

SUPPLEMENTARY DATA

A genetic locus on chromosome 2q24 predicting peripheral neuropathy risk in type 2 diabetes: results from the ACCORD and BARI 2D studies.

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Appendix ACCORD

Members of the ACCORD DSMB included Antonio M. Gotto Jr. (chair), Kent Bailey, Dorothy Gohdes, Steven Haffner, Roland Hiss, Kenneth Jamerson, Kerry Lee, David Nathan, James Sowers, and LeRoy Walters. The following companies provided study medications, equipment, or supplies: Abbott Laboratories (Abbott Park, IL), Amylin Pharmaceuticals (San Diego, CA), AstraZeneca (Wilmington,

SUPPLEMENTARY DATA

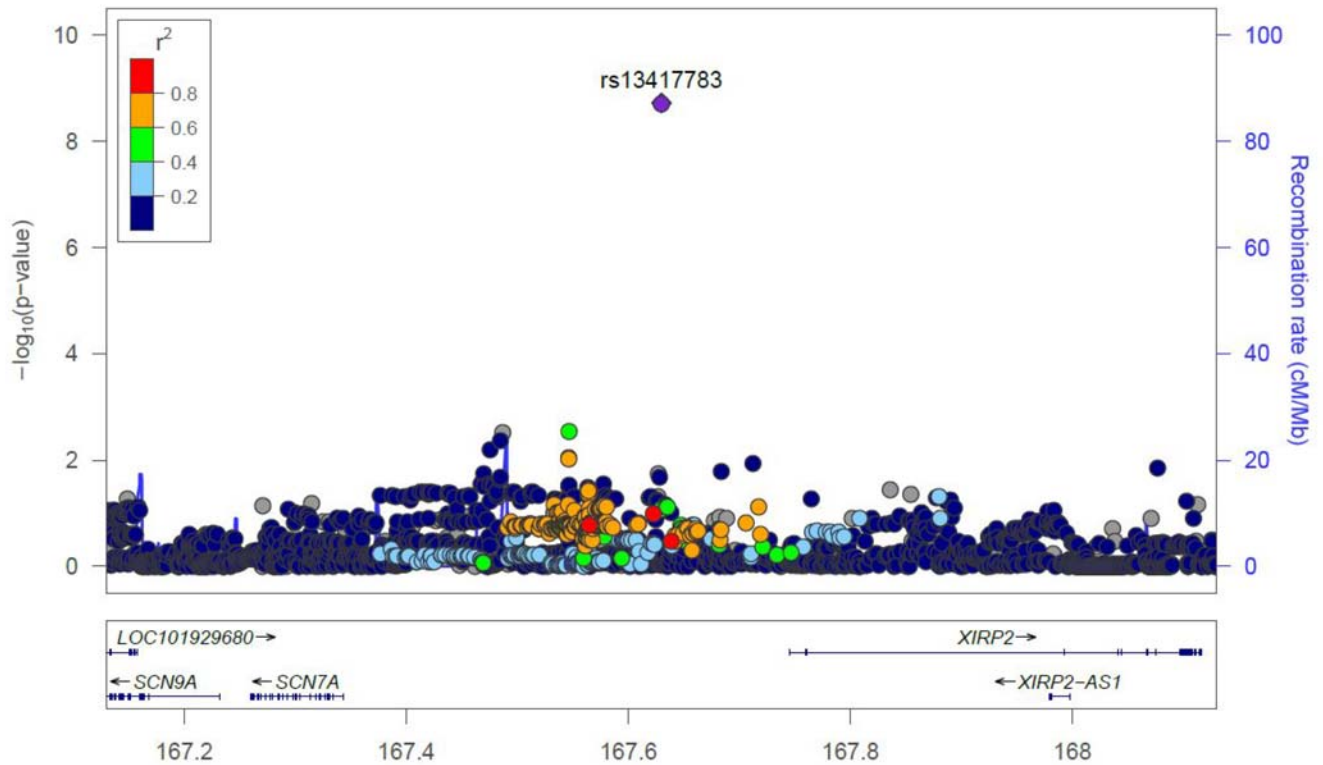
DE), Bayer (Tarrytown, NY), Closer Healthcare (Tequesta, FL), GlaxoSmithKline (Philadelphia, PA), King Pharmaceuticals (Bristol, TN), Merck (Whitehouse Station, NJ), Novartis (East Hanover, NJ), NovoNordisk (Princeton, NJ), Omron Healthcare (Schaumburg, IL), Sanofi (Bridgewater, NJ), Schering-Plough (Kenilworth, NJ), and Takeda Pharmaceuticals (Deerfield, IL). None of these companies had an interest or bearing on the genome-wide analysis of the ACCORD data.

