Epigenome-Wide Associations Between Observed Maternal Sensitivity and Offspring DNA Methylation: A Population-Based Prospective Study in Children

SELF-ARCHIVING VERSION

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ABSTRACT

Background: Experimental work in animals has shown that DNA methylation (DNAm), an epigenetic mechanism regulating gene expression, is influenced by typical variation in maternal care. While emerging research in humans supports a similar association, studies to date have been limited to candidate gene and cross-sectional approaches, with a focus on extreme deviations in the caregiving environment.

Methods: Here, we investigated the prospective association between typical variation in maternal sensitivity and offspring epigenome-wide DNAm, in a population-based cohort of children (N = 235). Maternal sensitivity was observed when children were three- and four-years-old. DNAm, quantified with the Infinium 450K array, was extracted at age six (whole blood). The influence of methylation quantitative trait loci (mQTLs), DNAm at birth (cord blood), and confounders (socioeconomic status, maternal psychopathology) was considered in follow-up analyses.

Results: Genome-wide significant associations between maternal sensitivity and offspring DNAm were observed at 13 regions ($p < 1.06e^{-07}$), but not at single sites. Follow-up analyses indicated that associations at these regions were in part related to genetic factors, confounders, and baseline DNAm levels at birth, as evidenced by the presence of mQTLs at five regions and estimate attenuations. Robust associations with maternal sensitivity were found at four regions, annotated to *ZBTB22*, *TAPBP*, *ZBTB12*, and *DOCK4*.

Conclusions: These findings provide novel leads into the relationship between typical variation in maternal caregiving and offspring DNA methylation in humans, highlighting robust regions of associations, previously implicated in psychological and developmental problems, immune functioning, and stress responses.

INTRODUCTION

Parental sensitivity, i.e. the responsiveness to children's signals and communications, is an important predictor of developmental outcomes across the behavioral, emotional, and cognitive domains [1–3]. Low sensitivity of primary caregivers - typically mothers - has been associated with a host of negative outcomes, including higher risk for child psychopathology [4,5], externalizing and internalizing problems [1,6], and lower cognitive abilities [7]. This influence can be long-lasting, as shown by prospective human studies [8,9] and experimental work in animals [10]. Yet, the molecular mechanisms underlying the enduring effects of maternal care on neurodevelopmental and behavioral outcomes in humans remain unclear.

Previous studies have provided initial support for DNA methylation (DNAm) - an epigenetic modification regulating gene expression - as a mechanism of interest for these processes [11–13]. DNAm involves the addition of a methyl group to DNA base pairs, primarily to the 5-carbon of cytosine nucleotides, resulting in 5-methylcytosine. DNAm is sensitive to both environmental and genetic influences [13–15], with the latter being evidenced by changes in the methylome due to DNA variation, named methylation quantitative trait loci (mQTLs) [16]. Further, DNAm plays an essential role in healthy development and functioning by modulating the programming of wider biological systems (e.g. neural and immune functioning) and by coordinating key cellular processes (e.g. tissue differentiation) [17]. DNAm might thus represent a mechanism by which genetic and environmental factors, including the early caregiving environment, jointly and/or independently predict developmental outcomes [14].

Most evidence of maternal care effects on DNAm comes from animal models. In a seminal study by Weaver et al. [13], low levels of maternal care in the first week of life – operationalized as the frequency of licking/grooming and arched-back nursing behaviors - altered DNAm patterns in offspring at the glucocorticoid receptor (*gr*, also known as *nr3c1*), a key regulator of stress response [18]. Importantly, these epigenetic changes were long-lasting, but could be reversed via cross-fostering or chemical interventions, leading to a normalization of physiological and behavioral responses to stress [13,19]. These findings generated widespread interest, as they indicated *(i)* a causal role of maternal care on offspring's epigenetic dysregulation and downstream phenotypes, independent of genetic liability, and *(ii)* the possibility of influencing developmental trajectories through environmental interventions, mediated by DNAm. Since this initial work, other studies have replicated the effects of maternal care on *gr* methylation in rodents [20] and extended findings to demonstrate DNAm changes in other tissues and genes [21–23] (e.g. brain derived neurotrophic factor (*bdnf*) and oxytocin receptor (*oxtr*)) as well as in other species such as rhesus macaques [24].

Although rodents and primates widely differ from humans in their caregiving, a number of similarities in maternal-infant relationships have been observed across mammalian species [25,26]. Parallels at the sensory, hormonal, behavioral, and brain circuit levels have been noted [25–27], including the touch-based behavior characterizing rodents, primates, and humans in the early caregiving and the involvement of the limbic network in maternal-infant relationships (Feldman, 2016). Guided by the animal literature, a growing number of studies have sought to determine the extent to which different forms of caregiving and adversities affect DNAm in humans.

Human studies have focused on different forms of adversities [28] including poly-victimization [29], and on extreme deviations in the early caregiving environment, such as maltreatment [30–34], institutionalization [35], and maternal psychopathology [36]. Generally, literature

focusing on the caregiving environment has provided preliminary support in line with animal findings, identifying, for example, similar increases in *GR* methylation in both *postmortem* hippocampal tissue and peripheral tissues from individuals exposed to childhood maltreatment or early-life stress [20]. Studies also indicate that epigenetic patterns associated with the caregiving environment extend beyond *GR*, implicating other genes related to, among other processes, neurodevelopment and stress, such as *OXTR* and *BDNF*. Moreover, by leveraging epigenome-wide DNAm, novel genes were identified (e.g. *KCNQ2, miR124-3*) in relation to maltreatment and child abuse in individuals with post-traumatic stress disorder [32], borderline personality disorder [33], and depression [34].

While these results are promising and suggest a role of the caregiving environment in the human methylome, the current evidence in humans is limited in a number of key ways. First, since research has mostly focused on extreme deviations in the caregiving environment in selected samples, little is known about how typical variation in maternal sensitivity associates with offspring DNAm in the general population. Second, while studies on extreme deviations in maternal care have leveraged epigenome-wide approaches, literature on normative variation in maternal care has solely focused on candidate genes. This has impeded the identification of novel DNAm loci associated with maternal sensitivity, which might instead be detected with a hypothesis-free approach by performing an epigenome-wide association study (EWAS). Third, studies have typically relied on cross-sectional designs, in which the early caregiving environment is measured retrospectively via the use of questionnaires, raising doubts about the directionality of observed associations and about the validity of measurements, which may be prone to recall bias [37,38]. Moreover, previous studies rarely investigated whether the identified associations may be confounded by genetic background shared between parents and offspring. The examination of the relationship between maternal care and DNAm might indeed capture intergenerational genetic transmission. Lastly, the influence on offspring DNAm of factors preceding postnatal maternal care, including the prenatal environment, remains unexplored.

To address these gaps, we firstly examined how typical variation in observed maternal sensitivity prospectively associates with epigenome-wide DNAm patterns in a general population of children. Secondly, with a series of follow-up analyses, we explored the extent to which associations reflected genetic influences as well as confounding by "baseline" DNAm levels at birth, which precede exposure to postnatal maternal care and might constitute a biological indicator of the prenatal environment as well as of genetic effects on the methylome.

