SUPPLEMENTARY DATA

Supplementary Table S1. Summary of DNA methylation array data generation and processing across the cohorts

Cohort	**EPIC-Norfolk**	**LOLIPOP**	**FHS**
Sample size	1264	1,074 (incident T2DM)/ 1,590 (controls)	2741
DNA source	whole blood	whole blood	whole blood
Methylation array	Illumina HM450k	Illumina HM450k	Illumina HM450k
normalisation	quantile normalisation	quantile normalisation	DASEN
QC method	Ref. 17	Ref. 17	Ref. 19
Statistical model	T2DM status ~ methylation + age + sex + estimated white blood cell counts + sample plate	T2DM status ~ methylation + control probes + bisulfite conversion batch + measured white blood cells + imputed white blood cell subsets + 5 PCA (corrected for genomic control inflation factor).	Methylation ~ T2DM status + age + sex + white blood cell counts + technical covariates + batch effects +BMI

Supplementary Table S2. Confirmation in EPIC-Norfolk of the 5 MVPs with consistent associations with incident T2DM reported by Chambers *et al.* (2015)

*These additional two MVPs were reportedly not significantly associated (P>0.05) with T2DM in their European replication samples.
MVPs with confirmed association *P*<7.1E-03 (=0.05/7) are highlighted.

				Chambers et al. 2015				**EPIC-Norfolk Study**		
CpG	**Chr**	**Position**	**Gene(s)**	**RR (Indian Asians)**	**P (Indian Asians)**	**RR (Europeans)**	**P (Europeans)**	**OR**	**CI 95%**	**P**
cg19693031	1	145441552	*TXNIP*	0·92 (0·91–0·94)	1.0E-13	0·96 (0·94–0·98)	2.50E-05	0.524	[0.46-0.6]	2.7E-21
cg06500161	21	43656587	*ABCG1*	1·08 (1·06–1·10)	2.2E-13	1·04 (1·02–1·06)	1.2E-04	1.655	[1.45-1.89]	6.4E-14
cg11024682	17	17730094	*SREBF1*	1·06 (1·04–1·08)	8.4E-09	1·03 (0·95–0·99)	5.4E-03	1.556	[1.35-1.79]	6.0E-10
cg02650017	17	47301614	*PHOSPHO1*	0·94 (0·92–0·96)	2.1E-09	0·97 (0·95–0·99)	1.2E-03	0.863	[0.76-0.97]	1.8E-02
cg18181703	17	76354621	*SOCS3*	0·95 (0·93–0·97)	2.1E-07	0·97 (0·95–0·99)	1.6E-03	0.909	[0.81-1.02]	1.2E-01
Reported inconsistent associations										
* cg04999691	7	150027050	*C7orf29*	0·95 (0·93–0·96)	1.4E-08	1·00 (0·98–1·02)	7.1E-01	0.999	[0.88-1.14]	9.9E-01
* cg09152259	2	128156114	*PROC*	0·95 (0·93–0·97)	9.3E-08	0·99 (0·97–1·01)	3.2E-01	0.799	[0.71-0.91]	4.2E-04

Supplementary Table S3. Conditional models for the top 18 MVPs associated with incident T2DM - adjusted for baseline BMI (B), HbA1c (C), BMI & HbA1c (D), in the EPIC-Norfolk study

Model A: adjusted for age, sex, estimated cell counts and technical covariates (Discovery).
Model B: model A + adjustment for baseline BMI.
Model C: model A + adjustment for baseline HbA1c.
Model D: model A + adjustement for baseline HbA1c and BMI.
OR: Odds Ratio per +1 SD in normalised methylation intensity; CI 95%: 95% Confidence Interval; Attentn: % Attenuation in the odds ratio from Model A.

				Model A			**Model B (n=1260)**				**Model C (n=1262)**				**Model D (n=1256)**			
CpG ID	**Chr**	**Position**	**Gene**	**OR**	**CI 95%**	**P-value**	**OR**	**CI 95%**	**P-value**	**Attentn.**	**OR**	**CI 95%**	**P-value**	**Attentn.**	**OR**	**CI 95%**	**P-value**	**Attentn.**
cg19693031	1	144152909	*TXNIP*	0.52	[0.46-0.6]	2.7E-21	0.55	[0.47-0.63]	2.5E-16	5%	0.68	[0.57-0.81]	8.5E-06	33%	0.68	[0.57-0.81]	1.9E-05	33%
cg06500161	21	42529656	*ABCG1*	1.65	[1.45-1.89]	6.4E-14	1.47	[1.27-1.69]	1.2E-07	29%	1.48	[1.25-1.75]	4.5E-06	26%	1.36	[1.13-1.62]	8.0E-04	46%
cg14476101	1	120057515	*PHGDH*	0.67	[0.59-0.76]	2.8E-10	0.78	[0.68-0.9]	4.4E-04	35%	0.68	[0.58-0.8]	4.1E-06	5%	0.76	[0.64-0.91]	1.9E-03	29%
cg14020176	17	70276580	*SLC9A3R1*	1.63	[1.4-1.9]	3.3E-10	1.48	[1.26-1.75]	3.6E-06	24%	1.36	[1.11-1.65]	2.4E-03	44%	1.26	[1.02-1.55]	3.1E-02	59%
cg11024682	17	17670819	*SREBF1*	1.56	[1.35-1.79]	6.0E-10	1.43	[1.23-1.67]	3.4E-06	22%	1.31	[1.08-1.57]	4.7E-03	45%	1.25	[1.03-1.52]	2.4E-02	55%
cg06397161	22	38090005	*SYNGR1*	1.51	[1.32-1.73]	4.5E-09	1.44	[1.23-1.68]	3.3E-06	14%	1.30	[1.09-1.56]	4.4E-03	41%	1.26	[1.04-1.53]	1.6E-02	49%
cg00574958	11	68364198	*CPT1A*	0.69	[0.61-0.78]	5.2E-09	0.79	[0.69-0.9]	5.5E-04	31%	0.73	[0.63-0.86]	1.0E-04	14%	0.81	[0.69-0.96]	1.3E-02	39%
cg06235429	11	67129690	*NDUFV1*	1.49	[1.3-1.7]	5.5E-09	1.38	[1.2-1.6]	1.2E-05	22%	1.32	[1.11-1.57]	1.9E-03	35%	1.25	[1.04-1.5]	1.6E-02	48%
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	7.4E-09	1.57	[1.3-1.91]	5.1E-06	17%	1.41	[1.12-1.78]	3.6E-03	41%	1.35	[1.06-1.72]	1.6E-02	50%
cg11376147	11	57017774	*SLC43A1*	0.68	[0.59-0.77]	1.3E-08	0.72	[0.62-0.84]	1.4E-05	14%	0.66	[0.55-0.79]	5.2E-06	-4%	0.68	[0.56-0.82]	6.8E-05	2%
cg04816311	7	1033176	*C7orf50*	1.51	[1.31-1.75]	1.7E-08	1.47	[1.26-1.72]	1.4E-06	8%	1.18	[0.98-1.43]	7.4E-02	64%	1.19	[0.98-1.44]	8.2E-02	63%
cg02711608	19	51979804	*SLC1A5*	0.69	[0.6-0.79]	4.5E-08	0.77	[0.67-0.89]	5.5E-04	27%	0.79	[0.66-0.93]	5.0E-03	31%	0.84	[0.7-1.01]	6.3E-02	50%
cg08309687	21	34242466	-	0.68	[0.6-0.78]	4.5E-08	0.75	[0.64-0.87]	1.4E-04	20%	0.79	[0.67-0.95]	1.0E-02	35%	0.86	[0.71-1.03]	1.1E-01	56%
cg13514042	7	1158728	-	1.42	[1.25-1.61]	4.5E-08	1.33	[1.16-1.53]	4.0E-05	20%	1.36	[1.16-1.59]	1.9E-04	15%	1.30	[1.1-1.54]	2.3E-03	28%
cg08994060	10	6254032	*PFKFB3*	0.65	[0.55-0.76]	5.2E-08	0.67	[0.56-0.79]	4.5E-06	6%	0.73	[0.59-0.89]	2.1E-03	23%	0.74	[0.59-0.91]	5.1E-03	25%
cg01676795	7	75424284	*POR*	1.56	[1.33-1.84]	6.5E-08	1.48	[1.24-1.77]	1.3E-05	14%	1.34	[1.08-1.67]	7.6E-03	39%	1.28	[1.02-1.61]	3.3E-02	50%
cg25130381	1	27313308	*SLC9A1*	1.49	[1.29-1.73]	6.7E-08	1.42	[1.22-1.67]	1.0E-05	14%	1.23	[1.02-1.48]	3.2E-02	54%	1.21	[1-1.48]	5.3E-02	57%
cg11183227	15	89256411	*MAN2A2*	1.49	[1.29-1.72]	7.0E-08	1.42	[1.21-1.66]	1.7E-05	14%	1.18	[0.99-1.42]	6.8E-02	62%	1.16	[0.96-1.41]	1.3E-01	67%

Supplementary Table S4. Significant gene-set enrichment analysis results for the EWAS result with MAGENTA. Significance is based on the FDR 75% cut-off. For further details see the original paper (Segrè *et al.* 2010).

