G	A	0.29	0.070	0.008	1.12E-18
rs5029990	3	186,721,030	G	C	0.21	0.076	0.010	3.11E-14
rs62120372	19	18,194,375	A	T	0.18	0.059	0.009	6.56E-11
rs75157919	15	78,955,738	A	G	0.16	0.079	0.012	7.42E-11
rs61991538	14	92,859,499	A	C	0.09	0.059	0.009	9.26E-11
rs55954186	3	58,450,749	A	G	0.15	0.052	0.008	2.04E-10

**Table S13:** Summary of MR analysis of the effect of Pro-cathepsin H on AAD

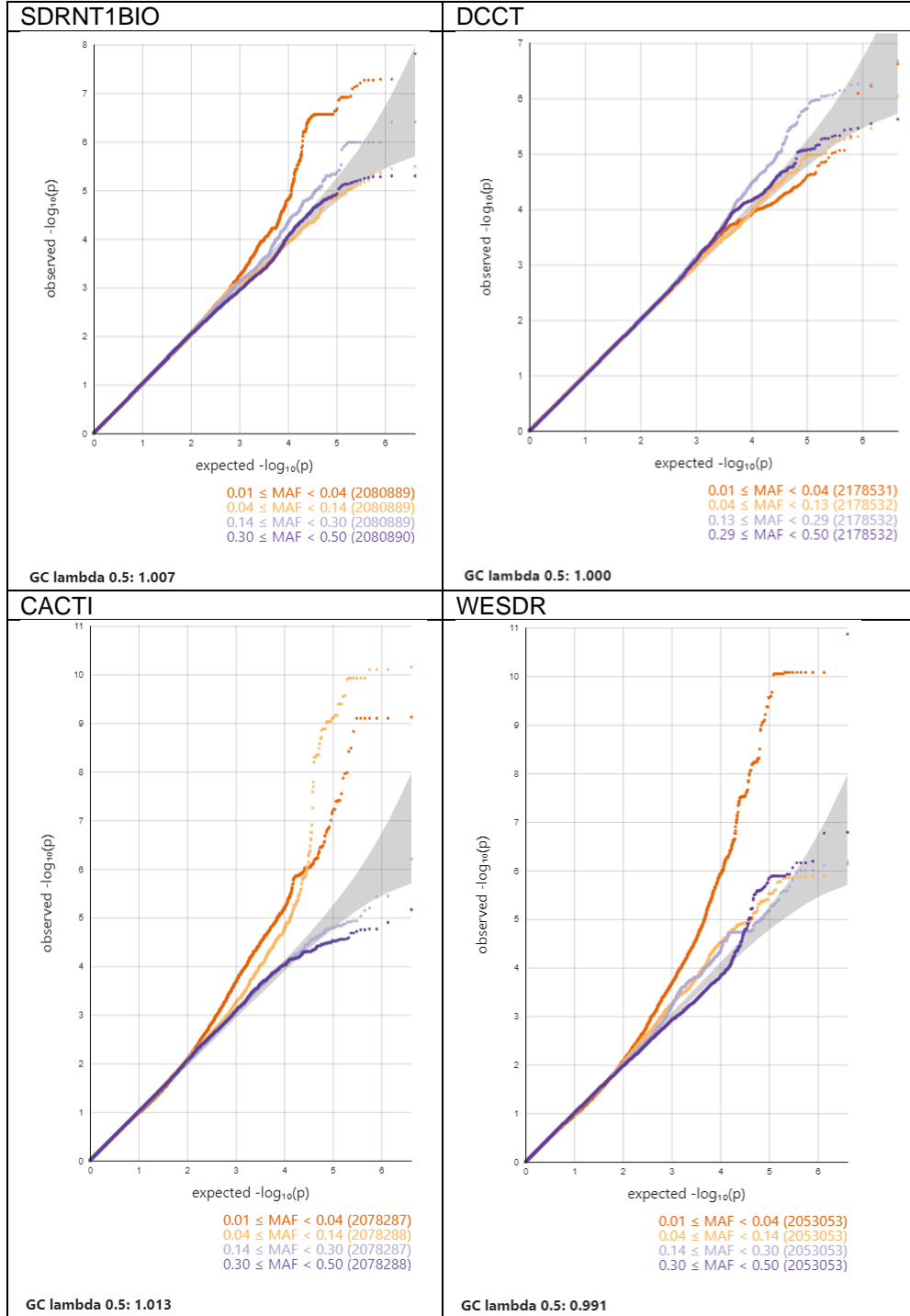
Method	Number of Instruments	Effect	SE	P
Simple median	8	-0.06	0.15	0.68
Inverse variance weighted	8	-0.07	0.06	0.23
Simple mode	8	-0.10	0.14	0.50

