Research Paper

Identification of novel functional CpG-SNPs associated with Type 2 diabetes and birth weight

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ABSTRACT

Genome-wide association studies (GWASs) have identified hundreds of genetic loci for type 2 diabetes (T2D) and birth weight (BW); however, a large proportion of the total trait heritability remains unexplained. The previous studies were generally focused on individual traits and largely failed to identify the majority of the variants that play key functional roles in the etiology of the disease. Here, we aim to identify novel functional loci for T2D, BW and the pleiotropic variants shared between them by performing a targeted conditional false discovery rate (cFDR) analysis that integrates two independent GWASs with summary statistics for T2D (*n* = 26,676 cases and 132,532 controls) and BW (*n* = 153,781) which entails greater statistical power than individual trait analyses. In this analysis, we considered CpG-SNPs, which are SNPs that may influence DNA methylation status, and are therefore considered to be functionally important. We identified 103 novel CpG-SNPs for T2D, 182 novel CpG-SNPs for BW (cFDR < 0.05), and 52 novel pleiotropic loci for both (conjunction cFDR [ccFDR] < 0.05). Among the identified novel CpG-SNPs, 33 were annotated as methylation quantitative trait loci (meQTLs) in whole blood, and 145 displayed at least some effects on meQTL, metabolic QTL (metaQTL), and/or expression QTL (eQTL). These findings may provide further insights into the shared biological mechanisms and functional genetic determinants that overlap between T2D and BW, thereby providing novel potential targets for treatment/intervention development.

INTRODUCTION

Type 2 diabetes (T2D) is a common chronic metabolic disorder characterized by hyperglycemia, insulin resistance, and impaired insulin secretion [1] It is estimated that in 2017 there were 451 million people suffering from diabetes worldwide [2] 90% of which were classified as T2D [3] Due to the reduced quality of life, increased mortality, and a significant burden on the healthcare system, T2D represents a severe global public health concern. Therefore, it is imperative to gain a better understanding of the pathophysiological mechanisms

involved in the onset of T2D for the enhanced development of intervention/treatment strategies.

Birth weight (BW) is a clinical indicator of a variety of metabolic conditions that manifest with age. Studies have demonstrated that low BW is associated with the increased risk of developing T2D [4, 5]. The concept of "developmental programming" holds that events occurring during the early development of an individual and specifically during intrauterine life have profound consequences on future disease such as diabetes [6, 7]. Both T2D and BW are believed to be highly influenced by genetic factors with heritability estimates of over 50% and 37%, respectively [8, 9]. Additionally, the phenotypic correlation between T2D and BW suggests that these traits may share overlapping genetic determinants [10]. Several studies have also proposed the genetic correlation between BW and T2D. For instance, a Mendelian randomization study demonstrated the genetic effects on retarded fetal growth and increased diabetes risk by showing that lower birth weight was associated with increased risk of T2D and higher fasting glucose concentration [11]. Our previous study also identified several loci that associated with both T2D and BW [12]. Therefore, studying genetic relationships between BW and T2D could yield insights into the genetic regulation of T2D risk during the fetal stage.

Hundreds of single nucleotide polymorphisms (SNPs) associated with T2D or BW have been identified by genome-wide association studies (GWASs) [13, 14]. However, these SNPs can only explain a small proportion of the total heritability for T2D (~10%) [15] and BW (~25%) [16]. The large majority of the missing heritability is likely attributed to the well-documented limitations of the single-trait GWAS analysis [17]. Due to the polygenic architecture of most complex traits, many SNPs have associations too weak to be identified with the relatively small sample sizes of current GWASs [18]. Therefore, it is essential to employ statistical approaches that can increase the effective sample size by incorporating more information embedded in the existing univariate datasets. For example, by incorporating the pleiotropic effects among correlated traits, it may be possible to augment the sample sizes of standard GWAS for individual traits and identify more trait-associated loci that would otherwise be missed.

Previous studies suggest that epigenetic mechanisms, which are a crucial link between the genetic factors and environmental exposures [19], may also account for some of the missing heritability [20]. DNA methylation occurs mainly at the fifth position of the cytosine ring in CpG dinucleotides [21], and SNPs that are associated with methylation status are commonly referred to as CpG-SNPs. Although it was previously believed that methylation of the promoter region is responsible for transcriptional silencing, emerging evidence suggests that DNA methylation is closely related to the expression across all genomic regions [19]. DNA methylation is the most well-explored epigenetic mark and is also involved in T2D pathogenesis [22]. For instance, Ma *et al*. [23] identified 30 CpGs representing the whole blood DNA methylation signatures that are associated with cardiovascular disease risk factors and all-cause mortality. Our previous work also proposed that peripheral blood-derived meQTL loci were related to the increasing risk of diabetes and coronary artery disease [23, 24]. Focusing on these CpG-SNPs may be an effective strategy to improve the detection of novel potential functional variants associated with T2D and BW.

A genetic-pleiotropy-informed conditional false discovery rate (cFDR) method was developed to improve the gene discovery in complex traits by integrating two independent GWASs for related traits [25]. A major advantage of this approach is that it only requires the summary statistics rather than the individual level genotype data, which are usually not easily accessible, as well as improves statistical power for identifying novel polygenic effects [25]. Using this approach, our group has analyzed multiple sets of genetically associated traits and successfully identified many novel trait-associated loci [12, 26].

In this study, we applied a targeted cFDR analysis on CpG-SNPs for T2D and BW [13, 14] to identify novel functional loci that are shared between these two traits. Our findings will provide novel insights into the shared pathophysiology between T2D and BW.

RESULTS

Assessment of pleiotropic enrichment

We observed a clear separation between each curve in the conditional Q-Q plot, and the enrichment of effects in T2D varied on different levels of association for BW (Figure 1A and 1C). We can intuitively observe and graphically assess a strong enrichment of T2D-associated SNPs conditioning on various strengths of associations with the BW. The similar separation between the different curves and similar enrichment pattern was also observed in BW conditioned on T2D (Figure 1B and 1D). This result indicates a strong pleiotropy between T2D and BW, regardless of whether T2D is conditioned on BW or BW is conditioned on T2D.

T2D loci identified by cFDR

Conditional on association with BW, we identified 127 significant CpG-SNPs (cFDR $\leq$ 0.05) for T2D variation,

which were located on 21 different chromosomes and annotated to 110 genes (Figure 2A, Supplementary Table 1). Among these significant SNPs, 103 were not reported compared with the original T2D GWAS study [13], our earlier work [12] and other previous studies [15, 27]. Using the more conservative threshold of cFDR ≤ 0.01, 64 significant loci remained.

To explore the potential regulatory functions of these CpG-SNPs, we conducted a series of bioinformatics analyses. Our results found that 27 CpG-SNPs showed significant meQTL effects in whole blood (Supplementary Table 2). Additionally, there were 18 loci that mapped to metaQTLs. Interestingly, two novel SNPs (rs677042 and rs7816345) were associated with bile acids (i.e., ursodeoxycholate, hyodeoxycholate), and a third novel SNP (rs10774563) was related to branched chain fatty acids (i.e., ethylmalonate, methylsuccinate). Bile acid and branched-chain fatty acids are known to be involved in the mechanisms of glucose metabolism [28]. Multiple recent studies reported that short-chain fatty acids and branched short-chain fatty acids may have beneficial health effects on adipocyte lipid and glucose metabolism that can contribute to improved insulin sensitivity in individuals with disturbed metabolism [29, 30]. Furthermore, the SNP rs11659412 (Supplementary Table 3) has associations with methylamine, which has previously been shown to have connections with susceptibility for T2D [31].

We also detected four pathways associated with the metabolites that are linked to the metaQTLs. Pathway analysis suggested that these metabolites were linked

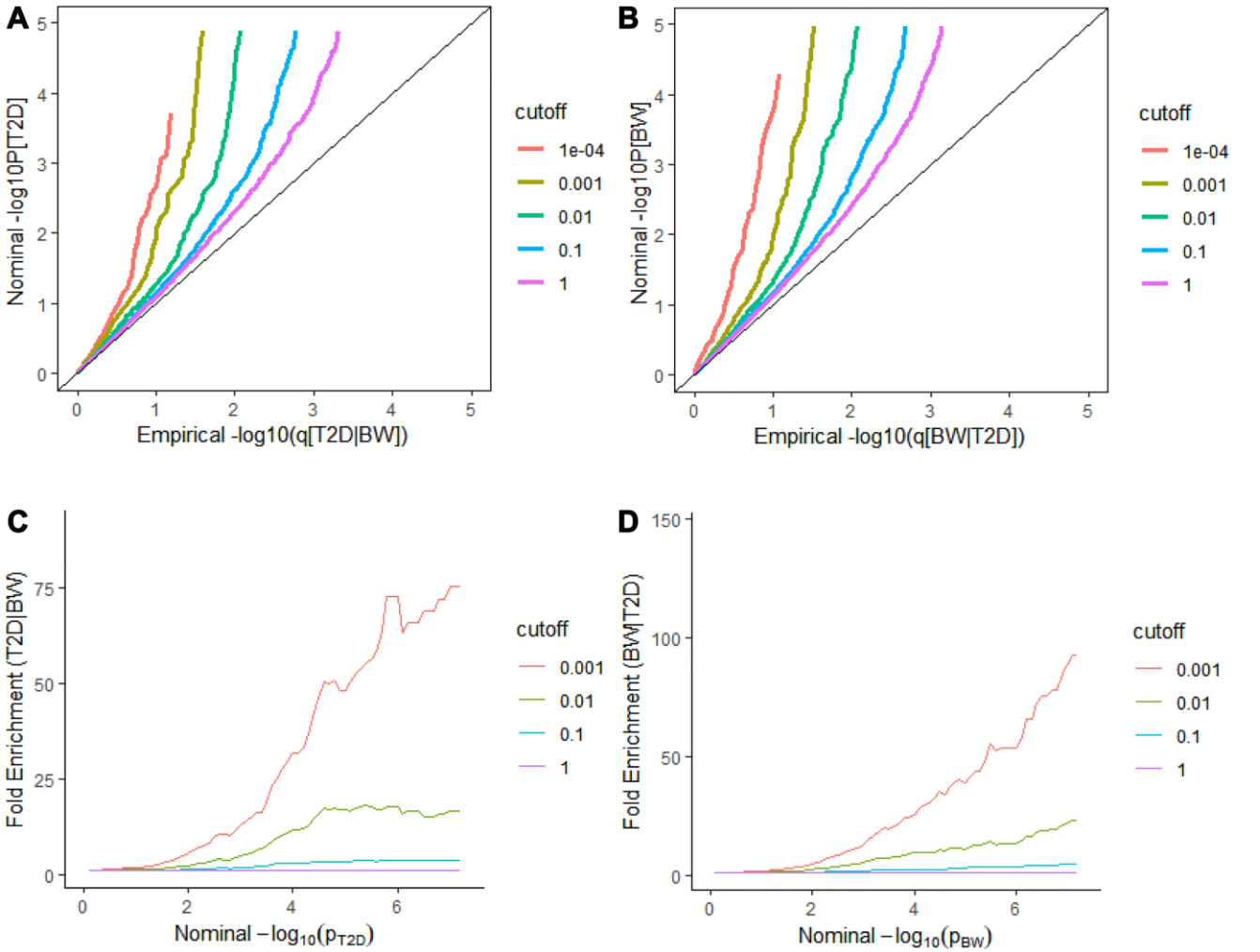

Figure 1. Stratified Q-Q plots and fold-enrichment plots. Stratified Q-Q plots of nominal versus empirical -log10(*p*) values in T2D (**A**) as a function of the significance of the association with BW at the level of -log10(*p*) > 0, -log10(*p*) > 1, -log10(*p*) > 2, -log10(*p*) > 3 corresponding to $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$, and $p \leq 0.0001$, respectively. and (**B**) reversely BW as a function of the significance of the association with T2D. Fold-enrichment plots of enrichment versus nominal -log10p-values (corrected for inflation) corresponding to levels of $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$, respectively in (**C**) T2D as a function of significance of the association with BW; and in (**D**) BW as a function of significance with T2D. Dashed lines indicate the null-hypothesis.

mainly to the lipid metabolism (alpha-Linolenic acid metabolism and Glycerophospholipid metabolism), energy metabolism (Methane metabolism), and genetic Information Processing (aminoacyl-tRNA biosynthesis) (Supplementary Table 4). Lastly, we detected the SNPs enriched in the eQTLs, which may regulate gene expression levels. Eight CpG-SNPs showed the eQTL effect and were associated with enhancer, promoter, and DNAse elements in various tissues. Notably, two novel CpG-SNPs, rs7787720, and rs579459 showed meQTL, eQTL, and metaQTL effects simultaneously (Table 2).

BW loci identified with cFDR

We identified a total of 188 significant CpG-SNPs (cFDR ≤ 0.05) for BW variation on their association with T2D, which were mapped to 20 different chromosomes (Figure 2B, Supplementary Table 5). Other than seven confirmed CpG-SNPs for BW [12, 14], the remaining 182 are novel CpG-SNPs. Using the more conservative threshold of conditional cFDR ≤ 0.01, 85 significant loci remained.

Likewise, we performed the analysis to explore the potential regulatory functions of these identified CpG-SNPs. We found 34 CpG-SNPs that showed significant meQTL effects in whole blood (Supplementary Table 2), and 20 CpG-SNPs that showed metaQTL effects. Among these SNPs identified by the metaQTL analysis, three were associated with bile acids, and one was associated with fatty acids. For the metabolites associated with these CpG-SNPs, two significant pathways were detected, including aminoacyl-tRNA biosynthesis and glycerophospholipid metabolism (Supplementary Table 3, Supplementary Table 4). Lastly, nine novel CpG-SNPs (i.e., rs6687139, rs863818, rs579459, rs3750640, rs4980661, rs11079803, rs4647887, rs2586211, and rs2261988) were identified as eQTL SNPs and were associated with enhancer, promoter, and DNAse elements in various tissues. There was one novel CpG-SNP, rs492602, which showed meQTL, eQTL, and metaQTL effects simultaneously (Table 2). To further verify the eQTL effects of identified loci, we applied LocusCompare method (see methods). Using this method, we identified 11 eQTL loci in T2D and 15 eQTL loci in BW

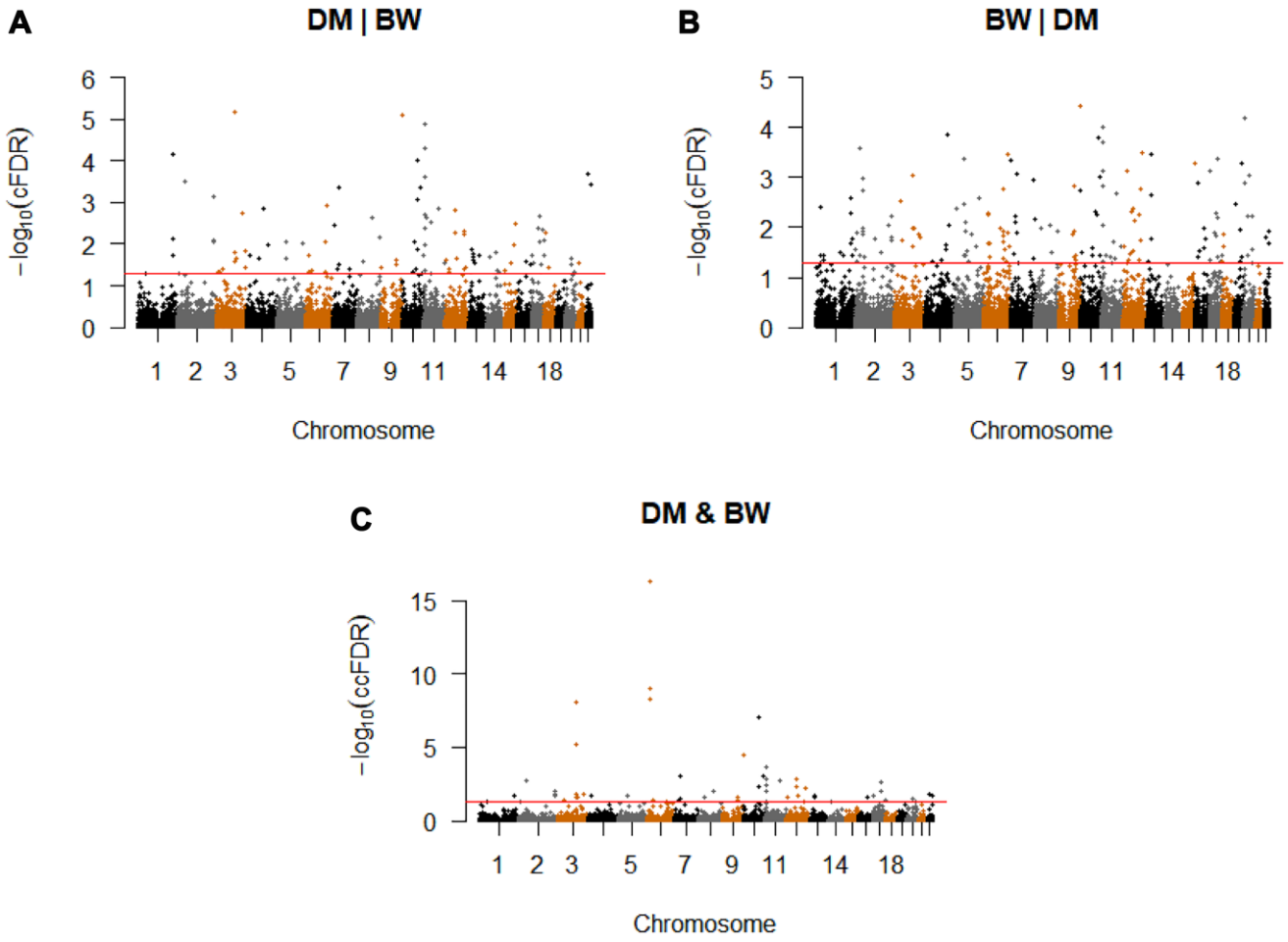

Figure 2. Conditional Manhattan plot. Conditional Manhattan plot of conditional -log10(FDR) values for (**A**) T2D given BW (T2D|BW), (**B**) BW given T2D (BW|T2D), (**C**) T2D and BW. The red line marks the conditional -log10(FDR) values of 1.3 corresponds to a cFDR ≤ 0.05.

Table 1. Conjunction cFDR for 55 pleiotropic CpG-SNPs in T2D and BW (ccFDR ≤ 0.05).