Database	Gene Set	Nominal GSEA P-val 75% cut-off	FDR 75% cut-off	Exp. Genes above 75% cutoff	Obs. Genes above 75% cutoff
Ingenuity	JAK.Stat.Signaling	3.00E-04	3.90E-03	3	8
Ingenuity	Erythropoietin.Signaling	4.00E-04	4.50E-03	4	10
Ingenuity	Insulin.Receptor.Signaling	1.17E-04	5.60E-03	9	19
Ingenuity	Fc.Epsilon.RI.Signaling	3.00E-04	6.20E-03	4	10
Ingenuity	PI3K.AKT.Signaling	1.20E-03	1.03E-02	7	15
Ingenuity	T.Cell.Receptor.Signaling	2.10E-03	1.26E-02	8	16
Ingenuity	Integrin.Signaling	1.00E-03	1.29E-02	9	18
Ingenuity	B.Cell.Receptor.Signaling	2.20E-03	1.32E-02	8	16
Ingenuity	Neuregulin.Signaling	2.10E-03	1.56E-02	6	13
Ingenuity	IGF-1.Signaling	6.10E-03	2.10E-02	5	10

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Supplementary Table S5. Evaluation of the top 18 T2DM-associated MVPs with glycemic traits in the Framingham Heart Studies and with BMI in Wahl *et al.*, 2017

Direction of methylation: Associations are aligned to T2DM-increasing methylation changes. MVPs with associations P<0.05 are highlighted in bold.

*Adjusted for age, sex, PC1-3 (calculated from methylation data), batch and family structure.

** Additionally adjusted for BMI.

				Fasting glucose (n=2117)*			**Fasting insulin (n=2151)****			**HbA1c (n=2156)***			**BMI Wahl (n=10,261)**		
CpG ID	**Chr**	**Gene**	**Direction of methylation**	**beta**	**se**	**p**	**beta**	**se**	**p**	**beta**	**se**	**p**	**beta**	**se**	**p**
cg19693031	1	*TXNIP*	Decreasing	**7.4E-04**	**1.2E-04**	**4.0E-10**	**3.4E-03**	**1.5E-03**	**2.1E-02**	**1.1E-02**	**3.9E-03**	**6.0E-03**	**-9.8**	**2.0**	**1.5E-06**
cg06500161	21	*ABCG1*	Increasing	**5.8E-04**	**7.9E-05**	**4.6E-13**	**8.3E-03**	**9.5E-04**	**3.9E-18**	**1.4E-02**	**2.6E-03**	**2.0E-07**	**34.8**	**2.3**	**1.7E-53**
cg14476101	1	*PHGDH*	Decreasing	**8.5E-04**	**1.6E-04**	**9.5E-08**	**5.5E-03**	**1.9E-03**	**4.4E-03**	-1.4E-03	5.3E-03	7.9E-01	**-14.5**	**1.6**	**4.1E-20**
cg14020176	17	*SLC9A3R1*	Increasing	6.9E-05	6.7E-05	3.1E-01	**2.2E-03**	**8.4E-04**	**7.9E-03**	**7.0E-03**	**2.2E-03**	**1.9E-03**	**17.5**	**3.0**	**3.3E-09**
cg11024682	17	*SREBF1*	Increasing	**3.5E-04**	**6.9E-05**	**6.9E-07**	**5.4E-03**	**8.4E-04**	**1.5E-10**	**9.6E-03**	**2.3E-03**	**3.0E-05**	**32.5**	**3.0**	**3.6E-27**
cg06397161	22	*SYNGR1*	Increasing	8.6E-05	9.7E-05	3.8E-01	**3.7E-03**	**1.2E-03**	**2.2E-03**	6.1E-03	3.2E-03	6.1E-02	**13.6**	**2.2**	**5.7E-10**
cg00574958	11	*CPT1A*	Decreasing	**2.6E-04**	**3.6E-05**	**4.4E-13**	**3.2E-03**	**4.3E-04**	**4.4E-13**	**3.6E-03**	**1.2E-03**	**2.4E-03**	**-40.2**	**3.1**	**1.4E-38**
cg06235429	11	*NDUFV1*	Increasing	7.5E-05	5.8E-05	1.9E-01	3.2E-04	7.1E-04	6.5E-01	1.5E-03	1.9E-03	4.3E-01	**15.5**	**3.9**	**8.3E-05**
cg05778424	17	*AKAP1*	Increasing	**2.1E-04**	**7.1E-05**	**3.5E-03**	**3.3E-03**	**8.8E-04**	**2.1E-04**	**7.5E-03**	**2.4E-03**	**1.6E-03**	**21.6**	**2.8**	**1.2E-14**
cg11376147	11	*SLC43A1*	Decreasing	**1.5E-04**	**5.5E-05**	**5.8E-03**	1.1E-03	6.8E-04	1.2E-01	2.5E-03	1.8E-03	1.7E-01	**-25.3**	**3.0**	**2.9E-17**
cg04816311	7	*C7orf50*	Increasing	**4.8E-04**	**1.4E-04**	**6.7E-04**	**6.2E-03**	**1.7E-03**	**3.6E-04**	**1.8E-02**	**4.7E-03**	**1.7E-04**	**9.3**	**1.8**	**1.9E-07**
cg02711608	19	*SLC1A5*	Decreasing	**1.7E-04**	**7.3E-05**	**2.2E-02**	**2.8E-03**	**9.1E-04**	**2.4E-03**	-8.2E-04	2.4E-03	7.3E-01	**-17.2**	**2.4**	**1.3E-12**
cg08309687	21	-	Decreasing	**6.6E-04**	**1.3E-04**	**7.9E-07**	**6.9E-03**	**1.7E-03**	**3.0E-05**	**1.7E-02**	**4.4E-03**	**9.6E-05**	**-15.2**	**1.9**	**9.4E-16**
cg13514042	7	-	Increasing	1.2E-04	6.3E-05	5.9E-02	8.8E-04	7.7E-04	2.6E-01	2.8E-03	2.1E-03	1.8E-01	**14.7**	**4.4**	**9.1E-04**
cg08994060	10	*PFKFB3*	Decreasing	**3.4E-04**	**1.1E-04**	**2.2E-03**	**4.2E-03**	**1.4E-03**	**3.0E-03**	**9.7E-03**	**3.8E-03**	**9.7E-03**	**-7.2**	**1.7**	**1.8E-05**
cg01676795	7	*POR*	Increasing	1.6E-04	1.0E-04	1.2E-01	**3.1E-03**	**1.3E-03**	**1.5E-02**	**1.3E-02**	**3.5E-03**	**1.3E-04**	**10.7**	**2.4**	**7.9E-06**
cg25130381	1	*SLC9A1*	Increasing	**1.6E-04**	**7.6E-05**	**3.2E-02**	**3.5E-03**	**9.4E-04**	**2.0E-04**	**6.1E-03**	**2.6E-03**	**1.7E-02**	**14.1**	**2.5**	**3.1E-08**
cg11183227	15	*MAN2A2*	Increasing	**2.6E-04**	**9.0E-05**	**4.4E-03**	**3.1E-03**	**1.1E-03**	**4.9E-03**	5.5E-03	3.0E-03	6.4E-02	**18.9**	**2.8**	**3.0E-11**

Supplementary Table S6. Evaluation of the top 18 T2DM-associated MVPs with cross-sectional differences in DNA methylation intensity between monozygous twin pairs discordant for Type 1 diabetes (T1DM).