BARI 2D

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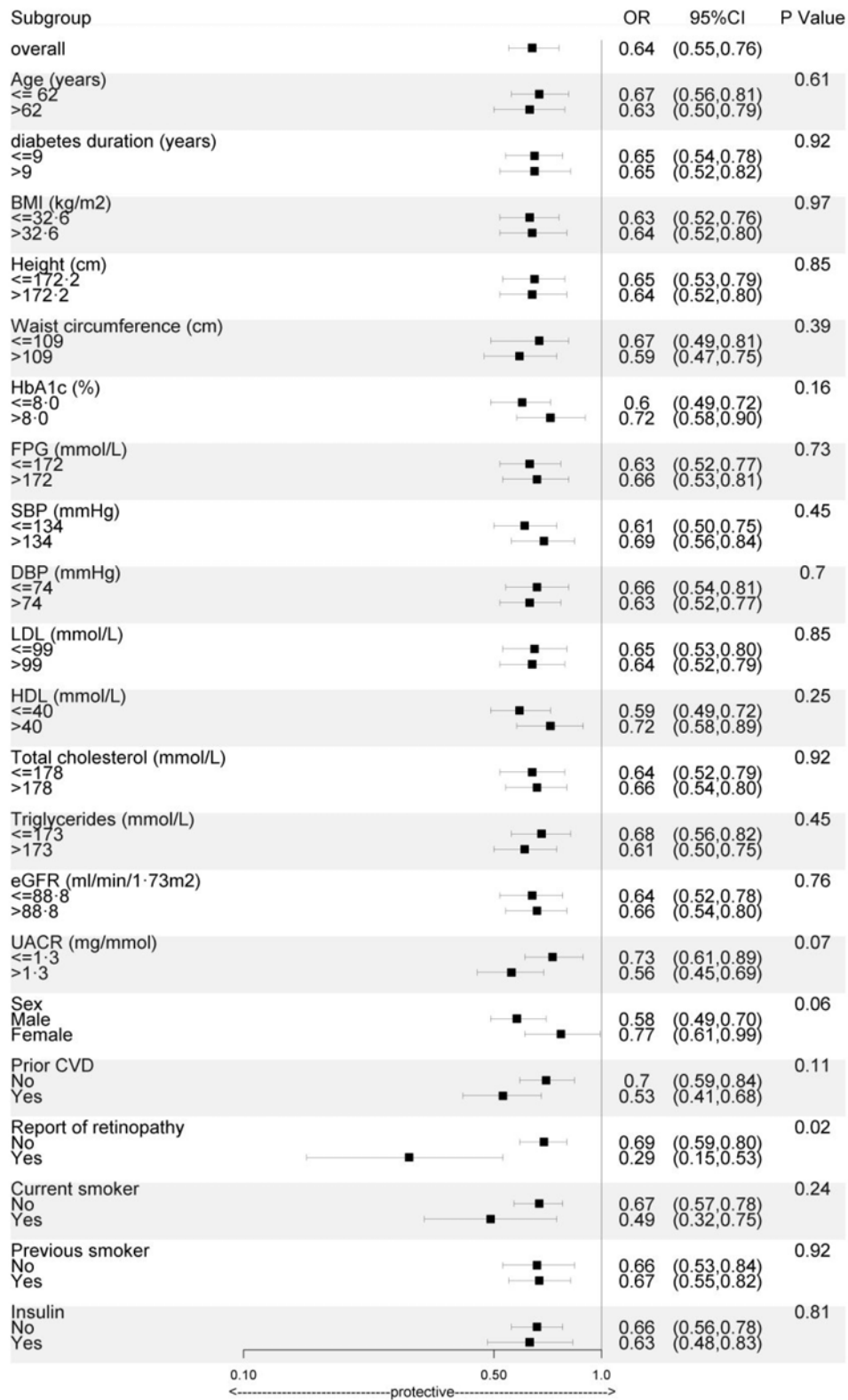
SUPPLEMENTARY DATA

Supplementary Figure S1. Regional association plot for locus 2q24 (± 500 kbp of lead SNP, rs13417783) after conditioning on lead SNP.



SUPPLEMENTARY DATA

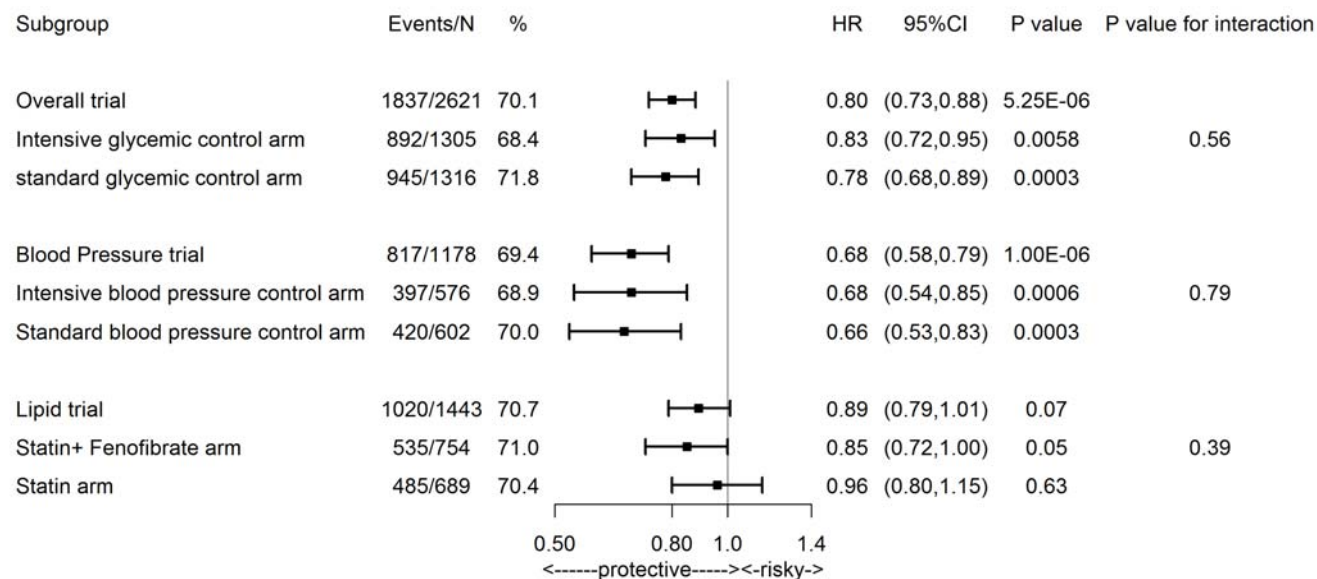
Supplementary Figure S2. Effect of the lead DPN SNP according to baseline characteristics in the Discovery Set.



For continuous variables, subgroups were defined based on median cut-offs. P values are for the interaction between clinical characteristics and SNP.

SUPPLEMENTARY DATA

Supplementary Figure S3. Interaction between DPN-associated SNP rs13417783 and interventions tested in ACCORD.