**Table S14:** Summary of MR analysis of the effect of Pro-cathepsin H on C-peptide

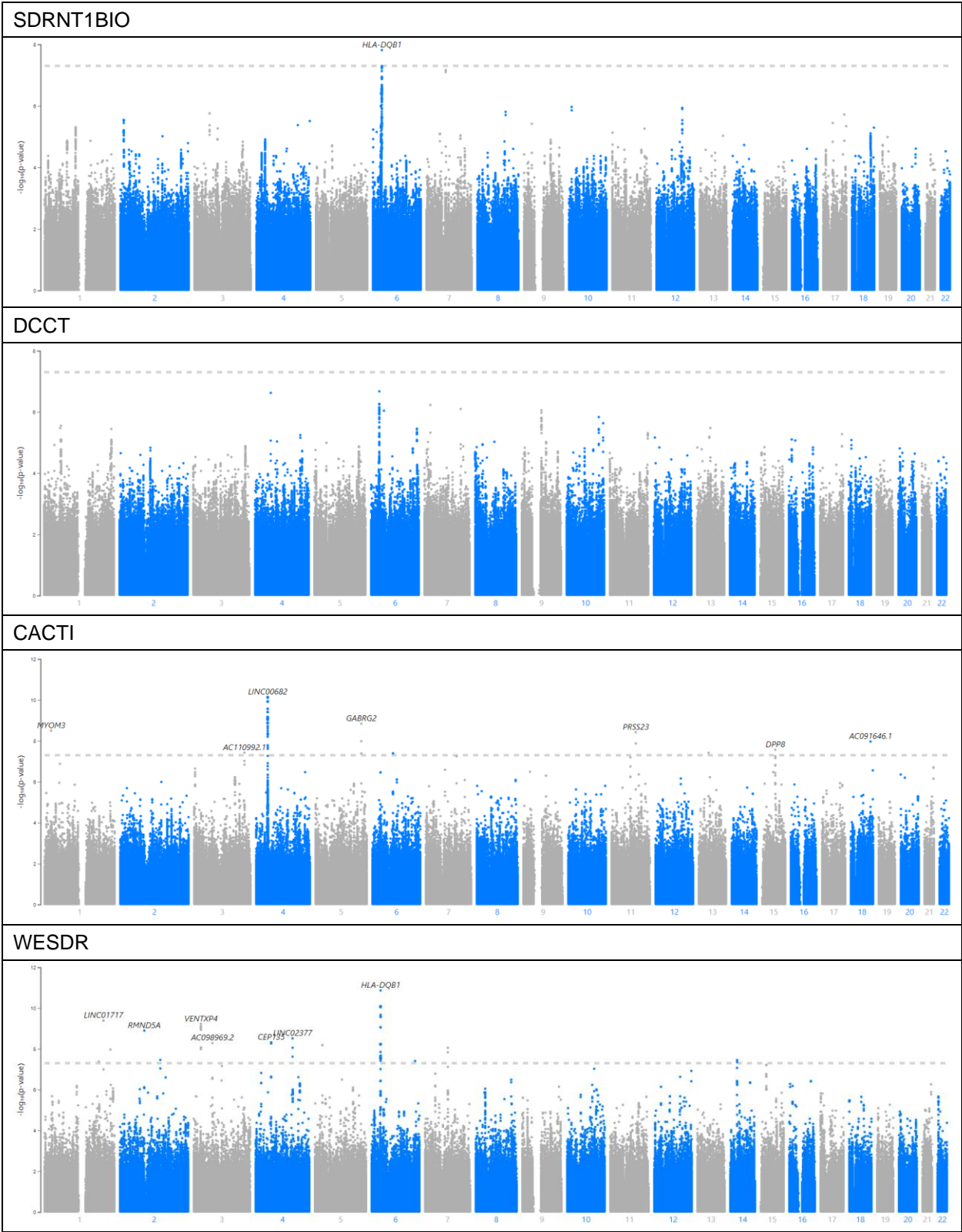
Method	Number of Instruments	Effect	SE	P
Simple median	8	-0.13	0.23	0.57
Inverse variance weighted	8	-0.08	0.10	0.44
Simple mode	8	0.03	0.22	0.88

