# Supplemental Material

# Supp Fig. 1

A close up of a map

Description automatically generated

Scree plot showing the proportion of the total variation in the individual glucose and insulin values captured by the principal components (PCs). Six glucose/insulin measures were available during a 75-g oral glucose tolerance test (OGTT) performed in the second trimester in mothers from the Gen3G study: fasting glucose, 1h-glucose, 2h-glucose post load, and fasting insulin, 1h-insulin and 2h-insulin post load. In the scree plot, the first three PCs have eigen values close to 1.0 (range 0.93 to 1.67), and together they capture 80% of the total variation in maternal glycemia in the OGTT (percent variance range 14 to 47).

# Supp Fig. 2

A picture containing boat

Description automatically generated

Histogram showing the distribution of top three PCs derived from maternal glucose and insulin values measured at each time-point (fasting, 1-h and 2-h) during a 75-g OGTT (2nd trimester). N= 430 mother-child pairs included in the PC analysis.

# Supp Fig. 3

A close up of a map

Description automatically generated

Biplot showing the relative contribution of each of the six glycemic traits measured in the OGTT to the first two components derived from the PC analysis (Dim1= PC1 and Dim2 = PC2). Arrows in the plot correspond to the loading values or the correlation between glycemic traits and the two components. For PC1, the colored legend indicates from blue to red, the increasing contribution of a trait to this PC. For instance, the trait with the largest loading value or contribution to PC1 is 2-h insulin, followed by 1-h and 2-h glucose, whereas fasting insulin has the smallest contribution to PC1 but the largest to PC2.

# Supp Fig. 4

Chart, bubble chart

Description automatically generated

Plot of loading values showing the position of measured glycemic traits (OGTT) in the two-dimensional space for three components estimated using a PC analysis. For PC1, 2-h post-load insulin showed the largest contribution or loading value, for PC2 it was fasting insulin, and for PC3 it was fasting glucose.

# Supp Fig. 4 (*Continuation*)

Chart, scatter chart

Description automatically generated

# Supp Fig. 5



Summary plots of the EWAS of PC1 and cord blood DNA methylation (in M-values) (N = 430). Results correspond to the model adjusted for maternal age, gestational week at 2nd visit, gravidity, gestational age at delivery, child sex, maternal smoking and cellular heterogeneity (7 cell types from cord blood). Associations were Bonferroni significant at P value < 6.9x10-8 and “suggestive” at P value ≤ 1.0x10-6.

# Supp Fig. 6

A screenshot of a cell phone

Description automatically generated

Summary plots of the EWAS of PC2 (A) and PC3 (B) in association with cord blood DNA methylation (in M-values) (N = 430). Results correspond to the model adjusted for maternal age, gestational week at 2nd visit, gravidity, gestational age at delivery, child sex, maternal smoking in pregnancy and cellular heterogeneity (7 cell types from cord blood). Associations were Bonferroni significant at P value < 6.9x10-8 and “suggestive” at P value ≤ 1.0x10-6.

# Supp Fig. 7

A screenshot of a cell phone

Description automatically generated

Manhattan plot summarizing results of the EWAS of six individual glycemic traits measured during the OGTT in the second trimester (N= 430 mother-child pairs) in association with cord blood DNAm (in M-values). Results correspond to the model adjusted for maternal age, gestational week at 2nd visit, gravidity, gestational age at delivery, child sex, maternal smoking in pregnancy and cellular heterogeneity (7 cell types from cord blood). Horizontal red line is the Bonferroni threshold at P value < 6.9x10-8 or -log10 (P value) = 7.2; blue line is the ‘suggestive’ threshold set at P value ≤1.0x10-6 or -log10 (P value) = 6.0. Genomic inflation factor in EWAS of fasting glucose (λ=0.84), 1-h post-load glucose (λ=0.87), 2-h post-load glucose (λ=1.14), fasting insulin (λ=1.19), 1-h post-load insulin (λ=0.79) and 2-h post-load insulin (λ=0.83).