MATERIALS AND METHODS

Participants

The present research was embedded in the Generation R Study, a prospective population-based cohort study from fetal life onwards in Rotterdam, The Netherlands [39] (Supplementary Information 1). Ethical approval was obtained from the Medical Ethics Committee of Erasmus MC, University Medical Center Rotterdam. For the purposes of this study, children within the Generation R Study with data on maternal sensitivity (at three and/or four years) and DNAm (at six years) were selected (N = 235). Since 5 sibling-pairs were present, we later excluded one sibling per pair (N = 230) to ensure genetic relatedness did not impact results.

Participant characteristics are shown in Supplementary Table 1. Participants with data on both maternal sensitivity and DNAm (age six) differed from participants invited to the age six assessment in gestational age at birth ($M_{subsample}$ = 40.3 weeks (SD = 1.4), $M_{fullsample}$ = 39.8 (SD = 1.9), t = 5.6, p = 6.50e^{-08}), but not other covariates.

Measures

Maternal sensitivity

Maternal sensitivity was assessed at ages three and four years through observations of mother-child interactions during teaching tasks too complex for the age of the child. These involved *(i)* building a tower and *(ii)* completing an etch-a-sketch drawing. Mother-child interactions were recorded and subsequently coded, according to the revised Erickson 7-point rating scales [40], based on two interdependent subscales: intrusiveness (IN) and supportive presence (SP), which together form the maternal sensitivity construct. Inter-coder reliability amounted to 0.81 at age three and 0.84 at age four [41].

Eight measures of maternal sensitivity (i.e. IN and SP scales x two tasks x two time-points) were available. IN scores were reversed, and both IN and SP scores were standardized. An overall maternal sensitivity score was calculated, for participants with data at age three and/or four, by averaging such standardized measures [42]. This was done in line with previous literature [41], due to the stability of the maternal sensitivity scores between age three and four years [1], the temporality of these assessments, which both precede DNAm at age six, and to maximize our sample size. Cronbach's alpha reliability of the obtained measure was acceptable (Cronbach's α = 0.70) [43].

DNA methylation

DNAm in whole blood at age six was used for our epigenome-wide analyses. This was selected due to it being the closest DNAm assessment after maternal sensitivity observations (age three and four years), and to test the prospective association of maternal sensitivity with DNAm. Based on previous studies in animals, which found maternal care to have long-lasting influences on the methylome [13], we expected for maternal care effects to endure in early childhood.

To obtain DNAm data, DNA extraction and bisulfite conversion via the EZ-96 DNA Methylation kit (Shallow) (Zymo Research Corporation, Irvine, USA) were performed, and samples were processed with the Illumina Infinium HumanMethylation450 BeadChip (Infinium 450K), which measures 485 577 CpGs. The incorporating control probe adjustment and reduction of global correlation pipeline [44] was employed for the preparation and normalization of the data using R. Firstly, the *minfi* package [45] in R was used to read the idat files. Probes that had a detection p-value above background (based on the sum of methylated and unmethylated intensity values) $\geq$ 1e^{-16} were set to missing per array. Next, the intensity values were stratified by autosomal and non-autosomal probes and quantile normalized for each of the six probe-type categories separately: type II red/green, type I methylated red/green and type I unmethylated red/green. For each probe, DNAm levels were indexed by beta values (i.e. the ratio of methylated signal divided by the sum of the methylated and unmethylated signal [M/(M + U + 100)]). Quality control procedures were additionally performed (e.g. check for sex mismatch). Only arrays with a call rate above 95% per sample were considered for additional processing.

DNAm data was winsorized (> 3 SD) to reduce the influence of potential outliers. In total, we obtained information on 457 872 autosomal sites in 493 six-year-olds.

We additionally used DNAm data collected at birth in cord blood for a follow-up analysis. This was subject to the same pipeline as the DNAm data at age six and was also measured based on the Infinium 450K BeadChip. Only CpGs identified as significant or within DNAm significant regions were selected for these analyses.

Covariates

All analyses were adjusted for a key set of potential covariates guided by previous literature [46–49], including batch effects (plate number), sex, gestational age at birth, maternal smoking during pregnancy (never smoked, smoked until pregnancy known, continued during pregnancy), and estimated cell-type proportions [50] (Supplementary Information 1). We additionally adjusted for two sets of covariates: *(i)* maternal education (highest level completed) as proxy for socioeconomic status, and postnatal maternal psychopathology (Brief Symptom Inventory), and *(iii)* DNAm levels at birth (cord blood tissue), together with respective cell-type and batch effect adjustments (Supplementary Information 1).

Statistical Analyses

Analyses were performed in R (version 4.0.0) and are described in-depth in Supplementary Information 1. A *probe-level EWAS* (multiple linear regression models) was run with the CpGassoc R package [51], to test for associations of maternal sensitivity with each DNAm site individually (Bonferroni epigenome-wide significance threshold: $p < 1.09e^{-07}$). To account for potential bias and inflation, the *BACON* R package [52] was used.

Moreover, to capture correlations across CpGs, reduce data dimensionality, and attenuate the multiple testing burden, a *regional-level EWAS* was performed by using the R package DMRff [53]. This estimates correlations across nominally-significant probes within a 500 bp window (default setting) and combines the EWAS summary statistics of such neighboring CpGs to identify differentially methylated regions while accounting for multiple testing with a Bonferroni procedure in both gene regions and sub-regions [54].

A *candidate gene look-up* was also performed to maximize comparability with previously reported DNAm-maternal care associations. To date, DNAm levels of four genes have been associated with maternal care in humans [55–58], by at least one study: *GR*, *BDNF*, the serotonin receptor (*SLC6A4*), and *OXTR*. We looked-up the EWAS results for probes located within these genes, as annotated in the HumanMethylation450 v1.2 Manifest File. Following previous studies [29,59], gene-level Bonferroni correction was used as significance threshold (i.e. $p < .05$/number of annotated probes).

To identify enriched biological pathways, we performed an in-house *gene ontology (GO) analysis* [59–61] on sites with $p < .001$ in the probe-level EWAS, in line with previous literature [59,60,62,63]. We performed p-value adjustments based on default procedures [61]. Enriched pathways were confirmed by an independent GO approach from the missMethyl R package [64] ($p < .05$).

