

SUPPLEMENTARY DATA

Supplementary Table 1. SNPs for GRS construction and single marker association with diabetes progression.

index_SNP	chr	position	OR	Function	gene	m_snpsym	g_snpsym	r ²	D'	MAF	SNP Allele	HR	P
rs10923931	1	120319482	1.08		NOTCH2	rs10923931	rs10923931			0.112	rs10923931_T	0.99	0.986
rs2075423	1	212221342	1.07	B	PROX1	rs2075423	rs2075423			0.332	rs2075423_G	1.03	0.600
rs780094	2	27594741	1.06	I	GCKR	rs780094	rs780094			0.365	rs780094_C	0.95	0.337
rs10203174	2	43543534	1.14	B	THADA	rs10203174	rs10203174			0.100	rs10203174_C	0.98	0.840
rs243088	2	60422249	1.07		BCL11A	rs243088	rs243090	1	1	0.460	rs243088_T	0.98	0.753
rs7569522	2	161054693	1.05		RBMS1	rs7569522	rs7569522			0.461	rs7569522_A	0.94	0.255
rs13389219	2	165237122	1.07	I	GRB14	rs6717858	rs6717858	0.933	1	0.392	rs6717858_T	0.89	0.020
rs2943640	2	226801829	1.1	I	IRS1	rs2943640	rs2943640			0.336	rs2943640_C	1.14	0.019
rs1801282	3	12368125	1.13	I	PPARG	rs1801282	rs1801282			0.124	rs1801282_C	0.97	0.690
rs1496653	3	23429794	1.09	B	UBE2E2	rs1496653	rs1496653			0.201	rs1496653_A	0.91	0.149
rs12497268	3	64065403	1.03		PSMD6	rs12497268	rs12497268			0.166	rs12497268_G	0.99	0.902
rs6795735	3	64680405	1.08		ADAMTS9	rs6795735	rs6795735			0.391	rs6795735_C	0.99	0.976
rs11717195	3	124565088	1.11	B	ADCY5	rs11717195	rs11717195			0.238	rs11717195_T	1.02	0.749
rs4402960	3	186994381	1.13	B	IGF2BP2	rs4402960	rs4402960			0.328	rs4402960_T	0.98	0.670
rs17301514	3	188096103	1.05		ST64GAL1	rs17301514	rs7648806	0.941	1	0.097	rs17301514_A	1.06	0.458
rs4458523	4	6340887	1.1	I	WFS1	rs4458523	rs4458523			0.398	rs4458523_G	1.02	0.654
rs459193	5	55842508	1.08		ANKRD55	rs40271	rs40271	0.953	1	0.258	rs40271_T	1.00	0.952
rs7756992	6	20787688	1.17	B	CDKAL1	rs7756992	rs7756992			0.276	rs7756992_G	1.08	0.148
rs4299828	6	38285645	1.04		ZFAND3	rs4299828	rs4299828			0.187	rs4299828_A	0.99	0.812
rs3734621	6	39412189	1.07		KCNK16	rs3734621	rs3734621			0.029	rs3734621_C	1.33	0.033
rs17168486	7	14864807	1.11	B	DGKB	rs17168486	rs17168486			0.160	rs17168486_T	1.07	0.328
rs849135	7	28162938	1.11		JAZF1	rs864745	rs864745	0.967	1	0.495	rs864745_T	0.98	0.641
rs13233731	7	130088229	1.05		KLF14	rs13234407	rs13233731	1	1	0.489	rs13234407_G	0.98	0.646
rs516946	8	41638405	1.09		ANK1	rs516946	rs516946			0.221	rs516946_C	1.04	0.524
rs7845219	8	96006678	1.06		TP53INP1	rs7845219	rs7845219			0.496	rs7845219_T	0.95	0.338
rs3802177	8	118254206	1.14	B	SLC30A8	rs3802177	rs3802177			0.303	rs3802177_G	0.99	0.891
rs10758593	9	4282083	1.06		GLIS3	rs4237150	rs4237150	1	1	0.384	rs4237150_C	0.99	0.835