# Supp Table 1.

Comparison of baseline characteristics between participants in Gen3G included and those excluded from our study of maternal glucose tolerance and newborn DNA methylation (DNAm). In total, 813 mother-child pairs in the cohort had complete glucose values in the OGTT (2nd visit) and delivery data, from which 430 pairs had also DNAm data measured from full-term (gestational age at birth ≥ 37 weeks) cord blood samples, passed all QC steps, and were therefore included in the analyses.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Included in DNAm analysis (N=430) | | Excluded from DNAm analysis (N=383) | | P-value b |
|  | N | Mean (SD) or n [%] a | N | Mean (SD) or n [%] a |
| Maternal age (years) | 430 | 28.2 (4.2) | 383 | 28.5 (4.5) | 2.90E-01 |
| Gravidity [% primigravid] | 430 | 140 [32.6] | 383 | 142 [37.1] | 2.00E-01 |
| Ethnicity [% European descent] | 430 | 428 [99.5] | 383 | 351 [91.6] | 5.50E-08 |
| Smoking in early pregnancy [% smoker] | 430 | 37 [8.6] | 383 | 40 [10.4] | 4.40E-01 |
| 1st trimester |  |  |  |  |  |
| Gestational age (weeks) | 430 | 9.7 (2.3) | 383 | 9.5 (2.2) | 2.10E-01 |
| Body mass index (kg/m2) | 430 | 23.7 (16.1, 54.1) | 383 | 24.6 (16.6, 44.6) | 3.70E-01 |
| 2nd trimester |  |  |  |  |  |
| Gestational age (weeks) | 430 | 26.4 (1.0) | 383 | 26.4 (1.0) | 9.30E-01 |
| Body mass index (kg/m2) | 429 | 26.5 (18.8, 54.1) | 383 | 27.1 (18.6, 46.5) | 6.60E-01 |
| *Glucose challenge 75-gram* |  |  |  |  |  |
| Fasting glucose (mmol/L) | 430 | 4.2 (3.4, 7.3) | 383 | 4.2 (3.4, 5.8) | 3.10E-01 |
| 1-h glucose (mmol/L) | 430 | 7.1 (1.6) | 383 | 7.2 (1.6) | 8.70E-01 |
| 2-h glucose (mmol/L) | 430 | 5.8 (1.3) | 383 | 5.9 (1.4) | 1.70E-01 |
| Fasting Insulin (pg/mL) | 430 | 281.5 (27.29, 3258.0) | 383 | 281.0 (36.7, 7565.0) | 4.20E-01 |
| 1-h Insulin (pg/mL) | 430 | 1918 (126.0, 5803.0) | 383 | 1857 (295.0, 10953.0) | 5.30E-01 |
| 2-h Insulin (pg/mL) | 430 | 1594 (176.0, 7801.0) | 383 | 1612 (275.0, 14005.0) | 6.30E-01 |
| GDM [% cases] | 430 | 38.0 [8.8] | 383 | 29.0 [7.6] | 6.00E-01 |
| **Offspring variables** |  |  |  |  |  |
| Gestational age at delivery (weeks) | 430 | 39.5 (37.0, 41.5) | 383 | 39.3 (29.2, 41.5) | 6.80E-04 |
| Child sex [% males] | 430 | 225.0 [52.3] | 383 | 198.0 [51.7] | 9.10E-01 |
| Birth weight (g) | 430 | 3446.6 (422.9) | 382 | 3347.3 (541.4) | 4.00E-03 |
| Birth length (cm) | 427 | 51.1 (2.0) | 378 | 50.7 (2.5) | 2.00E-02 |
| Cord blood C-peptide (pg/mL) | 429 | 414 (23.9, 1844.0) | 208 | 398.5 (49.4, 2955.0) | 1.00E+00 |
| Cord blood Insulin (pg/mL) | 429 | 306 (78.5, 1838.0) | 208 | 327 (86.5, 4758.0) | 3.50E-02 |

a Continuous non-parametric trait. Continuous parametric traits were described using the mean (SD), non-parametric traits using the median (range), and categorical traits using the frequency and %. b P value calculated using *X*2 test for categorical data, and the t-test or Mann-Whitney test for continuous parametric and non-parametric data, respectively.