*Odds ratio for incident T2DM in the discovery EPIC Norfolk study
FDR: false-discovery rate, based on paired T-tests. Delta Beta: Controls minus T1DM
No T1DM data were available for cg06397161 (SYNGR1) or cg02711608 (SLC1A5)

			Monocyte				**B cell**				**T cell**			
CpG ID	**Gene**	**OR for T2DM***	**Beta Controls**	**Beta T1DM**	**Delta Beta**	**FDR**	**Beta Controls**	**Beta T1DM**	**Delta Beta**	**FDR**	**Beta Controls**	**Beta T1DM**	**Delta Beta**	**FDR**
cg19693031	***TXNIP***	**0.52**	**0.680**	**0.744**	**-0.064**	**2.1E-05**	**0.886**	**0.919**	**-0.033**	**4.3E-04**	0.806	0.803	0.003	7.9E-01
cg06500161	*ABCG1*	1.65	0.741	0.740	0.001	8.7E-01	0.491	0.481	0.010	3.2E-01	0.705	0.713	-0.009	3.5E-01
cg14476101	*PHGDH*	0.67	0.658	0.649	0.009	5.3E-01	0.806	0.804	0.002	8.7E-01	0.883	0.883	0.001	9.0E-01
cg14020176	***SLC9A3R1***	**1.63**	**0.639**	**0.624**	**0.015**	**4.3E-04**	0.862	0.854	0.009	8.6E-01	0.905	0.903	0.002	7.9E-01
cg11024682	***SREBF1***	**1.56**	**0.414**	**0.405**	**0.010**	**2.9E-02**	0.504	0.500	0.004	8.6E-01	0.525	0.516	0.009	3.5E-01
cg00574958	***CPT1A***	**0.69**	0.032	0.033	-0.001	8.5E-01	0.034	0.032	0.001	8.6E-01	**0.136**	**0.157**	**-0.021**	**8.3E-03**
cg06235429	*NDUFV1*	1.49	0.891	0.889	0.002	8.2E-01	0.936	0.934	0.002	8.6E-01	0.942	0.946	-0.004	3.5E-01
cg05778424	*AKAP1*	1.69	0.087	0.084	0.004	8.2E-01	0.764	0.769	-0.005	8.6E-01	0.929	0.926	0.003	7.9E-01
cg11376147	*SLC43A1*	0.68	0.304	0.301	0.003	8.2E-01	0.246	0.245	0.001	9.3E-01	0.164	0.165	0.000	9.0E-01
cg04816311	***C7orf50***	**1.51**	**0.360**	**0.333**	**0.026**	**2.6E-02**	0.328	0.333	-0.005	8.6E-01	0.940	0.941	-0.001	7.9E-01
cg08309687	***NA***	**0.68**	**0.657**	**0.689**	**-0.032**	**4.0E-03**	0.634	0.657	-0.022	1.1E-01	0.069	0.067	0.002	7.9E-01
cg13514042	*NA*	1.42	0.814	0.813	0.001	8.7E-01	0.854	0.850	0.004	8.6E-01	0.912	0.910	0.002	7.9E-01
cg08994060	***PFKFB3***	**0.65**	**0.090**	**0.105**	**-0.015**	**2.0E-02**	**0.334**	**0.377**	**-0.043**	**1.2E-05**	**0.576**	**0.594**	**-0.018**	**4.7E-02**
cg01676795	*POR*	1.56	0.901	0.900	0.001	8.7E-01	0.960	0.963	-0.002	8.6E-01	0.982	0.980	0.002	3.5E-01
cg25130381	*SLC9A1*	1.49	0.676	0.665	0.011	3.0E-01	0.819	0.817	0.002	8.7E-01	0.436	0.428	0.008	5.1E-01
cg11183227	*MAN2A2*	1.49	0.981	0.981	-0.001	8.2E-01	0.976	0.975	0.001	8.6E-01	0.983	0.982	0.002	3.5E-01

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Supplementary Table S7. Spearman correlations in DNA methylation intensity between whole blood and liver, pancreas, adipose tissue or muscle at the top 18 T2DM-associated MVPs.

Liver and Pancreas samples are from 6 cadaveric samples; Spearman Rho values >=0.5 are highlighted in bold
Fat and muscle samples are from 14 and 16 twin pairs, respectively; correlations at P<0.05 are highlighted in bold

BLOOD (T2DM EPIC-Norfolk)			**LIVER**		**PANCREAS**		**FAT**		**MUSCLE**	
CpG ID	**Chr**	**Gene**	**Rho**	***P-value***	**Rho**	***P-value***	**Rho**	***P-value***	**Rho**	***P-value***
cg19693031	1	***TXNIP***	**0.7**	0.23	**0.8**	0.33	-0.2	*0.24*	0.2	*0.25*
cg06500161	21	*ABCG1*	-0.7	0.23	0.2	0.92	0.1	*0.68*	0.0	*0.87*
cg14476101	1	***PHGDH***	**0.7**	0.23	0.2	0.92	0.2	*0.23*	-0.1	*0.78*
cg14020176	17	***SLC9A3R1***	**0.7**	0.23	**0.8**	0.33	**0.4**	***0.05***	0.0	*0.81*
cg11024682	17	***SREBF1***	0.4	0.52	0.0	1.00	**0.5**	***0.01***	0.0	*0.79*
cg06397161	22	***SYNGR1***	0.3	0.68	0.0	1.00	**0.5**	***0.01***	0.2	*0.18*
cg00574958	11	***CPT1A***	**0.5**	0.45	-0.4	0.75	**0.5**	***0.01***	-0.2	*0.21*
cg06235429	11	*NDUFV1*	-0.8	0.13	0.4	0.75	0.3	*0.08*	0.0	*0.85*
cg05778424	17	*AKAP1*	-0.5	0.45	-0.8	0.33	0.2	*0.20*	0.0	*0.95*
cg11376147	11	***SLC43A1***	**0.7**	0.23	0.4	0.75	0.2	*0.40*	-0.2	*0.20*
cg04816311	7	***C7orf50***	**0.6**	0.35	0.2	0.92	-0.1	*0.64*	0.1	*0.63*
cg02711608	19	***SLC1A5***	**1.0**	**0.02**	0.0	1.00	0.2	*0.37*	-0.1	*0.47*
cg08309687	21	***NA***	0.1	0.95	0.2	0.92	**0.7**	***0.0001***	0.0	*0.95*
cg13514042	7	*NA*	-0.5	0.45	0.2	0.92	-0.1	*0.76*	0.0	*0.95*
cg08994060	10	***PFKFB3***	0.0	1.00	-0.4	0.75	0.2	*0.24*	**0.4**	***0.03***
cg01676795	7	*POR*	-0.9	0.08	1.0	0.08	0.2	*0.43*	-0.2	*0.37*
cg25130381	1	*SLC9A1*	-0.3	0.68	0.0	1.00	0.2	*0.32*	-0.1	*0.58*
cg11183227	15	***MAN2A2***	**0.7**	0.23	**0.6**	0.42	**0.4**	***0.02***	0.1	*0.63*

SUPPLEMENTARY DATA

Supplementary Table S8. Individual methQTLs identified in the BIOS-QTL browser for 16 of the 18 T2DM-associated MVPs. Methylation quantitative trait loci (methQTLs) are SNPs with a genome-wide significant association (FDR< 5%) with any of the 18 T2DM-associated MVPs.

* aligned to increasing T2DM.