## Supplementary Figures

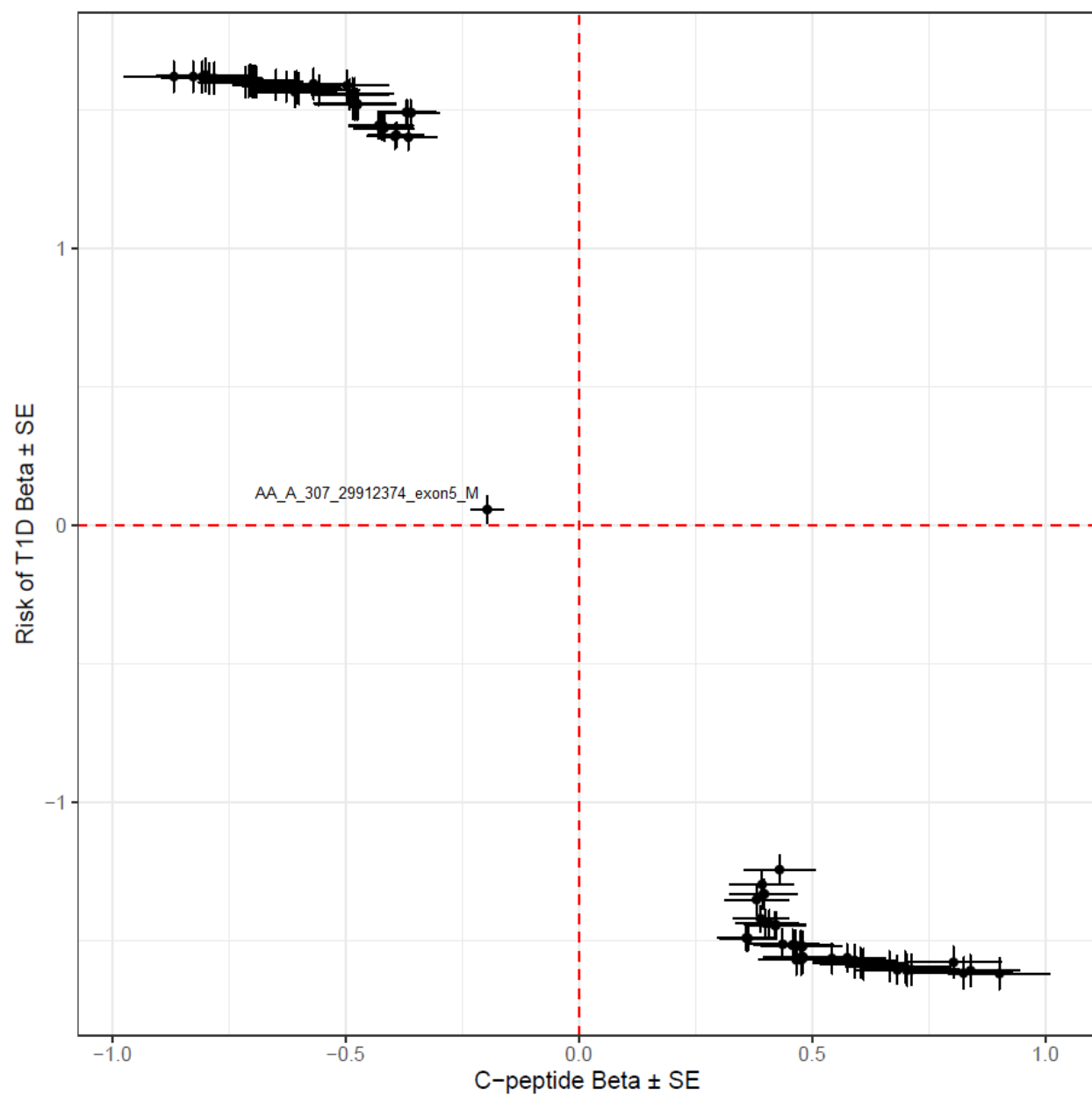
**Figure S1:** QQ-plots regarding C-peptide GWAS