Cox proportional regression models were adjusted by assignment to other interventions, seven clinical center networks, and top three principal components. The analysis is restricted to the prospective ACCORD cohorts – 1837 DPN cases and 784 controls. The intervention and control arms were : 1) Glycemia trial- intensive glycemic control versus standard glycemic control; 2) Blood pressure trial- intensive blood pressure control versus standard glycemic control; 3) Lipid trial: fenofibrate + statin versus placebo + statin. Hazard ratios, 95% confidence intervals and p values are provided for marginal associations of SNP with progression to DPN in each of the trial arms. P values for interaction between SNP x intervention are also provided.

SUPPLEMENTARY DATA

Supplementary Table S1. Baseline characteristics in prevalent cases and incident cases controls in the Discovery Set (ACCORD).

Baseline Characteristics	prevalent cases	incident cases	p value
	(N= 2,547)	(N= 1,837)	
Female	855 (33.6)	683 (37.2)	0.02
Age (years)	63.8 ± 6.5	62.8 ± 6.2	<0.0001
DM duration (years)	11.5 ± 7.8	10.1 ± 6.9	<0.0001
BMI (kg/m ²)	33.4 ± 5.2	32.8 ± 5.2	0.003
Waist circumference (cm)	111.0 ± 13.0	108.6 ± 12.6	<0.0001
Height (cm)	172.4 ± 9.5	170.7 ± 9.3	<0.0001
HbA1c (%)	8.22 ± 0.92	8.21 ± 0.95	0.52
Fasting serum glucose (mmol/L)	9.96 ± 2.91	9.89 ± 2.7	0.42
SBP (mmHg)	135.6 ± 16.8	134.7 ± 16.6	0.0750
DBP (mmHg)	73.6 ± 10.3	74.8 ± 10.5	0.0011
LDL (mmol/L)	2.65 ± 0.84	2.68 ± 0.83	0.21
HDL (mmol/L)	1.03 ± 0.26	1.05 ± 0.27	0.0040
Women	1.15 ± 0.28	1.17 ± 0.29	0.19
Men	0.97 ± 0.22	0.98 ± 0.23	0.15
Total cholesterol (mmol/L)	4.73 ± 1.04	4.75 ± 1.03	0.28
Triglycerides (mmol/L)†	1.97 (1.36-2.85)	1.95 (1.38-2.77)	0.71
eGFR (ml/min/1.73 m ²)	87.8 ± 22.2	87.8 ± 20.9	0.94
UACR (mg/mmol)†	1.5 (0.7-5.0)	1.3 (0.7-3.2)	<0.0001
Previous cardiovascular event	939 (36.9)	617 (33.6)	0.03
Report of retinopathy	317 (13.9)	122 (7.6)	<0.0001
Current smoker	353 (13.9)	213 (11.6)	0.03
Previous smoker	1303 (58.7)	891 (54.6)	0.02
Insulin therapy	1013 (39.9)	585 (32.0)	<0.0001
ACCORD glycaemia trial			
Standard	1282 (50.3)	945 (51.4)	0.49

SUPPLEMENTARY DATA

Intensive	1265 (49.7)	892 (48.6)	
ACCORD blood pressure trial	1045 (41.0)	817 (44.5)	0.03
Standard	506 (48.4)	420 (51.4)	0.75
Intensive	539 (51.6)	397 (48.6)	
ACCORD lipid trial	1502 (59.0)	1020 (55.5)	0.03
Fibrate	759 (51.5)	535 (52.5)	0.65
Placebo	743 (49.5)	485 (47.5)	

†median (IQR)

SUPPLEMENTARY DATA

Supplementary Table S2. Effects of GWAS significant ($p < 5 \times 10^{-8}$) SNPs in the two ACCORD genotyping sets

				ANYSET(3,554 cases/830 controls)					ACCSET(600 cases/184 controls)					Meta-analysis of ANYSET and ACCSET				
SNP	Chr:bp	Minor /major allele	MAF	Type*	info†	effect	SE	p	type	info	effect	SE	P	beta	SE	P	Dire-ction	P value For Hetero-geneity
rs13417783	2:167629849	T/C	0.148	I	0.991	-0.50	0.08	1.38×10^{-9}	I	0.96	-0.23	0.17	0.16	-0.45	0.07	1.91×10^{-9}	--	0.16
rs145971945	2:167677755	TAC /T	0.134	I	0.988	-0.51	0.09	1.45×10^{-9}	I	0.967	-0.24	0.17	0.15	-0.46	0.08	2.00×10^{-9}	--	0.15
rs13000447	2:167717280	G/C	0.145	I	0.983	-0.48	0.08	8.32×10^{-9}	I	0.951	-0.32	0.16	0.05	-0.45	0.07	2.29×10^{-9}	--	0.37
rs10164425	2:167706169	C/T	0.136	I	0.983	-0.51	0.08	1.7×10^{-9}	I	0.961	-0.23	0.17	0.17	-0.45	0.08	2.63×10^{-9}	--	0.14
rs13392463	2:167652676	A/G	0.136	G	1	-0.51	0.08	2.09×10^{-9}	I	0.971	-0.23	0.17	0.17	-0.45	0.08	3.09×10^{-9}	--	0.15
rs13031854	2:167638666	G/C	0.134	I	0.961	-0.53	0.09	9.77×10^{-9}	I	0.922	-0.19	0.17	0.28	-0.46	0.08	3.39×10^{-9}	--	0.08
rs13421469	2:167653868	G/A	0.135	I	0.998	-0.51	0.08	2.51×10^{-9}	I	0.971	-0.23	0.17	0.16	-0.45	0.08	3.55×10^{-9}	--	0.16
rs2390487	2:167660965	C/T	0.136	I	0.999	-0.50	0.08	2.45×10^{-9}	I	0.975	-0.23	0.17	0.17	-0.45	0.08	3.63×10^{-9}	--	0.15
rs536046332	2:167681464	-/TA	0.136	I	0.993	-0.50	0.08	3.47×10^{-9}	I	0.971	-0.24	0.17	0.14	-0.45	0.08	3.98×10^{-9}	--	0.17
rs13026906	2:167682431	C/T	0.136	I	0.995	-0.50	0.08	2.88×10^{-9}	I	0.973	-0.23	0.17	0.16	-0.45	0.08	3.98×10^{-9}	--	0.15
rs13034083	2:167683463	C/T	0.136	I	0.995	-0.50	0.08	2.88×10^{-9}	I	0.973	-0.23	0.17	0.16	-0.45	0.08	3.98×10^{-9}	--	0.15
rs16852695	2:167662782	C/G	0.135	I	0.999	-0.50	0.08	3.02×10^{-9}	I	0.974	-0.23	0.17	0.17	-0.45	0.08	4.27×10^{-9}	--	0.15
rs10183769	2:167661550	T/C	0.136	I	0.999	-0.50	0.08	3.09×10^{-9}	I	0.974	-0.23	0.17	0.17	-0.45	0.08	4.37×10^{-9}	--	0.15
rs10178966	2:167642185	G/A	0.136	I	0.99	-0.50	0.09	3.39×10^{-9}	I	0.966	-0.23	0.17	0.17	-0.45	0.08	4.68×10^{-9}	--	0.16