MVP and its observed association with T2DM						SNP to Methylation							
MVP	**chr**	**position**	**Gene**	**OR*$_{MVP-T2DM}$**	**CI 95%**	**SNP**	**chr**	**position**	**Type**	**A1**	**A2**	**Z-score $_{A1-to-MVP}$**	**P-value**
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs1047891	2	211540507	trans	A	C	-8.23	1.93E-16
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs715	2	211543055	trans	C	T	-8	1.20E-15
cg14020176	17	70276580	*SLC9A3R1*	1.63	[1.4-1.9]	rs7529925	1	199007208	trans	C	T	6.64	3.12E-11
cg11183227	15	89256411	*MAN2A2*	1.49	[1.29-1.72]	rs9790517	4	106084778	trans	T	C	-6.48	9.44E-11
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs2216405	2	211616894	trans	G	A	-6.44	1.20E-10
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs1544196	1	224632782	trans	A	G	-6.43	1.26E-10
cg08309687	21	34242466		1.46	[1.28-1.68]	rs6763931	3	141102833	trans	A	G	5.7	1.23E-08
cg08309687	21	34242466		1.46	[1.28-1.68]	rs1991431	3	141133450	trans	A	G	5.69	1.25E-08
cg08309687	21	34242466		1.46	[1.28-1.68]	rs724016	3	141105570	trans	G	A	5.69	1.25E-08
cg08309687	21	34242466		1.46	[1.28-1.68]	rs6440003	3	141094209	trans	A	G	5.63	1.84E-08
cg00574958	11	68364198	*CPT1A*	1.45	[1.28-1.64]	rs964184	11	116648917	trans	G	C	-5.54	2.99E-08
cg08994060	10	6254032	*PFKFB3*	1.55	[1.32-1.81]	rs6763931	3	141102833	trans	A	G	5.48	4.30E-08
cg00574958	11	68364198	*CPT1A*	1.45	[1.28-1.64]	rs3741298	11	116657561	trans	C	T	-5.48	4.34E-08
cg08309687	21	34242466		1.46	[1.28-1.68]	rs9310736	3	24350811	trans	A	G	-5.48	4.36E-08
cg08994060	10	6254032	*PFKFB3*	1.55	[1.32-1.81]	rs6440003	3	141094209	trans	A	G	5.46	4.70E-08
cg08994060	10	6254032	*PFKFB3*	1.55	[1.32-1.81]	rs724016	3	141105570	trans	G	A	5.43	5.72E-08
cg02711608	19	51979804	*SLC1A5*	1.45	[1.27-1.66]	rs4948102	7	56097265	trans	C	G	-5.41	6.25E-08
cg08994060	10	6254032	*PFKFB3*	1.55	[1.32-1.81]	rs1991431	3	141133450	trans	A	G	5.29	1.23E-07
cg11024682	17	17670819	*SREBF1*	1.56	[1.35-1.79]	rs7701414	5	131585958	trans	G	A	5.21	1.94E-07
cg11024682	17	17670819	*SREBF1*	1.56	[1.35-1.79]	rs7529925	1	199007208	trans	C	T	-5.15	2.62E-07
cg11183227	15	89256411	*MAN2A2*	1.49	[1.29-1.72]	rs1544196	1	224632782	trans	A	G	-5.15	2.65E-07
cg08994060	10	6254032	*PFKFB3*	1.55	[1.32-1.81]	rs592866	10	6205922	cis	A	T	-41.2	3.27E-310
cg04816311	7	1033176	*C7orf50*	1.51	[1.31-1.75]	rs56048221	7	1092533	cis	G	A	32.6	4.80E-233
cg14476101	1	120057515	*PHGDH*	1.50	[1.32-1.7]	rs11583993	1	120255370	cis	A	G	-32.2	3.85E-228
cg01676795	7	75424284	*POR*	1.56	[1.33-1.84]	rs10954750	7	75664921	cis	C	G	-22.8	7.21E-115
cg06397161	22	38090005	*SYNGR1*	1.51	[1.32-1.73]	rs2069235	22	39747780	cis	A	G	-17.5	1.72E-68

cg08309687	21	34242466		1.46	[1.28-1.68]	rs8128167	21	35307200	cis	C	T	17.5	1.92E-68
cg13514042	7	1158728		1.42	[1.25-1.61]	rs2949204	7	1200845	cis	G	A	16.1	4.85E-58
cg06235429	11	67129690	*NDUFV1*	1.49	[1.3-1.7]	rs4244823	11	67361356	cis	A	G	-13.9	1.24E-43
cg14020176	17	70276580	*SLC9A3R1*	1.63	[1.4-1.9]	rs12601504	17	72754829	cis	C	T	13.5	2.02E-41
cg06397161	22	38090005	*SYNGR1*	1.51	[1.32-1.73]	rs1569499	22	39769818	cis	T	C	-13.4	3.50E-41
cg04816311	7	1033176	*C7orf50*	1.51	[1.31-1.75]	rs12701708	7	1090333	cis	T	C	-12.4	4.25E-35
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs2160115	17	55165612	cis	C	T	-12.1	7.15E-34
cg08309687	21	34242466		1.46	[1.28-1.68]	rs2051387	21	35364046	cis	A	T	-10.9	1.22E-27
cg13514042	7	1158728		1.42	[1.25-1.61]	rs13226093	7	1168754	cis	C	T	-10.1	8.45E-24
cg11024682	17	17670819	*SREBF1*	1.56	[1.35-1.79]	rs8070432	17	17480474	cis	C	T	8.92	4.83E-19
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs148596028	17	55210022	cis	T	C	-8.45	2.87E-17
cg14476101	1	120057515	*PHGDH*	1.50	[1.32-1.7]	rs41276626	1	120262112	cis	A	G	7.59	3.14E-14
cg01676795	7	75424284	*POR*	1.56	[1.33-1.84]	rs239950	7	75581714	cis	G	A	-6.85	7.24E-12
cg08309687	21	34242466		1.46	[1.28-1.68]	rs75586969	21	35265459	cis	T	C	-6.64	3.03E-11
cg04816311	7	1033176	*C7orf50*	1.51	[1.31-1.75]	rs7784559	7	1002973	cis	A	G	-6	1.99E-09
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs3094438	17	55188373	cis	C	G	5.92	3.13E-09
cg14476101	1	120057515	*PHGDH*	1.50	[1.32-1.7]	rs34291690	1	120099137	cis	A	G	5.34	9.22E-08
cg04816311	7	1033176	*C7orf50*	1.51	[1.31-1.75]	rs13226093	7	1168754	cis	C	T	-5.24	1.64E-07
cg11376147	11	57017774	*SLC43A1*	1.48	[1.29-1.69]	rs2511984	11	57278733	cis	T	C	-5.22	1.76E-07
cg01676795	7	75424284	*POR*	1.56	[1.33-1.84]	rs10954672	7	75481823	cis	A	G	-5.07	3.94E-07
cg01676795	7	75424284	*POR*	1.56	[1.33-1.84]	rs59882870	7	75638421	cis	A	G	-4.74	2.11E-06
cg01676795	7	75424284	*POR*	1.56	[1.33-1.84]	rs7777399	7	75618797	cis	T	C	-4.28	1.88E-05
cg05778424	17	52524507	*AKAP1*	1.69	[1.42-2.02]	rs72843415	17	55163250	cis	T	C	-4.14	3.51E-05
cg06235429	11	67129690	*NDUFV1*	1.49	[1.3-1.7]	rs12799746	11	67246630	cis	T	C	-4.1	4.06E-05
cg08994060	10	6254032	*PFKFB3*	1.55	[1.32-1.81]	rs584797	10	6220496	cis	A	G	4.06	4.98E-05
cg13514042	7	1158728		1.42	[1.25-1.61]	rs55633977	7	1122645	cis	T	C	-4.05	5.14E-05
cg01676795	7	75424284	POR	1.56	[1.33-1.84]	rs73145061	7	75353969	cis	C	G	-4.02	5.81E-05
cg25130381	1	27313308	SLC9A1	1.49	[1.29-1.73]	rs34079867	1	27407850	cis	T	C	-3.88	0.000105

Supplementary Table S9. Genetically predicted effects of methylation intensity at 16 MVPs on T2DM.

No of methQTLs: number of methQTLs used in Mendelian Randomization analysis after clumping the SNPs using the R package *TwoSampleMR*. The remaining columns are generated using the *TwoSampleMR* package in R. Beta's indicate the log-odds ratios per 1 unit increase normalised methylation intensity.