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index_SNP	chr	position	OR	Function	gene	m_snpsym	g_snpsym	r ²	D'	MAF	SNP_Allele	HR	P
rs16927668	9	8359533	1.04		PTPRD	rs16927668	rs16927668			0.204	rs16927668_T	1.04	0.546
rs944801	9	22041670	1.08		CDKN2A/B	rs7030641	rs944801	0.966	1	0.420	rs7030641_T	1.04	0.476
rs10811661	9	22124094	1.18		CDKN2A/B	rs10811661	rs10811661			0.159	rs10811661_T	0.96	0.623
rs17791513	9	81095410	1.12		TLE4	rs17791513	rs13292347	1	1	0.054	rs17791513_A	1.07	0.588
rs2796441	9	83498768	1.07		TLE1	rs2796441	rs2796441			0.406	rs2796441_G	1.01	0.795
rs11257655	10	12347900	1.07	B	CDC123/CAMK1	rs4747969	rs4747969	0.918	1	0.192	rs4747969_C	1.02	0.805
rs12242953	10	70535348	1.07		VPS26A	rs12242953	rs12242953			0.065	rs12242953_G	0.86	0.125
rs12571751	10	80612637	1.08		ZMIZ1	rs12571751	rs12571751			0.445	rs12571751_A	0.99	0.986
rs1111875	10	94452862	1.11		HHEX/IDE	rs1111875	rs1111875			0.389	rs1111875_C	0.89	0.027
rs7903146	10	114748339	1.39	B	TCF7L2	rs4506565	rs4506565	0.892	1	0.326	rs4506565_T	0.98	0.714
rs2334499	11	1653425	1.04		DUSP8	rs2334499	rs4752781	0.834	0.929	0.431	rs2334499_T	1.00	0.998
rs231361	11	2648076	1.09	B	KCNQ1	rs463924	rs463924	0.657	1	0.325	rs463924_T	0.99	0.893
rs163184	11	2803645	1.09	B	KCNQ1	rs163177	rs163177	0.776	0.926	0.483	rs163177_C	0.99	0.936
rs5215	11	17365206	1.07		KCNJ11	rs5215	rs5215			0.363	rs5215_C	0.98	0.642
rs1552224	11	72110746	1.11	B	ARAP1(CENTD	rs17244499	rs17244499	0.799	0.926	0.178	rs17244499_A	1.07	0.341
rs10830963	11	92348358	1.1	B	MTNR1B	rs10830963	rs10830963			0.269	rs10830963_G	1.02	0.669
rs11063069	12	4244634	1.08		CCND2	rs11063069	rs11063069			0.198	rs11063069_G	1.01	0.864
rs10842994	12	27856417	1.1		KLHDC5	rs10842994	rs10842994			0.188	rs10842994_C	0.95	0.371
rs2261181	12	64498585	1.13	I	HMG A2	rs2261181	rs2261181			0.100	rs2261181_T	0.96	0.637
rs7955901	12	69719560	1.07		TSPAN8/LGR5	rs7138300	rs7138300	0.904	1	0.445	rs7138300_C	0.96	0.437
rs12427353	12	119911284	1.08		HNF1A(TCF1)	rs7965349	rs7965349	0.766	0.932	0.191	rs7965349_C	0.97	0.669
rs1359790	13	79615157	1.08	B	SPRY2	rs1359790	rs1359790			0.298	rs1359790_G	0.95	0.345
rs4502156	15	60170447	1.06	B	C2CD4A	rs4502156	rs6494307	0.967	1	0.432	rs4502156_T	1.05	0.324
rs7177055	15	75619817	1.08		HMG20A	rs7177055	rs7177055			0.286	rs7177055_A	1.01	0.838
rs11634397	15	78219277	1.05		ZFAND6	rs11634397	rs11634397			0.332	rs11634397_G	1.04	0.459
rs2007084	15	88146339	1.02		AP3S2	rs2007084	rs17240268	0.929	1	0.088	rs2007084_G	1.03	0.716
rs12899811	15	89345080	1.08		PRC1	rs11073964	rs11073964	0.71	1	0.379	rs11073964_T	0.98	0.638
rs9936385	16	52376670	1.13	I	FTO	rs8050136	rs8050136	0.935	1	0.408	rs8050136_A	0.96	0.425
rs7202877	16	73804746	1.12		BCAR1	rs3743614	rs3743614	0.808	0.899	0.086	rs3743614_C	1.10	0.314