Variant	Chr	Pos	Alt	Gene	Location	eQTL/meQTL/metaQTL	SNP Type	Gene Type	cFDR_T2D	cFDR_BW	ccFDR
rs10449766	1	42070125	A/G	HNRNPFP1	28396 upstream	-	novel	novel	4.99E-02	3.73E-02	4.99E-02
rs340883	1	213972363	C/T	PROX1-AS1	non-coding intronic	-	T2D	novel	7.04E-05	2.13E-02	2.13E-02
rs7553890	1	213832562	T/C	PROX1-AS1	non-coding	-	novel	novel	1.89E-02	2.53E-03	1.89E-02
rs1515114	2	226233671	A/G	AC062015.1	48300 downstream	eQ-TL	novel	novel	8.17E-03	1.82E-02	1.82E-02
rs1522812	2	226132738	A/G	AC062015.1	47306 downstream	eQTL	novel	novel	7.43E-04	1.55E-02	1.55E-02
rs2894593	2	226325601	T/C	AC062015.1	140230 upstream	eQTL	novel	novel	9.16E-03	6.05E-03	9.16E-03
rs7605661	2	43397939	T/C	THADA	intronic	meQTL	novel	T2D	3.21E-04	1.87E-03	1.87E-03
rs17361324	3	123412407	C/T	ADCY5	intronic	meQTL	novel	pleiotropic	8.40E-09	1.20E-18	8.40E-09
rs4677887	3	123381376	T/G	ADCY5	intronic	eQTL	pleiotropic	pleiotropic	6.80E-06	2.91E-11	6.80E-06
rs4677889	3	123424425	G/A	ADCY5	intronic	-	novel	pleiotropic	2.53E-02	1.02E-02	2.53E-02
rs569255	3	125207090	G/A	SLC12A8	intronic	eQTL	novel	novel	2.27E-02	1.01E-02	2.27E-02
rs6770420	3	170931960	G/A	KLF7P1	20890 downstream	eQTL,metaQTL	novel	novel	1.75E-03	1.63E-02	1.63E-02
rs6794193	3	47073414	T/C	SETD2	intronic	eQTL,meQTL	novel	novel	3.92E-02	3.02E-03	3.92E-02
rs9289218	3	123345984	C/T	ADCY5	intronic	eQTL	novel	pleiotropic	1.60E-02	8.91E-04	1.60E-02
rs7663887	4	17901297	C/A	LCORL	intronic	eQTL	novel	BW	1.89E-02	5.90E-07	1.89E-02
rs10514870	5	59055501	A/G	PDE4D, AC092343.1	intronic,intronic	-	novel	novel	2.18E-02	4.17E-04	2.18E-02
rs1012635	6	20675064	A/G	CDKAL1	intronic	-	pleiotropic	pleiotropic	2.64E-14	1.00E-09	1.00E-09
rs12526403	6	41676676	C/T	TFEB	7302 downstream	-	novel	novel	4.50E-02	3.83E-02	4.50E-02
rs2206734	6	20694653	C/T	CDKAL1	intronic	meQTL	novel	pleiotropic	9.60E-27	4.80E-17	4.80E-17
rs2745929	6	20754530	T/C	CDKAL1	intronic	-	novel	pleiotropic	2.10E-09	4.77E-09	4.77E-09
rs4897378	6	130217352	C/T	SAMD3	5upstream	eQTL	novel	novel	4.54E-02	1.20E-02	4.54E-02
rs17689040	7	40880714	C/G	SUGCT	19951 upstream	-	novel	novel	3.04E-02	1.31E-02	3.04E-02
rs6948511	7	27939096	T/C	JAZF1	intronic	eQTL, metaQTL	novel	T2D	4.02E-02	5.80E-03	4.02E-02
rs7723	7	44578194	G/A	TMED4	3utr	eQTL, metaQTL	T2D	novel	4.22E-04	8.40E-04	8.40E-04
rs7004862	8	94864735	T/G	INTS8	intronic	eQTL, metaQTL	novel	T2D	2.26E-03	9.35E-03	9.35E-03
rs7816345	8	36988591	C/T	AC090453.1	179 upstream	eQTL, metaQTL	novel	novel	2.68E-02	1.05E-02	2.68E-02
rs10739970	9	94134010	A/G	PTPDC1	24154 upstream	-	novel	novel	3.18E-02	3.78E-02	3.78E-02
rs10990568	9	95651855	A/G	AL354861.2	non-coding intronic	-	novel	novel	2.46E-02	1.19E-02	2.46E-02
rs579459	9	133278724	T/C	ABO	3510 upstream	eQTL,meQTL, metaQTL	novel	T2D	8.22E-06	3.60E-05	3.60E-05
rs2421019	10	122391070	C/T	PLEKHA1	5upstream	eQTL	novel	pleiotropic	1.17E-06	9.45E-04	9.45E-04
rs2488071	10	92739820	A/G	Y_RNA	29212 upstream	eQTL, metaQTL	T2D	novel	1.96E-10	9.00E-08	9.00E-08
rs7070786	10	92363930	C/T	MARCH5	9966 upstream	eQTL	novel	novel	9.54E-05	4.80E-03	4.80E-03
rs1447351	11	92984997	A/G	MTNR1B	3utr	metaQTL	novel	pleiotropic	1.47E-03	2.05E-03	2.05E-03
rs151216	11	2659585	C/T	KCNQ1, KCNQ1OT1	intronic,non-coding	-	novel	pleiotropic	1.33E-05	1.97E-04	1.97E-04
rs163177	11	2817183	T/C	KCNQ1	intronic	eQTL,meQTL	T2D	pleiotropic	2.07E-10	1.52E-03	1.52E-03
rs231354	11	2685121	T/C	KCNQ1, KCNQ1OT1	intronic,non-coding	eQTL,meQTL	pleiotropic	pleiotropic	2.40E-04	9.10E-03	9.10E-03
rs234857	11	2831299	T/C	KCNQ1	intronic	-	T2D	pleiotropic	1.09E-06	4.67E-02	4.67E-02
rs3213225	11	2135306	G/A	IGF2, INS-IGF2	intronic,intronic	eQTL,meQTL	novel	pleiotropic	4.15E-03	9.59E-05	4.15E-03
rs1042725	12	65964567	C/T	HMGA2	3utr,	-	T2D	pleiotropic	1.54E-03	1.90E-29	1.54E-03
rs10774202	12	4168281	A/G	AC007207.1	50149 upstream	-	novel	novel	2.42E-02	2.32E-02	2.42E-02
rs10862960	12	77030355	C/T	E2F7	intronic	eQTL	novel	novel	2.14E-02	7.30E-03	2.14E-02
rs10878353	12	65988752	T/C	HMGA2	22457 upstream	-	novel	pleiotropic	5.34E-03	1.04E-06	5.34E-03
rs4930718	12	123428886	A/G	RILPL2	intronic	eQTL	novel	novel	6.05E-03	3.28E-04	6.05E-03

rs12865243	13	40104683	G/A	LINC00598	non-coding intronic	-	novel	novel	2.44E-02	3.32E-04	2.44E-02
rs9532498	13	40104306	G/C	LINC00598	non-coding intronic	-	novel	novel	2.05E-02	2.22E-03	2.05E-02
rs4625714	16	55607701	C/T	LPCAT2	21031 upstream	-	novel	novel	2.64E-02	1.05E-02	2.64E-02
rs1531798	17	78826049	A/G	USP36	intronic	eQTL	novel	novel	7.84E-03	3.72E-02	3.72E-02
rs198542	17	50567176	G/A	CACNA1G	intronic	-	novel	novel	9.15E-03	6.42E-03	9.15E-03
rs390200	17	7206676	A/G	DLG4	intronic	eQTL	novel	novel	1.88E-02	6.89E-10	1.88E-02
rs6565531	17	81049580	G/A	BAIAP2	intronic	eQTL,meQTL	novel	novel	1.88E-02	3.61E-02	3.61E-02
rs878619	17	50555910	A/G	SPATA20	58 upstream	eQTL,meQTL	novel	novel	2.23E-03	4.24E-04	2.23E-03
rs2426778	20	58718421	G/A	NPEPL1	non-coding	eQTL	novel	novel	4.76E-02	6.10E-03	4.76E-02
rs926345	20	41143307	T/C	PLCG1	intronic	eQTL,meQTL	novel	novel	3.11E-02	9.32E-04	3.11E-02
rs137848	22	50001867	T/C	IL17REL	intronic	eQTL,meQTL	novel	novel	3.55E-04	2.08E-02	2.08E-02
rs6006393	22	30194037	T/C	AC002378.1	non-coding intronic	eQTL	novel	novel	2.14E-04	1.53E-02	1.53E-02

Abbreviations: Chr, chromosome; Pos, chromosomal position (GRCh38/hg38); Alt, reference allele/alter allele; eQTL, expression quantitative trait locus; meQTL, methylation quantitative trait locus (including associated SNPs with an LD $r^2 \geq 0.8$, Supplementary Table 3); metaQTL, metabolic quantitative trait locus. T2D, type 2 diabetes; BW, birth weight; cFDR, conditional false discovery rate; ccFDR, conjunctional conditional false discovery rate. The allele was exhibited as reference allele/alter allele; SNP type and gene type means whether identified CpG-SNPs and genes have been reported in previous GWAS or in our previous related cFDR studies.

Table 2. Functional annotation for 17 CpG-SNPs showing significant effects in meQTL, eQTL, and metaQTL.

rsID	GENCODE genes	Traits	meQTL (*p*)	eQTL hits	mQTL (metabolics)	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed
rs579459	ABO	Pleiotropic	1.45E-09	5 hits	glycylglycine	BLD	GI	4 tissues	NFYA, POL2	Hmx, Nkx2
rs6446490	PPP2R2C	T2D	2.81E-16	7 hits	-	LIV	4 tissues	4 tissues	7 bound proteins	-
rs7787720	AC005019.2	T2D	2.04E-22	1 hit	salicyluric glucuronide	-	MUS, LNG, SKIN	-	-	Mef2
rs12245680	TCF7L2	T2D	8.59E-05	-	-	15 tissues	17 tissues	29 tissues	FOXA1	-
rs11819995	ETS1	T2D	5.19E-05	-	-	19 tissues	9 tissues	15 tissues	POL2	NRSF
rs2237892	KCNQ1	T2D	1.45E-10	-	#gamma-g, **N2, N2-d	-	5 tissues	KID, MUS	-	8 altered motifs
rs2334499	FAM99B	T2D	4.05E-09	2 hits	-	LIV	ADRL, LIV	MUS, MUS	-	GR, PU.1, RXRA
rs2291725	GIP	T2D	1.62E-06	29 hits	-	11 tissues	14 tissues	22 tissues	16 bound proteins	Sin3Ak-20
rs6687139	LINC01681	BW	1.90E-05	1 hit	-	FAT	7 tissues	4 tissues	-	-
rs863818	PIK3R1	BW	-	-	1-methylxanthine	BLD	15 tissues	HRT	-	-
rs3750640	ASB13	BW	-	2 hits	phenylalanylserine	GI	7 tissues	IPSC, THYM, GI	-	PPAR
rs4980661	AP000439.2	BW	1.02E-04	-	-	SPLN	HRT, MUS, LIV	LNG, BLD	-	-
rs11079803	PNPO	BW	5.25E-09	57 hits	-	19 tissues	13 tissues	11 tissues	-	6 altered motifs
rs4647887	SNHG16	BW	6.23E-20	33 hits	-	5 tissues	16 tissues	14 tissues	GATA1	-
rs2586211	GNAL	BW	-	-	allantoin	LIV	9 tissues	9 tissues	CTCF, CMYC	CEBPB, GATA
rs2261988	UHRF1	BW	1.83E-05	7 hits	-	21 tissues	10 tissues	24 tissues	POL2, POL24H8	4 altered motifs
rs492602	FUT2	BW	2.50E-07	31 hits	*ADp	-	-	-	-	Znf143

Abbreviations: meQTL, methylation quantitative trait locus (including associated SNPs with an LD $r^2 \geq 0.8$, Supplementary Table 3); eQTL, expression quantitative trait locus; metaQTL, metabolic quantitative trait locus. DNAse, deoxyribonuclease; *ADp, ADpSGEGDFXAEGGGVR; #gamma-g, gamma-glutamylvaline; **N2, N2-d, N2, N2-dimethylguanosine.

(Supplementary Table 6). Two of these loci are overlapped with our results: *JAZF1* ($p = 8.7 \times 10^{-9}$), and *PLEKHA1* ($p = 5.2 \times 10^{-8}$), indicating that these two genes are more likely to be the eQTL loci.

Pleiotropic loci in T2D and BW identified with ccFDR

We computed ccFDR and constructed a ccFDR Manhattan plot to investigate whether any of the CpG-SNPs were associated with both T2D and BW. We found 55 independent pleiotropic SNPs detected by our analysis (The detailed annotations are listed in Supplementary Table 1 and 5), which were located on 16 chromosomes that reached a significance level of ccFDR ≤ 0.05 (Figure 2C, Table 1). With the more stringent significance threshold of ccFDR ≤ 0.01, 23 pleiotropic CpG-SNPs remained. Among the identified loci, 52 CpG-SNPs were suggested to be novel. In total, five SNPs have been associated with T2D, while none of these SNPs has previously been identified for BW. All the identified CpG-SNPs annotated to 45 different genes, and 35 of these were not detected as pleiotropic genes in previous related research [12]. Finally, we found 35 SNPs have at least one eQTL, meQTL, or metaQTL effect. One pleiotropic CpG-SNP, rs579459 (*ABO*), showed eQTL, meQTL, and metaQTL effects simultaneously (Table 2).

GO enrichment analysis and protein-protein interaction analysis.

We conducted GO enrichment analysis for the T2D- and BW- associated genes that were annotated to the identified CpG-SNPs to explore the potential regulatory functions. The identified SNPs were enriched in biological processes related to "response to oxygen-containing compound" and a molecular function of "scaffold protein binding". We also found that genes associated with T2D were significantly enriched in the pathway of "regulation of hormone levels" (FDR = 3.04×10^{-3}) and "regulation of insulin secretion" (FDR = 4.19×10^{-3}) (Supplementary Table 7). Using STRING 11.0 database, we performed protein-protein interaction analysis to further investigated the functional partnership among identified T2D- and BW- associated genes (Figure 3**)**, respectively. PPI results showed several genes were well-connected in the interaction network in both traits, such as *ADCY5*, *KCNQ1*, *IGF2*, and *CDKAL1*, suggesting these genes are essential in the genetic network that coupling of both traits.

Results of the validation study

For cFDR analysis between BW and FG, we observed similar significant separation between the different curves, which indicates a strong pleiotropy between

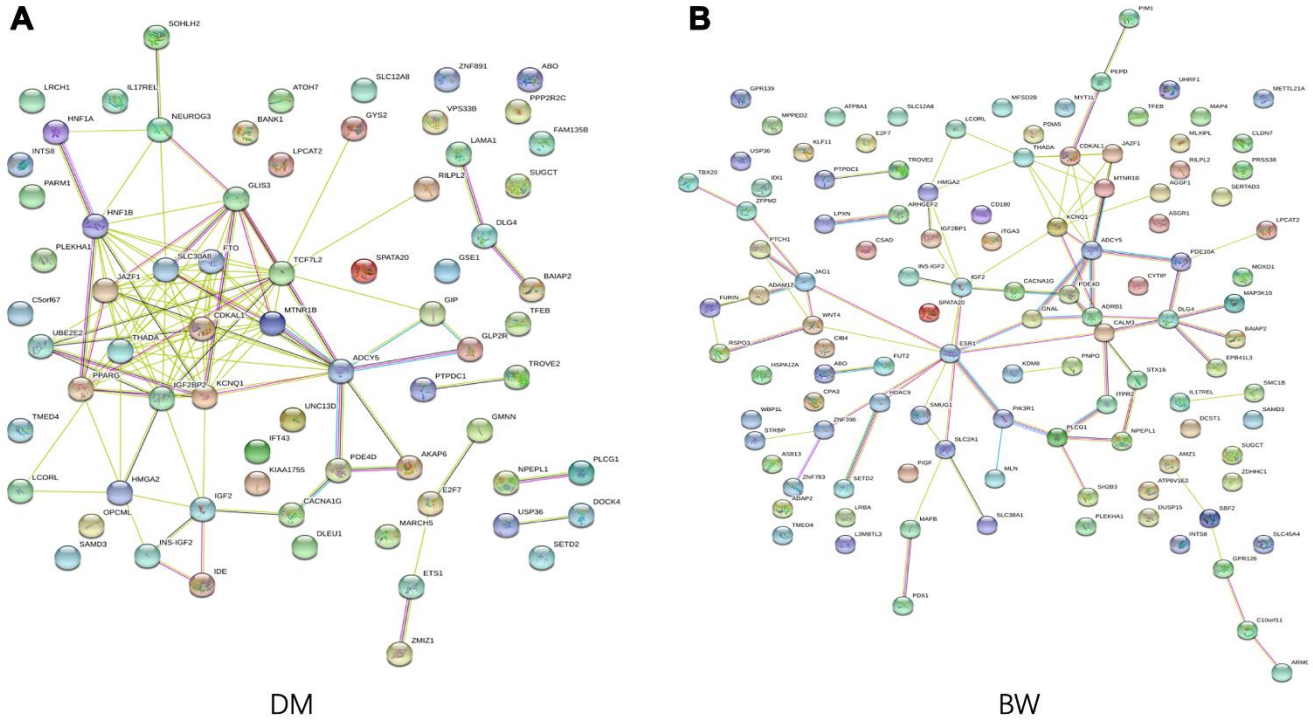

Figure 3. Functional protein association network analysis. Connections are based on evidence with a STRING 11.0 summary score above 0.4. Each network nodes represent a gene; edges between nodes indicate protein-protein interactions between protein products of the corresponding genes in (**A**) T2D and (**B**) BW, edge colors indicate the types of interaction.

those two traits (Supplementary Figure 1A and 1B). Conditional on association with FG, we identified 160 significant CpG-SNPs (cFDR ≤ 0.05) for BW variation, and 131 of them were replicated compared with the main cFDR analysis. We identified a total of 104 significant CpG-SNPs for FG variation on their association with BW, and 25 of them were replicated. And we replicated 18 pleiotropic CpG-SNPs for FG and BW (Supplementary Table 8).

For cFDR analysis between BW and FI, we identified clearly separation between the different curves, which indicates a strong pleiotropy between those two traits (Supplementary Figure 1C and 1D). Conditional on association with FI, we identified 140 significant CpG-SNPs for BW variation, and 125 of them were replicated compared with the main cFDR analysis. We identified a total of 13 significant CpG-SNPs for FI variation on their association with BW, and 5 of them were replicated. And we replicated 3 pleiotropic CpG-SNPs for FI and BW (Supplementary Table 9).

For cFDR analysis between BW_maternal and T2D_corBMI, significant deflection between curves suggested strong pleiotropy between those two phenotypes (Supplementary Figure 2A and 2B). Conditional on association with T2D_corBMI, we identified 90 CpG-SNPs for BW_ maternal variation, and 13 of them were replicated compared with the main cFDR analysis. We identified a total of 622 significant CpG-SNPs for T2D_corBMI variation on their association with BW_ maternal, and 79 of them were replicated. And we replicated 8 pleiotropic CpG-SNPs for BW_ maternal and T2D_corBMI (Supplementary Table 10).

For cFDR analysis between BW_fetal and T2D_corBMI, similar deflection between curves demonstrated significant pleiotropy between those two phenotypes (Supplementary Figure 2C and 2D). Conditional on association with T2D_corBMI, we identified 133 CpG-SNPs for BW_fetal variation, and 59 of them were replicated compared with the main cFDR analysis. We identified a total of 669 significant CpG-SNPs for T2D_corBMI variation on their association with BW_ fetal, and 87 of them were replicated. And we replicated 25 pleiotropic CpG-SNPs for BW_ fetal and T2D_corBMI (Supplementary Table 11).

MR results

Finally, 46 independent SNPs were left for MR analysis (Table 3). IVW results suggested causal association between BW and T2D (OR = 1.554, se = 0.207, 95% CI (1.036, 2.330), P = 0.033), MR-Egger regression demonstrated no pleiotropy among selected IVs (P = 0.450). However, other approaches did not identify any causal association (Table 4). Our bi-directional MR analysis also suggested no causal association between T2D and BW.