				Predicted effect			**Heterogeneity**			**Directional pleiotropy**		
MVP	**Gene**	**No. of methQTLs**	**MR model**	**b**	**se**	**P**	**Q**	**df**	**P-val**	**Egger_intercept**	**se**	**P**
cg08994060	*PFKFB3*	2	Inverse variance weighted	-0.003	0.029	0.92	0	1	1			
cg11183227	*MAN2A2*	2	Inverse variance weighted	0.026	0.038	0.50	0	1	1			
cg02711608	*SLC1A5*	1	Wald ratio	0.018	0.064	0.78						
cg08309687	-	3	MR Egger	0.001	0.085	0.99	6.62	1	0.01	-0.01	0.02	0.68
cg08309687	-	3	Inverse variance weighted	-0.039	0.034	0.25	4.32	2	0.12			
cg14020176	*SLC9A3R1*	2	Inverse variance weighted	-0.027	0.022	0.22	0	1	1			
cg06397161	*SYNGR1*	1	Wald ratio	0.017	0.020	0.40						
cg00574958	*CPT1A*	1	Wald ratio	-0.142	0.056	0.01						
cg11376147	*SLC43A1*	1	Wald ratio	-0.028	0.067	0.68						
cg25130381	*SLC9A1*	1	Wald ratio	-0.150	0.091	0.10						
cg11024682	*SREBF1*	3	MR Egger	0.058	0.054	0.48	0.20	1	0.65	-0.01	0.01	0.45
cg11024682	*SREBF1*	3	Inverse variance weighted	0.004	0.028	0.88	0.77	2	0.68			
cg05778424	*AKAP1*	3	MR Egger	0.022	0.108	0.87	0.04	1	0.85	-0.01	0.03	0.86
cg05778424	*AKAP1*	3	Inverse variance weighted	-0.002	0.019	0.94	0.04	2	0.98			
cg14476101	*PHGDH*	2	Inverse variance weighted	-0.005	0.010	0.65	0	1	1			
cg04816311	*C7orf50*	2	Inverse variance weighted	-0.010	0.011	0.39	0	1	1			
cg01676795	*POR*	4	MR Egger	-0.013	0.041	0.79	6.18	2	0.05	0.00	0.01	0.89
cg01676795	*POR*	4	Inverse variance weighted	-0.007	0.021	0.73	4.17	3	0.24			
cg06235429	*NDUFV1*	1	Wald ratio	0.017	0.025	0.50						
cg13514042	-	1	Wald ratio	-0.011	0.021	0.59						

Supplementary Table S10. Mendelian Randomisation tests for determinants of the 18 T2DM-associated MVPs.

Results for the MR associations for the inverse-variance weighted and MR-Egger methods using 2 hour glucose (Saxena *et al*., 2010), BMI (Locke *et al*., 2015), fasting glucose (Manning *et al*., 2012), fasting insulin (Scott *et al*., 2012), fasting insulin adjusted for BMI (Manning *et al*., 2012), insulin secretion (Prokopenko *et al*., 2014), insulin resistance (Lotta *et al*., 2016), T2DM status (Morris *et al*., 2012) and waist hip ratio (Shungin *et al*., 2015) associated SNPs instrument variables.

Potential Determinant	**MVP**	**IVW MR**			**Heterogenity**		**Egger MR**					
		Beta	**SE**	**p-value**	**Coch Q**	**Coch Q p-value**	**Beta**	**SE**	**p-value**	**intercept**	**SE intercept**	**p-value intercept**
2 hour glucose	cg00574958	0.06	0.28	0.82	72.31	2.37E-05	-0.33	0.51	0.52	0.01	0.01	0.35
2 hour glucose	cg01676795	0.15	0.27	0.58	58.10	1.56E-03	-0.42	0.49	0.39	0.02	0.01	0.09
2 hour glucose	cg02711608	0.22	0.20	0.26	5.44	0.71	0.37	0.81	0.65	-0.01	0.06	0.85
2 hour glucose	cg04816311	-0.06	0.20	0.76	5.65	0.69	0.69	0.77	0.37	-0.06	0.06	0.31
2 hour glucose	cg05778424	0.26	0.18	0.15	4.55	0.80	-0.15	0.70	0.83	0.03	0.06	0.55
2 hour glucose	cg06235429	-0.10	0.18	0.57	3.08	0.93	-0.56	0.67	0.40	0.04	0.05	0.44
2 hour glucose	cg06397161	0.31	0.20	0.12	5.25	0.73	0.95	0.77	0.22	-0.05	0.06	0.39
2 hour glucose	cg06500161	0.02	0.20	0.90	5.39	0.72	0.68	0.78	0.39	-0.05	0.06	0.39
2 hour glucose	cg08309687	-0.35	0.19	0.06	4.45	0.81	-0.18	0.76	0.81	-0.01	0.06	0.82
2 hour glucose	cg08994060	0.14	0.18	0.42	3.48	0.90	0.69	0.67	0.30	-0.05	0.05	0.36
2 hour glucose	cg11024682	-0.17	0.18	0.34	2.88	0.94	-0.76	0.67	0.26	0.05	0.04	0.25
2 hour glucose	cg11183227	-0.04	0.18	0.80	3.02	0.93	0.48	0.67	0.48	-0.04	0.04	0.31
2 hour glucose	cg11376147	-0.20	0.28	0.48	10.85	0.21	-0.73	1.14	0.52	0.04	0.09	0.63
2 hour glucose	cg13514042	0.43	0.18	0.01	1.98	0.98	-0.03	0.67	0.96	0.04	0.04	0.30
2 hour glucose	cg14020176	0.36	0.23	0.12	8.81	0.36	0.38	0.96	0.69	0.00	0.08	0.98
2 hour glucose	cg14476101	-0.05	0.17	0.78	3.44	0.90	-0.51	0.67	0.44	0.04	0.05	0.46
2 hour glucose	cg19693031	-0.31	0.20	0.12	6.26	0.62	-1.37	0.71	0.05	0.09	0.06	0.12
2 hour glucose	cg25130381	0.17	0.18	0.33	2.45	0.96	0.69	0.68	0.31	-0.04	0.04	0.27
BMI	cg00574958	-0.14	0.17	0.44	176.24	5.1E-08	-0.80	0.42	0.06	0.02	0.01	0.08
BMI	cg01676795	-0.18	0.17	0.29	161.10	2.4E-06	-0.04	0.40	0.91	0.00	0.01	0.71
BMI	cg02711608	-0.12	0.17	0.46	161.70	2.1E-06	-0.25	0.41	0.53	0.00	0.01	0.73
BMI	cg04816311	-0.19	0.17	0.27	173.55	1.0E-07	-0.43	0.42	0.31	0.01	0.01	0.54
BMI	cg05778424	-0.19	0.18	0.29	184.66	5.3E-09	-0.29	0.43	0.50	0.00	0.01	0.79
BMI	cg06235429	-0.02	0.17	0.90	157.40	5.8E-06	-0.53	0.41	0.19	0.01	0.01	0.15
BMI	cg06397161	0.06	0.17	0.71	155.59	8.8E-06	-0.14	0.41	0.72	0.01	0.01	0.57