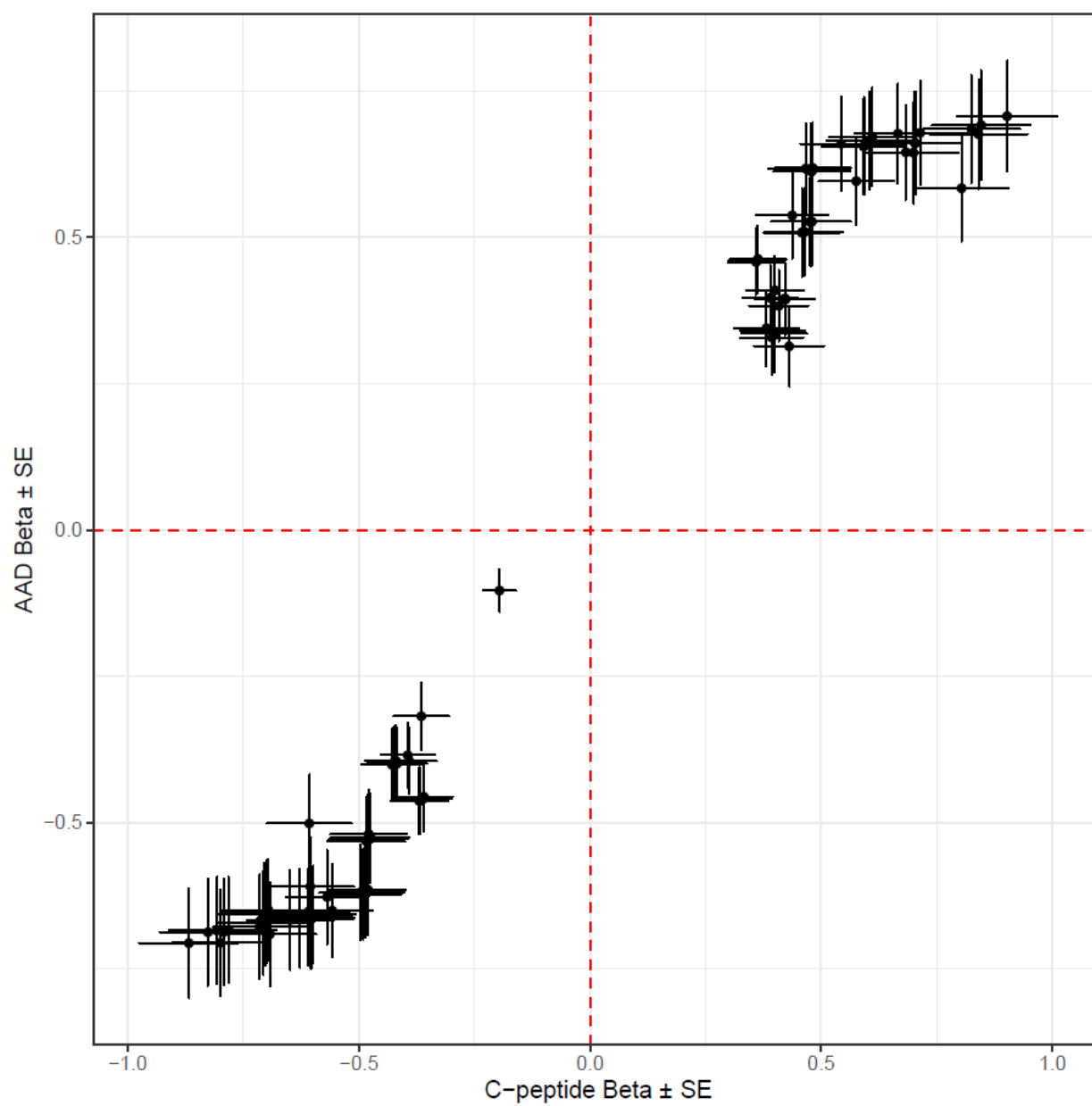
**Figure S2:** Manhattan plots regarding C-peptide GWAS