DISCUSSION

In this study, by performing the cFDR on the two independent GWAS datasets from T2D and BW, we identified 103 novel loci for T2D and 182 for BW when focusing on CpG-SNPs. Meanwhile, we identified 55 pleiotropic CpG-SNPs suggesting a shared genetic mechanism among them. Interestingly, only three of these CpG SNPs were identified as pleiotropic loci in the previous studies.

Since the genetic variants located at CpG-SNPs could affect the gene expression and regulation via epigenetic mechanisms, we investigated these 103 CpG-SNPs, which were regarded as novel SNPs associated with T2D. Among those CpG-SNPs, 55 showed at least one effect on meQTL, metaQTL, and/or eQTL, and 35 of them were located at novel risk genes for T2D. For example, rs11073964 is a novel CpG-SNP which showed both eQTL and meQTL effects and mapped to *VPS33B* (15q26.1). The relationship between *VPS33B* and T2D is unknown, although *VPS33B* is expressed in pancreas tissue, and encodes Vascular Protein Sorting-associated protein 33B [32]. The function of *VPS33B* refers to intracellular protein trafficking and membrane fusion mechanisms [33]. It also plays critical roles in bile acids metabolism [34], which could contribute to the regulation of glucose homeostasis [28]. Therefore, it is conceivable that *VPS33B* might influence pancreatic cell function through epigenetic mechanisms.

Another novel CpG-SNP (rs12786533), also showed both meQTL and eQTL effects and was located at the gene *KCNQ1DN* (*KCNQ1* downstream neighbor). *KCNQ1DN*, which imprinted and mapped between *CDKN1C* and *KCNQ1* on chromosome 11p15.5, is usually associated with Wilms' tumor [35]. Other imprinted genes in 11p15.5, including *KCNQ1* and *IGF2*, are candidates for involvement in T2D [36, 37]. We also detected seven CpG-SNPs (rs151216, rs163171, rs163177, rs2237892, rs231354, rs234857, and rs3852527) which were annotated to *KCNQ1*. Two of these loci (rs163177 and rs231354) were shown to have eQTL and meQTL effects, and another SNP (rs2237892) was shown to have metaQTL effect. It is plausible that these multiple neighboring CpG-SNPs might synergistically regulate gene expression and play some roles in T2D.

We also investigated the significant CpG-SNPs associated with BW conditioned on T2D, in which 120

Table 3. Characteristics of the instrumental variables used in MR analysis.

SNP	ea_E	oa_E	ea_O	oa_O	beta.E	beta.O	eaf.E	eaf.O	se.O	pval.O	outcome	se.E	pval.E	exposure
rs10818797	C	T	C	T	0.0345	0.0953102	0.14	0.141	0.076	0.3	T2D	0.0054	1.20E-10	BW
rs10830963	G	C	G	C	0.0232	0	0.28	0.276	0.039	0.27	T2D	0.0042	2.90E-08	BW
rs10872678	C	T	C	T	-0.0375	-0.040822	0.28	0.277	0.04	0.31	T2D	0.0041	6.90E-20	BW
rs10935733	C	T	C	T	-0.0221	-0.0953102	0.59	0.606	0.034	0.092001	T2D	0.0039	9.20E-09	BW
rs111778406	G	A	G	A	0.0492	-0.0202027	0.068	0.072	0.13	0.89	T2D	0.0075	5.80E-11	BW
rs113086489	T	C	T	C	0.0307	0	0.56	0.545	0.034	0.94	T2D	0.0038	9.10E-16	BW
rs11720108	T	C	T	C	0.046	0	0.23	0.249	0.045	0.61	T2D	0.0043	3.40E-26	BW
rs11765649	C	T	C	T	-0.0267	0	0.25	0.263	0.042	0.37	T2D	0.0043	5.80E-10	BW
rs1187118	T	A	T	A	-0.0299	0	0.83	0.833	0.058	0.73	T2D	0.0051	3.60E-09	BW
rs12543725	A	G	A	G	-0.0231	0	0.41	0.412	0.033	0.41	T2D	0.0038	1.20E-09	BW
rs12906125	A	G	A	G	-0.0228	-0.0100503	0.32	0.326	0.037	0.88	T2D	0.004	1.70E-08	BW
rs13266210	G	A	G	A	-0.0308	-0.0512933	0.21	0.212	0.051	0.36	T2D	0.0045	1.30E-11	BW
rs134594	T	C	T	C	-0.0227	0.0100503	0.65	0.65	0.036	0.77	T2D	0.004	1.00E-08	BW
rs1351394	C	T	C	T	-0.0436	0	0.51	0.511	0.032	0.760001	T2D	0.0037	1.90E-32	BW
rs1411424	A	G	A	G	0.0212	0.0202027	0.52	0.524	0.033	0.62	T2D	0.0038	2.20E-08	BW
rs1415701	A	G	A	G	-0.0253	0	0.26	0.269	0.041	0.9	T2D	0.0043	2.60E-09	BW
rs144843919	A	G	A	G	-0.066	-0.0100503	0.035	0.035	0.27	0.98	T2D	0.0116	1.40E-08	BW
rs17034876	T	C	T	C	0.0471	0.0304592	0.7	0.699	0.039	0.42	T2D	0.0042	2.60E-29	BW
rs1819436	C	T	C	T	0.0329	0.0100503	0.87	0.877	0.076	0.93	T2D	0.0057	6.30E-09	BW
rs2131354	A	G	A	G	0.0259	0	0.53	0.526	0.033	0.52	T2D	0.0037	4.10E-12	BW
rs2168443	A	T	A	T	-0.0228	0.0725707	0.62	0.621	0.035	0.053001	T2D	0.0039	3.50E-09	BW
rs2229742	C	G	C	G	-0.036	-0.040822	0.13	0.104	0.084	0.62	T2D	0.006	2.20E-09	BW
rs2306547	T	C	T	C	-0.0211	0	0.46	0.467	0.033	0.92	T2D	0.0037	1.80E-08	BW
rs2473248	C	T	C	T	0.0325	0	0.87	0.881	0.079	0.94	T2D	0.0057	1.00E-08	BW
rs2497304	T	C	T	C	-0.0282	0	0.48	0.478	0.033	0.97	T2D	0.0037	2.60E-14	BW
rs28530618	G	A	G	A	-0.0261	-0.0953102	0.51	0.529	0.033	0.041	T2D	0.0038	7.70E-12	BW
rs2946179	C	T	C	T	0.024	0	0.73	0.74	0.042	0.27	T2D	0.0042	1.30E-08	BW
rs35261542	A	C	A	C	-0.0444	-0.127833	0.27	0.263	0.039	0.00063	T2D	0.0041	4.40E-27	BW
rs3753639	C	T	C	T	0.0306	0.0953102	0.24	0.245	0.046	0.25	T2D	0.0045	7.30E-12	BW
rs3780573	A	G	A	G	0.0555	0.0953102	0.096	0.096	0.099	0.22	T2D	0.0064	7.00E-18	BW
rs4144829	T	C	T	C	-0.0341	0	0.73	0.739	0.043	0.56	T2D	0.0042	5.30E-16	BW
rs6016377	T	C	T	C	0.0239	0	0.43	0.446	0.035	0.53	T2D	0.0039	9.50E-10	BW
rs6040076	C	G	C	G	0.0231	-0.0512933	0.49	0.494	0.033	0.1	T2D	0.0039	2.00E-09	BW
rs72480273	C	A	C	A	0.0313	-0.0512933	0.17	0.189	0.056	0.38	T2D	0.0051	8.00E-10	BW
rs72833480	A	G	A	G	0.0226	-0.0304592	0.29	0.295	0.039	0.49	T2D	0.0041	4.60E-08	BW
rs72851023	T	C	T	C	0.0476	0	0.073	0.077	0.13	0.74	T2D	0.0075	2.90E-10	BW
rs7402982	G	A	G	A	-0.0232	0.0100503	0.57	0.586	0.034	0.67	T2D	0.0039	2.30E-09	BW
rs740746	A	G	A	G	0.0364	0	0.73	0.734	0.041	0.62	T2D	0.0042	3.80E-18	BW
rs753381	C	T	C	T	-0.0205	0	0.55	0.55	0.033	0.52	T2D	0.0037	2.80E-08	BW
rs7575873	G	A	G	A	-0.0384	-0.0618754	0.12	0.13	0.071	0.42	T2D	0.0057	1.20E-11	BW
rs7854962	G	C	G	C	-0.0279	-0.040822	0.22	0.216	0.047	0.36	T2D	0.0046	1.90E-09	BW
rs79237883	C	T	C	T	0.0371	-0.0833816	0.08	0.076	0.1	0.39	T2D	0.0067	3.50E-08	BW
rs7964361	A	G	A	G	0.0391	-0.105361	0.085	0.088	0.096	0.25	T2D	0.0067	4.70E-09	BW
rs798498	G	T	G	T	-0.0229	0	0.31	0.307	0.038	0.709999	T2D	0.004	1.30E-08	BW
rs7998537	A	G	A	G	-0.0222	0	0.32	0.321	0.037	0.35	T2D	0.004	3.90E-08	BW
rs854037	G	A	G	A	-0.0268	0.0953102	0.19	0.186	0.055	0.37	T2D	0.0048	2.20E-08	BW
rs900399	G	A	G	A	-0.0523	0	0.39	0.393	0.038	0.47	T2D	0.0039	2.20E-41	BW
rs9368777	C	G	C	G	0.0215	0.0304592	0.58	0.575	0.033	0.31	T2D	0.0038	2.20E-08	BW

Notes:

E: exposure; O: outcome; ea: effect_allele; oa: other_allele.

Table 4. MR analysis results.

Outcome	Exposure	Method	nsnp	b	se	pval	or	or_lci95, or_uci95
T2D	BW	MR Egger	46	0.968	0.723	0.187	2.632	0.639, 10.845
T2D	BW	Weighted median	46	0.000	0.309	1.000	1.000	0.546, 1.831
T2D	BW	Inverse variance weighted	46	0.441	0.207	0.033	1.554	1.036, 2.330
T2D	BW	Simple mode	46	0.009	0.527	0.986	1.009	0.359, 2.834
T2D	BW	Weighted mode	46	0.009	0.431	0.983	1.009	0.434, 2.347

CpG-SNPs were novel loci and annotated to genes that were not reported in previous study [13]. All these SNPs showed at least one effect on eQTL, meQTL, and/or metaQTL. There were two notable SNPs, rs3184504, which was located on the gene *SH2B3*, and rs492602, which was located on the gene *FUT2*. Both SNPs showed eQTL, meQTL, and metaQTL effects simultaneously. The gene *SH2B3* acts as a negative regulator of cytokine signaling and cell proliferation [38], which is known to be associated with type 1 diabetes and celiac disease [39]. The gene *FUT2* encodes a specific fucosyltransferase enzyme, which is crucial for the synthesis of histo-blood group antigens [40]. Whether these genes have a function on BW is unclear, but our findings imply that epigenetic alteration deserves attention and presents new insights for further exploration.

Importantly, 19 of the 55 pleiotropic variants were novel loci that showed at least one QTL effect. Notably, seven of these 19 loci (rs6770420 in *KLF7P1*, rs6794193 in *SETD2*, rs7816345 in *AC090453.1*, rs6565531 in *BAIAP2*, rs878619 in *SPATA20*, rs926345 in *PLCG1*, and rs137848 in *IL17REL*) showed eQTL and either metaQTL or meQTL effect. These facts suggest that these SNPs might be involved in the shared pathogenesis of both T2D and BW.

There are several advantages in the current study. First, identifying shared genetic factors between these two traits can facilitate our understanding of the genetic correlation between BW and T2D. To our knowledge, this study is the first to use a targeted cFDR method by focusing on functional CpG-SNPs that are associated with both T2D and BW. Compared with our previous work on the same two traits [12], this work was based on the updated GWAS datasets with a larger population and sophisticated study design [13, 14]. Second, in this study, we only focused on functional genetic variants-CpG-SNPs, which not only significantly reduced the multiple testing burden but also shed light on the biological interpretation of the results. Furthermore, we performed the analysis on meQTL, metaQTL, and eQTL effects, which facilitate the identification of candidate functional variants associated with T2D and/or BW. Third, our MR analysis IVW approach showed causal association between BW and T2D while other methods did not, therefore, we cannot define the direct causal relationship between BW and T2D. This result suggested that instead of acting like a direct risk factor, the BW might regulate T2D through multiple intermediate variants such as DNA methylation or regulation of metabolism, as we demonstrated in this study. Fourth, considering BW is influenced both by inherited fetus genotypes and maternal genotypes, we performed validation analysis by using GWAS datasets of direct fetal and indirect maternal genetic effects, which further support the story. Finally, multiple validations in different GWAS datasets were performed in the current study to partially support our findings, which demonstrated the credibility and significance of these findings.

There are also some limitations to our study. First, we are unable to evaluate the effect estimates of pleiotropic SNPs on the traits due to our inability to access the individual-level data. Second, it is difficult to distinguish between the pleiotropic scenarios where a SNP directly influences both BW and T2D, or the SNP affects BW, and the resulting change in phenotype influences T2D susceptibility. However, our MR analysis results may suggest that the SNPs affect T2D susceptibility via affecting BW. Thirdly, although using LD $r^2 \geq 0.2$ as the threshold for SNP pairwise pruning is a common practice in similar integration studies [41–43], some of our findings could still be secondary to the signals, especially for SNPs identified in the same gene without special features such as eQTL (e.g., rs151216, rs234857 in *KCNQ1*). However, since the identified SNPs are functional CpG-loci, the CpG-SNPs identified in this study are more likely to be the leading signals, compared with the previous results. Finally, these findings are based on a bioinformatics analysis of GWAS data. Without further molecular validation, some of these results are suggestive rather than conclusive, such as suggested CpG-loci or functional genes. The aim of our study was to find more potential novel T2D associated variants, so we hope that this limitation could partially be addressed in the future by follow up with fine-mapping studies or molecular validation experiments.

In conclusion, by using cFDR method on functional CpG-SNPs, we successfully improved the identification of novel genetic variants of both T2D and BW. Our findings offer an improved understanding of the potential shared genetic mechanisms in T2D and BW, which may provide a new direction for further biological studies and clinical trials.

MATERIALS AND METHODS

GWAS datasets

We obtained GWAS summary statistics for T2D and BW from publicly available sources [13, 14]. The dataset for T2D contained meta-analysis summary statistics from 18 studies performed by DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium (n = 26,676 case and 132,532 control, European) [13]. The dataset for BW contained meta-analysis summary statistics from 37 studies conducted by Early Growth Genetics (EGG) Consortium (n = 153,781, predominantly European) [14]. Both of these datasets have large enough sample sizes (n > 100,000) for statistical power. Each dataset contains summary statistics for each SNP with the p values that have undergone genomic control at the individual study level. The detailed inclusion criteria and phenotype characteristics from different GWAS are described in the original publications.

Identification of potentially functional CpG-SNPs

The CpG-SNPs in the human genome were identified by interrogating the comprehensive catalog of both common and rare genetic variants from the 1000 Genomes reference panel [44], and our in-house whole-genome high-coverage deep re-sequencing study [45]. A SNP is defined as a CpG-SNP if it introduces or disrupts a CpG site. A total of 50,278,228 CpG-SNPs was identified throughout the human genome. The details of the identification of potentially functional CpG-SNPs were described in our previous study [46].

Data processing

First, we combined the 8,099,761 common SNPs included in these two datasets, then overlapped these common SNPs with the above-identified CpG-SNPs and retrieved a total of 2,478,365 common CpG-SNPs with association summary statistics for both T2D and BW. We then used HapMap 3 genotypes as a reference, and performed a linkage disequilibrium (LD) based pruning method by PLINK 1.9 to remove pairs of SNPs with substantial correlations [47]. The process begins using a window of 50 SNPs, where LD between each pair of SNPs is calculated. If pairs have an $R^2 > 0.2$, one of that pair of SNPs is removed. Following this initial removal of SNPs, the window shifts 5 SNPs forward, and the process is repeated until there are no pairs of SNPs that are in high LD. After pruning, 96,312 independent CpG-SNPs remained to be used in the subsequent analysis.

Statistical analysis

We constructed conditional quantile-quantile plots (Q-Q plot) to evaluate the enrichment of pleiotropic effects by evaluating the increase in the number of trait-associated SNPs for the first trait (principal trait) when conditioning on SNPs with varying strengths of association in the second trait (conditional trait). We also constructed fold-enrichment plots, which quantify the pleiotropic enrichment within each conditional subset compared with the baseline group, which includes all SNPs.

By leveraging two GWASs from T2D and BW, we applied the cFDR approach to obtain the probability that a random SNP is null for association with the principal phenotype given that the p-values for the principal and conditional phenotypes are both less than observed p-values. The method was applied for both orderings of the two phenotypes, cFDR(T2D|BW) and cFDR (BW|T2D). Then, we computed the conjunction cFDR (ccFDR), taken to be the maximum of the two cFDR values, to identify pleiotropic SNPs for both T2D and BW. Finally, we present conditional Manhattan plots to visualize the localization of the SNPs associated with T2D conditional on the strength of association with BW and the reverse. We also present a conjunction Manhattan plot to visualize the locations of the variants with a pleiotropic effect on both phenotypes. We identified a SNP as novel if it has not been reported in previous GWASs [13, 14] or our previous cFDR studies [12]. The details were presented in the Supplementary Materials and Methods.

Functional annotation of the pleiotropic CpG-SNPs

To explore the biological functions of the individual trait associated CpG-SNPs and pleiotropic CpG-SNPs, we annotated each identified CPG-SNP to corresponding DNA features or regulatory elements using functional analysis tools such as HaploReg (http://www.broadinstitute.org/mammals/haploreg/haploreg.php) and SNPnexus (http://www.snp-nexus.org/). These tools provide the ENCODE [48] and RoadMap [49] annotations for the CpG-SNPs of interest as well as other SNPs in high LD ($r^2 \geq 0.8$).

We further determined whether the identified CpG-SNPs or other SNPs in high LD ($r^2 \geq 0.8$) have expression quantitative trait loci (eQTL), methylation QTL

(meQTL), or metabolic QTL (metaQTL) effects. First, we obtained the eQTL hits from HaploReg based on GTEx and other eQTL results. Then, we acquired the independent cis- and trans- meQTLs in whole blood from Bonder's study (https://genenetwork.nl/biosqtlbrowser/). Last, we obtained the metaQTLs from SNiPA (https://snipa.helmholtz-muenchen.de/snipa3/), which summarized recently published metaQTL studies. We also used the metabolites associated with these metaQTLs to perform a pathway analysis using MetaboAnalyst 4.0 (https://www.metaboanalyst.ca/). The eQTL results were further confirmed using a web tool "LocusCompare" [50]. This method calculates the colocalization between GWAS and eQTL results and identifies significant loci (GWAS lead SNP p-value $< 5 \times 10^{-8}$ and eQTL lead SNP *p*-value $< 1 \times 10^{-6}$). We used the original GWAS summary statistics we chose in this study as GWAS input, while using eQTL from adipose tissue as eQTL input (eQTL_Adipose_Subcutaneous_GTEx_v7) for BW and T2D are closely associated with adipocyte biology [51, 52].

The gene ontology (GO) terms database (http://omicslab.genetics.ac.cn/GOEAST/index.php) was used to perform gene enrichment analysis among the list of genes associated with pleiotropic CpG-SNPs. Among the significant genes we identified gene sets enriched in certain biological processes, cellular components, and molecular functions. To investigate the interaction and functional relationship of the identified T2D and BW genes, protein-protein interaction analyses were constructed by using the STRING 11.0 database (http://string-db.org/).