SUPPLEMENTARY DATA

rs10189266	2:167645439	C/A	0.136	I	0.992	-0.50	0.08	3.24×10^{-9}	I	0.967	-0.23	0.17	0.17	-0.45	0.08	4.68×10^{-9}	--	0.15
rs12993796	2:167649537	C/T	0.136	G	1	-0.50	0.08	3.63×10^{-9}	I	0.969	-0.23	0.17	0.16	-0.45	0.08	4.79×10^{-9}	--	0.16
rs35762912	2:167659769	C/CT	0.136	I	0.999	-0.50	0.08	3.47×10^{-9}	I	0.974	-0.23	0.17	0.17	-0.45	0.08	5.01×10^{-9}	--	0.16
rs12692848	2:167658191	G/A	0.136	I	1	-0.50	0.08	3.55×10^{-9}	I	0.976	-0.23	0.17	0.17	-0.45	0.08	5.13×10^{-9}	--	0.16
rs12692849	2:167658309	G/A	0.136	I	1	-0.50	0.08	3.55×10^{-9}	I	0.975	-0.23	0.17	0.17	-0.45	0.08	5.13×10^{-9}	--	0.16
rs76036953	2:167649160	T/A	0.136	I	1	-0.50	0.08	4.07×10^{-9}	I	0.97	-0.23	0.17	0.17	-0.44	0.08	5.62×10^{-9}	--	0.16
rs7558617	2:167655841	T/A	0.136	I	1	-0.50	0.08	4.07×10^{-9}	I	0.974	-0.23	0.17	0.17	-0.44	0.08	5.75×10^{-9}	--	0.16
rs34867578	2:167642067	T/C	0.136	I	0.989	-0.50	0.09	5.37×10^{-9}	I	0.966	-0.22	0.17	0.19	-0.44	0.08	8.13×10^{-9}	--	0.16
rs34148223	2:167682742	C/A	0.137	I	0.989	-0.49	0.08	5.5×10^{-9}	I	0.966	-0.22	0.17	0.19	-0.44	0.08	8.71×10^{-9}	--	0.15
rs16852735	2:167719276	T/C	0.139	I	0.986	-0.48	0.08	1.62×10^{-8}	I	0.956	-0.25	0.16	0.12	-0.43	0.08	1.29×10^{-8}	--	0.23
rs148112563	2:167657499	GGATA /G	0.133	I	0.987	-0.49	0.09	1.66×10^{-8}	I	0.967	-0.24	0.17	0.15	-0.44	0.08	1.74×10^{-8}	--	0.21
rs10200297	2:167657230	C/T	0.138	I	1	-0.48	0.08	1.38×10^{-8}	I	0.984	-0.20	0.17	0.23	-0.42	0.08	2.57×10^{-8}	--	0.14
rs10193273	2:167633880	A/C	0.257	I	0.992	-0.39	0.07	2.75×10^{-8}	I	0.96	-0.17	0.13	0.22	-0.34	0.06	4.57×10^{-8}	--	0.15
rs4629176	2:167635250	T/C	0.257	I	0.991	-0.39	0.07	2.75×10^{-8}	I	0.959	-0.16	0.13	0.22	-0.34	0.06	4.57×10^{-8}	--	0.15

*G: genotyped, I:imputed. †Info represents quality of imputation in IMPUTE V2. Values closer to 1 indicate good quality of imputation.

SUPPLEMENTARY DATA

Supplementary Table S3. Effects of Top loci ($P < 1 \times 10^{-5}$) associated with diabetic peripheral neuropathy in ACCORD : Adjustment by age, duration of diabetes, BMI.