# Supp Table 2.

Pairwise Pearson correlations of measured glycemic traits in the OGTT (fasting, 1-h and 2-h post-load insulin and glucose levels) and top three principal components (PCs) derived from these variables, with different birth outcomes. Highlighted in bold are pairwise comparisons with P value < 0.03.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Maternal variables** | PC1 | PC2 | PC3 | Gluc\_0 | Gluc\_1h | Gluc\_2h | Insul\_0 | Insul\_1h | Insul\_2h |
| Gluc\_0a | **0.55** | **0.16** | **0.72** | **1.00** | **0.34** | **0.25** | **0.31** | **0.24** | **0.29** |
| Gluc\_1ha | **0.73** | **-0.46** | 0.09 | **---** | **1.00** | **0.63** | 0.11 | **0.38** | **0.42** |
| Gluc\_2ha | **0.70** | **-0.56** | 0.04 | **---** | **---** | **1.00** | 0.10 | **0.18** | **0.57** |
| Insul\_0a | **0.49** | **0.67** | **0.18** | **0.31** | 0.11 | **0.10** | **1.00** | **0.33** | **0.38** |
| Insul\_1ha | **0.71** | **0.34** | **-0.43** | **0.24** | **0.38** | **0.18** | **---** | **1.00** | **0.66** |
| Insul\_2ha | **0.85** | 0.09 | **-0.32** | **0.29** | **0.42** | **0.57** | **---** | **---** | **1.00** |
| **Offspring variables** | PC1 | PC2 | PC3 | Gluc\_0 | Gluc\_1h | Gluc\_2h | Insul\_0 | Insul\_1h | Insul\_2h |
| Birth weight (g) | **0.17** | 0.03 | 0.13 | **0.18** | 0.10 | **0.13** | 0.14 | 0.06 | 0.10 |
| Birth weight (z-score) | **0.24** | **0.01** | **0.12** | **0.20** | **0.16** | **0.20** | **0.18** | **0.10** | **0.17** |
| Birth length (cm) | 0.08 | 0.01 | 0.09 | 0.12 | 0.03 | **0.07** | 0.06 | -0.01 | 0.06 |
| Newborn total body fat mass (g) b | 0.10 | 0.06 | 0.08 | 0.19 | 0.05 | 0.01 | 0.05 | 0.09 | 0.09 |
| Placenta weight (g) | **0.17** | -0.04 | 0.07 | **0.15** | **0.17** | **0.11** | 0.04 | 0.11 | 0.10 |
| Cord blood glucose (mmol/l) b | -0.20 | -0.05 | 0.14 | 0.04 | -0.16 | -0.17 | -0.32 | -0.20 | -0.17 |
| Cord blood C-peptide (pg/ml) | **0.27** | -0.02 | 0.14 | **0.30** | **0.22** | **0.17** | 0.07 | **0.18** | **0.18** |
| Cord blood insulin (pg/ml) | **0.26** | -0.07 | 0.14 | **0.28** | **0.22** | **0.19** | 0.04 | 0.14 | **0.18** |

a Gluc\_0 & Insul\_0: fasting glucose and fasting insulin; Gluc\_1h & Insul\_1h: 1-h, post load glucose and insulin values; Gluc\_2h & Insul\_2h: 2-h, post load glucose and insulin values. Glucose was measured in mmol/l, insulin in pg/ml. b Total body fat mass and cord blood glucose were available for a subsample of 128 and 26 newborns, respectively.

# Supp Table 3.

Additional adjustment for maternal BMI in early pregnancy at PC1-associated CpG sites in cord blood previously detected in our main EWAS model using as covariates maternal age, gestational week at the 2nd visit, gravidity, gestational age at delivery (weeks), child sex, maternal smoking in pregnancy and estimated cell-type distribution (7 cell types from cord blood). Results correspond to the multiple linear regression model with DNAm in M-values (N= 430).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| CpG | Chr | Position | Mapped  Gene | Genomic  context | Effect estimates  (SE) using DNAm M-values | *P* |
| cg02988288 | 1 | 145440445 | *TXNIP;* *NBPF20* | Body | -0.05 (0.01) | 1.8x10-4 |
| cg26974062 | 1 | 145440734 | *TXNIP;* *NBPF20* | Body | -0.06 (0.01) | 7.4x10-6 |
| cg27301328 | 1 | 166845490 | *TADA1* | 1st Exon | -0.04 (0.01) | 5.4x10-8 |

# Supp Table 4.

Look-ups of previously reported associations of cord blood DNAm with gestational diabetes (GDM) or maternal hemoglobin A1c (HbA1c) in pregnancy, in our EWAS of PC1. In total, 119 CpGs were extracted from five publications, with 101 of them with actual summary data available in our EWAS of PC1 (N= 430). We presented comparison in the direction of associations (higher levels of HbA1c/GDM/PC1) across studies: we observed consistent direction of association at 41/101 CpGs across studies (indicated in bold).