Finally, a series of *follow-up analyses* were run. Firstly, the influence of genetic factors on our top hits (i.e. Bonferroni-significant sites or sites within Bonferroni-significant DNAm regions) was assessed by drawing on an *mQTL database* [16] (www.mqtldb.org). We examined whether hits were associated with known mQTLs during childhood, based on the results from a

genome-wide complex trait conditional analysis. Secondly, we explored the robustness of top hits to *additional adjustments* for *(i)* postnatal maternal education and maternal psychopathology (*N* = 223) and *(ii)* pre-exposure DNAm (*N* = 226). The latter was done to account for the effect of DNAm at birth on DNAm at age six and to capture potential pre-existing influences (e.g. intrauterine exposures) on DNAm in childhood. Spearman correlations between DNAm at birth and age six were also calculated, per CpG. Thirdly, based on a list of our CpG hits, the in-house *gene ontology analysis* and missMethyl validation were run, with the same procedures as the main GO analysis specified above. Finally, to understand the relevance of our findings to the brain, which is linked to the caregiving environment [13,41], we looked up *brain-blood concordance* values for our top hits using the BECon online tool (https://redgar598.shinyapps.io/BECon/) [65].

RESULTS

Probe-level EWAS

Maternal sensitivity was not associated with any single CpGs at age six, after genome-wide correction ($p < 1.09e^{-07}$) (Figure 1, Supplementary Table 2). BACON analysis revealed a normal lambda ($\lambda = 1.00$), minimal bias (Bayesian estimate of bias = - 0.002) and deflation in the test results – indicative of low power (Bayesian inflation factor = 0.925) (Supplementary Figure 1). Following BACON correction for deflation, one intergenic CpG reached genome-wide significance: cg25628898 (estimate = - 0.008; SE = 0.002; $p = 1.03e^{-07}$) (Supplementary Table 2).

Regional-level EWAS

With a regional-level EWAS, we identified 13 DNAm regions associated with maternal sensitivity ($p < 1.09e^{-07}$; $\alpha = 0.05$) (Table 1, Figure 2, Supplementary Table 3), spanning 143 CpGs. The top three DNAm regions coincided with the *ANKMY1*, *RNF39*, and *ZBTB22* and *TAPBP* genes (Table 1). The largest estimates were shown at regions encompassing *COLEC11* and *DOCK4.* None of the CpGs within our significant regions was related to prenatal maternal smoking, based on previous research in neonates and children (Joubert et al., 2016 Rzehak et al., 2016), suggesting adjustments in the EWAS accounted for its confounding role. When siblings (*N* = 230) were excluded all but one region (annotated to *RNF5P1, RNF5, AGPAT1*) remained significantly associated with maternal sensitivity.

Candidate gene look-up

The candidate gene look-up showed that, of the four selected genes (*NR3C1, BDNF, SLC6A4, OXTR*), which included 14 to 74 sites, no CpG met Bonferroni-adjusted gene-wide significance in association with maternal sensitivity (Table 2, Supplementary Table 4). Only three sites reached nominal significance ($p < .05$).

Gene ontology

The in-house GO analysis, based on sites with $p < 0.001$ in the probe-level EWAS, revealed enrichment for 148 pathways. Yet, this threshold might have been overinclusive. Thirty-nine of the 148 pathways were confirmed by the missMethyl GO method ($p < 0.05$) (Supplementary Table 5). Both methods indicated enrichment for, among others, calcium ion channels functioning, phosphorylation, and tissue and cell polarity.

Follow-up analyses

Firstly, an mQTL search revealed that five of the 13 significant DNAm regions contained at least one CpG associated with one or more known SNPs (Table 3, Supplementary Table 6). Eight regions, including *ZBTB22/TAPBP* (one of our top regions), did not present any mQTLs. Of the 143 sites within the 13 significant regions, 22% (n = 31) associated with one or more known SNPs. All associations were in *cis*.

Secondly, after additional adjustments for socioeconomic status and maternal psychopathology, associations attenuated at seven regions (median = -1%, range = - 44% - 13%). Regions which did not decrease in effect were *TAPBP*, *RNF39*, two non-annotated regions, *ANKMY1*, and *ALOX12P2* (Supplementary Table 7). When adjusting for pre-exposure DNAm levels, (Supplementary Table 8), associations attenuated at ten regions (median = -45%, range = -97% - 17%), with *RNF39* being the most affected. Regions whose estimates did not decrease were *ZBTB12, FBXO44/FBXO2*, and a non-annotated region (chromosome 7). The median correlation between each CpG DNAm levels at birth and age six was of Rho = 0.43 (range: 0.11 – 0.86) (Supplementary Table 9).

Thirdly, in a follow-up GO analysis, based on the sites within the significant DNAm regions (n = 143), enrichment was found at 63 pathways (in-house method). Of these, 33 were validated by missMethyl ($p < 0.05$). Both methods indicated enrichment for, among others, several lipoprotein processes (e.g. particle remodeling), and peptide binding (Supplementary Table 10).

Lastly, of the 13 significant DNAm regions, six contained half or more sites with greater than average blood-brain tissue concordance [65] in at least one brain tissue (for BA7 $r > |.36|$, for BA10 $r > |.40|$, for BA20 $r > |.33|$), for a total of 67 sites (Supplementary Table 11) (not empirically tested).

DISCUSSION

This is the first epigenome-wide study investigating the prospective association between typical variation in maternal sensitivity (observed) and offspring DNAm, in a general population of children. Genome-wide significant associations were observed at 13 DNAm regions, four of which did not contain mQTLs and were minimally affected by adjustments for postnatal confounders and by pre-exposure DNAm levels, thus showing robustness in associations.

Summary of Key Findings

Our first aim was to examine the prospective relationship between maternal sensitivity and child DNAm using complementary approaches. Firstly, no individual CpG was identified in the *probe-level EWAS* after genome-wide correction. This might indicate that associations at a site-level are subtle and challenging to identify, especially considering this study assessed typical variation in maternal care as opposed to extreme deviations (e.g. abuse). The high multiple testing correction burden that probe-level EWASs entail may also impede the detection of single sites of small effect, which could be uncovered with larger samples. For instance, with our sample ($N = 235$) and model (multiple linear regression, 10 predictors), 80% power, and a genome-wide threshold, only moderate estimates (as small as 0.27) could be detected.

When employing a *regional approach*, which can detect weaker but more widespread signals by accounting for correlations across CpGs, 13 DNAm regions were significantly

associated with maternal sensitivity ($p < 1.06e^{-07}$, $\alpha = .05$). These findings support the presence of offspring methylomic signatures of maternal care, which may be best uncovered through hypothesis-free approaches with methods capturing the correlational patterns of DNAm. Yet, replication of these findings is needed, and the possibility of false-positive findings should not be excluded. Notably, when considering a more stringent significance threshold ($p < 2.18e^{-09}$; $\alpha = .001$), as suggested to reduce false-positive rates [68], most of the regions (77%, $N = 10$) remained significantly related to maternal sensitivity.

Further, we failed to detect an association between maternal sensitivity and DNAm variation at *candidate genes* previously identified by studies of maternal care in humans [55–58]. Inconsistencies may reflect several factors, including differences in sample characteristics (e.g. psychiatric vs. population-based samples), maternal care assessments (retrospective vs. prospective reports) and analysis (e.g. gene regions covered by pyrosequencing vs. Infinium 450K). Lastly, candidate gene studies may be particularly vulnerable to false positives, as shown in the genetic field [69].