SNP	Position‡	Closest gene	MA**	Primary model*		Full model†	
				OR (95%CI)	P	OR (95%CI)	P
rs13417783	2:167629849	XIRP2	T	0.64 (0.55-0.74)	1.9×10^{-9}	0.65 (0.56-0.78)	1.2×10^{-8}
rs12988669	2:240275570	HDAC4	C	0.71 (0.62-0.82)	2.7×10^{-6}	0.70 (0.61-0.82)	3.0×10^{-6}
rs60770880	3:8037416	LOC101-927394	A	0.75 (0.66-0.84)	5.0×10^{-6}	0.75 (0.66-0.85)	1.8×10^{-5}
rs11932946	4:45140214	GUF1	G	0.69 (0.59-0.82)	9.6×10^{-6}	0.70 (0.60-0.83)	3.9×10^{-5}
rs1202660	7:70658177	WBSCR-17	T	0.74 (0.65-0.84)	6.2×10^{-6}	0.73 (0.63-0.83)	2.8×10^{-6}
rs13265430	8:4165607	CSMD1	A	0.64 (0.52-0.76)	1.0×10^{-6}	0.65 (0.54-0.78)	7.6×10^{-6}
rs2491019	10:70776987	KIAA12-79	A	1.31 (1.17-1.47)	4.4×10^{-6}	1.31 (1.16-1.47)	7.1×10^{-6}
rs77494074	11:132794801	OPCML	T	0.61 (0.50-0.74)	1.0×10^{-6}	0.60 (0.48-0.78)	8.9×10^{-7}
rs201655918	14:76791306	ESRRB	C	0.75 (0.66-0.85)	6.9×10^{-6}	0.75 (0.65-0.85)	9.3×10^{-6}
rs11073752	15:88423051	NTRK3	C	0.76 (0.67-0.85)	2.1×10^{-6}	0.76 (0.67-0.86)	6.6×10^{-6}
rs9948095	18:12018665	IMPA2	C	0.71 (0.61-0.82)	3.6×10^{-6}	0.72 (0.62-0.84)	1.9×10^{-5}
rs10555080	19:32043170	THEG5	A	1.32 (1.17-1.49)	6.9×10^{-6}	1.30 (1.15-1.48)	3.5×10^{-5}
rs34948558	21:42825856	MX1	A	0.76 (0.67-0.85)	4.7×10^{-6}	0.76 (0.67-0.85)	7.8×10^{-6}

* Primary model is reported in the main manuscript in Table 2: additive genetic model, adjusted by assignment to ACCORD interventions, seven clinical centers, and top three principal components.

† Primary model + age, duration of diabetes and BMI.

‡ Position is chromosome:bp according to the National Center for Biotechnology Information assembly build GRCh37/hg19.

**MA is minor or effect allele.

SUPPLEMENTARY DATA

Supplementary Table S4. Association between top loci in the GoDarts GWAS and DPN in ACCORD.

SNP	Chr:bp*	Minor/major allele	MAF	ACCORD Model		GoDarts Model**	
				OR(95%CI)	P	OR(95%CI)	P
12:5391393	12:5391393	A/G	0.125	0.94 (0.79,1.11)	0.44	0.95 (0.81,1.12)	0.56
12:5393329	12:5393329	T/C	0.125	0.94 (0.79,1.10)	0.43	0.95 (0.81,1.12)	0.56
12:5400620	12:5400620	T/C	0.126	0.91 (0.78,1.07)	0.28	0.93 (0.79,1.09)	0.36
12:5401196	12:5401196	G/A	0.127	0.92 (0.78,1.08)	0.32	0.93 (0.79,1.09)	0.36
12:5401450	12:5401450	G/T	0.126	0.91 (0.78,1.08)	0.28	0.93 (0.79,1.09)	0.36
12:5402869	12:5402869	C/T	0.131	0.91 (0.77,1.07)	0.23	0.92 (0.79,1.08)	0.29
12:5405457	12:5405457	T/C	0.128	0.92 (0.78,1.09)	0.34	0.94 (0.80,1.10)	0.44
rs4872521	8:21707713	G/C	0.266	1.07 (0.94,1.22)	0.28	1.09 (0.96,1.23)	0.17
rs4872522	8:21707844	C/A	0.266	1.07 (0.94,1.21)	0.31	1.09 (0.96,1.23)	0.20
rs10098807	8:21708824	A/G	0.265	1.08 (0.95,1.22)	0.26	1.09 (0.96,1.23)	0.17
rs11774105	8:21710146	C/T	0.265	1.08 (0.95,1.22)	0.25	1.09 (0.97,1.24)	0.16
rs17428041	8:21711431	C/T	0.265	1.07 (0.95,1.22)	0.27	1.09 (0.96,1.23)	0.17
rs17615364	8:21711580	A/G	0.265	1.07 (0.95,1.22)	0.27	1.09 (0.96,1.23)	0.17
rs11776842	8:21711651	C/A	0.266	1.07 (0.94,1.21)	0.32	1.08 (0.96,1.22)	0.22
rs12545534	8:21712401	A/G	0.265	1.08 (0.95,1.22)	0.25	1.09 (0.97,1.24)	0.17
rs11780601	8:21717841	T/G	0.231	1.10 (0.96,1.26)	0.15	1.13 (0.99,1.29)	0.07

*Position is chromosome:bp according to the NCBI assembly build GRCh37/hg19.

** Fisher's exact test integrated in PLINK.

SUPPLEMENTARY DATA

Supplementary Table S5. Association between significant loci in candidate gene studies and DPN in ACCORD.

