

Extended Data Table 1. Clinical characteristics of the 192 samples (96 cases + 96 controls) included in the discovery cohort. Quantitative traits were compared between cases and controls using unadjusted linear regression and binary traits* were compared using Fisher exact test.

Traits (unit)	Controls (n=96)	T2D cases (n=96)	p-value
	Mean (SD) or n (%)	Mean (SD) or n (%)	
cg14496282 methylation (%)	60.3% (17.2%)	41.3% (12.2%)	9.27×10^{-16}
PDGFA expression (SD)	0.79 (0.35)	1.04 (0.40)	1.7×10^{-6}
Age (years)	46.7 (7.0)	48.2 (6.3)	0.13
BMI (kg/m ²)	47.1 (7.4)	49.1 (7.5)	0.06
Fasting glucose (mmol/l)	5.2 (0.4)	8.5 (3.2)	2.2×10^{-19}
Fasting insulin (pmol/l)	78.7 (36.497)	270.5 (854.2)	0.029
HOMA2-B (unitless)	112.6 (34.8)	71.5 (42.4)	4.67×10^{-11}
HOMA2-IR (unitless)	1.5 (0.7)	2.1 (1.435)	8.0×10^{-5}
QUICKI (unitless)	0.34 (0.03)	0.31 (0.04)	3.83×10^{-7}
Steatosis (%)	21.3% (20.1%)	42.4% (23.8%)	4.77×10^{-10}
NASH* (Yes/ No)	4 (4.2%)	17 (18%)	4.44×10^{-3}
Hepatic fibrosis* (Yes/ No)	21 (22%)	45 (47%)	6.55×10^{-4}
Alanine aminotransferase (UI/L)	27.11 (15.8)	34.3 (19.8)	6.04×10^{-3}
Aspartate aminotransferase (UI/L)	22.344 (7.04)	26.9 (14.3)	5.5×10^{-3}

Extended Data Table 2. Clinical characteristics of the 65 selected samples (12 cases + 53 controls) used for replication. Quantitative traits were compared between cases and controls using unadjusted linear regression and binary traits* were compared using Fisher exact test.

Traits (unit)	Controls (n=53)	T2D cases (n=12)	p-value
	Mean (SD) or n (%)	Mean (SD) or n (%)	
cg14496282 methylation (%)	63.3%	41.4%	3.59×10 ⁻⁴
	(19.2%)	(11.6%)	
Age (years)	46.7	54.6	0.063
	(13)	(13)	
Sex (female)*	42	5	0.014
	(79.2%)	(71.4%)	
BMI (kg/m ²)	40.5	43.2	0.542
	(13.6)	(11.5)	

Extended Data Table 3. Association between fasting insulin raising alleles and DNA methylation at cg14496282. Associations were assessed using linear regression with methylation as response variable. All models were adjusted for age, BMI, total cholesterol, HDL cholesterol, triglycerides and fasting glucose. Effect sizes are reported as percentage of DNA methylation per allele.