Validation study using different GWAS datasets

Considering the long duration of action between BW and T2D, we re-performed cFDR analysis between BW and diabetes-related indicators (fasting glucose (FG), and fasting insulin (FI) [53]) to validate the results of the main cFDR analysis, and QQ plots were also generated to demonstrate the pleiotropic enrichment.

Additionally, considering BMI may be highly related with both birth weight and T2D, and BW is influenced both by inherited fetus genotypes and maternal genotypes with intrauterine environment. We further conducted cFDR analysis between BW_maternal [54] and BW_fetal [54] with T2D with correction of BMI (T2D_corBMI) [55], separately."

Bi-directional Mendelian Randomization (MR) analysis

First, we selected independent SNPs ($r^2 < 0.001$) that achieved genome-wide significance ($p < 5 \times 10-8$) in the BW GWAS datasets as instrumental variables (IVs), then summary statistics of those SNPs were further extracted from T2D GWAS datasets. Next, inverse variance weighted (IVW) regression [56] was performed as main MR analysis to estimate the causal relationship between BW and T2D. MR-Egger regression [57] was performed to estimate the pleiotropy effect among selected SNPs. Simple mode, weighted mode and weighted median [56] were then conducted to validate the main results. *P* values less than 0.05 was considered significant. Then bi-directional MR analysis was repeated using T2D as exposure, BW as outcome.

Ethics approval and patient consent

We obtained genome-wide association study (GWAS) results published online. The relevant institutional review boards or ethics committees approved the research protocol of the individual GWAS used in the current analysis, and all human participants gave written informed consent, which was demonstrated in the respective original papers.

AUTHOR CONTRIBUTIONS

Hong-Wen Deng conceived and initiated this study，he is responsible for the general development and design of the study and contributed to critical revisions. Jie Shen gave constructive suggestions and finalization of the manuscript. Rui-ke Liu is the first author who performed data analysis and drafted the manuscript. Xu Lin and Chuan Qiu contributed to data analysis. Zun Wang, Jonathan Greenbaum, and Chun-Ping Zeng contributed to critical revisions. Yong-Yao Zhu gave constructive suggestions during the whole process. All authors have given approval to the final version of the manuscript. All authors agree to be accountable for the work and ensure that any questions relating to the accuracy and integrity of the paper are investigated and properly resolved.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary Materials And Methods

Pleiotropic enrichment estimation

We performed conditional Q-Q plots based on varying levels of significance in the conditional phenotype to visualize the difference between observed distribution in the principal trait and theoretical distribution. We plotted the QQ curve for the quantile of nominal -log10(p) values for the association of the subset of SNPs that were below each different significance threshold in the conditional phenotype. The quantile of the nominal p-values are plotted on the x-axis, and the nominal -log10(p) values are plotted on the y-axis for T2D and BW respectively. Under the null hypothesis, the strength of pleiotropy enrichment can be reflected by the degree of the leftward shift from the null line. The Q-Q plot falls on the X = Y, which means no enrichment of pleiotropic genetic effect. By contrast, an earlier leftward shift from the null line indicates the existence of pleiotropic enrichment. Greater spacing in the Q-Q plots shows a stronger trend of pleiotropic enrichment shared between the principal and conditional phenotypes.

Then, we presented fold-enrichment plots with "ggplot2 package in R software" [1] to assess further the pleiotropic enrichment between T2D and BW. The plots were formed by nominal -log10(p) values at different stratifications which were divided by the p-value of SNPs for the conditional phenotype ($p \leq 1$; $p \leq 0.1$; $p \leq 0.01$; $p \leq 0.001$). Nominal p values (-log10(p)) are plotted on the x-axis and fold enrichments are plotted on the y-axis. In each cut-off category, we computed the fold-enrichment values (En, as defined below) for all possible p values on the x-axis (between 0 and 10),

$$\mathrm{En[i]} = \frac{N_i}{N_o}$$

and N_i is the proportion of SNPs with -log10(p) $\geq x$, N_0 is the number of all SNPs in each cut-off category, and i is from 1 to N_0. We can observe an upward shift from the expected baseline as the presence of pleiotropy. Also, the greater separation between different stratification indicated a stronger pleiotropy.

The calculation of cFDR and conjunctional cFDR (ccFDR)

The cFDR is an extension of traditional FDR, and this method is well-established and has been widely applied [2], [3–5]. We performed to integrating the two independent GWASs with summary statistics to assess the probability that an SNP has a false positive association with the principal phenotypes under the given p-value for both the principal and conditional phenotypes are smaller than the pre-defined significance thresholds. cFDR was expressed as:

$$\mathrm{cFDR}(p_i|p_j) = \Pr\,(H_0^{(i)}|P_i \leq p_i, P_j \leq p_j)$$

Where p_i is the strength of association for the SNP with the 'principal phenotype', and p_j is the strength of association for the same SNP with the 'conditional phenotype'. Then the $H_0^{(i)}$ stand for the null hypothesis that there is no association between this given SNP and the principal trait. After the data preparation, we computed the cFDR for each SNP where T2D is the principal phenotype conditioned on the strength of association with BW (T2D|BW) and vice versa (BW|T2D). Using this approach, we identified the loci significantly associated with T2D and BW (FDR < 0.5), respectively.

After the calculation of cFDR, we computed the conjunction cFDR (ccFDR) to find the pleiotropic loci. The maximum cFDR value of the two traits was token as the ccFDR value of each variant. An SNP with the ccFDR value smaller than 0.05 was considered to be significantly associated with both T2D and BW.

Manhattan plots for conditional statistics and conjunction statistics

Using "qqman" package in R software [6], we constructed Manhattan plots to visualize the locations of the genetic markers. All SNPs were present in relation to their chromosomal locations. We plotted locations of the 22 chromosomal on the x-axis, and plotted the −log10 the SNPs' values on the y-axis. The SNP with a -log10(cFDR) $\geq$ 1.3 was considered as a locus associated with the principal phenotype given the conditional phenotype. Then, an SNP with − log10 conjunction FDR value is > 1.3 was determined to be associated with both the principal trait.

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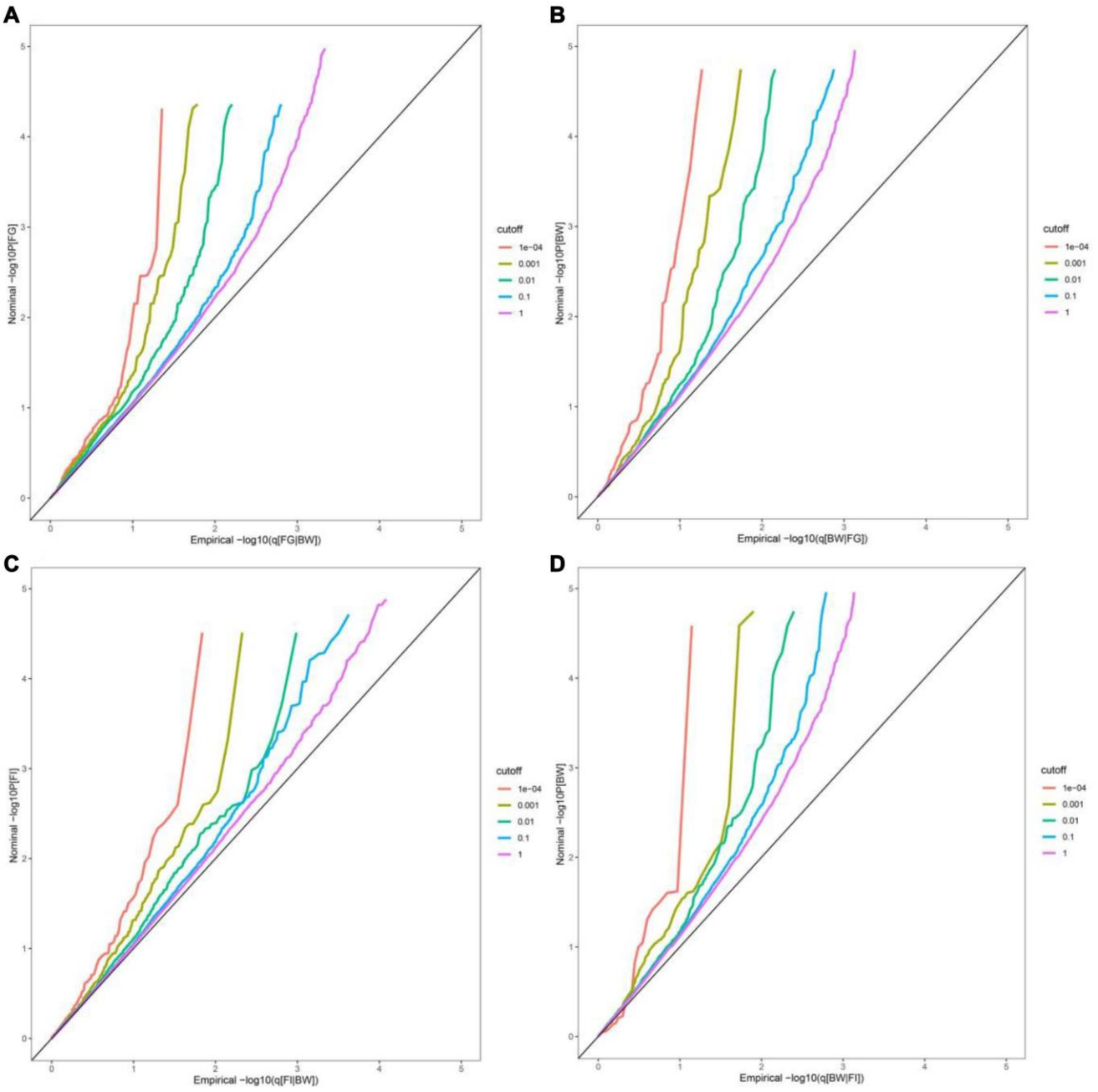
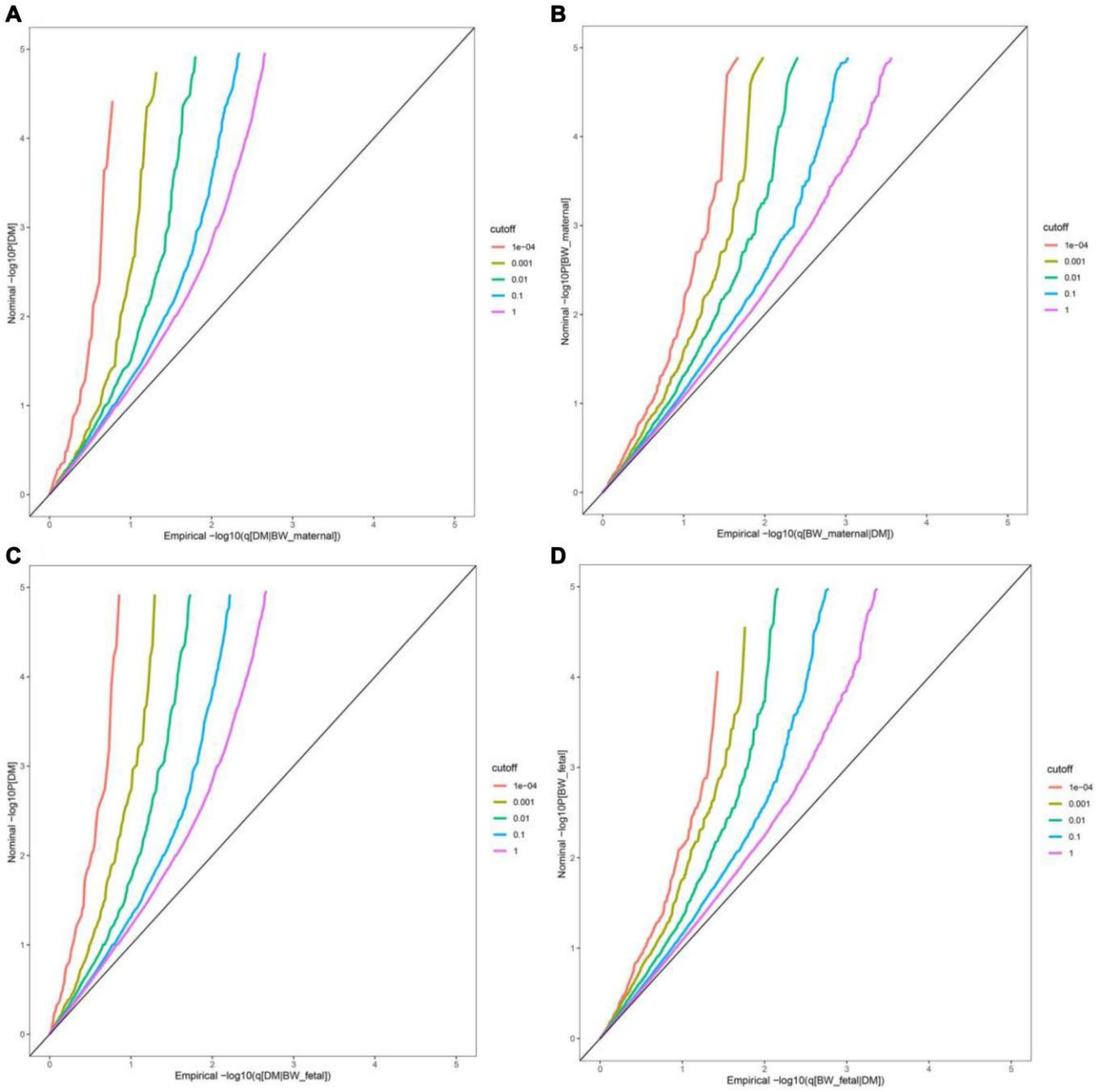
Supplementary Figures



Supplementary Figure 1. Stratified Q-Q plots. Stratified Q-Q plots of nominal versus empirical -log10(*p*) values in FG (**A**) as a function of the significance of the association with BW at the level of -log10(*p*) > 0, -log10(*p*) > 1, -log10(*p*) > 2, -log10(*p*) > 3 corresponding to $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$, and $p \leq 0.0001$, respectively. and (**B**) reversely BW as a function of the significance of the association with FG. in (**C**) FI as a function of significance of the association with BW; and in (**D**) BW as a function of significance with FI.



Supplementary Figure 2. Stratified Q-Q plots. Stratified Q-Q plots of nominal versus empirical -log10(*p*) values in T2D (**A**) as a function of the significance of the association with BW_maternal at the level of -log10(*p*) > 0, -log10(*p*) > 1, -log10(*p*) > 2, -log10(*p*) > 3 corresponding to $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$, and $p \leq 0.0001$, respectively. and (**B**) reversely BW_maternal as a function of the significance of the association with T2D. in (**C**) T2D as a function of significance of the association with BW_fetal; and in (**D**) BW_fetal as a function of significance with T2D.

Supplementary Tables

Supplementary Table 1. Conditional FDR value of 127 CpG-SNPs for T2DM given the BW (cFDR < 0.05).

Variant	chr	Pos	Alt	Gene	Annotation	Snp Type	Gene Type	eQTL/ meQTL/ metaQTL	*P*	cFDR
rs10449766	1	42070125	A/G	HNRNPFP1	28396 upstream	novel	novel		2.60E-03	4.99E-02
rs1415991	1	219625290	A/G	ZC3H11B	12145 upstream	novel	novel		8.60E-06	7.40E-03
rs340883	1	213972363	C/T	PROX1-AS1	non-coding intronic	confirmed	novel		3.80E-07	7.04E-05
rs7553890	1	213832562	T/C	PROX1-AS1	non-coding	novel	novel		2.20E-03	1.89E-02
rs1515114	2	226233671	A/G	AC062015.1	48.3kb upstream	novel	novel	eQTL	1.80E-04	8.17E-03
rs1522812	2	226132738	A/G	AC062015.1	47306 downstream	novel	novel	eQTL	9.30E-06	7.43E-04
rs2894593	2	226325601	T/C	AC062015.1	140230 upstream	novel	novel	eQTL	4.90E-04	9.16E-03
rs7605661	2	43397939	T/C	THADA	intronic	novel	confirmed	meQTL	1.30E-05	3.21E-04
rs12631028	3	12299907	C/T	PPARG	intronic	novel	confirmed	eQTL/meQTL	4.90E-05	4.81E-02
rs17013266	3	23449390	A/G	UBE2E2	intronic	novel	confirmed		1.90E-04	4.85E-02
rs17361324	3	123412407	C/T	ADCY5	intronic	novel	confirmed	meQTL	2.80E-09	8.40E-09
rs2290066	3	185728054	T/C	IGF2BP2, IGF2BP2-AS1	intronic, non-coding intronic	novel	confirmed	eQTL	4.90E-05	3.82E-02
rs4677887	3	123381376	T/G	ADCY5	intronic	confirmed	confirmed	eQTL	3.40E-06	6.80E-06
rs4677889	3	123424425	G/A	ADCY5	intronic	novel	confirmed		2.00E-03	2.53E-02
rs569255	3	125207090	G/A	SLC12A8	intronic	novel	novel	eQTL	1.70E-03	2.27E-02
rs6770420	3	170931960	G/A	KLF7P1	20890 downstream	novel	novel	eQTL/metaQTL	2.40E-05	1.75E-03
rs6794193	3	47073414	T/C	SETD2	intronic	novel	novel		6.60E-03	3.92E-02
rs6795735	3	64719689	C/T	ADAMTS9-AS2	non-coding intronic	confirmed	novel		2.10E-08	3.85E-05
rs720390	3	185830895	G/A	IGF2BP2	5839 upstream	confirmed	confirmed		1.40E-05	1.42E-02
rs9289218	3	123345984	C/T	ADCY5	intronic	novel	confirmed	eQTL	2.50E-03	1.60E-02
rs11097755	4	101788151	T/C	BANK1	intronic	novel	novel		1.60E-06	1.37E-03
rs1216373	4	128576009	C/T	AC078850.1	5478 upstream	novel	novel	metaQTL	6.60E-05	1.07E-02
rs3822109	4	75012761	C/T	PARM1, AC110760.1	coding nonsyn, non-coding intronic	novel	novel		3.20E-05	2.21E-02
rs6446490	4	6322920	G/A	PPP2R2C	3utr	confirmed	novel	eQTL/meQTL	1.70E-10	1.33E-06
rs7663887	4	17901297	C/A	LCORL	intronic	novel	novel	eQTL	8.80E-03	1.89E-02
rs10514870	5	59055501	A/G	PDE4D, AC092343.1	intronic, non-coding intronic	novel	novel		4.20E-03	2.18E-02
rs1650504	5	158602542	G/A	AC091939.1	13996 upstream	novel	novel		8.10E-05	9.88E-03
rs6867983	5	56558326	C/T	C5orf67	intronic	novel	confirmed		7.80E-06	9.07E-03
rs1012635	6	20675064	A/G	CDKAL1	intronic	confirmed	confirmed		4.40E-15	2.64E-14
rs12526403	6	41676676	C/T	TFEB	7302 downstream	novel	novel		1.90E-03	4.50E-02
rs1262557	6	126733443	C/T	RPS4XP9	49596 upstream	novel	novel		6.20E-05	8.80E-03
rs2206734	6	20694653	C/T	CDKAL1	intronic	novel	confirmed	meQTL	2.40E-27	9.60E-27
rs2307306	6	24781507	C/T	GMNN	coding nonsyn	novel	novel	eQTL	3.00E-05	1.82E-02
rs2745929	6	20754530	T/C	CDKAL1	intronic	novel	confirmed		4.50E-10	2.10E-09
rs4897378	6	130217352	C/T	SAMD3	5upstream, intronic	novel	novel	eQTL	4.80E-03	4.54E-02
rs6918311	6	136966564	A/G	RPL35AP3	7366 downstream	confirmed	novel	eQTL/meQTL	6.70E-07	1.16E-03
rs6941340	6	16037321	C/T	AL365265.1	4060 downstream	novel	novel		6.70E-05	4.75E-02
rs10244051	7	15024208	T/G	GTF3AP5	38.1kb upstream	novel	novel		2.40E-08	2.54E-05
rs17158736	7	111692378	G/C	DOCK4	33732 downstream	novel	novel		3.40E-05	3.89E-02
rs17689040	7	40880714	C/G	SUGCT	19951 upstream	novel	novel		2.70E-03	3.04E-02
rs6948511	7	27939096	T/C	JAZF1	intronic	novel	confirmed	metaQTL	5.70E-03	4.02E-02