Gene	Original locus associated with DPN	Reference	SNP in ACCORD	Chr	bp	Minor allele*	Major Allele	MAF	OR	95%CI	P value
ACE	I/D intron 19	Li et al, 2014	rs4341	17	61565990	C	CG	0.462	1.03	(0.92,1.15)	0.64
AKR1B1	-106 C/T	Sivenius et al., 2004	rs759853	7	134143958	A	G	0.397	1.08	(0.96,1.21)	0.19
APOE	rs429358	Tzuzuki et al., 1998	rs429358	19	45411941	C	T	0.132	0.99	(0.84,1.16)	0.88
APOE	rs7412	Tzuzuki et al, 1998	rs7412	19	45412079	T	C	0.077	0.99	(0.8,1.21)	0.89
GPX1	rs1050450	Tang et al, 2012	rs1050450	3	49394834	A	G	0.308	0.98	(0.87,1.10)	0.74
IFNG	874 A/T	Kolla et al, 2009	rs2430561	12	68552522	A	T	0.465	1.03	(0.92,1.15)	0.63
IL10	-1082 G/A	Kolla et al, 2009	rs1800896	1	206946897	C	T	0.471	1.09	(0.97,1.21)	0.13
MTHFR	677 C/T	Yigit et al, 2013	rs1801133	1	11856378	A	G	0.351	0.99	(0.88,1.11)	0.81
NOS1AP	rs1963645	Margolis et al, 2014	rs1963645	1	162333990	G	A	0.373	0.84	(0.76,0.94)	0.003
NOS1AP	rs16849113	Margolis et al, 2014	rs16849113	1	162040878	T	C	0.059	0.90	(0.72,1.13)	0.37
NOS1AP	rs6659759	Margolis et al, 2014	rs6659759	1	162037609	C	T	0.293	1.04	(0.92,1.17)	0.53
NOS1AP	rs880296	Margolis et al, 2014	rs880296	1	162128446	G	C	0.216	1.04	(0.91,1.19)	0.57
TLR4	1196 C/T	Rudofsky et al., 2004	rs4986791	9	120475602	T	C	0.061	1.06	(0.84,1.34)	0.60
UCP2	-866 G/A	Yamasaki et al., 2006	rs659366	11	73694754	T	C	0.363	1.02	(0.91,1.14)	0.73

*Effect allele

SUPPLEMENTARY DATA

Supplementary Table S6. Association of 2q24 variants with DPN in Whites and African Americans.

	Whites								African-Americans			
	MAF	r ²	ACCORD		BARI 2D		ACCORD+BARI2D		ACCORD			
			OR	P	OR	P	OR	P	MAF	r ²	OR	P
rs13417783	0.148	-	0.64	1.9 × 10 ⁻⁹	0.57	8.9 × 10 ⁻⁴	0.63	7.9 × 10 ⁻¹²	0.077	-	1.04	0.813
rs145971945	0.134	0.74	0.63	2.0 × 10 ⁻⁹	0.58	2.6 × 10 ⁻³	0.62	2.1 × 10 ⁻¹¹	0.036	0.12	0.96	0.871
rs13000447	0.145	0.66	0.64	2.3 × 10 ⁻⁹	0.68	2.8 × 10 ⁻²	0.65	2.1 × 10 ⁻¹⁰	0.242	0.16	0.94	0.575
rs10164425	0.136	0.73	0.64	2.6 × 10 ⁻⁹	0.58	2.2 × 10 ⁻³	0.63	2.4 × 10 ⁻¹¹	0.144	0.31	0.83	0.132
rs13392463	0.136	0.75	0.64	3.1 × 10 ⁻⁹	0.60	3.8 × 10 ⁻³	0.63	4.6 × 10 ⁻¹¹	0.121	0.42	0.82	0.138
rs13031854	0.134	0.82	0.63	3.4 × 10 ⁻⁹	0.61	6.2 × 10 ⁻³	0.63	7.5 × 10 ⁻¹¹	0.203	0.28	0.93	0.513
rs13421469	0.135	0.74	0.64	3.6 × 10 ⁻⁹	0.59	2.7 × 10 ⁻³	0.63	3.9 × 10 ⁻¹¹	0.038	0.28	0.98	0.933
rs2390487	0.136	0.73	0.64	3.6 × 10 ⁻⁹	0.57	1.3 × 10 ⁻³	0.63	2.1 × 10 ⁻¹¹	0.145	0.32	0.85	0.178
rs536046332	0.136	0.74	0.64	4.0 × 10 ⁻⁹	0.61	5.0 × 10 ⁻³	0.63	7.5 × 10 ⁻¹¹	0.125	NA	0.84	0.195
rs13026906	0.136	0.75	0.64	4.0 × 10 ⁻⁹	0.60	3.8 × 10 ⁻³	0.63	5.9 × 10 ⁻¹¹	0.124	0.36	0.81	0.123
rs13034083	0.136	0.75	0.64	4.0 × 10 ⁻⁹	0.60	3.8 × 10 ⁻³	0.63	5.9 × 10 ⁻¹¹	0.124	0.39	0.83	0.148
rs16852695	0.135	0.75	0.64	4.3 × 10 ⁻⁹	0.60	3.8 × 10 ⁻³	0.63	6.2 × 10 ⁻¹¹	0.124	0.37	0.83	0.162
rs10183769	0.136	0.74	0.64	4.4 × 10 ⁻⁹	0.60	3.8 × 10 ⁻³	0.63	6.3 × 10 ⁻¹¹	0.124	0.40	0.82	0.123
rs10178966	0.136	0.75	0.64	4.7 × 10 ⁻⁹	0.60	3.8 × 10 ⁻³	0.63	6.9 × 10 ⁻¹¹	0.122	0.41	0.83	0.162
rs10189266	0.136	0.75	0.64	4.7 × 10 ⁻⁹	0.60	4.1 × 10 ⁻³	0.63	7.3 × 10 ⁻¹¹	0.122	0.41	0.81	0.105
rs12993796	0.136	0.74	0.64	4.8 × 10 ⁻⁹	0.60	4.2 × 10 ⁻³	0.63	7.6 × 10 ⁻¹¹	0.182	0.26	0.93	0.490