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index_SNP	chr	position	OR	Function	gene	m_snpsym	g_snpsym	r ²	D'	MAF	SNP_Allele	HR	P
rs11651052	17	33176494	1.1		HNF1B(TCF2)	rs11651755	rs11651755	1	1	0.489	rs11651755_C	1.03	0.558
rs12970134	18	56035730	1.08		MC4R	rs12970134	rs12970134			0.263	rs12970134_A	0.99	0.886
rs10401969	19	19268718	1.13		CILP2	rs10401969	rs10401969			0.073	rs10401969_C	0.95	0.548
rs8108269	19	50850353	1.07		GIPR	rs8108269	rs8108269			0.269	rs8108269_G	0.89	0.034
rs4812829	20	42422681	1.06		HNF4A	rs4812829	rs16988991	1	1	0.151	rs4812829_A	0.86	0.039

Index_SNP, gene SNP_allele and OR were the SNP ID, annotated gene, risk allele and odds ratio for type 2 diabetes as retrieved from the latest DIAGRAM publication (1); chr and position were chromosome and position of the index SNP on genome build 37; m_snpsym and g_snpsym were the SNPs selected from metabochip and Affymetrix 6 respectively; r² and D' were the measurement of linkage disequilibrium between the index SNP and the proxy SNP when no direct genotyping data were available; MAF was the minor allele frequency in the combined data from the two arrays; HR and p_value were the hazard ratio and p value from a single marker test of association with diabetes progression in a Cox regression model (full phenotypic model, table 2); Function indicates whether the SNP is associated with insulin resistance (I) or beta cell function in the latest GWAS meta-analysis (2) .

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Supplementary Table 2a. Univariate Cox proportional hazards models for diabetes progression using only true insulin treatment events.

Covariate	Hazard Ratio [95% CI]	<i>P</i>	n
Females vs. males	1.22 [1.06,1.41]	0.007	5250
Smokers vs. non smokers	1.06 [0.89,1.27]	0.49	5250
Year of diagnosis (per 1 year)	0.89 [0.86,0.91]	<0.001	5250
Age at diagnosis (per 1 year)	0.96 [0.96, 0.97]	<0.001	5250
Social class (per 1 SIMD unit from most deprived to most affluent)	0.91 [0.86, 0.96]	<0.001	5191
Baseline HDL (per 1 mmol/L)	0.49 [0.38, 0.63]	<0.001	5222
Baseline LDL (per 1 mmol/L)*	1.06 [0.76, 1.48]	0.74	4306
Baseline TG (per 1 mmol/L)*	1.58 [1.39, 1.76]	<0.001	5114
Baseline ALT (per 1 mmol/L)*	1.27 [1.07, 1.50]	0.006	4504