rs7723	7	44578194	G/A	TMED4	3utr,3downstream	confirmed	novel	eQTL/metaQTL	2.50E-05	4.22E-04
rs7787720	7	13847029	C/T	AC005019.2	7326 downstream	confirmed	novel	eQTL/meQTL/ metaQTL	4.00E-06	3.66E-03
rs849135	7	28156794	G/A	JAZF1	intronic	confirmed	novel	eQTL/meQTL	6.60E-14	5.04E-10
rs1033129	8	138257741	T/C	FAM135B	intronic	novel	confirmed		4.70E-05	6.92E-03
rs2466311	8	117208857	G/C	SLC30A8	32143 upstream	novel	confirmed		1.20E-08	3.28E-05
rs7004862	8	94864735	T/G	INTS8	intronic	novel	confirmed	eQTL/metaQTL	5.50E-05	2.26E-03
rs7816345	8	36988591	C/T	AC090453.1	179 upstream	novel	novel	eQTL/metaQTL	2.30E-03	2.68E-02
rs10739970	9	94134010	A/G	PTPDC1	24154 upstream	novel	novel		9.90E-04	3.18E-02
rs10758593	9	4292083	G/A	GLIS3	intronic	confirmed	novel		2.90E-04	3.60E-02
rs10990568	9	95651855	A/G	AL354861.2	non-coding intronic	novel	novel		1.60E-03	2.46E-02
rs2383208	9	22132077	A/G	CDKN2B-AS1	10980 upstream	novel	confirmed	metaQTL	4.50E-13	2.77E-09
rs579459	9	133278724	T/C	ABO	3510 upstream	novel	confirmed	eQTL/meQTL/ metaQTL	8.50E-07	8.22E-06
rs7018475	9	22137686	T/G	CDKN2B-AS1	16589 upstream	novel	confirmed		7.20E-16	1.29E-11
rs10786044	10	92430823	A/G	MARK2P9	9948 upstream	novel	confirmed	eQTL/metaQTL	4.00E-05	1.36E-02
rs10885410	10	113064714	G/A	TCF7L2	intronic	novel	confirmed		1.60E-11	1.61E-07
rs11196229	10	113106413	G/A	TCF7L2	intronic	novel	confirmed		5.20E-09	2.70E-05
rs12245680	10	113060432	T/C	TCF7L2	intronic	confirmed	confirmed	meQTL	1.10E-10	7.90E-07
rs1225404	10	113154906	C/T	TCF7L2	intronic	novel	confirmed		1.80E-07	4.34E-04
rs1815314	10	79169036	G/A	ZMIZ1	intronic	novel	confirmed		2.90E-05	4.02E-02
rs1867567	10	68223370	G/A	ATOH7	7254 downstream	novel	novel		2.90E-04	4.87E-02
rs190925	10	69561187	G/A	NEUROG3	10511 downstream	novel	novel		4.20E-05	9.12E-03
rs2421019	10	122391070	C/T	PLEKHA1	5upstream	novel	confirmed	eQTL	3.50E-08	1.17E-06
rs2488071	10	92739820	A/G	Y_RNA	29212 upstream	confirmed	novel	eQTL/metaQTL	3.10E-11	1.96E-10
rs7070786	10	92363930	C/T	MARCH5	9966 upstream	novel	novel	eQTL	1.80E-06	9.54E-05
rs7899603	10	92465260	G/C	IDE	intronic	confirmed	confirmed	eQTL	3.80E-06	8.59E-04
rs7904519	10	113014168	A/G	TCF7L2	intronic	novel	confirmed	eQTL/meQTL	3.20E-38	2.00E-33
rs1002226	11	17384070	C/T	AC124798.1	0.5kb upstream	novel	novel	eQTL/meQTL	2.40E-06	2.28E-03
rs11037685	11	43857990	A/G	AC087521.2	non-coding intronic	novel	novel	eQTL	1.80E-06	3.08E-03
rs11819995	11	128519496	C/T	ETS1	intronic	novel	novel	meQTL	5.00E-05	2.86E-02
rs12786533	11	2875083	G/A	KCNQ1DN	2978 upstream	novel	novel	eQTL/meQTL	5.20E-05	4.34E-02
rs1447351	11	92984997	A/G	MTNR1B	3utr	novel	confirmed	metaQTL	8.20E-05	1.47E-03
rs151216	11	2659585	C/T	KCNQ1, KCNQ1OT1	intronic, non-coding	novel	comfirmed, novel		8.70E-07	1.33E-05
rs163171	11	2799835	T/C	KCNQ1	intronic	novel	confirmed	meQTL	8.90E-07	1.95E-03
rs163177	11	2817183	T/C	KCNQ1	intronic	confirmed	confirmed	eQTL	2.00E-12	2.07E-10
rs2237892	11	2818521	C/T	KCNQ1	intronic	novel	confirmed	meQTL/metaQ TL	1.10E-07	4.91E-05
rs231354	11	2685121	T/C	KCNQ1, KCNQ1OT1	intronic, non-coding	confirmed	comfirmed, novel	eQTL/meQTL	3.70E-06	2.40E-04
rs2334499	11	1675619	C/T	FAM99B	7650 downstream	confirmed	novel	eQTL/meQTL	7.30E-05	1.87E-02
rs234857	11	2831299	T/C	KCNQ1	intronic	confirmed	confirmed		2.00E-09	1.09E-06
rs3213225	11	2135306	G/A	IGF2,INS-IGF2	intronic,intronic	novel	confirmed	eQTL/meQTL	8.10E-04	4.15E-03
rs3852527	11	2805373	A/G	KCNQ1	intronic	confirmed	confirmed	eQTL	6.20E-06	1.02E-02
rs4937729	11	132833690	A/C	OPCML	intronic	novel	novel		1.30E-04	2.80E-02
rs1042725	12	65964567	C/T	HMGA2	3utr,3downstream	confirmed	confirmed	metaQTL	7.70E-04	1.54E-03
rs10774202	12	4168281	A/G	AC007207.1	50149 upstream	novel	novel		9.50E-04	2.42E-02
rs10774563	12	120622977	G/A	AC125616.1	6634 downstream	novel	novel	eQTL/metaQTL	3.30E-06	4.76E-03
rs10862960	12	77030355	C/T	E2F7	intronic	novel	novel	eQTL	1.70E-03	2.14E-02

rs10878353	12	65988752	T/C	HMGA2	2245 upstream	novel	confirmed		2.20E-03	5.34E-03
rs1169302	12	120994499	T/G	HNF1A	intronic	novel	novel	eQTL	2.60E-05	3.93E-02
rs12422899	12	133115743	T/C	ZNF891, AC026786.2	3utr, non-coding intronic	novel	novel, novel	eQTL/meQTL	4.90E-05	3.57E-02
rs192210	12	21615041	G/A	GYS2	10194 upstream	novel	novel	eQTL	1.10E-04	4.89E-02
rs3962536	12	22861176	A/G	AC084816.1	non-coding	novel	novel		1.50E-04	4.09E-02
rs4930718	12	123428886	A/G	RILPL2	intronic	novel	novel	eQTL	8.90E-04	6.05E-03
rs12865243	13	40104683	G/A	LINC00598	non-coding intronic	novel	novel		5.80E-03	2.44E-02
rs17202418	13	36163442	T/C	SOHLH2	4766 downstream	novel	novel	metaQTL	3.50E-05	1.31E-02
rs2066612	13	50171259	G/A	DLEU1	non-coding intronic	novel	novel	eQTL/metaQTL	2.70E-05	2.89E-02
rs4885692	13	80066087	C/T	AL158064.2	non-coding intronic	novel	novel		2.30E-05	1.90E-02
rs842379	13	46686202	C/T	LRCH1	intronic	novel	novel		1.60E-05	1.67E-02
rs9532498	13	40104306	G/C	LINC00598	non-coding intronic	novel	novel		2.80E-03	2.05E-02
rs10146260	14	76010803	G/T	IFT43	intronic	novel	novel		3.50E-05	1.57E-02
rs1285850	14	91419362	A/G	AL133153.2	non-coding intronic	confirmed	novel	eQTL	5.80E-05	4.61E-02
rs12894779	14	32835814	G/A	AKAP6	3utr	novel	confirmed		2.70E-04	2.05E-02
rs17117189	14	82713706	G/A	LINC02301	6881 upstream	novel	novel		1.20E-04	4.37E-02
rs11073964	15	91000531	C/T	VPS33B	coding nonsyn	novel	novel	eQTL/meQTL	2.10E-06	3.25E-03
rs1436955	15	62112183	C/T	NPM1P47	28878 upstream	novel	novel	eQTL	2.60E-05	2.87E-02
rs2682920	15	77577575	C/T	AC046168.2	non-coding intronic	novel	novel	eQTL	2.20E-05	1.02E-02
rs7497492	15	23782133	A/G	LOC107984793	intronic	novel	novel		1.90E-04	4.18E-02
rs4625714	16	55607701	C/T	LPCAT2	21031 upstream	novel	novel		1.90E-03	2.64E-02
rs7198093	16	85193257	A/G	GSE1	intronic	novel	novel		3.80E-05	3.09E-02
rs9940128	16	53766842	G/A	FTO	intronic	confirmed	confirmed		2.60E-22	5.61E-18
rs11651755	17	37739849	C/T	HNF1B	intronic	confirmed	confirmed		3.40E-08	2.27E-05
rs1402657	17	9886035	C/T	GLP2R	intronic	novel	confirmed	eQTL	4.50E-05	2.78E-02
rs1531798	17	78826049	A/G	USP36	intronic	novel	novel	eQTL	9.90E-05	7.84E-03
rs198542	17	50567176	G/A	CACNA1G	intronic	novel	novel		5.20E-04	9.15E-03
rs2290770	17	75834935	G/A	UNC13D	coding syn	novel	novel		3.80E-06	4.72E-03
rs2291725	17	48961770	T/C	GIP	coding nonsyn	novel	confirmed	eQTL/meQTL	7.10E-06	4.30E-03
rs390200	17	7206676	A/G	DLG4	intronic	novel	novel	eQTL	1.50E-02	1.88E-02
rs6565531	17	81049580	G/A	BAIAP2	intronic	novel	novel	eQTL/meQTL	3.90E-04	1.88E-02
rs878619	17	50555910	A/G	SPATA20	58 upstream	novel	novel	eQTL/meQTL	2.00E-04	2.23E-03
rs9303407	17	59299448	A/G	SNRPGP17	18105 upstream	novel	novel	eQTL	2.90E-04	3.20E-02
rs11659412	18	7063533	G/A	LAMA1	intronicc	novel	confirmed	metaQTL	1.70E-06	5.46E-03
rs7238644	18	29436831	C/T	AC074237.1	74868 upstream	novel	novel		4.30E-05	3.57E-02
rs1205438	20	38247165	C/T	KIAA1755	intronic	novel	novel	eQTL	1.10E-04	2.19E-02
rs2426778	20	58718421	G/A	NPEPL1	non-coding	novel	novel	eQTL	7.70E-03	4.76E-02
rs926345	20	41143307	T/C	PLCG1	intronic	novel	novel	eQTL/meQTL	5.70E-03	3.11E-02
rs11908784	21	19628605	A/G	AP000403.1	7060 upstream	novel	novel		5.80E-05	2.92E-02
rs137848	22	50001867	T/C	IL17REL	intronic	novel	novel	eQTL/meQTL	3.00E-06	3.55E-04
rs6006393	22	30194037	T/C	AC002378.1	non-coding intronic	confirmed	novel		2.00E-06	2.14E-04

Supplementary Table 2. meQTL associated effects of novel CpG-SNPs.

CpG-SNP	Traits	Chr	Allele	Gene	Pos	meQTL Type	*P* value
rs7605661	Pleiotropic	2	T/C	THADA	43397939	cis	3.23E-29
rs17361324	Pleiotropic	3	C/T	ADCY5	123412407	cis	1.77E-38
rs6794193(LD to rs295442)	Pleiotropic	3	T/C	SETD2	47073414	cis	1.06E-33
rs6794193(LD to rs295458)	Pleiotropic	3	T/C	SETD2	47073414	cis	6.79E-21
rs6794193(LD to rs4078466)	Pleiotropic	3	T/C	SETD2	47073414	cis	3.27E-310
rs6794193(LD to rs6785790)	Pleiotropic	3	T/C	SETD2	47073414	cis	3.27E-310
rs2206734	Pleiotropic	6	C/T	CDKAL1	20694653	trans	1.71E-07
rs579459	Pleiotropic	9	T/C	ABO	133278724	cis	1.45E-09
rs163177	Pleiotropic	11	T/C	KCNQ1	2799835	cis	1.71E-58
rs231354	Pleiotropic	11	T/C	KCNQ1, KCNQ1OT1	2685121	cis	1.43E-29
rs231354(LD to rs462402)	Pleiotropic	11	T/C	KCNQ1, KCNQ1OT1	2685121	cis	4.17E-46
rs3213225	Pleiotropic	11	G/A	IGF2, INS-IGF2	2135306	cis	4.24E-07
rs6565531	Pleiotropic	17	G/A	BAIAP2	81049580	cis	3.27E-310
rs878619(LD to rs989128)	Pleiotropic	17	A/G	SPATA20	50555910	cis	1.28E-43
rs926345(LD to rs4297946)	Pleiotropic	20	T/C	PLCG1	41143307	trans	1.61E-14
rs137848(LD to rs137864)	Pleiotropic	22	T/C	IL17REL	50001867	cis	5.70E-24
rs137848(LD to rs5771222)	Pleiotropic	22	T/C	IL17REL	50001867	cis	9.01E-147
rs12631028(LD to rs12493718)	DM	3	C/T	PPARG	12299907	cis	7.39E-07
rs6446490	DM	4	G/A	PPP2R2C	6322920	cis	2.81E-16
rs6918311(LD to rs947733)	DM	6	A/G	RPL35AP3	136966564	cis	7.58E-110
rs7787720(LD to rs17167582)	DM	7	C/T	AC005019.2	13847029	cis	2.04E-22
rs849135	DM	7	G/A	JAZF1	28156794	trans	1.22E-07
rs12245680	DM	10	T/C	TCF7L2	113060432	cis	8.59E-05
rs7904519(LD to rs7077247)	DM	10	A/G	TCF7L2	113014168	cis	9.91E-09
rs1002226(LD to rs2074314)	DM	11	C/T	AC124798.1	17384070	cis	5.01E-05
rs11819995	DM	11	C/T	ETS1	128519496	cis	5.19E-05
rs12786533(LD to rs16924912)	DM	11	G/A	KCNQ1DN	2875083	cis	1.48E-28
rs2237892(LD to rs2283228)	DM	11	C/T	KCNQ1	2818521	cis	1.45E-10
rs2334499	DM	11	C/T	FAM99B	1675619	cis	4.05E-09
rs12422899(LD to rs11147248)	DM	12	T/C	ZNF891, AC026786.2	133115743	cis	2.13E-12
rs11073964	DM	15	C/T	VPS33B	91000531	cis	5.73E-05
rs2291725(LD to rs3895874)	DM	17	T/C	GIP	48961770	cis	1.62E-06
rs10807805(LD to rs4719646)	BW	7	CA/C,CG	AMZ1	2714216	cis	6.51E-17
rs2886070	BW	1	G/A	ARHGEF2	156004180	cis	2.43E-11
rs6687139	BW	1	A/G	LINC01681	170204121	cis	1.90E-05
rs12623454(LD to rs1869026)	BW	2	G/C	AC073257.1	120568721	cis	5.30E-08
rs2952769(LD to rs2464975)	BW	2	T/C	METTL21A	207629538	cis	1.55E-154
rs4853831	BW	2	T/C	MYT1L, AC093390.2	1809892	cis	1.60E-77
rs6918981	BW	6	G/A	AL354740.1	34270737	trans	2.57E-07
rs7766106(LD to rs9491706)	BW	6	C/T	RSPO3	127133993	cis	1.41E-44
rs2191883(LD to rs4720169)	BW	7	T/C	TBX20	35233679	cis	5.16E-06
rs855715	BW	10	G/T	ADRB1	114063765	cis	2.48E-06
rs4980661(LD to rs12365305)	BW	11	G/A	AP000439.2	69491811	cis	1.02E-04
rs12306172(LD to rs35786993)	BW	12	G/A	SMUG1, SMUG1-AS1	54145221	cis	7.72E-05
rs2293429(LD to rs2272300)	BW	12	A/C	CSAD	53180119	cis	7.73E-36

rs3184504	BW	12	T/C	SH2B3	111446804	cis	6.30E-07
rs3184504(LD to rs10774625)	BW	12	T/C	SH2B3	111446804	trans	4.10E-16
rs3184504(LD to rs653178)	BW	12	T/C	SH2B3	111446804	trans	9.62E-17
rs8039305	BW	15	T/C	FURIN	90879313	cis	3.63E-29
rs11079803	BW	17	G/A	PNPO	47942535	cis	5.25E-09
rs3760318	BW	17	G/A	ADAP2	30920697	cis	3.46E-05
rs4647887	BW	17	A/G	SNHG16	76562724	cis	6.23E-20
rs12455403	BW	18	T/C	EPB41L3	5620115	cis	2.22E-07
rs2261988	BW	19	G/T	UHRF1	4910877	cis	1.83E-05
rs2261988(LD to rs2602710)	BW	19	G/T	UHRF1	4910877	cis	1.85E-17
rs2261988(LD to rs3786942)	BW	19	G/T	UHRF1	4910877	cis	6.37E-231
rs2261988(LD to rs4544355)	BW	19	G/T	UHRF1	4910877	cis	1.55E-154
rs492602	BW	19	A/G	FUT2	48703160	trans	2.50E-07
rs492602(LD to rs281379)	BW	19	A/G	FUT2	48703160	trans	8.68E-08
rs492602(LD to rs503279)	BW	19	A/G	FUT2	48703160	trans	6.56E-08
rs492602(LD to rs504963)	BW	19	A/G	FUT2	48703160	cis	7.75E-10
rs492602(LD to rs601338)	BW	19	A/G	FUT2	48703160	cis	1.61E-222
rs492602(LD to rs602662)	BW	19	A/G	FUT2	48703160	trans	2.42E-08
rs492602(LD to rs681343)	BW	19	A/G	FUT2	48703160	cis	2.64E-257
rs5765275(LD to rs2272804)	BW	22	A/G	SMC1B	45352459	cis	3.27E-310
rs5765275(LD to rs5765335)	BW	22	A/G	SMC1B	45352459	cis	3.27E-310

Supplementary Table 3. metabolic QTL (mQTL) Effect of Novel CpG-SNPs.