SUPPLEMENTARY DATA

rs35762912	0.136	0.74	0.64	5.0×10^{-9}	0.60	3.8×10^{-3}	0.63	7.2×10^{-11}	0.136	0.35	0.83	0.132
rs12692848	0.136	0.74	0.64	5.1×10^{-9}	0.58	2.2×10^{-3}	0.63	4.8×10^{-11}	0.126	0.39	0.83	0.151
rs12692849	0.136	0.74	0.64	5.1×10^{-9}	0.58	2.2×10^{-3}	0.63	4.8×10^{-11}	0.127	0.38	0.84	0.174
rs76036953 (rs35714834)	0.136	0.74	0.64	5.6×10^{-9}	0.58	2.5×10^{-3}	0.63	5.8×10^{-11}	0.185	0.25	0.95	0.631
rs7558617	0.136	NA	0.64	5.8×10^{-9}	NA	NA	0.64	5.8×10^{-9}	0.185	NA	0.94	0.603
rs34867578	0.136	0.74	0.64	8.1×10^{-9}	0.59	3.4×10^{-3}	0.64	1.1×10^{-10}	0.210	0.21	0.99	0.912
rs34148223	0.137	0.74	0.64	8.7×10^{-9}	0.61	5.3×10^{-3}	0.64	1.7×10^{-10}	0.124	0.39	0.82	0.138
rs16852735	0.139	0.67	0.65	1.3×10^{-8}	0.66	2.0×10^{-2}	0.65	8.0×10^{-10}	0.083	0.02	0.75	0.069
rs148112563	0.133	0.74	0.64	1.7×10^{-8}	0.58	2.9×10^{-3}	0.64	2.2×10^{-10}	0.184	0.24	0.94	0.562
rs10200297	0.138	0.73	0.66	2.6×10^{-8}	0.55	7.1×10^{-4}	0.64	1.1×10^{-10}	0.482	0.03	1.03	0.741
rs10193273	0.257	0.48	0.71	4.6×10^{-8}	0.69	1.0×10^{-2}	0.71	1.6×10^{-9}	0.265	0.23	1.01	0.891
rs4629176	0.257	0.48	0.71	4.6×10^{-8}	0.69	1.0×10^{-2}	0.71	1.6×10^{-9}	0.265	0.23	1.01	0.891

SUPPLEMENTARY DATA

Supplementary Table S7. Baseline characteristics of ACCORD DPN cases and controls according to rs13417783 genotypes.

Baseline Characteristics	rs13417783 genotype	Cases+ Controls			Cases			Controls		
		N	Mean ± SD	P	N	Mean ± SD	P	N	Mean ± SD	P
BMI (kg/m ²)	CC	3736	32.93 ± 5.23	0.44	3244	33.10 ± 5.26	0.25	492	31.87 ± 4.88	0.81
	CT	1322	33.02 ± 5.09		1051	33.34 ± 5.12		271	31.77 ± 4.75	
	TT	108	33.00 ± 4.76		87	33.00 ± 4.83		21	32.96 ± 4.61	
Height (cm)	CC	3737	171.46 ± 9.40	0.71	3245	171.73 ± 9.38	0.65	492	169.73 ± 9.36	0.19
	CT	1322	171.38 ± 9.78		1051	171.69 ± 9.81		271	170.17 ± 9.57	
	TT	108	171.53 ± 8.30		87	171.66 ± 8.35		21	170.98 ± 8.30	
Waist circumference (cm)	CC	3703	109.33 ± 13	0.64	3214	109.98 ± 13.01	0.91	489	105.10 ± 12.14	0.41
	CT	1308	109.15 ± 12.73		1037	110.14 ± 12.79		271	105.37 ± 11.77	
	TT	108	108.94 ± 11.22		87	109.13 ± 11.53		21	108.12 ± 10.09	
HbA1c (%)	CC	3736	8.21 ± 0.93	0.29	3245	8.22 ± 0.93	0.82	491	8.16 ± 0.95	0.13
	CT	1319	8.20 ± 0.92		1050	8.23 ± 0.92		269	8.09 ± 0.91	
	TT	108	8.07 ± 0.9		87	8.12 ± 0.86		21	7.89 ± 1.05	
Fasting serum glucose (mmol/L)	CC	3728	9.90 ± 2.81	0.94	3239	9.93 ± 2.81	0.85	489	9.75 ± 2.78	0.74
	CT	1317	9.92 ± 2.86		1048	9.96 ± 2.87		269	9.78 ± 2.75	
	TT	107	9.74 ± 2.73		87	9.86 ± 2.78		20	9.23 ± 2.51	
SBP (mmHg)	CC	3726	135.38 ± 16.65	0.37	3236	135.42 ± 16.68	0.68	490	135.07 ± 16.45	0.39
	CT	1314	134.51 ± 16.64		1045	134.59 ± 16.71		269	134.21 ± 16.42	
	TT	108	135.31 ± 17.7		87	135.90 ± 17.96		21	132.90 ± 16.78	
DBP (mmHg)	CC	3726	74.16 ± 10.48	0.19	3236	74.06 ± 10.44	0.29	490	74.81 ± 10.7	0.72
	CT	1314	74.34 ± 10.33		1045	74.13 ± 10.21		269	75.19 ± 10.78	
	TT	108	75.09 ± 10.3		87	75.01 ± 10.3		21	75.43 ± 10.55	
LDL (mmol/L)	CC	3722	2.67 ± 0.85	0.38	3235	2.66 ± 0.85	0.69	487	2.67 ± 0.84	0.30
	CT	1318	2.68 ± 0.84		1049	2.68 ± 0.83		269	2.70 ± 0.91	
	TT	107	2.67 ± 0.72		87	2.60 ± 0.72		20	2.98 ± 0.65	
HDL (mmol/L)	CC	3723	1.05 ± 0.27	0.16	3236	1.05 ± 0.27	0.36	487	1.09 ± 0.29	0.04
	CT	1318	1.03 ± 0.26		1049	1.02 ± 0.26		269	1.05 ± 0.28	
	TT	107	1.05 ± 0.30		87	1.05 ± 0.30		20	1.06 ± 0.30	
Total cholesterol (mmol/L)	CC	3722	4.74 ± 1.07	0.09	3235	4.73 ± 1.06	0.19	487	4.75 ± 1.09	0.34
	CT	1318	4.78 ± 1.06		1049	4.77 ± 1.04		269	4.81 ± 1.14	
	TT	107	4.75 ± 0.89		87	4.67 ± 0.90		20	5.10 ± 0.80	
Triglycerides (mmol/L) †	CC	3722	1.93 (1.34-2.76)	0.01	3235	1.94 (1.36-2.76)	0.05	487	1.82 (1.25-2.68)	0.05
	CT	1318	2.02 (1.39-2.96)		1049	2.00 (1.39-2.94)		269	2.03 (1.32-2.98)	
	TT	107	1.99 (1.33-2.96)		87	1.99 (1.33-2.90)		20	1.95 (1.31-3.28)	
eGFR (ml/min/1.73 m ²) †	CC	3727	88.3 (72.9-103.3)	0.03	3238	88.0 (72.1-103.2)	0.12	489	90.0 (77.2-104.4)	0.27
	CT	1317	89.8 (76.1-104.9)		1048	89.5 (75.4-104.7)		269	90.7 (77.8-105.4)	
	TT	107	87.4 (72.1-104.8)		87	87.3 (72.4-102.3)		20	98.55 (70.2-106.4)	
UACR (mg/mmol) †	CC	3594	1.4 (0.7-4.1)	0.03	3122	1.4 (0.7-4.4)	0.05	472	1.0 (0.6-2.6)	0.80
	CT	1248	1.3 (0.7-3.7)		997	1.3 (0.7-3.7)		251	1.4 (0.7-3.6)	
	TT	101	1.2 (0.7-2.8)		80	1.6 (0.8-3.1)		21	0.7 (0.5-1.0)	