BMI	cg06500161	-0.15	0.18	0.42	200.01	6.9E-11	-0.05	0.44	0.91	0.00	0.01	0.81
BMI	cg08309687	0.03	0.17	0.87	180.81	1.5E-08	-0.37	0.42	0.38	0.01	0.01	0.30
BMI	cg08994060	0.12	0.19	0.52	200.93	5.3E-11	0.69	0.45	0.12	-0.02	0.01	0.16
BMI	cg11024682	-0.05	0.17	0.76	147.76	5.2E-05	0.06	0.41	0.88	0.00	0.01	0.75
BMI	cg11183227	-0.12	0.17	0.48	152.55	1.8E-05	-0.02	0.41	0.96	0.00	0.01	0.78
BMI	cg11376147	-0.03	0.17	0.86	175.42	6.4E-08	-0.39	0.42	0.34	0.01	0.01	0.34
BMI	cg13514042	-0.38	0.17	0.02	156.25	7.6E-06	-0.93	0.41	0.02	0.02	0.01	0.12
BMI	cg14020176	-0.30	0.18	0.08	178.84	2.6E-08	-0.83	0.42	0.05	0.02	0.01	0.17
BMI	cg14476101	-0.10	0.17	0.54	145.63	8.4E-05	-0.33	0.40	0.41	0.01	0.01	0.52
BMI	cg19693031	0.29	0.17	0.08	137.76	4.3E-04	0.19	0.40	0.64	0.00	0.01	0.77
BMI	cg25130381	0.13	0.17	0.44	165.30	8.5E-07	0.62	0.41	0.13	-0.01	0.01	0.19
Fasting glucose	cg00574958	0.06	0.28	0.82	72.31	2.4E-05	-0.33	0.51	0.52	0.01	0.01	0.35
Fasting glucose	cg01676795	0.15	0.27	0.58	58.10	1.6E-03	-0.42	0.49	0.39	0.02	0.01	0.09
Fasting glucose	cg02711608	0.13	0.27	0.64	59.01	1.2E-03	0.15	0.49	0.76	0.00	0.01	0.96
Fasting glucose	cg04816311	0.31	0.27	0.26	59.63	1.0E-03	0.31	0.50	0.54	0.00	0.01	0.99
Fasting glucose	cg05778424	0.19	0.34	0.57	89.54	7.7E-08	1.22	0.57	0.03	-0.03	0.02	0.03
Fasting glucose	cg06235429	-0.15	0.27	0.59	57.27	1.9E-03	-0.18	0.49	0.71	0.00	0.01	0.92
Fasting glucose	cg06397161	0.12	0.29	0.68	71.23	3.3E-05	0.26	0.54	0.62	0.00	0.01	0.75
Fasting glucose	cg06500161	0.17	0.27	0.52	60.28	8.5E-04	-0.38	0.49	0.44	0.02	0.01	0.14
Fasting glucose	cg08309687	-0.15	0.27	0.59	68.39	8.0E-05	-0.31	0.49	0.52	0.01	0.01	0.67
Fasting glucose	cg08994060	0.50	0.31	0.11	106.42	1.8E-10	0.29	0.57	0.61	0.01	0.02	0.65
Fasting glucose	cg11024682	0.05	0.27	0.86	59.01	1.2E-03	0.21	0.49	0.68	-0.01	0.01	0.69
Fasting glucose	cg11183227	-0.04	0.28	0.89	74.19	1.3E-05	-0.41	0.49	0.41	0.01	0.01	0.37
Fasting glucose	cg11376147	0.17	0.32	0.60	89.35	8.2E-08	0.17	0.58	0.77	0.00	0.02	1.00
Fasting glucose	cg13514042	0.08	0.31	0.79	78.59	3.1E-06	-0.09	0.56	0.87	0.01	0.02	0.70
Fasting glucose	cg14020176	0.07	0.27	0.81	72.23	2.4E-05	-0.15	0.50	0.77	0.01	0.01	0.61
Fasting glucose	cg14476101	0.06	0.28	0.82	72.52	2.2E-05	-0.02	0.51	0.97	0.00	0.01	0.85
Fasting glucose	cg19693031	0.09	0.27	0.73	62.25	4.9E-04	-0.93	0.49	0.06	0.03	0.01	3.9E-03
Fasting glucose	cg25130381	0.19	0.31	0.54	103.78	4.7E-10	-0.15	0.56	0.79	0.01	0.02	0.46
Fasting insulin (adj BMI)	cg00574958	0.25	0.68	0.71	32.92	4.8E-03	-3.13	2.94	0.29	0.05	0.04	0.17
Fasting insulin (adj BMI)	cg01676795	0.54	0.77	0.49	57.78	6.0E-07	8.83	2.94	0.00	-0.13	0.04	1.0E-03
Fasting insulin (adj BMI)	cg02711608	-0.31	0.79	0.69	59.60	3.0E-07	-1.68	3.52	0.63	0.02	0.05	0.69
Fasting insulin (adj BMI)	cg04816311	-0.56	0.81	0.49	69.28	6.0E-09	2.37	3.56	0.51	-0.04	0.05	0.40

Fasting insulin (adj BMI)	cg05778424	0.19	0.68	0.78	29.63	1.3E-02	1.38	2.95	0.64	-0.02	0.04	0.62
Fasting insulin (adj BMI)	cg06235429	-1.01	0.70	0.15	47.01	3.7E-05	0.06	3.13	0.98	-0.02	0.05	0.72
Fasting insulin (adj BMI)	cg06397161	0.68	0.68	0.32	44.07	1.1E-04	0.02	3.01	0.99	0.01	0.04	0.82
Fasting insulin (adj BMI)	cg06500161	-0.38	0.68	0.58	24.40	0.06	0.89	2.95	0.76	-0.02	0.03	0.56
Fasting insulin (adj BMI)	cg08309687	-0.61	0.83	0.46	69.62	5.2E-09	3.63	3.56	0.31	-0.06	0.05	0.22
Fasting insulin (adj BMI)	cg08994060	-0.54	0.68	0.42	44.25	1.0E-04	-2.13	2.94	0.47	0.02	0.04	0.58
Fasting insulin (adj BMI)	cg11024682	-0.02	0.68	0.97	12.04	0.68	-1.30	2.95	0.66	0.02	0.02	0.41
Fasting insulin (adj BMI)	cg11183227	0.06	0.72	0.93	48.31	2.3E-05	5.90	2.95	0.05	-0.09	0.04	0.03
Fasting insulin (adj BMI)	cg11376147	0.45	0.68	0.50	40.16	4.3E-04	-0.04	2.95	0.99	0.01	0.04	0.86
Fasting insulin (adj BMI)	cg13514042	0.04	0.92	0.96	78.15	1.5E-10	-9.01	3.27	0.01	0.14	0.05	4.5E-03
Fasting insulin (adj BMI)	cg14020176	-0.11	0.91	0.90	73.26	1.2E-09	2.14	4.04	0.60	-0.03	0.06	0.57
Fasting insulin (adj BMI)	cg14476101	0.18	0.68	0.80	31.53	0.01	-0.64	2.94	0.83	0.01	0.04	0.75
Fasting insulin (adj BMI)	cg19693031	-1.75	0.82	0.03	64.11	4.9E-08	-0.42	3.68	0.91	-0.02	0.05	0.71
Fasting insulin (adj BMI)	cg25130381	0.45	0.68	0.51	25.93	0.04	1.69	2.95	0.57	-0.02	0.03	0.58
Insulin secretion	cg00574958	-0.27	0.18	0.13	15.65	0.55	-0.60	0.47	0.20	0.02	0.03	0.45
Insulin secretion	cg01676795	0.10	0.16	0.52	7.56	0.98	0.00	0.42	0.99	0.01	0.02	0.70
Insulin secretion	cg02711608	-0.05	0.19	0.81	19.98	0.28	0.02	0.52	0.97	0.00	0.03	0.89
Insulin secretion	cg04816311	0.17	0.17	0.31	16.88	0.46	0.61	0.45	0.18	-0.03	0.03	0.30
Insulin secretion	cg05778424	-0.05	0.19	0.80	16.72	0.47	-0.03	0.51	0.95	0.00	0.03	0.98
Insulin secretion	cg06235429	0.22	0.16	0.17	18.89	0.33	1.14	0.42	0.01	-0.06	0.02	4.6E-04
Insulin secretion	cg06397161	-0.13	0.20	0.52	29.53	0.03	0.14	0.54	0.80	-0.02	0.03	0.59
Insulin secretion	cg06500161	0.05	0.16	0.78	14.19	0.65	-0.31	0.43	0.47	0.02	0.03	0.37
Insulin secretion	cg08309687	0.02	0.16	0.91	10.09	0.90	0.11	0.42	0.80	-0.01	0.02	0.79
Insulin secretion	cg08994060	-0.38	0.21	0.07	26.33	0.07	-0.29	0.55	0.59	-0.01	0.03	0.87
Insulin secretion	cg11024682	0.31	0.16	0.06	27.82	0.05	0.75	0.43	0.08	-0.03	0.03	0.26
Insulin secretion	cg11183227	0.14	0.16	0.38	12.52	0.77	-0.08	0.42	0.85	0.01	0.03	0.56
Insulin secretion	cg11376147	0.00	0.21	1.00	27.54	0.05	-1.02	0.50	0.04	0.07	0.03	0.03
Insulin secretion	cg13514042	0.09	0.20	0.64	21.36	0.21	-0.44	0.53	0.41	0.04	0.03	0.28
Insulin secretion	cg14020176	-0.13	0.17	0.45	20.05	0.27	0.60	0.42	0.15	-0.05	0.03	0.06
Insulin secretion	cg14476101	0.05	0.16	0.76	8.58	0.95	-0.32	0.42	0.45	0.02	0.02	0.15
Insulin secretion	cg19693031	-0.03	0.16	0.87	18.43	0.36	1.00	0.42	0.02	-0.07	0.02	9.6E-04
Insulin secretion	cg25130381	0.09	0.16	0.58	9.34	0.93	0.44	0.42	0.29	-0.02	0.02	0.27
Insulin resistance	cg00574958	-0.91	0.62	0.14	238.85	1.3E-28	0.98	1.91	0.61	-0.02	0.02	0.30