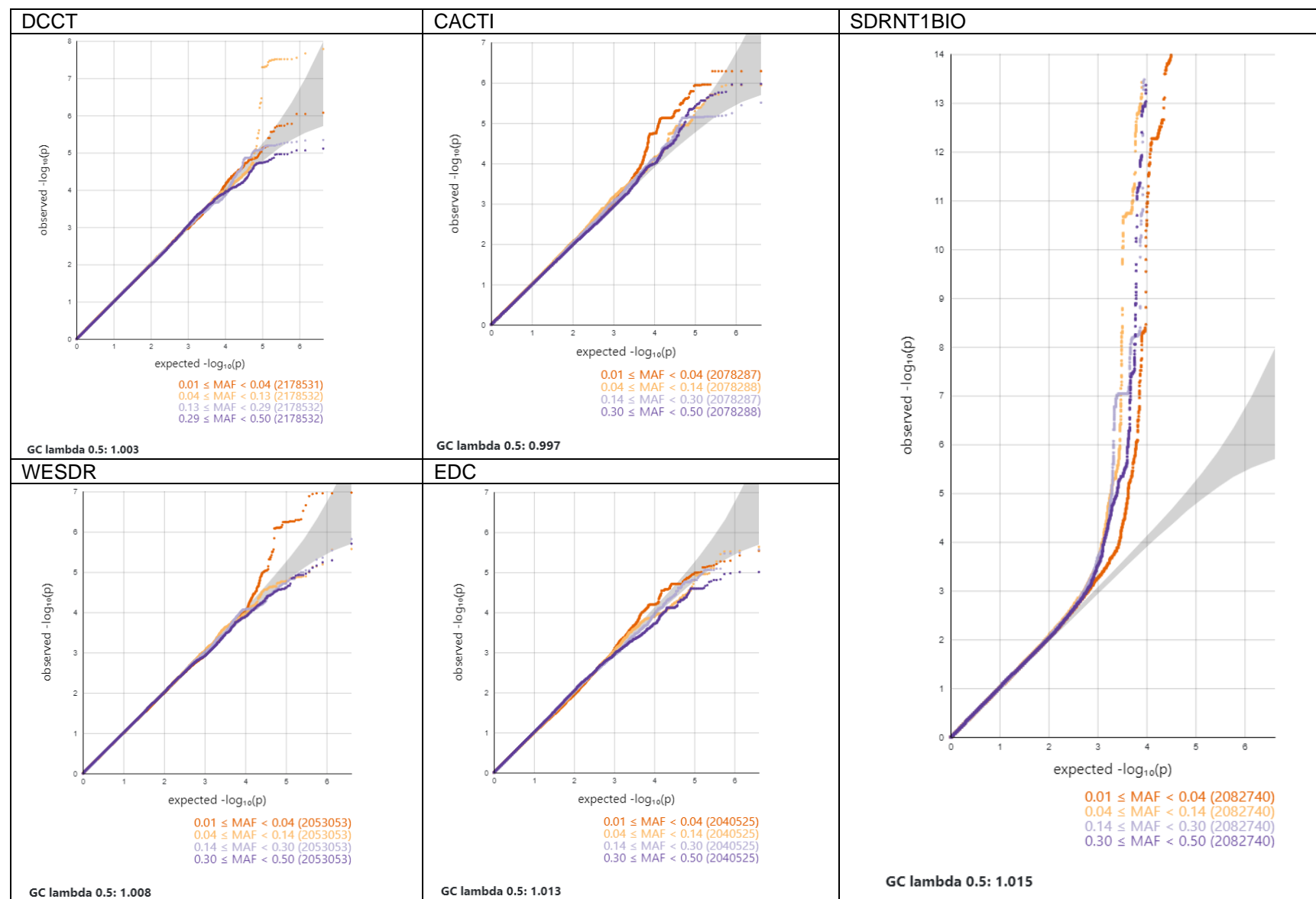
**Figure S3:** Association of HLA haplotypes, amino acid changes and SNP/indels associated with C-peptide at genome-wide significance threshold with risk of type 1 diabetes