SNP	Closest gene (locus)	Fasting insulin raising allele	Effect size (p-value) in Controls	Effect size (p-value) in T2D cases	I ² statistic (p-value)	Fixed effect meta-analysis effect size (p-value)
rs459193	ANKRD55	G	-1.85 (0.483)	-0.87 (0.691)	0% (0.776)	-1.27% (0.448)
rs4865796	MAP3K1	A	-3.53 (0.216)	0.96 (0.656)	37.49% (0.206)	-0.68% (0.692)
rs3822072	ARL15	A	-2.89 (0.267)	0.12 (0.953)	0% (0.353)	-0.97% (0.532)
rs1421085	FAM13A1	C	-0.66 (0.794)	-2.83 (0.124)	0% (0.486)	-2.09% (0.158)
rs10195252	FTO	T	-0.27 (0.913)	0.22 (0.91)	0% (0.876)	0.03% (0.983)
rs1167800	GRB14	A	2.31 (0.414)	0.54 (0.793)	0% (0.611)	1.15% (0.486)
rs2943645	HIP1	T	-1.66 (0.552)	-0.73 (0.698)	0% (0.783)	-1.02% (0.511)
rs4846565	IRS1	G	-6.69 (0.006)	1.49 (0.483)	85.03% (0.01)	-2.15% (0.171)
rs6822892	LYPLAL1	A	-0.88 (0.731)	-1.03 (0.62)	0% (0.963)	-0.97% (0.546)
rs731839	PDGFC	G	-3.69 (0.197)	-0.95 (0.643)	0% (0.432)	-1.88% (0.256)
rs17036328	PEPD	T	-6.3 (0.122)	-4.42 (0.115)	0% (0.701)	-5.02% (0.028)
rs2126259	PPARG	T	-0.24 (0.96)	-2.54 (0.418)	0% (0.69)	-1.86% (0.477)
rs2745353	PPP1R3B	T	-4.72 (0.056)	-1.23 (0.546)	17.56% (0.271)	-2.66% (0.088)
rs7903146	RSPO3	C	-1.66 (0.619)	-2.75 (0.172)	0% (0.78)	-2.46% (0.15)
rs974801	TCF7L2	G	4.32 (0.141)	-2.37 (0.229)	72.58% (0.056)	-0.29% (0.861)
rs6912327	TET2	T	-1.68 (0.576)	-3.87 (0.064)	0% (0.546)	-3.16% (0.062)
rs1530559	UHRF1BP1	A	3.94 (0.154)	-1.71 (0.356)	65.92% (0.087)	0.05% (0.974)
rs860598	YSK4	A	-5.39 (0.118)	3.6 (0.095)	79.95% (0.026)	1.09% (0.548)
rs780094	IGF1	C	0.21 (0.936)	1.35 (0.513)	0% (0.736)	0.92% (0.569)
Overall						
Meta-analysis	-	-	-1.63% (0.011)	-0.83% (0.079)	2.4% (0.428)	-1.11% (0.004)
(Cases + Controls)						
Genetic Risk Score (GRS)	-	-	-1.68% (0.010)	-0.74% (0.099)		-1.05% (0.004)

Extended Data Table 4. Correlation between multiple genetic risk scores (GRS) and PDGA methylation in 192 ABOS study participants. GRS are calculated as the number of trait/risk increasing alleles over N_{SNP} (number of SNPs) independent loci.

Traits	Publication identifying genome-wide associated SNPs	Correlation between GRS and PDGA DNA methylation at cg14496282 (p-value)
Type 2 diabetes ($N_{\text{SNP}}=65$)	Morris et al. Nat. Genet. (2012)	-0.07 (0.32)
BMI ($N_{\text{SNP}}=97$)	Locke et al. Nature (2015)	-0.01 (0.87)
Fasting glucose ($N_{\text{SNP}}=24$)	Vaxillaire et al. Diabetologia (2014)	-0.05 (0.51)
Fasting insulin ($N_{\text{SNP}}=19$)	Scott et al. Nat. Genet. (2012)	-0.21 (0.005)

Extended Data Table 5. List of deregulated genes within the network of PDGFA

Gene	Log2 Fold Change	p-value
PDGFRB	-0.68	3.2E-10
IL1RN	-0.59	3.0E-15
A2M	-0.33	2.2E-09
FGF2	-0.31	9.5E-03
VDR	-0.25	3.2E-02
PRKACB	-0.25	1.7E-03
IRS1	-0.21	1.1E-02
POU5F1	-0.19	6.0E-03
NFATC2	-0.17	2.7E-02
NR3C1	-0.14	4.4E-02
PRKACA	-0.13	2.1E-02
PDPK1	-0.13	1.8E-02
HDAC1	-0.12	3.9E-02
RXRΒ	-0.12	4.2E-02
PRKAR1A	-0.12	2.4E-02
SP1	-0.11	3.9E-02
NME2	0.11	2.6E-02
SSRP1	0.12	2.2E-02
SPP1	0.12	1.6E-02
NCL	0.12	8.2E-03
TAF4	0.16	8.2E-03
NFKB1	0.17	2.8E-03
FURIN	0.18	4.5E-02
VEGFB	0.20	1.5E-02
PDAP1	0.21	3.0E-03
HIF1A	0.22	6.4E-05
TGFB1	0.23	3.0E-04
MAP2K1	0.23	1.3E-04
MAP2K2	0.23	1.1E-02
DNM2	0.25	1.7E-04
RRAS	0.25	4.4E-02
TNFRSF1A	0.25	7.6E-06
GRB14	0.26	2.2E-02
NFIC	0.27	1.3E-02
NME1	0.28	1.1E-06
IL18	0.29	3.1E-02
PDGFB	0.43	1.2E-04
PCSK5	0.52	8.3E-12
EDN1	0.55	6.4E-05
VEGFA	0.56	5.8E-13
NES	0.64	1.2E-25
DUSP1	0.67	9.7E-11
PDGFA	0.80	1.1E-11
KLF5	0.87	3.6E-13
EGR1	1.13	2.2E-16