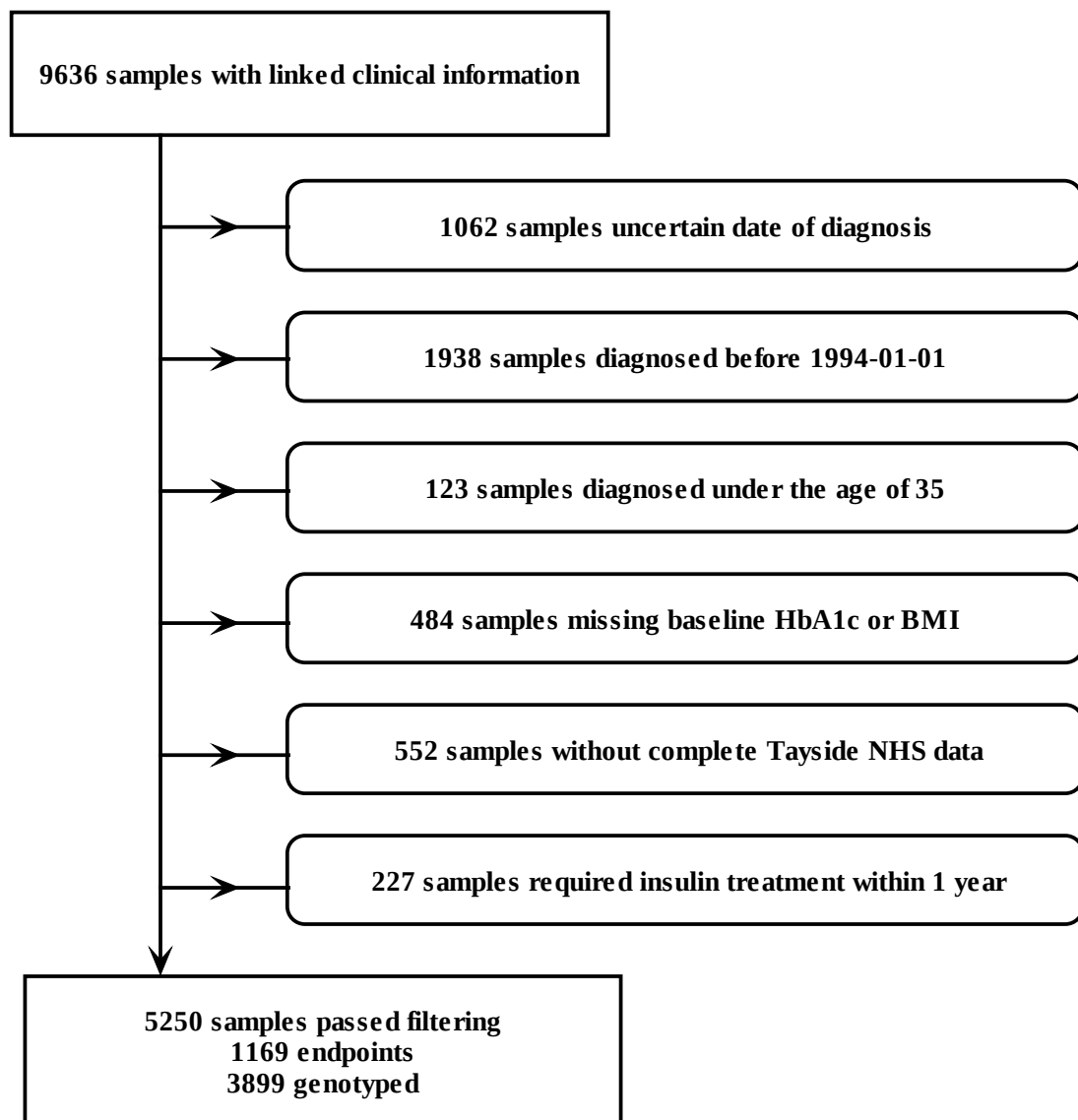
*log transformed

Supplementary Table 2b. Adjusted Cox proportional hazards models for diabetes progression using only true insulin treatment events.