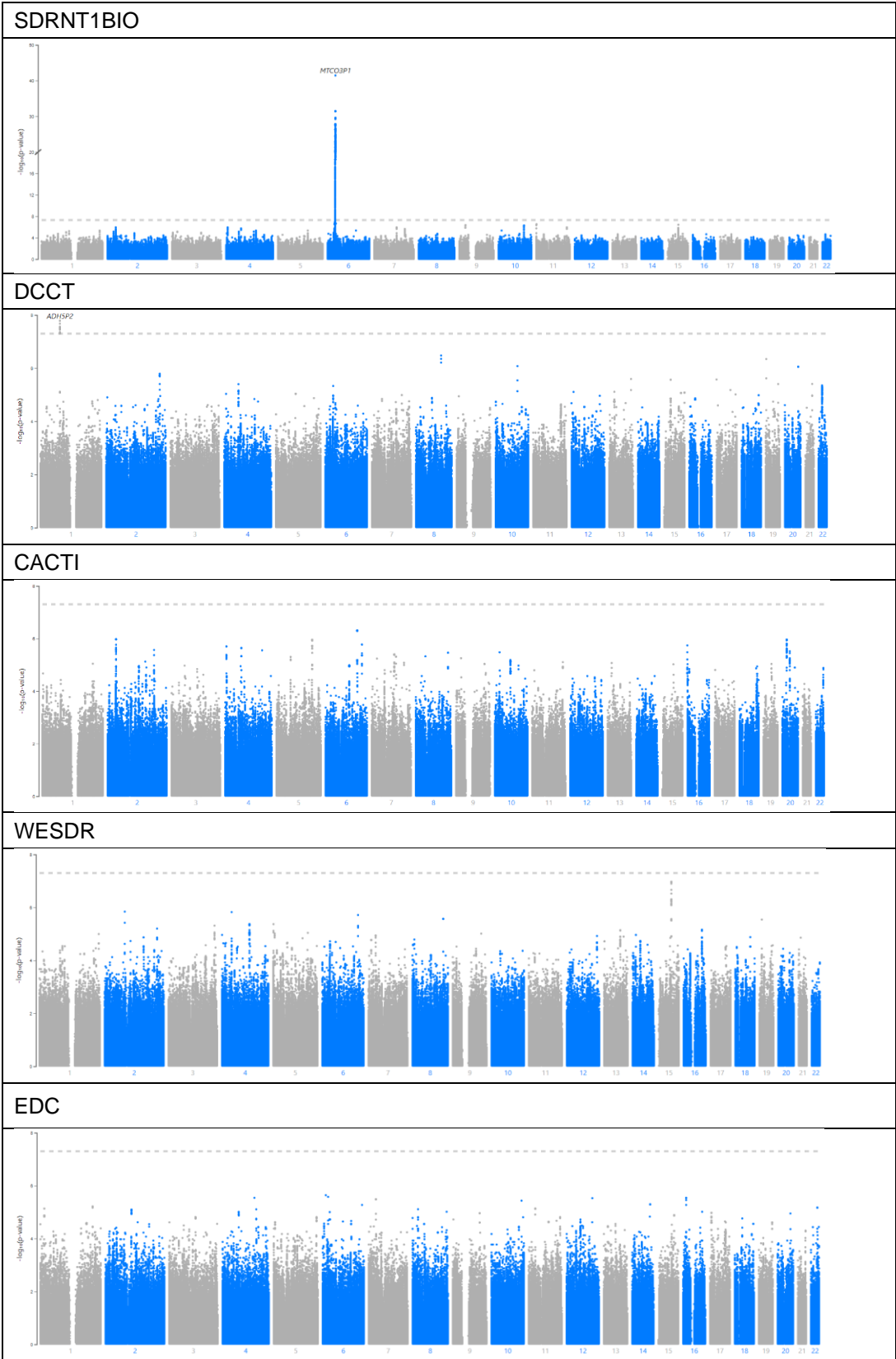
**Figure S4:** Association of HLA haplotypes, amino acid changes and SNP/indels associated with C-peptide at genome-wide significance threshold with age at type 1 diabetes diagnosis