Values are means ± SD or medians (IQR) (†). P values are according to an additive genetic model, adjusted by assignment to interventions, seven clinical center networks, and top three principal components.

SUPPLEMENTARY DATA

Supplementary Table S8. Effects of lead SNP rs13417783 on DPN in ACCORD after adjustment for risk factors.

Adjusted covariates*	OR (95%CI)	P
Age	0.66 (0.57,0.76)	1.45E-08
Duration of diabetes	0.66 (0.57,0.76)	9.65E-09
eGFR	0.66 (0.57,0.76)	1.23E-08
UACR	0.65 (0.56,0.75)	1.13E-08
Triglyceride	0.65 (0.56,0.75)	5.12E-09

* In ACCORD, the primary model was adjusted by assignment to interventions, 7 clinical center networks, and top 3 principal components. These covariates were added to the primary model.

SUPPLEMENTARY DATA

Supplementary Table S9. Effects of lead SNP rs13417783 on prevalent and incident microvascular outcomes.

Outcome	Events/ N	OR (95%CI)	HR (95% CI)	P
Neph1: Microalbuminuria (urine albumin:creatinine ratio \geq 3.4 mg/mmol) [†]	1,141/3,859	0.98 (0.85,1.12)	-	0.73
Neph2: Macroalbuminuria (urine albumin:creatinine ratio \geq 33.9 mg/mmol) [†]	304/4,693	0.96 (0.76,1.22)	-	0.74
Neph3: Renal failure (Initiation of Dialysis or ESRD, or renal transplantation, or rise of serum creatinine $>$ 291.72 μ mol/L in absence of an acute reversible cause) [‡]	142/5,146	-	0.95 (0.68,1.33)	0.78
Neph4: Doubling of baseline serum creatinine or $>$ 20 mL/min per 1.73 m ² decrease in estimated GFR [‡]	3,078/5,163	-	0.97 (0.91,1.05)	0.45
Neph5: Any of Neph2/Neph3/Neph4	3,204/5,159	0.95 (0.84,1.07)	-	0.39
Eye1: Photocoagulation or Vitrectomy to treat retinopathy [†]	647/5,168	0.95 (0.80,1.12)	-	0.52
Eye2: Surgery for Cataract Extraction [†]	1304/5,168	0.92 (0.81,1.04)	-	0.18
Eye3: 3-line Worsened Visual Acuity [‡]	2183/4996	-	1.02 (0.94,1.11)	0.66
Eye4: Severe Vision Loss (Snellen fraction $<$ 20/200) [†]	900/4,652	0.91 (0.78,1.06)	-	0.23
Progression to Diabetic Retinopathy in ACCORD EYE Study*	132/1707	0.99 (0.69-1.42)	-	0.97

[†]Prevalent + incident cases vs. controls (subjects without the outcome of interest at study entry and during follow-up).

[‡]Incident cases vs. controls at study entry and during follow-up. GFR estimation was done on the basis of the four variable MDRD GFR equation from Levey and colleagues.

*Progression of diabetic retinopathy defined by \geq 3 steps from baseline on the ETDRS (Early Treatment Diabetic Retinopathy Study Severity Scale) or the development of diabetic retinopathy requiring laser photocoagulation or vitrectomy.

All outcomes above were predefined in ACCORD as secondary microvascular outcomes. (1; 2)

SUPPLEMENTARY DATA

Supplementary Table S10. Effects of lead SNP rs13417783 on prevalent and incident cardiac autonomic neuropathy.

Outcome	Cases*/N	OR (95%CI)	P
CAN1	768/3,863	0.96 (0.82,1.13)	0.61
CAN2	314/3,847	1.11 (0.88,1.40)	0.37
CAN3	201/3,812	1.08 (0.82,1.44)	0.57

CAN1 is defined as the lowest quartile of standard deviation of N interval (SDNN) (<7.815 ms) and the highest quartile of QT-index (QTI) (>104.32%). Thresholds derived from the baseline electrocardiogram (ECG); CAN2 is defined as the lowest quartile of SDNN and the highest quartiles of QTI and resting heart rate (>99bpm); CAN3 is defined as the lowest quartile of SDNN and the highest quartiles of QTI and heart rate, in the presence of DPN (3).

*CAN1, CAN2, and CAN3 cases are those that met the criteria either at baseline or during follow-up, and controls are those that did not meet the criteria both at baseline and during follow-up.

SUPPLEMENTARY DATA

References

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