rsID	Traits	Metabolics	related disease or biofunctions (PMID)	Sample Type	*P*	Source	PMID
rs677042	Pleiotropic	ursodeoxycholate	Colorectal cancer (23940645)	serum	4.71E-05	SI data (Shin et al.)	24816252
rs6948511	Pleiotropic	X-11795		serum	3.30E-06	SI data (Shin et al.)	24816252
rs7723	Pleiotropic	1-oleoylglycerophosphocholine	T2D (2528830)	serum	2.12E-05	SI data (Shin et al.)	24816252
rs1042725	Pleiotropic	serine	Pancreatic cancer (20300169), Obesity (24740590)	serum	7.98E-07	SI data (Shin et al.)	24816252
rs1447351	Pleiotropic	X-13619		serum	4.98E-05	SI data (Shin et al.)	24816252
rs2488071	Pleiotropic	21-hydroxypregnenolone disulfate		serum	7.04E-07	SI data (Long et al.)	28263315
		leucine	Pancreatic cancer (20300169), Colorectal cancer (27275383)	serum	8.11E-05	SI data (Shin et al.)	24816252
rs579459	Pleiotropic	glycylglycine	Colorectal cancer (27275383), Alzheimer's disease (28951883)	serum	8.38E-10	SI data (Long et al.)	28263315
		phenylalanylserine	Colorectal cancer (27275383)	serum	2.78E-06	SI data (Long et al.)	28263315
		leucylalanine	Colorectal cancer (27275383), Pancreatic cancer (20300169), Uremia (22626821)	serum	8.62E-11	SI data (Long et al.)	28263315
		X-17178		serum	1.57E-09	SI data (Long et al.)	28263315
		alpha-glutamylglycine		serum	5.11E-09	SI data (Long et al.)	28263315
		X-14086		serum	5.15E-05	SI data (Shin et al.)	24816252
		ADpSGEGDFXAEGGGVR*	T2D (30372032)	serum	2.09E-19	SI data (Shin et al.)	24816252
		phenylalanylserine	Colorectal cancer (27275383)	serum	3.53E-07	SI data (Shin et al.)	24816252
		leucylalanine	Colorectal cancer (27275383), Pancreatic cancer (20300169), Uremia (22626821)	serum	1.26E-08	SI data (Shin et al.)	24816252
		alpha-glutamyltyrosine	Colorectal cancer (27275383)	serum	2.64E-05	SI data (Shin et al.)	24816252
		aspartylphenylalanine	Colorectal cancer (27275383)	serum	5.21E-07	SI data (Shin et al.)	24816252
		O-sulfo-L-tyrosine	CKD (26449609)	serum	3.03E-09	SI data (Shin et al.)	24816252
rs7004862	Pleiotropic	SM C24:0		serum	5.19E-05	SI data (Draisma et al.)	26068415
rs7816345	Pleiotropic	PC aa C34:4	Obesity (26910390)	serum	7.47E-05	SI data (Draisma et al.)	26068415
		hyodeoxycholate	Primary biliary cirrhosis (2621422)	serum	2.87E-05	SI data (Suhre et al.)	21886157
rs7787720	T2D	salicyluric glucuronide*		serum	9.33E-05	SI data (Shin et al.)	24816252
rs2383208	T2D	lysine	Pancreatic cancer (20300169), Colorectal cancer (20156336)	serum	8.79E-06	SI data (Shin et al.)	24816252
rs10786044	T2D	2-hydroxypalmitate	CKD (5672969)	serum	8.89E-05	SI data (Shin et al.)	24816252
rs2237892	T2D	gamma-glutamylvaline	Inflammatory Response (28691814)	serum	6.02E-05	SI data (Suhre et al.)	21886157
		N2,N2-dimethylguanosine	Kidney disease (9607216)	serum	9.42E-05	SI data (Shin et al.)	24816252

rs1216373	T2D	ergothioneine		serum	8.69E-05	SI data (Shin et al.)	24816252
rs10774563	T2D	butyrylcarnitine	Obesity (26910390)	serum	5.32E-121	SI data (Shin et al.)	24816252
		ethylmalonate	Anorexia nervosa (10197568), Malonyl-Coa decarboxylase deficiency (9177981)	serum	1.92E-62	SI data (Long et al.)	28263315
		butyrylcarnitine	Obesity (26910390)	serum	7.94E-50	SI data (Long et al.)	28263315
		methylsuccinate	Colorectal cancer (27275383)	serum	8.82E-19	SI data (Long et al.)	28263315
		butyrylcarnitine	Obesity (26910390)	serum	2.20E-16	SI data (Suhre et al.)	21886157
rs17202418	T2D	dihomo-linolenate (20:3n3 or n6)	oxidative stress (24760997)	serum	4.82E-05	SI data (Suhre et al.)	21886157
rs2066612	T2D	X-11847		serum	8.27E-05	SI data (Shin et al.)	24816252
rs11659412	T2D	X-23026		serum	9.85E-06	SI data (Long et al.)	28263315
		methylamine	Uremia (22626821), Crohn's disease (17269711)	urine	3.76E-05	SI data (Raffler et al.)	26352407
rs11125079	BW	HWESASXX*		serum	7.34E-05	SI data (Suhre et al.)	21886157
rs7701346	BW	X-11261		serum	4.81E-05	SI data (Shin et al.)	24816252
rs863818	BW	1-methylxanthine	Colorectal cancer (27275383)，Asthma (15537072)	serum	2.95E-05	SI data (Suhre et al.)	21886157
rs3750640	BW	phenylalanylserine	Colorectal cancer (27275383)	serum	1.85E-05	SI data (Shin et al.)	24816252
rs9416062	BW	2-hydroxyisobutyrate	Colorectal cancer (27275383)	urine	5.38E-05	SI data (Raffler et al.)	26352407
rs11051137	BW	X-24309		serum	7.93E-06	SI data (Long et al.)	28263315
rs3184504	BW	hypoxanthine	Colorectal cancer (27275383), Pancreatic cancer (20300169), Uremia (22626821)	serum	8.94E-07	SI data (Long et al.)	28263315
		C-glycosyltryptophan*		serum	1.66E-05	SI data (Shin et al.)	24816252
		gamma-glutamylleucine	Colorectal cancer (27275383)	serum	9.21E-05	SI data (Shin et al.)	24816252
		kynurenine	Crohn's disease (27609529), Ulcerative colitis (27609529)	serum	6.05E-18	SI data (Shin et al.)	24816252
		erythronate*	Colorectal cancer (27275383)	serum	8.62E-06	SI data (Shin et al.)	24816252
		laurate (12:0)		serum	8.19E-05	SI data (Suhre et al.)	21886157
rs7296248	BW	glycodeoxycholate	Colorectal cancer (27275383)	serum	7.18E-05	SI data (Shin et al.)	24816252
rs2586211	BW	allantoin	Crohn's disease (27609529), Colorectal cancer (25037050)	serum	5.80E-05	SI data (Shin et al.)	24816252
rs492602	BW	ADpSGEGDFXAEGGGVR*	T2D (30372032)	serum	2.62E-11	SI data (Shin et al.)	24816252
		X-08402		serum	2.03E-05	SI data (Shin et al.)	24816252
		citrulline	Crohn's disease (27609529), Gout (28270806)	serum	7.45E-05	SI data (Shin et al.)	24816252
rs533318		tiglyl carnitine		serum	4.81E-05	SI data (Suhre et al.)	21886157

Supplementary Table 4. metabolic pathway analysis (*P* < 0.05).

Traits	Pathway	Total	Hits	Impact	*P*-value	Details
T2D	Aminoacyl-tRNA biosynthesis	75	4	0.11268	9.15E-04	KEGG
	alpha-Linolenic acid metabolism	29	2	0.20335	1.34E-02	KEGG
	Methane metabolism	34	2	0.01778	1.81E-02	KEGG
	Glycerophospholipid metabolism	39	2	0.1037	2.35E-02	KEGG
BW	Aminoacyl-tRNA biosynthesis	75	3	0.05634	8.26E-03	KEGG
	Glycerophospholipid metabolism	39	2	0.1037	2.06E-02	KEGG

Supplementary Table 5. Conditional FDR value of 188 CpG-SNPs for BW given the T2DM (cFDR < 0.05).

Variant	Chr	Pos	Alt	Gene	Annotation	Snp Type	Gene Type	eQTL/meQTL/ metaQTL	*P*	cFDR
rs10449766	1	42070125	A/G	HNRNPFP1	28396 upstream	novel	novel		2.00E-03	3.73E-02
rs11264298	1	155036782	G/A	DCST1	intronic	novel	novel	eQTL	6.80E-05	3.07E-02
rs11537641	1	42930743	G/A	SLC2A1	coding syn	novel	novel		4.90E-05	4.43E-02
rs11589239	1	227849577	C/T	PRSS38	3107 upstream	novel	novel	eQTL	5.80E-04	3.77E-02
rs1415181	1	214857808	T/C	GAPDHP24	12926 downstream	novel	novel		3.70E-06	5.20E-03
rs2744718	1	22197234	T/C	WNT4	53265 upstream	novel	novel	eQTL	3.50E-06	4.00E-03
rs2886070	1	156004180	G/A	ARHGEF2	intronic	novel	novel	eQTL/meQTL	3.50E-08	3.39E-05
rs340883	1	213972363	C/T	PROX1-AS1	non-coding intronic	novel	novel		7.10E-03	2.13E-02
rs6687139	1	170204121	A/G	LINC01681	non-coding intronic	novel	novel	eQTL/meQTL	3.80E-05	3.54E-02
rs7527321	1	232632149	T/C	RNU6-1211P	68055 downstream	novel	novel		1.30E-05	1.64E-02
rs7542242	1	22151000	C/T	WNT4	7031 upstream	novel	novel	eQTL	3.80E-05	3.62E-02
rs7553890	1	213832562	T/C	PROX1-AS1	non-coding	novel	novel		6.70E-05	2.53E-03
rs10165908	2	157459117	T/C	CYTIP	intronic	novel	novel		5.40E-05	3.17E-02
rs11125079	2	46505076	C/T	ATP6V1E2	non-coding intronic	novel	novel	eQTL/metaQTL	9.50E-06	1.04E-02
rs12476224	2	56154789	A/G	AC011306.1, AC007744.1	non-coding intronic, non-coding intronic	novel	novel		2.40E-04	3.82E-02
rs12623454	2	120568721	G/C	AC073257.1	10612 upstream	novel	novel	meQTL	2.40E-05	1.66E-02
rs1515114	2	226233671	A/G	AC062015.1	48300 upstream	novel	novel	eQTL	2.60E-03	1.82E-02
rs1522812	2	226132738	A/G	AC062015.1	47306 downstream	novel	novel	eQTL	4.30E-03	1.55E-02
rs17745230	2	46263191	C/T	Metazoa_SRP	3499 downstream	novel	novel	eQTL	9.10E-07	1.01E-03
rs1901263	2	46591447	C/T	PIGF	intronic	novel	novel	eQTL	3.50E-05	1.21E-02
rs2894593	2	226325601	T/C	AC062015.1	140230 upstream	novel	novel	eQTL	3.80E-04	6.05E-03
rs2952769	2	207629538	T/C	METTL21A	3610 upstream	novel	novel	eQTL/meQTL	8.50E-06	8.79E-03
rs34367192	2	9502349	C/T	ADAM17	intronic	novel	novel	eQTL	2.50E-04	1.29E-02
rs4669521	2	10051809	G/A	KLF11	intronic	novel	novel	eQTL	6.20E-05	4.91E-02
rs4853831	2	1809892	T/C	MYT1L, AC093390.2	intronic, non-coding	novel	novel	eQTL/meQTL	5.10E-05	2.71E-02
rs6735418	2	43002048	A/G	AC016735.1	non-coding intronic	novel	novel	eQTL	1.00E-05	1.34E-02
rs7561273	2	24024644	A/G	MFSD2B	intronic	novel	novel	eQTL	2.10E-07	2.56E-04
rs7605661	2	43397939	T/C	THADA	intronic	novel	novel	meQTL	3.90E-04	1.87E-03
rs935172	2	26581379	T/C	CIB4	coding nonsyn	novel	novel		9.30E-05	3.71E-02
rs17290714	3	47854215	C/T	MAP4	intronic	novel	novel	eQTL	1.80E-05	1.87E-02
rs17361324	3	123412407	C/T	ADCY5	intronic	novel	novel	meQTL	8.00E-20	1.20E-18
rs2306531	3	157099873	C/T	LINC00880, LINC00881	non-coding intronic, 3downstream	novel	novel	eQTL	8.60E-06	1.34E-02
rs4677887	3	123381376	T/G	ADCY5	intronic	confirmed	confirmed	eQTL	2.30E-12	2.91E-11

rs4677889	3	123424425	G/A	ADCY5	intronic	novel	novel		4.50E-04	1.02E-02
rs4681161	3	148891258	T/C	AC092979.1, CPA3	non-coding intronic, intronic	novel	novel	eQTL	4.40E-09	3.45E-06
rs569255	3	125207090	G/A	SLC12A8	intronic	novel	novel	eQTL	4.50E-04	1.01E-02
rs6770420	3	170931960	G/A	KLF7P1	20890 downstream	novel	novel	eQTL/metaQTL	4.60E-03	1.63E-02
rs6794193	3	47073414	T/C	SETD2	intronic	novel	novel	eQTL/meQTL	4.20E-05	3.02E-03
rs870429	3	123159172	A/G	PDIA5	intronic	novel	novel	eQTL	1.20E-04	2.42E-02
rs900399	3	157080943	A/G	LINC00880	724 downstream	novel	novel	eQTL	2.90E-41	4.05E-37
rs9289218	3	123345984	C/T	ADCY5	intronic	novel	novel	eQTL	1.80E-05	8.91E-04
rs10020719	4	129331259	A/G	AC082650.1	26237 upstream	novel	novel		5.00E-05	2.21E-02
rs1129998	4	150798111	A/G	LRBA	coding syn	novel	novel		1.00E-05	9.19E-03
rs12502033	4	144701499	T/C	HHIP, GYPA	intron, intron	novel	novel		1.10E-07	1.39E-04
rs17447835	4	42592928	A/G	ATP8A1	intronic	novel	novel	eQTL	8.00E-05	4.72E-02
rs2301718	4	105088606	G/A	AC096577.1	non-coding intronic	novel	novel		6.60E-05	4.59E-02
rs7663887	4	17901297	C/A	LCORL	intronic	novel	novel	eQTL	2.70E-09	5.90E-07
rs7682893	4	130355629	G/A	LINC02479	20600 downstream	novel	novel		2.60E-05	2.68E-02
rs10514870	5	59055501	A/G	PDE4D, AC092343.1	intron, non-coding intronic	novel	novel		5.00E-06	4.17E-04
rs110873	5	57632548	A/G	AC008780.2	15117 upstream	novel	novel	eQTL	3.60E-05	3.52E-02
rs12653511	5	77014955	A/G	AGGF1	14296 downstream	novel	novel		3.00E-05	2.94E-02
rs13153101	5	68289314	A/C	PIK3R1	intronic	novel	novel		5.00E-06	7.86E-03
rs1705392	5	67204440	C/G	CD180	7641 upstream	novel	novel		6.90E-04	3.55E-02
rs4130707	5	85071655	G/T	AC114928.1	40687 downstream	novel	novel		9.50E-05	4.75E-02
rs4699908	5	57618434	G/A	AC008780.2	1003 upstream	novel	novel		4.50E-06	3.46E-03
rs6556350	5	158452481	C/T	AC091979.1	non-coding	novel	novel		2.30E-06	2.55E-03
rs7701346	5	134492665	A/G	AC005355.1	146 upstream	novel	novel	eQTL/metaQTL	4.20E-04	2.43E-02
rs7717779	5	8429660	C/T	LINC02226, C091965.1	non-coding intronic, non-coding intronic	novel	novel		3.40E-05	4.17E-03
rs845734	5	109687709	C/A	AC012603.1	93 downstream	novel	novel	eQTL	2.00E-05	1.36E-02
rs863818	5	68258195	A/G	PIK3R1	intronic	novel	novel	metaQTL	1.10E-05	1.22E-02
rs10080410	6	132289467	G/A	MOXD1	6588 downstream	novel	novel		8.60E-04	2.81E-02
rs1012635	6	20675064	A/G	CDKAL1	intronic	confirmed	confirmed		4.00E-10	1.00E-09
rs1040525	6	142382532	C/T	ADGRG6	intronic	novel	novel	eQTL	6.10E-05	4.91E-02
rs10946101	6	165751179	C/G	PDE10A	non-coding intronic	novel	novel		7.20E-04	2.46E-02
rs10947463	6	33879300	G/A	LINC01016	non-coding intronic	novel	novel	eQTL	2.20E-05	2.04E-02
rs10947659	6	37141909	C/A	PIM1	28294 downstream	novel	novel		1.80E-05	2.05E-02
rs12526403	6	41676676	C/T	TFEB	7302 downstream	novel	novel		2.10E-03	3.83E-02
rs1361024	6	151749793	G/A	ESR1	intronic	novel	novel		8.00E-06	1.25E-02
rs1415701	6	130024690	G/A	L3MBTL3	intronic	confirmed	novel	eQTL	4.00E-11	3.30E-07
rs1547669	6	33807864	A/G	MLN	3853 upstream	novel	novel	eQTL	1.00E-05	5.28E-03
rs2206734	6	20694653	C/T	CDKAL1	intronic	novel	novel	meQTL	2.40E-17	4.80E-17
rs2273669	6	108963986	A/G	ARMC2	intronic	novel	novel	eQTL	7.60E-06	1.07E-02
rs2745929	6	20754530	T/C	CDKAL1	intronic	novel	novel		1.10E-09	4.77E-09
rs2982570	6	151692613	C/T	ESR1	intronic	novel	novel		4.30E-07	3.38E-04
rs4897378	6	130217352	C/T	SAMD3	5upstream	novel	novel	eQTL	2.80E-04	1.20E-02
rs6918981	6	34270737	G/A	AL354740.1	non-coding intronic	novel	novel	eQTL/meQTL	1.10E-05	5.44E-03
rs6933511	6	130135793	A/C	L3MBTL3, KLF7P1	intronic, non-coding intronic	novel	novel	eQTL	2.60E-06	1.71E-03
rs7766106	6	127133993	C/T	RSPO3	intronic	novel	novel	eQTL/meQTL	2.60E-05	1.48E-02
rs9385532	6	130050082	T/C	L3MBTL3	intronic	novel	novel	eQTL	2.00E-04	4.18E-02