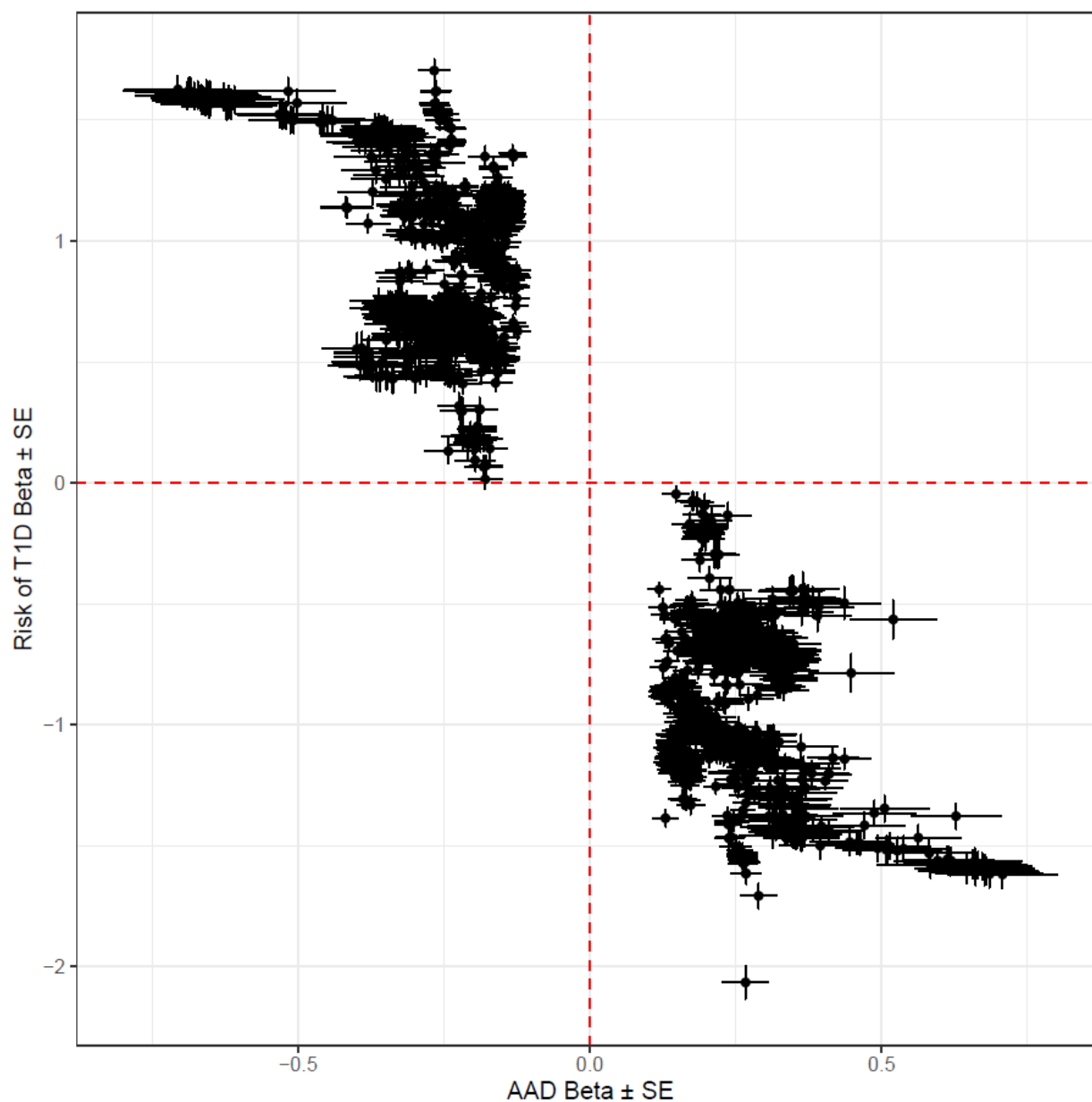
**Figure S5:** QQ-plots regarding AAD GWAS