As a second aim, we explored whether identified maternal sensitivity-DNAm associations may be influenced by genetic factors, based on mQTL mapping. Twenty-two percent of the sites in our significant regions were linked to known SNPs. This suggests that associations for those sites may be in part confounded by genetic factors and corroborates previous research highlighting DNAm responsiveness to both external exposures and genetic variation [14]. However, the presence of mQTLs alone does not preclude environmental effects. Indeed, recent studies have found that interindividual variability in DNAm is primarily explained by gene-environment combinations (additive and interactive effects) [70,71]. Moreover, mQTLs were identified based on a publicly available database, as our sample was underpowered to directly test for genetic confounding. Future studies employing genetically-sensitive designs could more precisely quantify the effect of maternal sensitivity on DNAm by directly modeling genetic influences.

When exploring the robustness of findings to additional adjustments, we observed attenuations at half of the regions, after controlling for socioeconomic status and maternal psychopathology. When considering pre-exposure DNAm levels, estimates attenuated at most regions. Although neonatal methylomic patterns were measured in cord blood at birth and not in peripheral blood (used at age six), which may lead to additional differences, these findings indicate that associations partly reflected pre-existing DNAm levels. This was clearly exemplified by *RNF39*, a region strongly associated with sensitivity, robust to postnatal confounders, and genetic influences. After adjustments, its estimate reduced by 97%, showing that associations did not result from postnatal caregiving, as they were already present at baseline (birth). These findings cast doubts on previous studies of caregiving which did not consider pre-exposure DNAm levels, and raise questions on the directionality of associations between maternal care and DNAm, as well as on the potential role of other confounders affecting child DNAm at birth and in childhood, and maternal sensitivity (e.g. shared genetics, maternal distress).

Here, we highlight four "high-confidence" associations with maternal caregiving, which were not linked to any mQTLs, and were most robust to adjustments for confounders and pre-exposure DNAm levels. These spanned *(i)* ZBTB22/*TAPBP*, *(ii) ZBTB12*, *(iii) DOCK4*, and *(iv)* a non-annotated region in chromosome four. All four genes are protein-coding [18]. *DOCK4* is

implicated in neuronal processes, such as neuronal migration, and dendritic arborization [72] and its DNAm region presented higher than average blood-BA10 concordance in this study. *ZBTB22* and *ZBTB12* are involved in transcriptional regulation and nuclear chromatin localization [73]. These two genes, together with *TAPBP*, are within the Major Histocompatibility Complex (MHC). While these associations should be carefully interpreted as the MHC is characterized by extensive linkage disequilibrium [74], this genomic region plays an important role in immune functioning and has been implicated in neuronal plasticity [75,76]. *TAPBP* specifically is involved in MHC class I protein complex assembly, gene expression regulation, and immunodeficiency [73]. In this study, enrichment for MHC class I protein assembly and peptide binding was found for maternal sensitivity, suggesting that such exposure might enact on *TAPBP*-related functions via DNAm.

Generally, our high-confidence genes have been previously associated with psychological and developmental problems, inflammation, and stress-responses. Molecular changes were shown at *TAPBP* for major depressive disorder and suicide [77], *TAPBP* and *DOCK4* for schizophrenia [78–80], *ZBTB22* for intellectual disability [73] and psychopathologies following hypercortisolism [81], and *DOCK4* for autism and dyslexia [82,83]. Enrichment for pathways including Dock4 has been repeatedly associated with stress-related responses in mice [84–86], while *ZBTB12* DNAm is related to markers of inflammation (e.g. white blood cell counts) [87].

Limitations and Suggestions for Future Research:

Our findings should be interpreted in light of several limitations. Firstly, identified associations may have been influenced by additional parental factors that we could not control for in the present study, either because this information was not available (e.g. parental temperament, parental genotype) or due to the low number of cases (e.g. maternal medication and substance use in pregnancy). Nevertheless, we did control for the most important maternal confounders (smoking during pregnancy, socioeconomic status, psychopathology). Secondly, if unmeasured changes in maternal sensitivity and covariates occurred during the two-to-three-year time-lag between our exposure and outcome, noise would be introduced in the identified associations. A prospective design, as opposed to a cross-sectional one, remains however preferable due to the possibility to better understand the directionality of associations. Nonetheless, repeated postnatal measurements of both DNAm and maternal sensitivity would be ideal to longitudinally examine how associations change over time and disentangle directionality. Thirdly, we did not have information on whether the mothers included in this study were primary or secondary caregivers (at four years only). Yet, within Generation R, most mothers are primary caregivers [88]. Additionally, while the use of the Infinium 450K provided novel insights into the genes affected by maternal sensitivity, future research should employ, when possible, the EPIC 850K array due to its wider and more diverse genomic coverage [89]. Lastly, our investigation solely focused on the association of maternal sensitivity on the child methylome. Related molecular signatures, such as transcription changes and epigenetic clocks, could be examined in future research to better understand the biological consequences of maternal care.

In conclusion, this population-based study supports a prospective association of typical variation in maternal sensitivity with epigenome-wide DNAm in children. We highlight four DNAm regions that showed the strongest associations with maternal sensitivity as well as minimal evidence of genetic and pre-exposure influences, and which should thus be prioritized in future research. These results permit further delineation of the relationship between DNA

methylation and maternal care in humans and warrant confirmation by future research with large, longitudinal, and genetically-sensitive studies.

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CONFLICT OF INTEREST

None.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Supplementary Information:

Epigenome-Wide Associations Between Observed Maternal Sensitivity and Offspring DNA Methylation:

A Population-Based Prospective Study in Children

List of Supplementary Information (SI):

Supplementary Information (SI):

SI1: Supplementary information on the methods

References: References for the supplementary information on the method

Supplementary Figures (SF):

SF1 A-C: BACON-corrected probe-level EWAS of the association between maternal sensitivity and DNAm

Supplementary Tables (ST):

ST1: Sample characteristics

ST2: Top sites from the probe-level EWAS with BACON-corrected estimates

ST3: Top regions from the regional-level EWAS

ST4: Candidate gene look-up

ST5: Gene ontology in-house results with MissMethyl validation

ST6: mQTLs associated with the CpGs within the significant DNAm regions

ST7: Associations between maternal sensitivity and DNA methylation at significant regions after adjustments for maternal education and psychopathology

ST8: Associations between maternal sensitivity and DNA methylation at significant regions after adjustments for baseline DNA methylation

ST9: Correlations of methylation values at birth with age 6 at significant regions

ST10: Gene ontology analysis based on the CpGs within the significant DNAm regions

ST11: BECon Brain-Blood Correlations

Text summary for the supplementary files:

Supplementary Information (SI):

SI1.Here we describe the details of our sample, covariates, and the analyses performed (e.g. candidate gene look-up, adjustments for DNAm at birth, brain-blood correlations)

Supplementary Figures (SF):

SF1. Minimal bias is depicted in panel A, where adjusted and unadjusted test statistics approximately overlap. Deflation in the original EWAS is evident in panel B, where the observed CpG *p*-values vary following BACON correction. After BACON-correction, a greater proportion of small as opposed to large p-values is present (panel C).