rs9492469	6	130169033	G/A	SAMD3	intronic	novel	novel	eQTL	1.80E-05	2.01E-02
rs10807805	7	2714216	CA/C,CG	AMZ1	3utr	novel	novel	eQTL/meQTL	1.40E-07	4.61E-04
rs12704091	7	149267936	A/G	ZNF783	intronic	novel	novel	eQTL	9.70E-07	1.10E-03
rs17401675	7	73643220	A/G	MLXIPL	18677 upstream	novel	confirmed	eQTL	1.50E-11	2.12E-08
rs17689040	7	40880714	C/G	SUGCT	19951 upstream	novel	novel		6.20E-04	1.31E-02
rs2191883	7	35233679	T/C	TBX20	intronic	novel	novel	meQTL	4.20E-06	7.90E-03
rs2389995	7	18933395	A/G	HDAC9	intronic	novel	novel		6.30E-05	3.34E-02
rs4143341	7	159262263	A/G	PIP5K1P2	28886 upstream	novel	novel	eQTL	3.20E-06	6.93E-03
rs6947302	7	149172403	T/C	ZNF398	intronic	novel	novel		5.40E-04	4.31E-02
rs6948511	7	27939096	T/C	JAZF1	intronic	novel	novel	metaQTL	9.50E-05	5.80E-03
rs7723	7	44578194	G/A	TMED4	3utr	novel	novel	eQTL/metaQTL	1.40E-04	8.40E-04
rs12677785	8	141243157	A/G	SLC45A4	intronic	novel	novel	eQTL	2.70E-05	1.20E-02
rs17217757	8	105601093	G/C	ZFPM2	intronic	novel	novel		5.90E-05	3.12E-02
rs6989280	8	125496504	G/A	AC091114.1	non-coding intronic	confirmed	novel		5.00E-08	1.10E-04
rs7004862	8	94864735	T/G	INTS8	intronic	novel	novel	eQTL/metaQTL	1.70E-03	9.35E-03
rs7816345	8	36988591	C/T	AC090453.1	179 upstream	novel	novel	eQTL/metaQTL	4.20E-04	1.05E-02
rs10739970	9	94134010	A/G	PTPDC1	24154 upstream	novel	novel		3.00E-03	3.78E-02
rs10816736	9	108835654	C/T	AL359692.1	679 downstream	novel	novel	eQTL	1.40E-04	3.67E-02
rs10990568	9	95651855	A/G	AL354861.2	non-coding intronic	novel	novel		5.30E-04	1.19E-02
rs2000244	9	123211138	A/G	STRBP	intronic	novel	novel	eQTL	1.80E-10	2.33E-07
rs2236407	9	95475514	A/G	PTCH1	intronic	novel	novel	eQTL	1.70E-08	2.48E-05
rs473902	9	95493953	T/G	PTCH1	intronic	novel	novel		6.70E-07	1.49E-03
rs534643	9	111276424	C/T	AL162414.1	non-coding intronic	novel	novel		1.20E-04	4.35E-02
rs579459	9	133278724	T/C	ABO	3510 upstream	novel	novel	eQTL/meQTL/ metaQTL	8.30E-06	3.60E-05
rs9721852	9	89748077	T/C	UNQ6494	28318 upstream	novel	novel		1.10E-05	1.39E-02
rs11250238	10	1043676	T/C	IDI2-AS1/IDI1	intron,intron	novel	novel	eQTL	4.00E-06	1.80E-03
rs1638410	10	116766015	T/C	HSPA12A	intronic	novel	novel		5.70E-05	3.56E-02
rs17566087	10	69219200	A/G	AL596223.1	non-coding intronic	novel	novel	eQTL	2.30E-05	2.50E-02
rs2421019	10	122391070	C/T	PLEKHA1	5upstream,intronic	novel	novel	eQTL	2.70E-04	9.45E-04
rs2488071	10	92739820	A/G	Y_RNA	29212 upstream	novel	novel	eQTL/metaQTL	2.70E-08	9.00E-08
rs3750640	10	5654519	G/A	ASB13	intronic	novel	novel	eQTL/metaQTL	3.00E-04	3.08E-02
rs7070786	10	92363930	C/T	5-Mar	9966 upstream	novel	novel	eQTL	1.50E-03	4.80E-03
rs7088711	10	102799509	G/A	WBP1L	intronic	novel	novel	eQTL	4.50E-05	5.71E-03
rs855715	10	114063765	G/T	ADRB1	16857 upstream	novel	novel	meQTL	1.50E-07	1.65E-04
rs9416062	10	75490730	A/G	LRMDA	intronic	novel	novel	eQTL/metaQTL	3.40E-04	3.70E-02
rs10840346	11	10041452	G/A	SBF2	intronic	novel	novel	eQTL	7.00E-07	7.60E-04
rs1447351	11	92984997	A/G	MTNR1B	3utr	novel	novel	metaQTL	2.30E-04	2.05E-03
rs151216	11	2659585	C/T	KCNQ1, KCNQ1OT1	intronic, non-coding	novel	novel		5.10E-05	1.97E-04
rs163177	11	2817183	T/C	KCNQ1	intronic	novel	novel	eQTL/meQTL	5.70E-04	1.52E-03
rs1944055	11	58575156	A/G	LPXN	intronic	novel	novel		3.80E-04	3.97E-02
rs231354	11	2685121	T/C	KCNQ1, KCNQ1OT1	intron, non-coding	confirmed	confirmed	eQTL/meQTL	2.80E-03	9.10E-03
rs234857	11	2831299	T/C	KCNQ1	intronic	novel	novel		2.00E-02	4.67E-02
rs3213225	11	2135306	G/A	IGF2, INS-IGF2	intronic, intronic	novel	novel	eQTL/meQTL	2.70E-06	9.59E-05
rs4980661	11	69491811	G/A	AP000439.2	11871 upstream	novel	novel	meQTL	1.00E-04	1.98E-02
rs546240	11	30512075	C/T	MPPED2	intronic	novel	novel	eQTL	4.40E-05	3.71E-02
rs6590039	11	124071072	G/T	OR10D5P	15365 upstream	novel	novel		2.20E-05	2.40E-02

rs936370	11	81264293	C/T	MTND4LP18	287933 downstream	novel	novel		3.10E-04	4.26E-02
rs1042725	12	65964567	C/T	HMGA2	3utr	confirmed	confirmed	metaQTL	7.10E-32	1.90E-29
rs10774202	12	4168281	A/G	AC007207.1	50149 upstream	novel	novel		1.60E-03	2.32E-02
rs10862960	12	77030355	C/T	E2F7	intronic	novel	novel	eQTL	2.50E-04	7.30E-03
rs10878353	12	65988752	T/C	HMGA2	22457 upstream	novel	novel		1.40E-08	1.04E-06
rs10878359	12	66010844	T/C	MIR6074	12776 downstream	novel	novel		4.90E-10	1.36E-06
rs11051137	12	30884947	G/A	AC010198.2	22768 upstream	novel	novel	metaQTL	6.80E-05	4.50E-02
rs11067591	12	115429745	T/C	AC078880.2	65000 upstream	novel	novel	eQTL	5.80E-04	1.84E-02
rs12306172	12	54145221	G/A	SMUG1, SMUG1-AS1	intronic, non-coding intronic	novel	novel	eQTL/meQTL	3.80E-06	4.75E-03
rs12828089	12	46210774	C/A,T	SLC38A1	intronic	novel	novel	eQTL	3.70E-05	3.48E-02
rs1870566	12	65818237	T/C	RPSAP52	intronic	novel	novel		7.50E-06	4.29E-03
rs2293429	12	53180119	A/C	CSAD	intronic	novel	novel	eQTL/meQTL	5.00E-05	3.16E-02
rs3184504	12	111446804	T/C	SH2B3	coding nonsyn	novel	novel	eQTL/meQTL/metaQTL	3.70E-06	1.75E-03
rs4930718	12	123428886	A/G	RILPL2	intronic	novel	novel	eQTL	1.10E-05	3.28E-04
rs703545	12	102549222	A/G	AC010202.1	35567 upstream	novel	novel		8.70E-06	5.74E-03
rs7296248	12	102683420	C/T	LINC00485	125860 downstream	novel	novel	metaQTL	3.20E-04	4.49E-02
rs7961772	12	26798318	C/T	ITPR2	intronic	novel	confirmed	eQTL	3.80E-07	7.43E-04
rs7965495	12	66037910	G/A	RPL21P18	196 upstream	novel	novel		1.10E-04	2.97E-02
rs12865243	13	40104683	G/A	LINC00598	non-coding intronic	novel	novel		3.00E-06	3.32E-04
rs452674	13	40080917	T/C	LINC00598	non-coding	novel	novel		8.50E-05	1.70E-02
rs7331478	13	27919720	T/G	PDX1	300 downstream	novel	novel		6.50E-05	4.79E-02
rs9532498	13	40104306	G/C	LINC00598	non-coding intronic	novel	novel		5.20E-05	2.22E-03
rs4965425	15	98638434	C/T	AC118658.1	8517 downstream	novel	novel		6.40E-07	5.30E-04
rs8039305	15	90879313	T/C	FURIN	intronic	novel	novel	eQTL/meQTL	4.90E-08	4.55E-05
rs13331339	16	20179928	C/T	AC092132.2	21537 upstream	novel	novel		1.50E-04	3.79E-02
rs2397775	16	55718812	A/G	CES1P2	9303 downstream	novel	novel		2.40E-05	2.54E-02
rs2521477	16	20016691	T/C	GPR139	14794 downstream	novel	confirmed	eQTL	4.70E-07	1.33E-03
rs4625714	16	55607701	C/T	LPCAT2	21031 upstream	novel	novel		3.70E-04	1.05E-02
rs908382	16	27204059	A/C	KDM8	intronic	novel	novel		5.20E-05	2.91E-02
rs9938631	16	67397901	C/T	ZDHHC1	intronic	novel	novel	eQTL	2.50E-05	1.67E-02
rs11079803	17	47942535	G/A	PNPO	intronic	novel	novel	eQTL/meQTL	9.70E-06	5.09E-03
rs1215	17	7260031	A/G	AC003688.1, CLDN7	intronic,3utr	novel	novel	eQTL	1.20E-04	4.53E-02
rs12939237	17	49067202	G/A	IGF2BP1	11552 upstream	novel	novel	eQTL	1.80E-04	1.45E-02
rs1531798	17	78826049	A/G	USP36	intronic	novel	novel	eQTL	8.90E-03	3.72E-02
rs198542	17	50567176	G/A	CACNA1G	intronic	novel	novel		4.50E-04	6.42E-03
rs34870220	17	7181592	C/T	ASGR1	2028 upstream	novel	novel	eQTL	9.90E-07	7.32E-04
rs3760318	17	30920697	G/A	ADAP2	5upstream	novel	novel	eQTL/meQTL	7.90E-05	1.26E-02
rs390200	17	7206676	A/G	DLG4	intronic	novel	novel	eQTL	1.20E-12	6.89E-10
rs4647887	17	76562724	A/G	SNHG16	non-coding intronic	novel	novel	eQTL/meQTL	2.80E-04	4.93E-02
rs4793636	17	50062136	G/A	ITGA3	intronic	novel	novel	eQTL	4.10E-05	3.82E-02
rs6565531	17	81049580	G/A	BAIAP2	intronic	novel	novel	eQTL/meQTL	3.50E-03	3.61E-02
rs878619	17	50555910	A/G	SPATA20	58 upstream	novel	novel	eQTL/meQTL	2.80E-05	4.24E-04
rs12455403	18	5620115	T/C	EPB41L3	intronic	novel	novel	meQTL	3.80E-05	2.32E-02
rs2586211	18	11872826	G/A	GNAL	intronic	novel	novel	metaQTL	4.00E-05	1.38E-02
rs4798774	18	932568	G/A	LINC01904	4575 upstream	novel	novel		2.80E-04	4.94E-02
rs10113	19	46609391	T/C	CALM3, AC093503.2	utr-3, non-coding intronic	novel	novel		1.20E-03	3.79E-02

rs2261988	19	4910877	G/T	UHRF1	5utr	novel	novel	eQTL/meQTL	7.10E-06	3.39E-03
rs34033973	19	40437876	A/G	SERTAD3	2968 downstream	novel	novel	eQTL	5.90E-05	4.70E-02
rs492602	19	48703160	A/G	FUT2	coding syn	novel	novel	eQTL/meQTL/metaQTL	4.10E-07	5.10E-04
rs533318	19	40161784	T/C	MAP3K10	29960 downstream	novel	novel	eQTL/metaQTL	1.80E-04	4.94E-02
rs8182579	19	33418945	C/T	PEPD	intronic	novel	confirmed	eQTL	1.80E-05	1.12E-02
rs17536052	20	10664057	G/A	JAG1	intronic	novel	novel		7.80E-07	1.27E-03
rs1886843	20	58669145	A/G	STX16, STX16-NPEPL1	intronic, intronic	novel	novel	eQTL	2.00E-04	2.74E-02
rs2426778	20	58718421	G/A	NPEPL1	non-coding	novel	novel	eQTL	9.70E-05	6.10E-03
rs6016377	20	40544088	C/T	MAFB	141760 downstream	confirmed	confirmed		3.60E-10	2.24E-06
rs6057610	20	32653587	T/C	C20orf203	5upstream	novel	novel	eQTL	3.00E-10	1.99E-06
rs6075924	20	22531891	T/C	LINC00261	15780 downstream	novel	novel		4.80E-06	5.87E-03
rs6077888	20	10712341	C/T	AL050403.2	non-coding intronic	novel	novel		8.00E-08	6.47E-05
rs8125378	20	31852354	G/A	DUSP15	intronic	novel	novel	eQTL	4.10E-05	3.57E-02
rs926345	20	41143307	T/C	PLCG1	intronic	novel	novel	eQTL/meQTL	1.10E-05	9.32E-04
rs137848	22	50001867	T/C	IL17REL	intronic	novel	novel	eQTL/meQTL	7.50E-03	2.08E-02
rs5765275	22	45352459	A/G	SMC1B	coding syn	novel	novel	eQTL/meQTL	9.20E-06	1.16E-02
rs6006393	22	30194037	T/C	AC002378.1	non-coding intronic	novel	novel	eQTL	5.10E-03	1.53E-02

Supplementary Table 6. Significant results in LocusCompare analysis.

GeneID	Gene Symbol	Chr	TSS	GWAS -log10(P)	eQTL -log10(P)	Traits
ENSG00000169047.5	IRS1	chr2	227596032	8.921	10.756	T2D
ENSG00000272622.1	RP11-395N3.2	chr2	227664861	8.921	8.641	T2D
ENSG00000153814.7	JAZF1	chr7	27870191	13.523	8.065	T2D
ENSG00000149084.7	HSD17B12	chr11	43577985	8.276	87.748	T2D
ENSG00000246250.2	RP11-613D13.5	chr11	43851258	8.276	11.800	T2D
ENSG00000107679.10	PLEKHA1	chr10	124134211	11.745	7.278	T2D
ENSG00000260196.1	RP1-239B22.5	chr11	17402195	7.367	10.564	T2D
ENSG00000188211.4	NCR3LG1	chr11	17373272	7.367	9.621	T2D
ENSG00000157895.7	C12orf43	chr12	121440315	7.444	26.424	T2D
ENSG00000153774.4	CFDP1	chr16	75327595	10.432	24.336	T2D
ENSG00000227117.2	CTA-85E5.10	chr22	30404730	8.409	15.734	T2D
ENSG00000163257.6	DCAF16	chr4	17802277	15.276	20.505	BW
ENSG00000254135.1	RP11-32D16.1	chr5	157912197	7.886	9.454	BW
ENSG00000146535.9	GNA12	chr7	2767745	7.886	8.225	BW
ENSG00000106635.3	BCL7B	chr7	72950685	10.237	12.136	BW
ENSG00000029534.15	ANK1	chr8	41510738	10.886	8.513	BW
ENSG00000226752.3	PSMD5-AS1	chr9	123587105	8.066	140.174	BW
ENSG00000213277.3	MARCKSL1P1	chr10	104935310	7.456	9.845	BW
ENSG00000107679.10	PLEKHA1	chr10	124134211	7.745	7.278	BW
ENSG00000182511.7	FES	chr15	91426924	7.770	10.397	BW
ENSG00000181885.14	CLDN7	chr17	7163259	15.041	16.767	BW
ENSG00000175826.7	CTDNEP1	chr17	7146909	15.041	9.632	BW
ENSG00000170291.10	ELP5	chr17	7155400	15.041	14.102	BW
ENSG00000264920.1	RP11-6N17.4	chr17	45968620	7.337	18.426	BW
ENSG00000175730.7	BAK1P1	chr20	31276722	11.114	13.738	BW
ENSG00000183762.8	KREMEN1	chr22	29469065	8.000	22.178	BW

Supplementary Table 7. Gene ontology (GO) terms enriched for SNP-annotated genes with FDR ≤ 0.05.

Traits	Pathway ID	Pathway description	Gene count	FDR
T2DM	GO:0097110	scaffold protein binding	6	9.62E-04
	GO:0010817	regulation of hormone levels	13	3.04E-03
	GO:0050796	regulation of insulin secretion	8	4.19E-03
	GO:0032409	regulation of transporter activity	9	4.43E-03
	GO:0046883	regulation of hormone secretion	9	4.95E-03
	GO:0031016	pancreas development	6	5.32E-03
	GO:0009746	response to hexose	7	5.56E-03
	GO:0090276	regulation of peptide hormone secretion	8	5.67E-03
	GO:0009749	response to glucose	7	5.96E-03
	GO:0034284	response to monosaccharide	7	6.11E-03
	GO:2001257	regulation of cation channel activity	7	6.74E-03
	GO:0032412	regulation of ion transmembrane transporter activity	8	6.92E-03
	GO:0051049	regulation of transport	21	6.93E-03
	GO:1901700	response to oxygen-containing compound	19	7.33E-03
	GO:0022898	regulation of cation transmembrane transport	9	7.42E-03
	GO:0022898	regulation of transmembrane transporter activity	8	7.43E-03
	GO:0048878	chemical homeostasis	16	7.44E-03
	GO:0032879	regulation of localization	26	8.59E-03
	GO:0009743	response to carbohydrate	7	8.70E-03
	GO:0034762	regulation of transmembrane transport	11	8.87E-03
	GO:0044057	regulation of system process	11	9.81E-03
	GO:0051046	regulation of secretion	13	1.11E-02
	GO:0034765	regulation of ion transmembrane transport	10	1.12E-02
	GO:0031018	endocrine pancreas development	4	1.92E-02
	GO:1903530	regulation of secretion by cell	12	2.21E-02
	GO:0001890	placenta development	6	2.35E-02
	GO:0042592	homeostatic process	18	3.29E-02
	GO:0050708	regulation of protein secretion	9	4.67E-02
BW	GO:0005515	protein binding	109	7.86E-04
	GO:0097110	scaffold protein binding	7	1.18E-03
	GO:0003674	molecular_function	136	4.33E-03
	GO:0008134	transcription factor binding	17	4.92E-03
	GO:0005158	insulin receptor binding	4	1.96E-02
	GO:0009653	anatomical structure morphogenesis	33	2.56E-02
	GO:1901653	cellular response to peptide	11	2.57E-02
	GO:1901652	response to peptide	13	2.58E-02
	GO:0071417	cellular response to organonitrogen compound	14	2.58E-02
	GO:0033500	carbohydrate homeostasis	9	2.67E-02
	GO:0045893	positive regulation of transcription, DNA-templated	26	2.86E-02
	GO:1901701	cellular response to oxygen-containing compound	20	3.26E-02
	GO:0042593	glucose homeostasis	9	3.41E-02
	GO:1901700	response to oxygen-containing compound	25	3.63E-02
	GO:0048729	tissue morphogenesis	14	3.87E-02
	GO:0051254	positive regulation of RNA metabolic process	27	3.94E-02
	GO:1902680	positive regulation of RNA biosynthetic process	26	4.12E-02
	GO:0051240	positive regulation of multicellular organismal process	29	4.13E-02

	GO:0005488	binding	122	4.27E-02
	GO:1901699	cellular response to nitrogen compound	14	4.33E-02
	GO:1903508	positive regulation of nucleic acid-templated transcription	26	4.39E-02
	GO:0048568	embryonic organ development	12	4.69E-02
	GO:0045944	positive regulation of transcription by RNA polymerase II	21	5.00E-02
Pleiotropic	GO:0097110	scaffold protein binding	6	3.63E-06

Supplementary Table 8. Conjunction cFDR for 35 pleiotropic CpG-SNPs in FG and BW (cFDR < 0.05).