Covariate	Hazard Ratio [95% CI]	<i>P</i>
Age at diagnosis (per 1 year)	0.96[0.95,0.97]	<0.001
Year of diagnosis (per 1 year)	0.91[0.88,0.93]	<0.001
Baseline TG (per 1 mmol/L)*	1.25[1.09,1.43]	0.002
Females vs. males	1.39[1.17,1.64]	<0.001
Baseline HDL (per 1 mmol/L)	0.73[0.54,0.98]	0.03
Smokers vs. non smokers	1.17[0.96,1.43]	0.12
Social class (per 1 SIMD unit from most deprived to most affluent)	0.95[0.89,1.00]	0.05

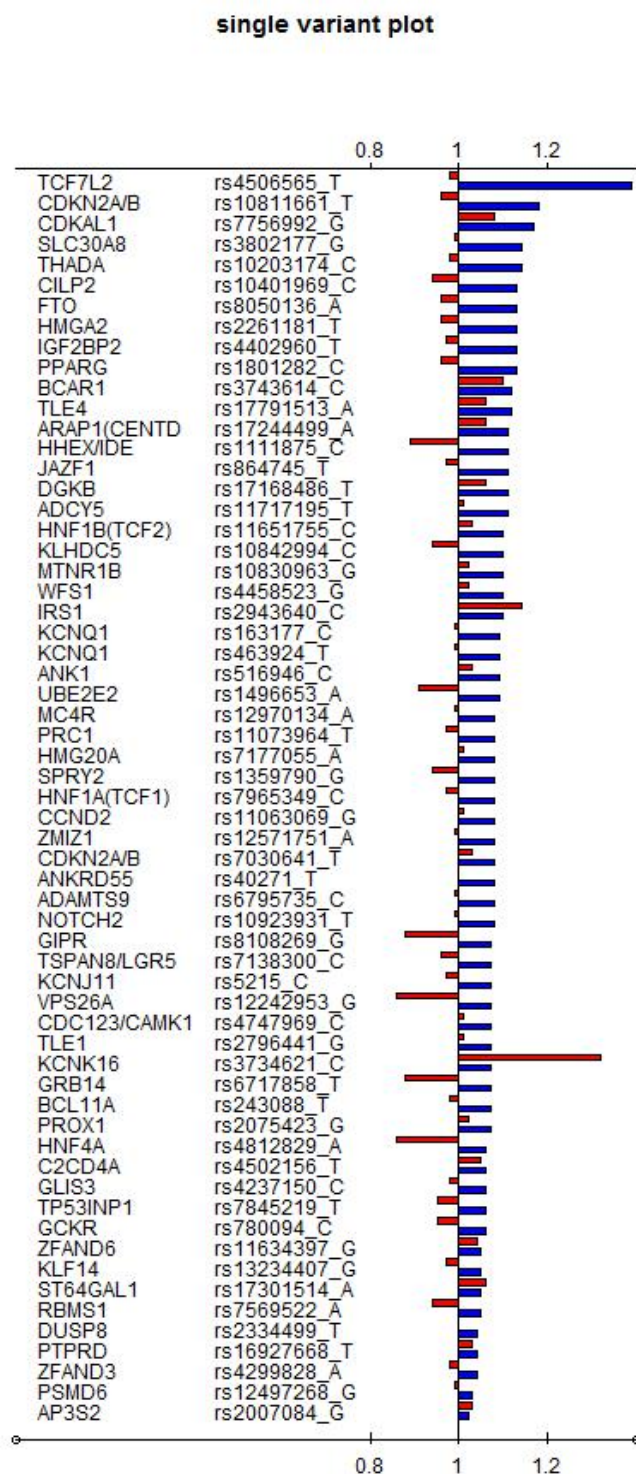
*log transformed. Analysis was stratified by HbA1c at diagnosis and BMI category

Supplementary Figure 1. Sample selection flow for the GoDARTS cohort.



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Supplementary Figure 2. Single variant association with diabetes progression on the 61 SNPs used for T2D GRS construction.



Red bars are HR for progression to insulin requirement (from a single marker test of association with diabetes progression in a Cox regression model (full phenotypic model, table 2)) and blue bars are OR for the t2d risk increase allele. All values are shown in supplementary table 1.

References

1. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet.* 2012;44(9):981-90.
2. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan J, et al. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. *Nat Genet.* 2012;44(9):991-1005.