\* DMRs (Differentially Methylated Regions). \*\* Candidate gene study.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | Reported Estimates | | Observed association in EWAS of PC1 | | | |
| CpG/DMR | Study | PubMed ID | Trait | Near Gene | Estimate/  Direction of association | P | Estimate  (in DNAm β-values) | SE | P | Consistent direction of association |
| **cg21645848** | Juvinao-Quintero et al. 2021 | 33406918 | HbA1c | *URGCP* | -1.70% | 3.9E-11 | **-0.075** | 0.043 | 0.129 | yes |
| Chr1:248100345- 248100614 \* | Howe C. et al. 2020 | 31601636 | GDM | *OR2L13* | - | 1.8E-09 |  |  |  |  |
| cg00785941 |  |  |  |  | - |  | 0.027 | 0.446 | 0.901 | no |
| cg03748376 |  |  |  |  | - |  | 0.008 | 0.533 | 0.715 | no |
| cg04028570 |  |  |  |  | - |  | NA | NA | NA | NA |
| cg08260406 |  |  |  |  | - |  | NA | NA | NA | NA |
| cg08944170 |  |  |  |  | - |  | 0.047 | 0.666 | 0.991 | no |
| cg20434529 |  |  |  |  | - |  | 0.043 | 0.476 | 0.820 | no |
| cg20507276 |  |  |  |  | - |  | 0.082 | 0.673 | 0.983 | no |

***Continuation*** **Supp Table 4.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | Reported Estimates | | Observed association in EWAS of PC1 | | | |
| CpG/DMR | Study | PubMed ID | Trait | Near Gene | Estimate/  Direction of association | P | Estimate  (in DNAm β-values) | SE | P | Consistent direction of association |
| Chr4:165878037- 165878219 \* | Howe C. et al. 2020 | 31601636 | GDM | *C4orf39, TRIM61* | - | 3.4E-05 |  |  |  |  |
| **cg00393585** |  |  |  |  | - |  | **-0.021** | 0.081 | 0.478 | yes |
| **cg06481168** |  |  |  |  | - |  | **-0.068** | 0.124 | 0.330 | yes |
| cg08992305 |  |  |  |  | - |  | NA | NA | NA | NA |
| **cg11630554** |  |  |  |  | - |  | **-0.111** | 0.139 | 0.161 | yes |
| **cg12861945** |  |  |  |  | - |  | **-0.071** | 0.131 | 0.348 | yes |
| **cg20697094** |  |  |  |  | - |  | **-0.055** | 0.121 | 0.410 | yes |
| Chr6:31148332- 31148666 \* | Howe C. et al. 2020 | 31601636 | GDM | *Open sea* | + | 2.6E-05 |  |  |  |  |
| cg03078486 |  |  |  |  | + |  | -0.188 | 0.243 | 0.440 | no |
| cg09179646 |  |  |  |  | + |  | -0.071 | 0.244 | 0.748 | no |
| cg09357589 |  |  |  |  | + |  | -0.051 | 0.226 | 0.773 | no |
| cg11805138 |  |  |  |  | + |  | -0.070 | 0.212 | 0.656 | no |
| cg11811828 |  |  |  |  | + |  | -0.037 | 0.336 | 0.853 | no |
| **cg14036627** |  |  |  |  | + |  | **0.034** | 0.315 | 0.942 | yes |
| cg17931227 |  |  |  |  | + |  | -0.032 | 0.209 | 0.882 | no |
| cg22291762 |  |  |  |  | + |  | -0.072 | 0.212 | 0.770 | no |
| cg22701603 |  |  |  |  | + |  | -0.085 | 0.231 | 0.696 | no |
| cg23252259 |  |  |  |  | + |  | NA | NA | NA | NA |
| cg24427850 |  |  |  |  | + |  | -0.021 | 0.196 | 0.939 | no |
| cg26668675 |  |  |  |  | + |  | -0.186 | 0.294 | 0.551 | no |
| **cg27547543** |  |  |  |  | + |  | **0.060** | 0.229 | 0.810 | yes |
| Chr10:135342218- 135342413 \* | Howe C. et al. 2020 | 31601636 | GDM | *CYP2E1* | - | 8.9E-03 |  |  |  |  |
| cg10862468 |  |  |  |  | - |  | NA | NA | NA | NA |
| cg25330361 |  |  |  |  | - |  | 0.166 | 0.181 | 0.153 | no |
| Chr15:74592566- 74592786 \* | Howe C. et al. 2020 | 31601636 | GDM | *CCDC33* | + | 8.0E-05 |  |  |  |  |
| cg04629595 |  |  |  |  | + |  | -0.036 | 0.152 | 0.825 | no |
| cg05926586 |  |  |  |  | + |  | -0.211 | 0.337 | 0.521 | no |
| cg21565421 |  |  |  |  | + |  | -0.062 | 0.148 | 0.667 | no |