Variant	chr	P_FG	P_bw	Gene	SNP Type	cFDR_FG	cFDR_BW	ccFDR
rs1012635	6	5.13E-07	4.00E-10	CDKAL1	pleiotropic/confirmed	0.04886625	0.01573	0.04886625
rs1042725	12	0.002725	7.10E-32	HMGA2	T2D/confirmed	2.79E-06	0.000144	0.000144
rs1447351	11	2.83E-93	0.00023	MTNR1B	novel/confirmed	0.0291375	1.40E-09	0.0291375
rs151216	11	0.003477	5.10E-05	KCNQ1,KCNQ1OT1	novel/confirmed	9.54E-10	1.20E-18	9.54E-10
rs17361324	3	3.18E-10	8.00E-20	ADCY5	novel/confirmed	0.0081405	0.0077625	0.0081405
rs2206734	6	8.27E-08	2.40E-17	CDKAL1	novel/confirmed	2.99E-09	0.01993333	0.01993333
rs231354	11	5.94E-05	0.0028	KCNQ1,KCNQ1OT1	pleiotropic/confirmed	2.05E-06	4.00E-09	2.05E-06
rs340883	1	1.45E-09	0.0071	PROX1-AS1	T2D/confirmed	3.55E-07	0.01893333	0.01893333
rs4677887	3	0.019425	2.30E-12	ADCY5	pleiotropic/confirmed	1.65E-07	2.64E-16	1.65E-07
rs569255	3	0.000243	0.00045	SLC12A8	novel/confirmed	0.01957829	0.00526	0.01957829
rs579459	9	4.85E-05	8.30E-06	ABO	novel/confirmed	0.02516222	0.01199333	0.02516222
rs6006393	22	0.00034	0.0051	AC002378.1	novel/confirmed	0.01744615	0.02262308	0.02262308
rs6770420	3	8.30E-12	0.0046	KLF7P1	novel/confirmed	0.00070325	0.00014733	0.00070325
rs7004862	8	4.00E-04	0.0017	INTS8	novel/confirmed	0.04133767	0.00349633	0.04133767
rs7605661	2	0.002355	0.00039	THADA	novel/confirmed	0.00461538	0.02184	0.02184
rs7723	7	0.000926	0.00014	TMED4	T2D/confirmed	5.15E-91	0.00046	0.00046
rs7816345	8	0.000871	0.00042	AC090453.1	novel/confirmed	0.00545	3.71E-29	0.00545
rs9289218	3	1.13E-07	1.80E-05	ADCY5	novel/confirmed	0.0249475	0.049725	0.049725
rs16856159	2	7.51E-24	0.0068			5.35E-21	0.0204	0.0204
rs2001350	2	0.000191	0.0018			0.01005355	0.02061818	0.02061818
rs7748736	6	0.00108	0.0029			0.04764	0.04575556	0.04764
rs1059288	6	0.002113	0.00027			0.0431052	0.012096	0.0431052
rs4143341	7	0.001696	3.20E-06			0.018232	0.0003032	0.018232
rs11145756	9	2.85E-06	0.0015			0.00021375	0.00792857	0.00792857
rs3812605	9	0.000481	0.0042			0.02704289	0.04456667	0.04456667
rs17566087	10	0.003405	2.30E-05			0.03490125	0.00173938	0.03490125
rs198476	11	7.94E-05	0.00046			0.0026996	0.005175	0.005175
rs2072114	11	1.04E-15	0.003			4.27E-13	0.0165	0.0165
rs4601728	11	0.00039	0.0033			0.0213525	0.03526875	0.03526875
rs703545	12	0.007068	8.70E-06			0.04790533	0.00107107	0.04790533
rs7331478	13	2.85E-09	6.50E-05			1.66E-07	0.0005525	0.0005525
rs11074093	15	0.000352	0.00038			0.010912	0.007695	0.010912
rs4965425	15	0.006996	6.40E-07			0.0461736	0.00014029	0.0461736
rs2429243	17	4.37E-05	0.00092			0.00250339	0.00893714	0.00893714
rs6075924	20	0.003485	4.80E-06			0.0296225	0.0004944	0.0296225

Supplementary Table 9. Conjunction cFDR for 6 pleiotropic CpG-SNPs in FI and BW (cFDR < 0.05).

Variant	chr	P_FI	P_bw	SNP Type	Gene	cFDR_FI	cFDR_BW	ccFDR
rs9289218	3	0.000476	1.80E-05	novel/confirmed	ADCY5	0.017374	0.000792	0.017374
rs17361324	3	0.003383	8.00E-20	novel/confirmed	ADCY5	0.0050745	1.91E-17	0.0050745
rs900399	3	0.002526	2.90E-41			0.002526	1.06E-38	0.002526
rs2206734	6	0.010898	2.40E-17	novel/confirmed	CDKAL1	0.01453067	1.09E-14	0.01453067
rs7766106	6	3.08E-05	2.60E-05			0.0013398	0.000169	0.0013398
rs703545	12	1.52E-06	8.70E-06			9.12E-05	4.35E-05	9.12E-05

Supplementary Table 10. Conjunction cFDR for 54 pleiotropic CpG-SNPs in T2D and BW_maternal (cFDR < 0.05).

Variant	chr	P_DM	P_BW	Gene	SNP Type	cFDR_DM	cFDR_BW	ccFDR
rs1447351	11	6.60E-18	1.22E-08	MTNR1B	novel/confirmed	5.94E-17	2.68E-07	2.68E-07
rs1515114	2	9.50E-17	0.009981	AC062015.1	novel/confirmed	1.66E-14	0.027725	0.027725
rs17361324	3	1.10E-25	1.29E-05	ADCY5	novel/confirmed	2.97E-24	0.00016705	0.00016705
rs2206734	6	4.70E-66	7.74E-05	CDKAL1	novel/confirmed	2.73E-64	0.00023226	0.00023226
rs2488071	10	1.30E-22	0.0005663	Y_RNA	T2D/confirmed	8.36E-21	0.00302027	0.00302027
rs340883	1	1.40E-13	0.005544	PROX1-AS1	T3D/confirmed	1.36E-11	0.019404	0.019404
rs4677887	3	0.0011	0.0001349	ADCY5	pleiotropic/confirmed	0.0053625	0.00738578	0.00738578
rs9289218	3	3.60E-17	5.01E-16	ADCY5	novel/confirmed	3.60E-17	1.15E-14	1.15E-14
rs934227	2	1.40E-09	2.03E-05			1.01E-08	0.00027148	0.00027148
rs2580770	2	0.00021	0.003075			0.00434	0.04930603	0.04930603
rs175238	2	0.0011	7.63E-05			0.00447857	0.00476813	0.00476813
rs10190207	2	0.0036	0.0005613			0.02973913	0.03628927	0.03628927
rs12631028	3	2.00E-08	9.40E-06			1.30E-07	0.00021843	0.00021843
rs1826215	3	3.80E-05	1.76E-05			0.00014356	0.00056061	0.00056061
rs6440003	3	7.50E-07	2.51E-07			2.44E-06	8.90E-06	8.90E-06
rs3852060	3	1.60E-09	0.003731			1.06E-07	0.02374273	0.02374273
rs7657332	4	0.0027	0.00067			0.023004	0.0340896	0.0340896
rs4146009	4	0.0022	0.0007345			0.019536	0.03402204	0.03402204
rs6827183	4	0.0031	0.0001024			0.01298125	0.008736	0.01298125
rs7715701	5	0.017	4.16E-05			0.0499375	0.01007051	0.0499375
rs7701346	5	3.80E-07	8.81E-07			1.43E-06	2.95E-05	2.95E-05
rs1650504	5	1.90E-05	0.001422			0.00041563	0.02141888	0.02141888
rs2842363	6	1.80E-09	0.002199			7.95E-08	0.01459336	0.01459336
rs13220047	6	0.006	0.0004588			0.04175	0.03765983	0.04175
rs1415701	6	4.20E-05	0.0004987			0.000534	0.01040146	0.01040146
rs6918311	6	2.10E-11	0.01142			3.10E-09	0.04663167	0.04663167
rs2392244	7	0.0041	6.29E-05			0.01522857	0.00718179	0.01522857
rs1127065	7	2.20E-08	0.001289			6.52E-07	0.01113227	0.01113227
rs10758593	9	1.60E-10	8.98E-07			8.53E-10	1.68E-05	1.68E-05
rs2811709	9	3.40E-05	0.001777			0.00075337	0.02590679	0.02590679
rs2383208	9	2.60E-67	0.001181			4.00E-65	0.001181	0.001181
rs10983319	9	0.0021	0.0005646			0.01823182	0.02917955	0.02917955
rs7904519	10	1.70E-135	0.0006389			3.49E-133	0.0006389	0.0006389
rs1225404	10	2.80E-20	0.004352			3.80E-18	0.01450667	0.01450667
rs2334499	11	3.60E-05	0.001989			0.00081	0.0280449	0.0280449

rs2762954	11	8.90E-07	0.00199	2.51E-05	0.01815875	0.01815875
rs474901	11	0.0065	7.76E-06	0.0186875	0.00203383	0.0186875
rs7102746	11	2.80E-06	0.005975	0.00013185	0.0478	0.0478
rs12819124	12	2.20E-05	0.003385	0.0007403	0.0423125	0.0423125
rs1826535	12	4.50E-05	0.0003167	0.00047769	0.00725974	0.00725974
rs17331697	12	3.20E-05	0.0003115	0.00039855	0.00775918	0.00775918
rs6489844	12	0.00023	3.40E-06	0.00065714	0.00023911	0.00065714
rs3184504	12	2.30E-07	1.22E-14	2.30E-07	7.87E-13	2.30E-07
rs1054852	12	3.10E-09	0.005067	2.03E-07	0.02859236	0.02859236
rs10781628	12	0.00026	0.001917	0.00441	0.03782388	0.03782388
rs9593509	13	0.0051	5.03E-05	0.01748571	0.00652662	0.01748571
rs8022758	14	0.00021	2.56E-05	0.000665	0.00100092	0.00100092
rs12442879	15	9.20E-05	1.49E-05	0.00031689	0.00059931	0.00059931
rs7343010	18	1.80E-05	0.0003404	0.00023564	0.00736502	0.00736502
rs3803915	19	8.80E-05	0.00193	0.00169878	0.03004087	0.03004087
rs7248104	19	0.0073	4.52E-06	0.0191625	0.00125827	0.0191625
rs7246440	19	3.60E-05	0.002804	0.00090313	0.03474522	0.03474522
rs2304130	19	1.90E-15	0.001429	8.41E-14	0.00464425	0.00464425
rs2708742	19	0.00061	0.0002167	0.00431067	0.00980929	0.00980929

Supplementary Table 11. Conditional FDR value of 133 CpG-SNPs for BW_fetal given the DM (cFDR < 0.05).

Variant	Chr	Gene	Snp Type	P	cFDR
rs1012635	6	CDKAL1	confirmed/confirmed	3.27E-11	1.80E-10
rs1042725	12	HMGA2	novel/confirmed	6.72E-21	9.75E-20
rs10840346	11	SBF2	novel/confirmed	1.93E-06	0.00040448
rs10878353	12	HMGA2	novel/confirmed	1.17E-07	1.30E-05
rs10878359	12	MIR6074	novel/confirmed	6.02E-11	2.63E-08
rs11264298	1	DCST1	novel/confirmed	0.0002617	0.03691187
rs12306172	12	SMUG1,SMUG1-AS1	novel/confirmed	3.96E-06	0.00736571
rs12623454	2	AC073257.1	novel/confirmed	8.48E-06	0.00016646
rs12677785	8	SLC45A4	novel/confirmed	1.82E-05	0.0219353
rs12704091	7	ZNF783	novel/confirmed	6.46E-05	0.03083022
rs12865243	13	LINC00598	novel/confirmed	0.001429	0.03875112
rs12939237	17	IGF2BP1	novel/confirmed	6.15E-05	0.0040557
rs137848	22	IL17REL	novel/confirmed	8.56E-05	0.00066145
rs1415181	1	GAPDHP24	novel/confirmed	1.94E-05	0.02138222
rs151216	11	KCNQ1,KCNQ1OT1	novel/confirmed	0.0005676	0.00502108
rs1515114	2	AC062015.1	novel/confirmed	8.29E-06	2.96E-05
rs1547669	6	MLN	novel/confirmed	1.52E-06	0.001656
rs163177	11	KCNQ1	novel/confirmed	0.003422	0.013688
rs17361324	3	ADCY5	novel/confirmed	2.80E-26	3.64E-25
rs17401675	7	MLXIPL	novel/confirmed	5.34E-10	6.74E-08
rs17689040	7	SUGCT	novel/confirmed	0.0003883	0.02320925
rs1886843	20	STX16,STX16-NPEPL1	novel/confirmed	6.68E-06	0.00281015
rs2000244	9	STRBP	novel/confirmed	2.20E-06	7.30E-05
rs2206734	6	CDKAL1	novel/confirmed	1.86E-19	5.57E-19
rs2236407	9	PTCH1	novel/confirmed	1.57E-07	1.62E-05
rs2426778	20	NPEPL1	novel/confirmed	6.77E-05	0.04231615
rs2488071	10	Y_RNA	novel/confirmed	4.86E-09	1.56E-08
rs2745929	6	CDKAL1	novel/confirmed	1.39E-09	5.55E-09
rs2886070	1	ARHGEF2	novel/confirmed	3.83E-07	0.00090853
rs2894593	2	AC062015.1	novel/confirmed	0.001014	0.002873
rs3213225	11	IGF2,INS-IGF2	novel/confirmed	2.82E-10	1.88E-08
rs340883	1	PROX1-AS1	novel/confirmed	0.0003724	0.00144822
rs390200	17	DLG4	novel/confirmed	2.37E-08	3.67E-05
rs452674	13	LINC00598	novel/confirmed	0.0002213	0.01337943
rs4625714	16	LPCAT2	novel/confirmed	7.11E-05	0.02681838
rs4677887	3	ADCY5	confirmed/confirmed	0.0003492	0.01456663
rs4677889	3	ADCY5	novel/confirmed	1.05E-05	0.00147809
rs492602	19	FUT2	novel/confirmed	6.51E-06	0.01085498
rs4965425	15	AC118658.1	novel/confirmed	1.76E-06	0.00393077
rs4980661	11	AP000439.2	novel/confirmed	9.89E-06	0.00659886
rs6016377	20	MAFB	confirmed/confirmed	1.41E-08	2.30E-05
rs6057610	20	C20orf203	novel/confirmed	1.05E-09	8.45E-07
rs6075924	20	LINC00261	novel/confirmed	7.58E-06	0.00628746
rs6770420	3	KLF7P1	novel/confirmed	0.002812	0.00723086
rs7004862	8	INTS8	novel/confirmed	0.001778	0.01012092

rs7088711	10	WBP1L	novel/confirmed	9.90E-05	0.02317354
rs7331478	13	PDX1	novel/confirmed	8.00E-06	0.00719778
rs7561273	2	MFSD2B	novel/confirmed	5.88E-06	0.01162883
rs7605661	2	THADA	novel/confirmed	0.007443	0.0302682
rs7766106	6	RSPO3	novel/confirmed	0.0005544	0.0422037
rs7816345	8	AC090453.1	novel/confirmed	0.002037	0.03783
rs7965495	12	RPL21P18	novel/confirmed	3.64E-06	0.00010424
rs8182579	19	PEPD	novel/confirmed	0.0001873	0.00181057
rs855715	10	ADRB1	novel/confirmed	1.12E-05	0.00390828
rs900399	3	LINC00880	novel/confirmed	1.55E-37	5.44E-34
rs926345	20	PLCG1	novel/confirmed	1.36E-05	0.00091218
rs9289218	3	ADCY5	novel/confirmed	9.89E-17	7.58E-16
rs935172	2	CIB4	novel/confirmed	0.0001418	0.01920556
rs9416062	10	LRMDA	novel/confirmed	0.007054	0.04856408
rs4655772	1			0.0004808	0.04171463
rs17407594	1			1.91E-05	0.00838113
rs2884428	1			9.98E-07	0.00240745
rs13020622	2			1.08E-05	0.00099688
rs10865186	2			0.0001158	0.03633099
rs895514	2			0.0002029	0.02075471
rs6749108	2			0.0003793	0.01269657
rs4664054	2			0.0001046	0.04485819
rs853770	2			1.78E-06	0.00387095
rs16856159	2			5.42E-05	0.02007762
rs1801123	2			0.0003899	0.03399758
rs332353	3			0.003545	0.0328976
rs13075511	3			0.0006302	0.018906
rs3852060	3			0.002468	0.01328923
rs7657332	4			2.54E-05	0.00170314
rs1460554	4			0.0008588	0.03377947
rs7666523	4			2.06E-05	0.01891119
rs10512645	5			1.40E-05	0.0278654
rs12658884	5			1.66E-05	0.02684736
rs13180312	5			0.0001105	0.03770582
rs17056278	5			0.0002935	0.03992283
rs16884481	6			0.001217	0.02822281
rs1466339	6			0.004848	0.02477867
rs9368716	6			0.00705	0.048222
rs13219530	6			0.0001734	0.038135
rs4236049	6			0.0002469	0.04212803
rs13220047	6			0.0007954	0.04123521
rs1262557	6			3.13E-06	1.72E-05
rs9457107	6			1.07E-05	0.01209444
rs2934849	6			6.75E-05	0.02081225
rs38205	7			0.001059	0.024357
rs6948977	7			0.0002126	0.03499508
rs2392244	7			0.0001059	0.00736235
rs1127065	7			0.002815	0.01573088

rs10265057	7	9.28E-07	0.00042795
rs42042	7	1.48E-05	0.00648605
rs10487687	7	7.50E-05	0.04762364
rs7016707	8	0.006436	0.04994336
rs551580	8	3.07E-05	0.00695603
rs13255921	8	0.0005765	0.02419165
rs7460241	8	1.80E-05	0.02264809
rs10758593	9	6.16E-08	4.31E-07
rs10992100	9	6.24E-05	0.03037422
rs357542	9	2.77E-05	0.00127327
rs17301196	9	0.0002614	0.01143281
rs11145846	9	0.003154	0.0184509
rs11145756	9	0.001304	0.010758
rs3812605	9	0.0009563	0.02798217
rs11009689	10	0.001576	0.03594297
rs2782979	10	0.00143	0.02403762
rs2292623	10	0.003152	0.04919371
rs3213223	11	3.84E-06	0.00072623
rs7483056	11	7.28E-05	0.01885261
rs9669403	12	0.000226	0.00652741
rs10878361	12	3.41E-05	0.00500507
rs7336104	13	0.0001887	0.0145299
rs9593509	13	0.000256	0.01604855
rs4899027	14	0.0002498	0.01131988
rs8022758	14	0.000625	0.01542763
rs11160605	14	1.65E-05	0.00235233
rs12442879	15	0.002313	0.03640461
rs7178220	15	1.82E-05	0.00565695
rs208569	16	0.0002637	0.04940443
rs13336802	16	8.31E-05	0.02231026
rs1242507	17	0.0003098	0.02684662
rs7220080	17	2.36E-06	0.00239079
rs11658711	17	0.0001492	0.03589127
rs7248104	19	3.01E-05	0.00305272
rs3786913	19	0.001317	0.01293759
rs2303088	19	3.83E-05	0.03451953
rs205894	20	0.0001576	0.04472151
rs6119294	20	2.06E-06	0.00367933
rs2766673	20	0.002079	0.04934889
rs911303	20	0.008403	0.02881029