Supplementary Tables (ST):

ST1. All children in the present study are of Dutch ethnicity. An approximately equal proportion of males and females participated. Most mothers obtained a higher education qualification and never smoked during pregnancy.

ST2. None of the top 30 CpGs identified in the probe-level EWAS surpassed genome-wide significance in the original EWAS. When BACON correction was applied, p-values decreased, with cg25628898, becoming statistically significant (estimate = - 0.008; SE = 0.002; p = 1.03e-07)

ST3. The top 30 maternal sensitivity-DNAm associations are shown. The regional-level EWAS, after Bonferroni correction, revealed 13 regions significantly associated with maternal sensitivity.

ST4. Probe-level EWAS findings at four genes, previously identified in association with maternal care in humans, were leveraged. Gene-wide significance thresholds were calculated for each gene separately: $p < 0.05$ / number of probes within the gene. There was no gene-wide significant probe. Only three probes reached nominal significance.

ST5. 148 significant pathways were identified as enriched by the in-house method, 39 of which were validated by the MissMethyl method (highlighted in green).

ST6. Twenty-two percent of the CpGs within the significant DNAm regions were significantly associated with one or more known SNPs. All associations were in cis.

ST7. Summary statistics before and after adjustments for maternal education and psychopathology, within a restricted sample with covariate data, are shown. After adjustments, estimates attenuated at approximately half of the regions.

ST8. Summary statistics before and after adjustments for DNA methylation at birth, within a restricted sample with DNAm at birth, are shown. After adjustments, estimates attenuated at 10 regions.

ST9. DNA methylation levels at birth and age six for our significant regions were generally moderate-to-strong: Rho = 0.43.

ST10. The follow-up gene ontology analysis, based on sites within our significant regions, identified 63 significant pathways, 33 of which were validated by MissMethyl.

ST11. We examined brain-blood correlations based on a publicly available database with information on DNAm levels across blood, Brodmann area (BA) 7, BA10 and BA20. Six regions presented half or more CpGs with correlations greater than the average value for all Infinium 450K probes, in at least one brain tissue.

SI1. Supplementary Information on the Methods

Participants:

Generation R was designed to shed light into environmental, genetic, and other pathways involved in (ab)normal development. For the purposes of this study, children within Generation R with data on maternal sensitivity (at three and/or four years) and DNAm (at six years) were selected. Maternal sensitivity assessments at ages three (N = 1247) and four (N = 752) years were both considered. This was done in line with previous literature [1], due to the stability of the maternal sensitivity scores between age 3 and 4 years [2], the temporality of these assessments, which both precede DNAm at age 6, and to maximize our sample size. Amongst children with maternal sensitivity data at either time point, 235 also had DNAm information at age six (i.e. the closest prospective DNAm assessment). Of note, this sample included 5 sibling-pairs and was the sample used for the main analyses. To ensure genetic relatedness did not impact results, one sibling per pair was later excluded in a sensitivity analysis. The excluded sibling presented the least covariate data.

In follow-up analyses, where additional adjustments for covariates were made, the main sample was further restricted to complete cases. For adjustments for maternal education and psychopathology, 223 children had data. For adjustments for DNAm levels at birth, 226 children had data.

Covariates

The main model in the epigenome-wide association study (EWAS) was adjusted for cell types, batch effects, sex, gestational age at birth, and maternal smoking during pregnancy. Further information on these variables is shown below.

Cell-type and Batch effects

Cell-type adjustments were performed, for analyses with DNAm at age six, for the following cell types: CD4 T lymphocytes, CD8 T lymphocytes, B lymphocytes, monocytes, natural killer cells. Of note, granulocyte cells were excluded due to multicollinearity. The sample plate was used as a measure of batch effects. This variable presented 17 levels.

Sex and gestational age at birth

Sex and gestational age were measured at child-birth. Sex was coded binarily into males and females. Gestational age at birth was measured continuously.

Maternal smoking during pregnancy

We analyzed maternal smoking during pregnancy as a three-level variable: *(i)* did not smoke during pregnancy, *(ii)* smoked until pregnancy was known, *(iii)* smoked throughout pregnancy. This was based on previous work from Joubert et al. [3] showing that sustained smoking throughout pregnancy has the strongest associations with offspring DNA methylation, with any smoking in pregnancy also showing significant associations, although not as strong. To ensure such variable was not subject to important bias, we additionally examined whether any of

our hits (i.e. significant sites or sites within significant regions) overlapped with CpGs related to smoking, based on previous literature. Given the sample at hand, we used the Pregnancy and Childhood Epigenetics (PACE) consortium prenatal smoking exposure reference [3]. In this publication, 6 074 genome-wide significant CpGs were identified in association with maternal smoking during pregnancy in cord blood. Additionally, since tissue- and age-specific effects might be present, we considered another EWAS of smoking carried out in childhood (age 5.5) in whole blood [4], which identified five genome-wide significant probes.

Maternal education and maternal psychopathology

In follow-up analyses, we additionally adjusted for maternal education and maternal psychopathology. Maternal education was coded into low, medium, and high, respectively denoting primary, secondary, and tertiary education levels. Maternal psychopathology (postnatal: child age six months) was measured according to the Beck Symptoms Inventory (BSI) which presents information on the total maternal psychopathology symptoms.

DNA methylation at birth

In another follow-up analysis, additional adjustments for DNAm levels at birth were performed. This was done for top hits only. Covariates which are key to appropriately measure DNAm levels were also included: batch effects (measured by sample plate) and cell types (CD4 T lymphocytes, CD8T lymphocytes, B lymphocytes, monocytes, natural killer cells, and nucleated red blood cells – a cell type present only in cord blood).

Statistical Analyses

Regional-level EWAS

The dmrff approach, based on simulations, performs better compared to other regional methods in terms of false positive control, statistical power, and replicability across datasets [5]. Of note, the probe- and regional-level EWASs were rerun after one sibling per sibling-pair was excluded.

Candidate gene look-up

For the candidate gene look-up, we selected genes based on previous literature. We searched the PubMed and Google Scholar engines by using a combination of the following terms: “maternal care” or "maternal sensitivity" with “DNA methylation”. Only studies in humans were considered. Review articles were excluded. Both epigenome-wide association studies (probe- and regional-level EWASs) as well as candidate gene studies were considered, yet, no EWAS had been performed to date on normative maternal care. Of the identified candidate gene studies, only those with statistically significant results were included, for a total of four publications [6–9]. Genes significantly related with maternal care/sensitivity included *NR3C1, BDNF, SLC6A4, OXTR, and 11B-HSD2*. Due to methylomic values not being available in our sample for *11B-HSD2*, such gene was excluded. Overall, four genes were selected based on previous literature.