***Continuation*** **Supp Table 4.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | Reported Estimates | | Observed association in EWAS of PC1 | | | |
| CpG/DMR | Study | PubMed ID | Trait | Near Gene | Estimate/  Direction of association | P | Estimate  (in DNAm β-values) | SE | P | Consistent direction of association |
|
| **cg04111177** | El Hajj et al. 2013\*\* | 23209187 | GDM | *NR3C1* | - | 1.20E-02 | **-0.009** | 0.017 | 0.647 | yes |
| **cg05556276** | El Hajj et al. 2013 | 23209187 | GDM | *MEST* | - | 5.60E-12 | **-0.224** | 0.153 | 0.262 | yes |
| cg05862114 | El Hajj et al. 2013 | 23209187 | GDM | *MEST* | - | 5.60E-12 | 0.149 | 0.131 | 0.299 | no |
| **cg15910486** | El Hajj et al. 2013 | 23209187 | GDM | *NR3C1* | - | 1.20E-02 | **-0.028** | 0.026 | 0.240 | yes |
| **cg17580798** | El Hajj et al. 2013 | 23209187 | GDM | *MEST* | - | 5.60E-12 | **-0.084** | 0.131 | 0.562 | yes |
| cg17860381 | El Hajj et al. 2013 | 23209187 | GDM | *NR3C1* | - | 1.20E-02 | NA | NA | NA | NA |
| **cg18068240** | El Hajj et al. 2013 | 23209187 | GDM | *NR3C1* | - | 1.20E-02 | **-0.002** | 0.006 | 0.709 | yes |
| cg00063535 | Haertle et al. 2017 | 28360945 | GDM | *TPCN1* | 1.75% | 4.9E-02 | -0.036 | 0.037 | 0.409 | no |
| **cg00273340** | Haertle et al. 2017 | 28360945 | GDM | *CCDC88B* | 1.45% | 4.6E-02 | **0.039** | 0.026 | 0.127 | yes |
| cg00730857 | Haertle et al. 2017 | 28360945 | GDM | *WHSC2* | 0.90% | 4.6E-02 | -0.003 | 0.023 | 0.970 | no |
| **cg01203331** | Haertle et al. 2017 | 28360945 | GDM | *NOP56; SNORD56* | 1.49% | 4.0E-02 | **0.046** | 0.043 | 0.281 | yes |
| **cg01205011** | Haertle et al. 2017 | 28360945 | GDM | *ZNF76* | -2.44% | 4.1E-02 | **-0.017** | 0.111 | 0.880 | yes |
| cg01955962 | Haertle et al. 2017 | 28360945 | GDM | *CpG island* | -0.64% | 4.1E-02 | 0.002 | 0.016 | 0.804 | no |
| cg01968402 | Haertle et al. 2017 | 28360945 | GDM | *North shore* | 0.58% | 4.4E-02 | -0.009 | 0.010 | 0.371 | no |
| **cg01993865** | Haertle et al. 2017 | 28360945 | GDM | *DSTN* | -0.78% | 2.8E-02 | **-0.006** | 0.004 | 0.236 | yes |
| cg02683621 | Haertle et al. 2017 | 28360945 | GDM | *North shore* | 1.59% | 3.5E-02 | -0.022 | 0.028 | 0.402 | no |
| cg02943336 | Haertle et al. 2017 | 28360945 | GDM | *CARD11* | 1.33% | 2.2E-02 | -0.016 | 0.021 | 0.644 | no |
| cg03246914 | Haertle et al. 2017 | 28360945 | GDM | *TUBB1* | -3.05% | 4.0E-02 | NA | NA | NA | NA |
| **cg03345925** | Haertle et al. 2017 | 28360945 | GDM | *ZC3H3* | 3.83% | 2.8E-02 | **0.021** | 0.076 | 0.865 | yes |
| cg04078644 | Haertle et al. 2017 | 28360945 | GDM | *North shelf* | -1.69% | 4.6E-02 | 0.027 | 0.031 | 0.516 | no |
| cg04514868 | Haertle et al. 2017 | 28360945 | GDM | *MTA1* | 1.08% | 4.6E-02 | -0.018 | 0.023 | 0.506 | no |
| cg05536286 | Haertle et al. 2017 | 28360945 | GDM | *ST8SIA2* | -1.22% | 4.6E-02 | 0.001 | 0.030 | 0.564 | no |
| cg05697697 | Haertle et al. 2017 | 28360945 | GDM | *XPNPEP1* | 0.62% | 2.8E-02 | -0.013 | 0.008 | 0.096 | no |
| **cg07018980** | Haertle et al. 2017 | 28360945 | GDM | *GAK* | 1.67% | 4.0E-02 | **0.005** | 0.020 | 0.686 | yes |
| cg07431064 | Haertle et al. 2017 | 28360945 | GDM | *CBX7* | 1.12% | 2.8E-02 | -0.009 | 0.027 | 0.624 | no |
| **cg07689396** | Haertle et al. 2017 | 28360945 | GDM | *PRKAR1B* | 1.42% | 3.5E-02 | **0.002** | 0.042 | 0.846 | yes |
| **cg08077807** | Haertle et al. 2017 | 28360945 | GDM | *PRKCH* | -2.53% | 3.7E-02 | **-0.003** | 0.034 | 0.904 | yes |
| cg08144943 | Haertle et al. 2017 | 28360945 | GDM | *PPM1M* | 1.91% | 4.9E-02 | -0.026 | 0.080 | 0.804 | no |