Insulin resistance	cg01676795	0.26	0.61	0.66	210.47	1.4E-23	1.37	1.89	0.47	-0.01	0.02	0.54
Insulin resistance	cg02711608	-0.58	0.69	0.40	272.93	8.6E-35	-1.14	2.16	0.60	0.01	0.02	0.78
Insulin resistance	cg04816311	0.39	0.61	0.52	214.72	2.6E-24	-0.05	1.92	0.98	0.00	0.02	0.81
Insulin resistance	cg05778424	0.52	0.59	0.38	159.10	6.1E-15	-0.15	1.83	0.93	0.01	0.02	0.66
Insulin resistance	cg06235429	-0.22	0.63	0.73	228.51	9.4E-27	-0.37	1.97	0.85	0.00	0.02	0.93
Insulin resistance	cg06397161	0.90	0.70	0.20	311.31	6.2E-42	2.57	2.18	0.24	-0.02	0.02	0.42
Insulin resistance	cg06500161	0.44	0.59	0.46	200.51	7.5E-22	1.14	1.83	0.53	-0.01	0.02	0.68
Insulin resistance	cg08309687	-0.30	0.61	0.63	210.36	1.5E-23	0.26	1.91	0.89	-0.01	0.02	0.76
Insulin resistance	cg08994060	-0.15	0.59	0.80	125.65	8.7E-10	-0.74	1.83	0.69	0.01	0.02	0.68
Insulin resistance	cg11024682	0.99	0.59	0.09	206.64	6.6E-23	1.37	1.83	0.45	0.00	0.02	0.82
Insulin resistance	cg11183227	-0.01	0.59	0.98	180.48	1.9E-18	-1.12	1.83	0.54	0.01	0.02	0.49
Insulin resistance	cg11376147	-0.28	0.59	0.64	205.12	1.2E-22	2.35	1.82	0.20	-0.03	0.02	0.13
Insulin resistance	cg13514042	0.52	0.65	0.43	236.40	3.7E-28	-1.72	2.01	0.39	0.02	0.02	0.24
Insulin resistance	cg14020176	0.15	0.71	0.83	294.11	1.0E-38	0.28	2.23	0.90	0.00	0.02	0.95
Insulin resistance	cg14476101	-0.24	0.59	0.69	178.26	4.5E-18	0.69	1.82	0.71	-0.01	0.02	0.57
Insulin resistance	cg19693031	-1.33	0.73	0.07	304.97	9.5E-41	-2.42	2.28	0.29	0.01	0.02	0.61
Insulin resistance	cg25130381	1.41	0.59	0.02	189.18	6.5E-20	1.25	1.83	0.50	0.00	0.02	0.92
Type 2 diabetes	cg00574958	-0.04	0.06	0.56	22.03	1.00	-0.07	0.15	0.66	0.00	0.01	0.83
Type 2 diabetes	cg01676795	0.10	0.06	0.11	22.89	0.99	0.01	0.15	0.94	0.01	0.02	0.50
Type 2 diabetes	cg02711608	0.07	0.07	0.35	25.51	0.98	0.01	0.17	0.95	0.01	0.02	0.70
Type 2 diabetes	cg04816311	0.03	0.06	0.59	21.60	1.00	0.01	0.15	0.95	0.00	0.01	0.84
Type 2 diabetes	cg05778424	0.08	0.06	0.17	17.59	1.00	0.05	0.14	0.71	0.00	0.01	0.77
Type 2 diabetes	cg06235429	0.01	0.06	0.83	22.21	0.99	0.05	0.14	0.73	0.00	0.01	0.77
Type 2 diabetes	cg06397161	-0.03	0.06	0.69	24.58	0.99	-0.06	0.15	0.67	0.00	0.01	0.78
Type 2 diabetes	cg06500161	0.06	0.06	0.34	20.50	1.00	0.19	0.14	0.17	-0.02	0.01	0.28
Type 2 diabetes	cg08309687	-0.08	0.06	0.18	18.68	1.00	-0.22	0.14	0.12	0.02	0.01	0.26
Type 2 diabetes	cg08994060	0.08	0.07	0.25	27.00	0.96	0.30	0.16	0.06	-0.02	0.02	0.13
Type 2 diabetes	cg11024682	0.00	0.07	0.95	27.30	0.96	0.05	0.15	0.72	-0.01	0.02	0.67
Type 2 diabetes	cg11183227	0.01	0.06	0.92	19.87	1.00	0.07	0.14	0.62	-0.01	0.01	0.60
Type 2 diabetes	cg11376147	-0.03	0.08	0.66	30.77	0.90	-0.03	0.18	0.86	0.00	0.02	0.98
Type 2 diabetes	cg13514042	-0.07	0.08	0.38	33.15	0.83	-0.01	0.18	0.95	-0.01	0.02	0.72
Type 2 diabetes	cg14020176	0.11	0.06	0.08	23.23	0.99	0.32	0.14	0.03	-0.02	0.01	0.11
Type 2 diabetes	cg14476101	-0.03	0.06	0.61	18.91	1.00	0.19	0.14	0.18	-0.02	0.01	0.06

Type 2 diabetes	cg19693031	-0.08	0.07	0.28	26.34	0.97	-0.02	0.16	0.91	-0.01	0.02	0.69
Type 2 diabetes	cg25130381	0.01	0.06	0.91	16.17	1.00	0.13	0.14	0.37	-0.01	0.01	0.27
WHR (adj. BMI)	cg00574958	-0.07	0.26	0.78	67.13	1.8E-03	-1.28	1.31	0.33	0.03	0.04	0.34
WHR (adj. BMI)	cg01676795	0.02	0.26	0.93	65.34	2.8E-03	1.14	1.31	0.38	-0.03	0.04	0.38
WHR (adj. BMI)	cg02711608	-0.01	0.28	0.98	70.11	8.2E-04	-1.28	1.39	0.35	0.04	0.04	0.35
WHR (adj. BMI)	cg04816311	-0.25	0.25	0.31	61.98	0.01	1.29	1.22	0.29	-0.04	0.03	0.20
WHR (adj. BMI)	cg05778424	0.00	0.24	0.99	49.18	0.09	-0.02	1.20	0.99	0.00	0.03	0.99
WHR (adj. BMI)	cg06235429	0.15	0.24	0.53	38.27	0.41	-1.38	1.21	0.25	0.04	0.03	0.10
WHR (adj. BMI)	cg06397161	0.09	0.24	0.70	59.73	0.01	-0.40	1.20	0.74	0.01	0.03	0.68
WHR (adj. BMI)	cg06500161	0.09	0.24	0.70	56.91	0.02	-1.06	1.20	0.38	0.03	0.03	0.31
WHR (adj. BMI)	cg08309687	-0.08	0.25	0.73	59.58	0.01	0.19	1.25	0.88	-0.01	0.03	0.82
WHR (adj. BMI)	cg08994060	0.15	0.25	0.55	61.49	0.01	-1.44	1.22	0.24	0.04	0.03	0.19
WHR (adj. BMI)	cg11024682	0.13	0.24	0.60	57.59	0.02	1.39	1.20	0.25	-0.04	0.03	0.28
WHR (adj. BMI)	cg11183227	-0.09	0.28	0.76	78.04	9.3E-05	-0.05	1.44	0.97	0.00	0.04	0.98
WHR (adj. BMI)	cg11376147	0.16	0.24	0.51	53.07	0.04	-1.70	1.20	0.16	0.05	0.03	0.09
WHR (adj. BMI)	cg13514042	-0.17	0.24	0.48	52.92	0.04	0.82	1.20	0.50	-0.03	0.03	0.40
WHR (adj. BMI)	cg14020176	-0.12	0.24	0.62	52.57	0.05	1.47	1.21	0.22	-0.04	0.03	0.16
WHR (adj. BMI)	cg14476101	0.10	0.24	0.68	37.83	0.43	0.29	1.20	0.81	-0.01	0.03	0.84
WHR (adj. BMI)	cg19693031	-0.28	0.24	0.24	57.56	0.02	-2.27	1.20	0.06	0.06	0.03	0.08
WHR (adj. BMI)	cg25130381	0.35	0.24	0.15	45.72	0.15	0.65	1.21	0.59	-0.01	0.03	0.77

SUPPLEMENTARY DATA

Supplementary Table S11. Gene annotations for the top 18 T2DM-associated MVPs.