Gene Ontology: In-House method

In this method, genes in the test list were tested in relation to pathway membership, with a logistic regression approach. We controlled for the number of probes annotated to each gene in the test list. The Gene Ontology website was utilized to obtain pathways. Genes annotated to parent terms were used too. A gene list was formed based on the probes associated with maternal sensitivity at a *p*-value threshold < 0.001, based on the probe-level EWAS. The Illumina UCSC gene annotation permitted the annotation of probes to genes. Genes were considered if they were included in, at minimum, one gene ontology pathway and presented at least one annotated probe. Pathways were considered if including from 10 to 2000 genes. Once this method was used for all pathways, the significant ones with overlapping genes were retested. Associations were retested in all significant pathways, after adjusting for the most significant term. In case the associations at such pathways were no longer significant, the most significant pathway was considered as explaining the relationship. In such situation, pathways were grouped together. This process was repeated, with the next most significant pathway being adjusted for, till all pathways were considered as the most significant one or were identified as pertaining to a more significant pathway. A minimum of two genes was necessary for GO terms to be interpreted.

Follow-up analyses

Firstly, the influence of genetic factors on DNAm was examined, based on an openly-accessible mQTL database. The database mQTL information was based on the results from the Accessible Resource for Integrative Epigenomics Studies (ARIES). The ARIES mQTL database includes data on the single nucleotide polymorphisms (SNPs) significantly affecting DNAm levels in cis or trans ($p < 1e^{-14}$, 1Mb window), at several lifespan stages, based on the Infinium 450K array. Here, we selected information for children, based on the results from a genome-wide complex trait conditional analysis.

Secondly, we adjusted for an additional set of parental confounders, maternal education and psychopathology, in a subsample of children with such information ($N = 223$). This was done on top hits only. To ensure estimate changes resulted from adjustments as opposed to the restriction to the subsample, firstly, we ran a multiple linear regression on our top hits, within the subsample of children with data on such confounders (Model A, $N = 223$). This model was still *un*adjusted for maternal education and psychopathology. Subsequently, adjustments for maternal education and psychopathology were performed on top hits, within the subsample (Model B, N = 223, adjusted model), with a multiple linear regression. The newly-obtained site summary statistics for both models were then inputted in DMRff, where the function dmrff.stats enables the recalculation of the statistics per DNAm region. The percent estimate change was then calculated ((estimate after adjustments – estimate before adjustments) / estimate before adjustments * 100).

The same procedure was employed for adjustments for DNAm levels at birth. Therefore, a multiple linear regression where, for each site, its own DNAm levels at baseline were used as covariates, was tested in association with maternal sensitivity: site DNAm at six ~ maternal sensitivity + main set of covariates + site DNAm at birth (Model B, $N = 226$). This was compared to a restricted *un*adjusted model (Model A, $N = 226$). Site statistics were inputted in dmrff.stats to obtain regional-level statistics.

Lastly, the BECon online tool used here includes information on tissue concordance between DNAm in blood and Brodmann Areas (BA) seven, 10 and 20, based on brain postmortem samples from 16 subjects.

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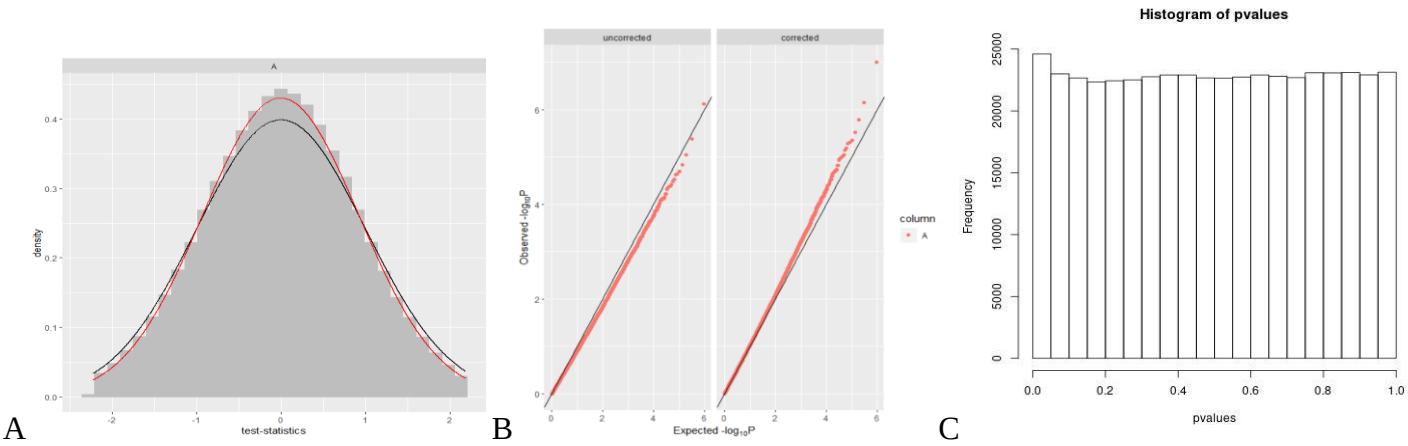

Supplementary Figure 1 A-C.
BACON-corrected probe-level EWAS of the association between maternal sensitivity and DNAm
Note. Panel A shows the test statistic histogram. This indicates minimal bias, as shown by the proximity of the black and red lines. Panel B depicts uncorrected and BACON-corrected QQ-plots. The uncorrected QQ-plot is from the main EWAS and shows no significant associations. The BACON-corrected QQ-plot suggests that values were originally deflated in the EWAS and that, after corrections, associations are present. Panel C is a histogram of *p*-values after BACON-correction, showing that there is a greater proportion of sites with low *p*-values compared to the proportion of sites with higher *p*-values, further suggesting that associations of maternal sensitivity with DNAm are present.

ST1. Sample characteristics

Child and maternal characteristics	**Percentage/Mean**
Child Characteristics	
Sex - females	49%
Child Ethnicity - Dutch	100%
Maternal Characteristics	
Observed maternal sensitivity	0.05
Maternal Education*	
Primary education	8%
Secondary education	21%
Higher education	71%
Gestational age at birth	40.31
Maternal prenatal smoking	
Never smoked	75%
Quit when pregnancy known	11%
Continued during pregnancy	14%
Maternal psychopathology*	0.15

Note. % = percentage

*Information was available only for a subsample (n = 223)