***Continuation*** **Supp Table 4.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | Reported Estimates | | Observed association in EWAS of PC1 | | | |
| CpG/DMR\* | Study | PubMed ID | Trait | Near Gene | Estimate/  Direction of association | P | Estimate  (in DNAm β-values) | SE | P | Consistent direction of association |
|
| cg08440349 | Haertle et al. 2017 | 28360945 | GDM | *ATP2C2* | 1.33% | 4.0E-02 | -0.027 | 0.038 | 0.553 | no |
| cg08542429 | Haertle et al. 2017 | 28360945 | GDM | *AGPAT1* | 1.42% | 4.6E-02 | -0.007 | 0.105 | 0.898 | no |
| cg08732684 | Haertle et al. 2017 | 28360945 | GDM | *ATF6B* | 2.20% | 3.5E-02 | -0.014 | 0.037 | 0.819 | no |
| cg09244071 | Haertle et al. 2017 | 28360945 | GDM | *CUX1* | 1.38% | 4.6E-02 | -0.020 | 0.028 | 0.486 | no |
| **cg10288510** | Haertle et al. 2017 | 28360945 | GDM | *CpG island* | -0.89% | 4.0E-02 | **-0.005** | 0.032 | 0.941 | yes |
| **cg10778517** | Haertle et al. 2017 | 28360945 | GDM | *MAD1L1* | 1.18% | 4.0E-02 | **0.015** | 0.014 | 0.307 | yes |
| cg11010397 | Haertle et al. 2017 | 28360945 | GDM | *AMPH* | -1.81% | 2.8E-02 | 0.000 | 0.022 | 0.921 | no |
| **cg11449134** | Haertle et al. 2017 | 28360945 | GDM | *CpG island* | -0.63% | 2.8E-02 | **-0.004** | 0.011 | 0.546 | yes |
| **cg11703745** | Haertle et al. 2017 | 28360945 | GDM | *TMCC2* | 1.87% | 4.0E-02 | **0.080** | 0.061 | 0.102 | yes |
| cg12841566 | Haertle et al. 2017 | 28360945 | GDM | *MADD* | 0.94% | 4.6E-02 | -0.003 | 0.026 | 0.966 | no |
| cg13153307 | Haertle et al. 2017 | 28360945 | GDM | *SEC16A* | 1.55% | 4.0E-02 | -0.065 | 0.044 | 0.145 | no |
| cg13706613 | Haertle et al. 2017 | 28360945 | GDM | *INPP5E* | 1.10% | 4.1E-02 | -0.021 | 0.024 | 0.551 | no |
| **cg14088574** | Haertle et al. 2017 | 28360945 | GDM | *VPS52* | 1.34% | 4.6E-02 | **0.016** | 0.047 | 0.685 | yes |
| cg14597908 | Haertle et al. 2017 | 28360945 | GDM | *GNAS* | 1.35% | 4.9E-02 | -0.003 | 0.110 | 0.993 | no |
| cg15737302 | Haertle et al. 2017 | 28360945 | GDM | *North shelf* | -1.85% | 3.9E-02 | 0.012 | 0.056 | 0.845 | no |
| cg16126178 | Haertle et al. 2017 | 28360945 | GDM | *AKT1* | 1.35% | 4.8E-02 | -0.005 | 0.028 | 0.814 | no |
| cg17881203 | Haertle et al. 2017 | 28360945 | GDM | *WDR18* | 1.40% | 4.9E-02 | -0.016 | 0.018 | 0.328 | no |
| **cg17921080** | Haertle et al. 2017 | 28360945 | GDM | *Open sea* | -2.36% | 3.5E-02 | **-0.047** | 0.048 | 0.305 | yes |
| cg18502630 | Haertle et al. 2017 | 28360945 | GDM | *PTGDS* | 1.35% | 4.0E-02 | -0.029 | 0.044 | 0.551 | no |
| cg18906596 | Haertle et al. 2017 | 28360945 | GDM | *ANKFY1* | -2.29% | 2.8E-02 | 0.090 | 0.053 | 0.099 | no |
| **cg19143209** | Haertle et al. 2017 | 28360945 | GDM | *CpG island* | -2.74% | 3.9E-02 | **-0.085** | 0.127 | 0.523 | yes |
| cg19169154 | Haertle et al. 2017 | 28360945 | GDM | *MFAP4* | 3.21% | 3.9E-02 | -0.005 | 0.086 | 0.944 | no |
| **cg19830000** | Haertle et al. 2017 | 28360945 | GDM | *NELL2* | -0.48% | 4.1E-02 | **-0.007** | 0.020 | 0.704 | yes |
| cg20935025 | Haertle et al. 2017 | 28360945 | GDM | *NFKBIA* | 2.70% | 4.9E-02 | -0.120 | 0.148 | 0.615 | no |
| **cg21143899** | Haertle et al. 2017 | 28360945 | GDM | *UCK2* | 1.53% | 3.5E-02 | **0.004** | 0.044 | 0.855 | yes |
| cg22865713 | Haertle et al. 2017 | 28360945 | GDM | *SLC17A4* | -3.38% | 2.8E-02 | 0.025 | 0.078 | 0.571 | no |
| cg23376861 | Haertle et al. 2017 | 28360945 | GDM | *ATP5A1* | -4.32% | 3.5E-02 | 0.046 | 0.084 | 0.727 | no |
| cg25871543 | Haertle et al. 2017 | 28360945 | GDM | *XAB2* | 1.41% | 4.1E-02 | NA | NA | NA | NA |