Extended Data Table 6. List of deregulated genes within the network related to the metabolism of carbohydrates

Gene	Log2 Fold Change	p-value	Gene	Log2 Fold Change	p-value	Gene	Log2 Fold Change	p-value
G6PC	-1,69	2,3E-36	FAS	-0,14	2,3E-02	TCF7L2	0,24	5,7E-04
PDGFRB	-0,68	3,2E-10	CPT1A	-0,14	1,9E-02	OAS1	0,25	2,3E-03
IL1RN	-0,59	3,0E-15	ALG2	-0,14	1,2E-02	SREBF1	0,25	8,4E-03
GPAM	-0,54	1,5E-18	ACADM	-0,14	2,2E-02	TIGAR	0,25	5,1E-04
SLC2A2	-0,53	3,8E-14	PIGF	-0,14	3,5E-02	HEXB	0,25	1,1E-05
CREB3L3	-0,51	1,8E-05	CHKB	-0,13	4,7E-02	ITGB1	0,25	6,3E-06
ENPP2	-0,47	2,5E-04	GM2A	-0,13	3,2E-02	TNFRSF1A	0,25	7,6E-06
GNMT	-0,47	2,9E-04	PDPK1	-0,13	1,8E-02	CTGF	0,25	7,8E-03
PPARGC1A	-0,46	1,3E-08	EXTL2	-0,12	4,2E-02	CHST6	0,26	2,9E-02
ETNK2	-0,44	1,3E-09	PHKB	-0,12	3,5E-02	UGP2	0,26	3,0E-04
SLC23A2	-0,41	2,2E-14	NAGA	-0,12	3,9E-02	GCNT3	0,26	5,4E-04
SH3YL1	-0,39	6,4E-07	MAN2A1	-0,11	4,8E-02	B3GNT3	0,27	8,0E-05
PXYLP1	-0,38	4,9E-04	B3GAT1	-0,11	3,5E-02	GYS1	0,27	4,5E-05
CYP3A5	-0,35	6,1E-03	PGM3	-0,10	4,3E-02	ADRBK1	0,28	2,0E-04
TRPV1	-0,35	2,0E-05	NQO1	0,10	4,6E-02	CSF1	0,29	3,5E-03
PGAP1	-0,34	1,7E-05	RHOA	0,10	3,8E-02	IL18	0,29	3,1E-02
PMM1	-0,34	3,0E-06	CLTC	0,10	4,5E-02	GPI	0,29	2,4E-08
NEU3	-0,33	7,4E-05	XBP1	0,10	2,9E-02	NR1D1	0,30	3,1E-03
PPP1R3F	-0,31	9,2E-03	SCD	0,11	3,6E-02	GAL	0,30	2,7E-02
ST6GAL1	-0,31	3,2E-10	SPP1	0,12	1,6E-02	B4GALNT1	0,30	5,2E-04
FGF2	-0,31	9,5E-03	PTGFRN	0,12	4,5E-02	SFN	0,31	1,5E-03
GALNT7	-0,29	3,6E-02	GNB1	0,12	5,2E-03	TPI1	0,31	5,5E-07
RGN	-0,29	1,6E-05	PTEN	0,13	3,5E-02	HBEGF	0,31	2,1E-02
PIGV	-0,27	9,9E-05	SH3KBP1	0,13	2,9E-02	IGF2	0,32	8,2E-05
SLC37A4	-0,27	1,2E-07	DSE	0,13	4,8E-02	GOT1	0,33	4,0E-07
PPARA	-0,27	4,3E-05	GALE	0,13	1,8E-02	SLC2A8	0,33	2,3E-04
GALT	-0,25	9,8E-05	AFF4	0,13	4,2E-02	PPARG	0,33	2,7E-04
IGF1R	-0,25	1,8E-05	PRPS1	0,13	3,0E-02	CHSY1	0,34	6,5E-08
NDST2	-0,25	1,2E-04	CDC42	0,14	1,5E-02	GMDS	0,36	1,5E-09
C5	-0,25	2,0E-04	SLC9A3R1	0,14	3,1E-02	PPP1R3C	0,37	1,8E-04