ST2. Top sites from the probe-level EWAS with BACON-corrected estimates

CpG	EWAS T-statistic	EWAS P-value	EWAS Estimate	EWAS Standard Error	Bacon T-statistic	Bacon P-value
cg25628898	-4.93	1.7E-06	-0.01	0.00	-5.32	0.000
cg00808563	-4.62	6.7E-06	-0.01	0.00	-4.99	0.000
cg27541515	4.43	1.5E-05	0.01	0.00	4.79	0.000
cg01567825	-4.34	2.2E-05	-0.02	0.00	-4.69	0.000
cg26554505	4.26	3.1E-05	0.00	0.00	4.60	0.000
cg21457839	4.20	3.9E-05	0.00	0.00	4.54	0.000
cg05637265	-4.19	4.2E-05	-0.01	0.00	-4.52	0.000
cg07439474	4.17	4.4E-05	0.00	0.00	4.51	0.000
cg02276600	4.17	4.4E-05	0.01	0.00	4.51	0.000
cg01200177	4.17	4.5E-05	0.02	0.01	4.51	0.000
cg04604420	-4.16	4.7E-05	-0.01	0.00	-4.49	0.000
cg05935283	4.16	4.7E-05	0.00	0.00	4.49	0.000
cg00079764	4.08	6.4E-05	0.01	0.00	4.41	0.000
cg09678349	-4.03	7.8E-05	-0.02	0.01	-4.35	0.000
cg14012059	-3.99	9.1E-05	-0.02	0.00	-4.31	0.000
cg25623347	-3.98	9.3E-05	-0.01	0.00	-4.30	0.000
cg02328660	3.98	9.4E-05	0.00	0.00	4.31	0.000
cg19755714	3.98	9.5E-05	0.01	0.00	4.30	0.000
cg12441928	-3.97	1.0E-04	0.00	0.00	-4.28	0.000
cg03113916	-3.94	1.1E-04	-0.01	0.00	-4.26	0.000
cg03810365	3.94	1.1E-04	0.01	0.00	4.26	0.000
cg09086615	-3.93	1.2E-04	-0.01	0.00	-4.24	0.000
cg10066481	-3.92	1.2E-04	-0.01	0.00	-4.23	0.000
cg10319073	-3.91	1.2E-04	-0.01	0.00	-4.23	0.000
cg20093139	3.91	1.2E-04	0.01	0.00	4.23	0.000
cg22798223	-3.91	1.3E-04	0.00	0.00	-4.22	0.000
cg24618910	3.90	1.3E-04	0.00	0.00	4.22	0.000
cg20959907	-3.88	1.4E-04	-0.02	0.00	-4.19	0.000
cg15871766	-3.87	1.5E-04	-0.02	0.01	-4.18	0.000

ST3. Top regions from the regional-level EWAS

Location	N CpGs	Estimate	Standard Error	P-value	Adj. P-value
chr2:241458886-241460002	8	-0.36	0.04	1.17E-17	5.61E-12
chr6:30039027-30039600	22	-0.23	0.03	5.03E-16	2.42E-10
chr6:33282879-33283184	17	-0.21	0.03	1.83E-15	8.77E-10
chr2:21266727-21267334	10	-0.30	0.04	2.83E-14	1.36E-08
chr2:3642629-3642867	6	-0.87	0.14	9.80E-11	4.71E-05
chr17:6797034-6797771	6	-0.57	0.09	1.00E-10	4.80E-05
chr7:111368367-111368847	4	-0.82	0.13	1.02E-10	4.90E-05
chr6:32145383-32146595	27	0.05	0.01	3.55E-10	1.71E-04
chr7:158749953-158751591	8	0.56	0.09	4.80E-10	2.31E-04
chr6:33280149-33280436	9	-0.28	0.05	8.89E-10	4.27E-04
chr6:31867757-31868169	19	-0.10	0.02	2.35E-08	1.13E-02
chr4:147164778-147165097	4	0.43	0.08	2.53E-08	1.21E-02
chr1:11714218-11714254	3	-0.44	0.08	5.82E-08	2.80E-02
chr4:1243980-1244086	6	1.04	0.20	1.19E-07	5.70E-02
chr7:158551048-158551361	4	-0.58	0.11	1.47E-07	7.07E-02
chr20:57225195-57225678	2	0.12	0.02	1.65E-07	7.92E-02
chr11:70672365-70672858	7	-0.28	0.05	2.27E-07	1.09E-01
chr7:63505638-63505871	6	0.84	0.16	2.56E-07	1.23E-01
chr20:36148615-36148928	14	-0.09	0.02	2.99E-07	1.43E-01
chr2:128616082-128616167	2	1.07	0.21	4.00E-07	1.92E-01
chr6:33245619-33246105	17	-0.10	0.02	4.75E-07	2.28E-01
chr10:82295394-82296191	6	0.45	0.09	5.63E-07	2.71E-01
chr2:20870087-20871002	5	-1.42	0.29	8.51E-07	4.09E-01
chr6:31856617-31856773	4	-0.39	0.08	9.10E-07	4.37E-01
chr7:44349704-44349955	3	0.91	0.19	1.15E-06	5.52E-01
chr19:57702479-57702772	6	0.23	0.05	1.19E-06	5.72E-01
chr7:6979239-6979488	2	-0.22	0.05	1.34E-06	6.42E-01
chr12:52404134-52404422	4	0.29	0.06	1.42E-06	6.82E-01

Note. adj. = adjusted; N = number.

ST4. Candidate gene look-up

Gene	Location	CPG.Labels	estimate	std.error	T.statistic	P.value	Genome_wide_sign	Gene_wide_sign	Nominal_sign
BDNF	chr11:27744816	cg18867480	-0.003	0.002	-1.63	0.105	No	No	No
BDNF	chr11:27744363	cg11718030	-0.003	0.003	-0.95	0.342	No	No	No
BDNF	chr11:27744049	cg15462887	0.002	0.003	0.72	0.475	No	No	No
BDNF	chr11:27744490	cg06046431	0.000	0.001	-0.50	0.619	No	No	No
BDNF	chr11:27744557	cg10022526	-0.001	0.002	-0.50	0.620	No	No	No
BDNF	chr11:27744759	cg24249411	-0.001	0.003	-0.35	0.729	No	No	No
BDNF	chr11:27743619	cg03167496	-0.002	0.002	-1.58	0.115	No	No	No
BDNF	chr11:27743664	cg25457956	0.001	0.002	0.68	0.494	No	No	No
BDNF	chr11:27743651	cg25381667	-0.001	0.001	-0.63	0.532	No	No	No
BDNF	chr11:27743648	cg14589148	-0.001	0.002	-0.56	0.577	No	No	No
BDNF	chr11:27742832	cg07704699	0.001	0.007	0.21	0.834	No	No	No
BDNF	chr11:27743258	cg27351358	-0.004	0.002	-1.63	0.105	No	No	No
BDNF	chr11:27740161	cg21010859	-0.002	0.001	-1.58	0.115	No	No	No
BDNF	chr11:27740813	cg13974632	0.004	0.003	1.45	0.149	No	No	No
BDNF	chr11:27739827	cg17413943	0.004	0.003	1.36	0.175	No	No	No
BDNF	chr11:27743348	cg02527472	0.002	0.002	1.21	0.226	No	No	No
BDNF	chr11:27742365	cg12448003	-0.001	0.002	-0.76	0.449	No	No	No
BDNF	chr11:27742355	cg01225698	0.003	0.003	0.76	0.451	No	No	No
BDNF	chr11:27742369	cg06684850	-0.003	0.004	-0.72	0.475	No	No	No
BDNF	chr11:27743476	cg01642653	0.001	0.002	0.63	0.528	No	No	No
BDNF	chr11:27740078	cg05818894	0.001	0.002	0.49	0.625	No	No	No
BDNF	chr11:27742454	cg04106006	0.003	0.007	0.41	0.684	No	No	No
BDNF	chr11:27740876	cg05733135	-0.001	0.002	-0.37	0.710	No	No	No
BDNF	chr11:27732958	cg11806762	-0.001	0.005	-0.28	0.779	No	No	No
BDNF	chr11:27743580	cg16257091	-0.001	0.006	-0.22	0.824	No	No	No
BDNF	chr11:27740495	cg04481212	0.000	0.002	0.12	0.907	No	No	No
BDNF	chr11:27742435	cg10635145	0.001	0.007	0.10	0.918	No	No	No
BDNF	chr11:27741077	cg22043168	0.002	0.002	0.95	0.341	No	No	No
BDNF	chr11:27741916	cg24650785	0.002	0.003	0.72	0.470	No	No	No
BDNF	chr11:27742138	cg25412831	-0.004	0.003	-1.49	0.139	No	No	No
BDNF	chr11:27742060	cg26949694	0.002	0.003	0.63	0.530	No	No	No
BDNF	chr11:27742219	cg06816235	0.000	0.002	-0.14	0.885	No	No	No
BDNF	chr11:27723290	cg26840770	0.005	0.002	2.36	0.019	No	No	Yes
BDNF	chr11:27723214	cg23497217	-0.005	0.003	-1.82	0.070	No	No	No
BDNF	chr11:27722722	cg03747251	-0.010	0.006	-1.58	0.116	No	No	No