MVP (CpG ID)	Chr	Position	P-value	Gene	Gene position	Full gene name	Gene function	Associated disorders
cg19693031	1	144152909	2.7E-21	*TXNIP*	3'UTR	thioredoxin interacting protein	The encoded protein inhibits the antioxidative function of thioredoxin resulting in the accumulation of reactive oxygen species and cellular stress. This protein also regulates cellular metabolism and endoplasmic reticulum (ER) stress, and may also function as a tumor suppressor.	
cg06500161	21	42529656	6.4E-14	*ABCG1*	Body	ATP-binding cassette, sub-family G (WHITE), member 1	The encoded protein is a member of the White subfamily of ATP-binding cassette (ABC) transporters, and is involved in macrophage cholesterol and phospholipids transport, and may regulate cellular lipid homeostasis in other cell types.	**Tangier disease**: Characterized by low levels of high-density lipoprotein cholesterol (HDL) in the blood and accordingly with moderately increased risk of cardiovascular disease. **Autosomal Recessive Nonsyndromic Deafness**
cg14476101	1	120057515	2.8E-10	*PHGDH*	Body	phosphoglycerate dehydrogenase	The encoded enzyme is involved in the early steps of L-serine synthesis in animal cells. L-serine is required for D-serine and other amino acid synthesis.	**Neu-Laxova Syndrome 1**: An autosomal recessive lethal multiple malformation syndrome. **Phosphoglycerate Dehydrogenase Deficiency**: characterized by microcephaly; impaired development of physical reactions, movements, and speech (psychomotor retardation); and recurrent seizures (epilepsy).
cg14020176	17	70276580	3.3E-10	*SLC9A3R1*	3'UTR	solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 1	Encodes a sodium/hydrogen exchanger regulatory cofactor, which regulates: the cystic fibrosis transmembrane conductance regulator, and G-protein coupled receptors such as the beta2-adrenergic receptor and the parathyroid hormone 1 receptor. Interacts with proteins that function as linkers between integral membrane and cytoskeletal proteins.	**Nephrolithiasis/osteoporosis, hypophosphatemic, 2**: Characterized by decreased renal phosphate absorption, renal phosphate wasting, hypophosphatemia, hyperphosphaturia, hypercalciuria, nephrolithiasis and osteoporosis.
cg11024682	17	17670819	6.0E-10	*SREBF1*	Body	sterol regulatory element binding transcription factor 1 [alias: sterol regulatory element binding protein 1; SREBP1	Encodes a transcription factor that binds to the sterol regulatory element-1 (SRE1), which is a decamer flanking the low density lipoprotein receptor gene and some genes involved in sterol biosynthesis. SREBP1 and SREBP2 (600481) are structurally related proteins that control cholesterol homeostasis by stimulating transcription of sterol-regulated genes.	This gene is located within the Smith-Magenis syndrome region (a developmental disorder characterised by intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems).
cg06397161	22	38090005	4.5E-09	*SYNGR1*	Body;TSS200	synaptogyrin 1	Encodes an integral membrane protein associated with presynaptic vesicles in neuronal cells. The exact function is unclear, but may function in synaptic plasticity.	

cg00574958	11	68364198	5.2E-09	*CPT1A*	5'UTR	carnitine palmitoyltransferase 1A (liver)	Initiates mitochondrial oxidation of long-chain fatty acids. CPT I is the key enzyme in the carnitine-dependent transport across the mitochondrial inner membrane. Its deficiency results in a decreased rate of fatty acid beta-oxidation.	**CPT deficiency, hepatic, type IA**: An autosomal recessive metabolic disorder of long-chain fatty acid oxidation characterized by severe episodes of hypoketotic hypoglycemia usually occurring after fasting or illness.
cg06235429	11	67129690	5.5E-09	*NDUFV1*	TSS1500	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa	Encodes a subunit of mitochondrial NADH:ubiquinone oxidoreductase complex I; a large complex that liberates electrons from NADH and channels them to ubiquinone. This subunit carries the NADH-binding site as well as flavin mononucleotide (FMN)- and Fe-S-biding sites.	**Mitochondrial Complex I Deficiency**: The most common enzymatic defect of the oxidative phosphorylation disorders. It causes a wide range of clinical disorders, including myopathies, encephalomyopathies, and neurodegenerative disorders.
cg05778424	17	52524507	7.4E-09	*AKAP1*	5'UTR	A kinase (PRKA) anchor protein 1	The encoded protein binds to type I and type II regulatory subunits of protein kinase A (PKA) and anchors them to the mitochondrion. This protein is speculated to be involved in the cAMP-dependent signal transduction pathway.	
cg11376147	11	57017774	1.3E-08	*SLC43A1*	Body	solute carrier family 43, member 1	Member of the system L family of plasma membrane carrier proteins that transports large neutral amino acids	
cg04816311	7	1033176	1.7E-08	*C7orf50*	Body	chromosome 7 open reading frame 50 (194 aa)		
cg02711608	19	51979804	4.5E-08	*SLC1A5*	1stExon;5'UTR;Body	solute carrier family 1 (neutral amino acid transporter), member 5 (541 aa)	Encodes a sodium-dependent neutral amino acid transporter that can act as a receptor for RD114/type D retrovirus	
cg08309687	21	34242466	4.5E-08	-	-			
cg13514042	7	1158728	4.5E-08	-	-			
cg08994060	10	6254032	5.2E-08	*PFKFB3*	Body	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	The encoded protein catalyses the synthesis and degradation of fructose-2,6-bisphosphate, a regulatory molecule that controls glycolysis in eukaryotes. It regulates cyclin-dependent kinase 1, linking glucose metabolism to cell proliferation and survival in tumor cells.	

cg01676795	7	75424284	6.5E-08	*POR*	Body	P450 (cytochrome) oxidoreductase	Encodes an endoplasmic reticulum membrane oxidoreductase with an FAD-binding domain and a flavodoxin-like domain. The protein binds two cofactors, FAD and FMN, which allow it to donate electrons directly from NADPH to all microsomal P450 enzymes.	**Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis**: a rare craniosynostosis syndrome characterized by radiohumeral synostosis. Other features include midface hypoplasia, choanal stenosis or atresia, multiple joint contractures, visceral anomalies (genitourinary system), and impaired steroidogenesis (specific to POR mutations). **Disordered steroidogenesis due to cytochrome P450 oxidoreductase**: A rare variant of congenital adrenal hyperplasia, due to apparent combined deficiency of P450C17 and P450C21 and accumulation of steroid metabolites. Affected girls are born with ambiguous genitalia, indicating intrauterine androgen excess. After birth, however, virilization does not progress and amounts of circulating androgens are low or normal. Affected boys are sometimes born undermasculinized.
cg25130381	1	27313308	6.7E-08	*SLC9A1*	Body	solute carrier family 9, subfamily A (NHE1, cation proton antiporter 1), member 1	Encodes a Na+/H+ antiporter, a plasma membrane transporter that is expressed in the kidney and intestine. Regulates pH homeostasis, cell migration and cell volume.	**Lichtenstein-Knorr syndrome**: An autosomal recessive neurologic disorder characterized by postnatal onset of severe progressive sensorineural hearing loss and progressive cerebellar ataxia. **Myocardial Stunning**: A state when some section of the myocardium (corresponding to area of a major coronary occlusion) shows a form of contractile abnormality.
cg11183227	15	89256411	7.0E-08	*MAN2A2*	Body	mannosidase, alpha, class 2A, member 2	The encoded protein catalyzes the first committed step in the biosynthesis of complex N-glycans. It controls conversion of high mannose to complex N-glycans; the final hydrolytic step in the N-glycan maturation pathway.	