GCKR	-0,25	1,0E-03	TALDO1	0,14	7,0E-03	NTSR1	0,37	4,9E-03
ONECUT1	-0,25	3,3E-02	ARF6	0,15	7,0E-03	GBE1	0,38	8,8E-06
LIPC	-0,25	5,7E-03	RPE	0,15	1,7E-02	DKK1	0,39	8,5E-08
GPLD1	-0,24	2,4E-03	GNPDA1	0,15	1,3E-02	SERINC2	0,39	3,3E-05
ENPP1	-0,24	3,9E-05	GK	0,15	4,2E-02	FOXA2	0,39	2,8E-07
NDST1	-0,24	7,4E-04	GLA	0,15	1,3E-02	PKM	0,40	1,6E-12
CTBS	-0,22	9,4E-03	SH3GLB1	0,16	1,1E-02	PLCH2	0,40	3,5E-03
H6PD	-0,22	8,5E-04	PYGB	0,16	3,0E-02	PGK1	0,42	5,4E-07
IRS1	-0,21	1,1E-02	HS2ST1	0,17	4,7E-03	PLAU	0,43	9,5E-04
ALDH5A1	-0,21	2,8E-04	GNE	0,17	6,1E-03	PDGFB	0,43	1,2E-04
S1PR2	-0,21	3,0E-02	CEBPB	0,17	3,6E-02	PLA2G3	0,44	5,4E-04
KHK	-0,21	3,6E-03	XYLT1	0,17	3,2E-02	PPP1R3G	0,45	1,6E-04
HDAC5	-0,20	3,4E-03	COQ2	0,17	2,2E-02	STBD1	0,45	2,6E-06
PPP1R3E	-0,20	2,2E-03	NFKB1	0,17	2,8E-03	ALDOA	0,45	6,8E-11
SIAE	-0,20	7,8E-04	FOXO1	0,18	2,4E-02	ICAM1	0,45	1,2E-17
PLCD1	-0,20	4,9E-02	G6PD	0,18	3,0E-02	ALDOC	0,46	1,3E-10
CHPT1	-0,19	6,3E-04	FUCA2	0,18	8,3E-04	DUSP6	0,46	2,0E-15
PIGZ	-0,19	2,9E-02	TKT	0,18	8,3E-03	SLC2A1	0,49	1,3E-18
SLC5A2	-0,19	1,8E-02	MTMR2	0,19	3,9E-03	GRB10	0,49	1,8E-06
CHST3	-0,17	1,4E-03	GYG1	0,19	5,5E-03	PFKP	0,52	3,8E-09
EPHX1	-0,17	3,3E-03	INPP5E	0,19	3,9E-02	AGPAT2	0,53	3,1E-06
FUCA1	-0,17	1,3E-02	ADORA2B	0,20	1,2E-02	SLC16A3	0,54	2,7E-10
LCAT	-0,17	4,3E-02	MYC	0,20	2,3E-04	EDN1	0,55	6,4E-05
PIGP	-0,16	3,2E-02	TRPV2	0,20	3,7E-03	ANGPTL8	0,56	1,6E-06
SULF2	-0,16	3,1E-02	NEU1	0,21	1,5E-05	HK1	0,57	2,1E-05
SERINC5	-0,16	2,6E-02	GAPDH	0,21	1,5E-04	CHST15	0,62	1,6E-10
TGFBR1	-0,16	1,3E-02	PLCG2	0,21	2,7E-02	CEMP	0,71	1,7E-20
HECTD4	-0,16	4,8E-02	PRKAA2	0,21	2,2E-03	PFKFB3	0,71	1,3E-07
DYRK2	-0,16	2,8E-02	HS6ST1	0,22	7,7E-03	IGFBP3	0,78	1,4E-08
CPS1	-0,15	1,1E-02	HIF1A	0,22	6,4E-05	PPP1R15A	0,80	3,5E-19
PLCB1	-0,15	2,7E-02	PFKFB2	0,22	5,3E-04	PDGFA	0,80	1,1E-11
EPM2AIP1	-0,15	1,2E-02	CHKA	0,22	1,9E-05	HK2	0,82	8,4E-23
SRD5A3	-0,14	3,9E-02	TGFB1	0,23	3,0E-04	NR4A1	0,86	1,0E-21
PLSCR1	-0,14	2,9E-02						