***Continuation*** **Supp Table 4.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | Reported Estimates | | Observed association in EWAS of PC1 | | | |
| CpG/DMR | Study | PubMed ID | Trait | Near Gene | Estimate/  Direction of association | P | Estimate  (in DNAm β-values) | SE | P | Consistent direction of association |
|
| cg25927444 | Haertle et al. 2017 | 28360945 | GDM | *TTC7A* | -1.91% | 4.6E-02 | 0.058 | 0.044 | 0.246 | no |
| **cg26001655** | Haertle et al. 2017 | 28360945 | GDM | *KIAA1530* | 1.25% | 2.8E-02 | **0.008** | 0.014 | 0.501 | yes |
| cg26406256 | Haertle et al. 2017 | 28360945 | GDM | *HERC3; NAP1L5* | 1.83% | 4.6E-02 | NA | NA | NA | NA |
| cg26828643 | Haertle et al. 2017 | 28360945 | GDM | *FAM38A* | 1.51% | 4.8E-02 | -0.003 | 0.041 | 0.949 | no |
| cg27509867 | Haertle et al. 2017 | 28360945 | GDM | *Open sea* | 1.42% | 4.6E-02 | NA | NA | NA | NA |
| **cg00510787** | Quilter et al. 2014 | 25145626 | GDM | *C6orf96* | -0.13 | 3.7E-38 | **-0.019** | 0.013 | 0.243 | yes |
| cg03169527 | Quilter et al. 2014 | 25145626 | GDM | *C3orf31* | -0.15 | 3.7E-38 | 0.000 | 0.013 | 0.920 | no |
| cg03849074 | Quilter et al. 2014 | 25145626 | GDM | *ZNF306* | 0.13 | 3.7E-38 | NA | NA | NA | NA |
| **cg03923277** | Quilter et al. 2014 | 25145626 | GDM | *TDG* | 0.14 | 3.7E-38 | **0.090** | 0.483 | 0.923 | yes |
| cg04721883 | Quilter et al. 2014 | 25145626 | GDM | *ESX1* | -0.14 | 3.7E-38 | NA | NA | NA | NA |
| **cg07011110** | Quilter et al. 2014 | 25145626 | GDM | *BTN1A1* | -0.12 | 3.7E-38 | **-0.325** | 0.218 | 0.187 | yes |
| **cg07404485** | Quilter et al. 2014 | 25145626 | GDM | *PON1* | 0.10 | 3.7E-38 | **0.220** | 0.221 | 0.280 | yes |
| **cg08471713** | Quilter et al. 2014 | 25145626 | GDM | *MEOX1* | -0.12 | 3.7E-38 | **-0.248** | 0.672 | 0.841 | yes |
| cg09303642 | Quilter et al. 2014 | 25145626 | GDM | *NFE2* | -0.11 | 3.7E-38 | 0.009 | 0.089 | 0.886 | no |
| **cg09419670** | Quilter et al. 2014 | 25145626 | GDM | *PSMD5* | -0.13 | 3.7E-38 | **-0.672** | 0.528 | 0.191 | yes |
| cg10591659 | Quilter et al. 2014 | 25145626 | GDM | *NYX* | -0.29 | 3.7E-38 | NA | NA | NA | NA |