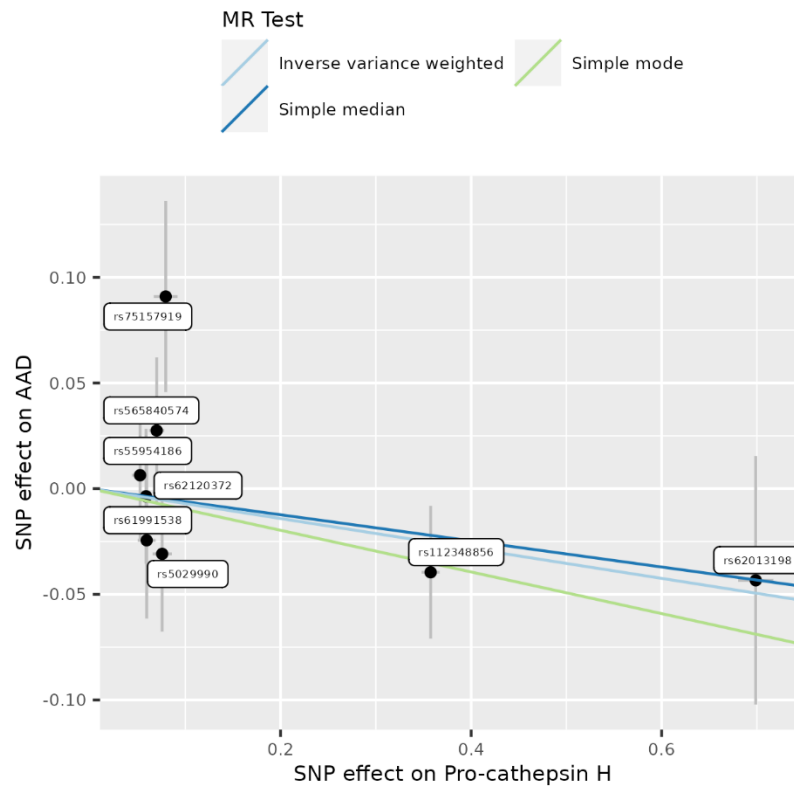
**Figure S6:** Manhattan plots regarding AAD GWAS



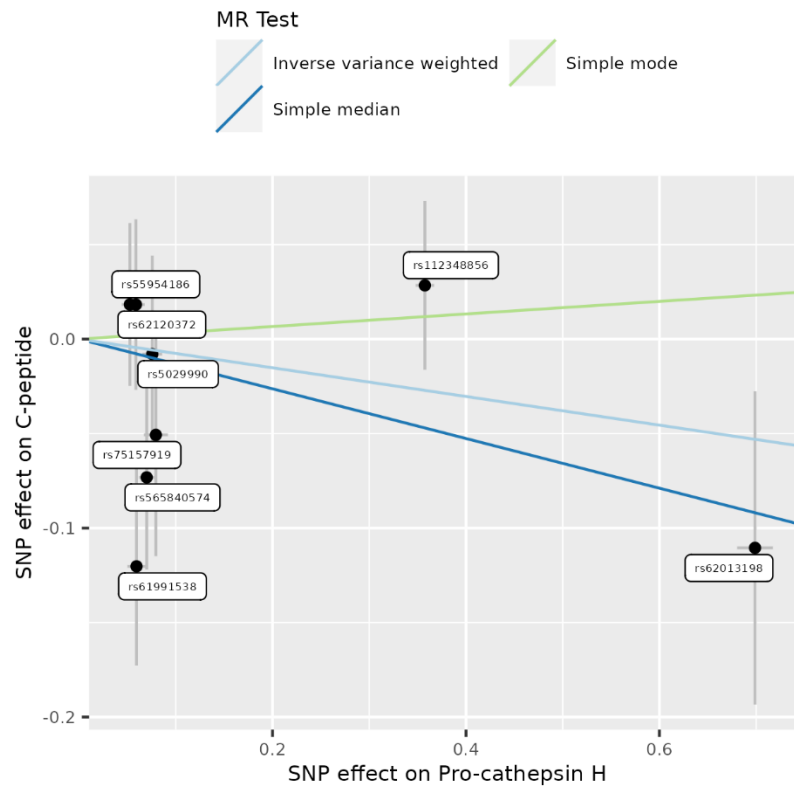
**Figure S7:** Association of HLA haplotypes, amino acid changes and SNP/indels associated with AAD at genome-wide significance threshold with type 1 diabetes risk



**Figure S8:** MR plot including scatter plot of the instrumental SNP effects on Pro-cathepsin H levels (exposure) vs. AAD (outcome). The lines correspond to MR fits for each of the methods used.



**Figure S9:** MR plot including scatter plot of the instrumental SNP effects on Pro-cathepsin H levels (exposure) vs. C-peptide (outcome). The straight lines correspond to MR fits for each of the methods used.



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