| cg12791554 | Quilter et al. 2014 | 25145626 | GDM | *TAS2R49* | -0.11 | 3.7E-38 | NA | NA | NA | NA |
| cg13334990 | Quilter et al. 2014 | 25145626 | GDM | *ENO2* | -0.11 | 3.7E-38 | NA | NA | NA | NA |
| cg14159672 | Quilter et al. 2014 | 25145626 | GDM | *FLJ32569* | 0.14 | 3.7E-38 | -1.097 | 0.853 | 0.231 | no |
| cg14893161 | Quilter et al. 2014 | 25145626 | GDM | *FLJ32569* | 0.15 | 3.7E-38 | -0.971 | 0.779 | 0.262 | no |
| **cg16474696** | Quilter et al. 2014 | 25145626 | GDM | *MGC3207* | -0.15 | 3.7E-38 | **-0.312** | 0.801 | 0.557 | yes |
| cg17439694 | Quilter et al. 2014 | 25145626 | GDM | *CP* | -0.13 | 1.3E-34 | 0.021 | 0.038 | 0.662 | no |
| cg18885346 | Quilter et al. 2014 | 25145626 | GDM | *PKHD1* | -0.11 | 3.7E-38 | NA | NA | NA | NA |
| cg19857457 | Quilter et al. 2014 | 25145626 | GDM | *RPL17* | -0.12 | 3.7E-38 | NA | NA | NA | NA |
| cg20507276 | Quilter et al. 2014 | 25145626 | GDM | *OR2L13* | -0.29 | 3.7E-38 | 0.082 | 0.673 | 0.983 | no |
| cg21649520 | Quilter et al. 2014 | 25145626 | GDM | *PMP2* | -0.13 | 1.9E-31 | 0.109 | 0.082 | 0.321 | no |
| **cg21717724** | Quilter et al. 2014 | 25145626 | GDM | *PSMD5* | -0.16 | 3.7E-38 | **-0.328** | 0.419 | 0.526 | yes |
| **cg24468890** | Quilter et al. 2014 | 25145626 | GDM | *HDAC1* | 0.13 | 3.7E-38 | **0.016** | 0.108 | 0.953 | yes |
| cg26130726 | Quilter et al. 2014 | 25145626 | GDM | *CYB5R4* | -0.12 | 3.7E-38 | 0.002 | 0.009 | 0.691 | no |
| **cg27105123** | **Quilter et al. 2014** | **25145626** | **GDM** | ***EPS8L1*** | **-0.13** | 3.7E-38 | **-0.816** | **0.381** | **0.031** | yes |

For the P-values reported in this table, Juvinao-Quintero *et al.* used Bonferroni correction, considering genome-wide significant sites at *P* < 6.9x10-8; Howe C. *et al.* reported significant regions at Sidak corrected *P* < 0.05; El Hajj *et al.* used the Holm method for multiple testing correction and reported sites at *P* < 0.05; Haertle *et al.* applied FDR correction and reported sites at *P* < 0.05; lastly, Quilter *et al.* used a *P* < 0.001 after correcting for multiple testing.