BDNF	chr11:27723218	cg05218375	0.004	0.003	1.21	0.228	No	No	No
BDNF	chr11:27722774	cg15914769	0.001	0.001	1.18	0.241	No	No	No
BDNF	chr11:27723237	cg06991510	-0.001	0.001	-0.64	0.525	No	No	No
BDNF	chr11:27723190	cg15688670	0.000	0.001	0.38	0.705	No	No	No
BDNF	chr11:27723409	cg24065044	0.000	0.003	0.16	0.869	No	No	No
BDNF	chr11:27723245	cg24377657	0.000	0.003	0.13	0.896	No	No	No
BDNF	chr11:27723385	cg01636003	0.000	0.002	0.04	0.967	No	No	No
BDNF	chr11:27723075	cg20340655	-0.002	0.001	-1.56	0.120	No	No	No
BDNF	chr11:27722971	cg09606766	0.001	0.001	0.90	0.370	No	No	No
BDNF	chr11:27723128	cg11241206	0.000	0.001	0.27	0.789	No	No	No
BDNF	chr11:27722889	cg04672351	0.000	0.002	0.19	0.848	No	No	No
BDNF	chr11:27720709	cg09492354	0.001	0.001	1.78	0.077	No	No	No
BDNF	chr11:27721277	cg26057780	-0.002	0.001	-1.49	0.137	No	No	No
BDNF	chr11:27722037	cg23947039	-0.002	0.001	-1.46	0.147	No	No	No
BDNF	chr11:27718978	cg20108357	-0.006	0.005	-1.34	0.181	No	No	No
BDNF	chr11:27722066	cg18117895	-0.001	0.001	-1.25	0.212	No	No	No
BDNF	chr11:27701991	cg18595174	-0.004	0.003	-1.15	0.251	No	No	No
BDNF	chr11:27721668	cg20954537	0.001	0.002	0.96	0.339	No	No	No
BDNF	chr11:27722636	cg08362738	0.001	0.001	0.88	0.379	No	No	No
BDNF	chr11:27722638	cg25328597	0.001	0.002	0.78	0.434	No	No	No
BDNF	chr11:27722620	cg15710245	0.002	0.004	0.66	0.511	No	No	No
BDNF	chr11:27721270	cg15313332	-0.001	0.001	-0.50	0.620	No	No	No
BDNF	chr11:27722617	cg03984780	0.001	0.003	0.42	0.676	No	No	No
BDNF	chr11:27721280	cg10558494	0.001	0.002	0.33	0.740	No	No	No
BDNF	chr11:27721350	cg06260077	-0.001	0.003	-0.19	0.847	No	No	No
BDNF	chr11:27721222	cg25962210	0.000	0.002	-0.17	0.867	No	No	No
BDNF	chr11:27722063	cg00298481	0.000	0.001	-0.03	0.977	No	No	No
BDNF	chr11:27721088	cg27193031	0.000	0.002	0.25	0.801	No	No	No
BDNF	chr11:27722523	cg07159484	0.000	0.002	-0.06	0.949	No	No	No
BDNF	chr11:27722549	cg06025631	0.001	0.001	1.03	0.302	No	No	No
BDNF	chr11:27677125	cg06979684	-0.006	0.004	-1.64	0.103	No	No	No
BDNF	chr11:27680480	cg05189570	-0.002	0.002	-0.98	0.330	No	No	No
BDNF	chr11:27679729	cg23426002	0.002	0.002	1.17	0.242	No	No	No
BDNF	chr11:27679469	cg01418645	-0.001	0.002	-0.71	0.478	No	No	No
BDNF	chr11:27681475	cg07238832	0.001	0.002	0.44	0.662	No	No	No
BDNF	chr11:27679632	cg08388004	0.000	0.002	-0.01	0.988	No	No	No
BDNF	chr11:27696004	cg18354203	0.001	0.005	0.30	0.762	No	No	No

BDNF	chr11:27683959	cg14291693	-0.004	0.004	-1.08	0.281	No	No	No
BDNF	chr11:27695210	cg15014679	0.000	0.004	-0.09	0.929	No	No	No
NR3C1	chr5:142786405	cg27345592	0.005	0.002	1.86	0.064	No	No	No
NR3C1	chr5:142815469	cg12466613	0.006	0.004	1.73	0.085	No	No	No
NR3C1	chr5:142815463	cg07589972	0.001	0.002	0.41	0.683	No	No	No
NR3C1	chr5:142788776	cg07528216	0.001	0.002	0.38	0.706	No	No	No
NR3C1	chr5:142785172	cg24026230	0.002	0.001	1.88	0.061	No	No	No
NR3C1	chr5:142784982	cg14558428	0.000	0.001	0.62	0.534	No	No	No
NR3C1	chr5:142785258	cg13648501	0.002	0.003	0.55	0.584	No	No	No
NR3C1	chr5:142814827	cg08818984	0.003	0.002	1.32	0.189	No	No	No
NR3C1	chr5:142814934	cg26720913	0.002	0.002	1.05	0.293	No	No	No
NR3C1	chr5:142780254	cg17342132	0.005	0.002	2.15	0.033	No	No	Yes
NR3C1	chr5:142658828	cg23273257	0.003	0.002	1.79	0.074	No	No	No
NR3C1	chr5:142784222	cg26464411	0.001	0.001	1.20	0.233	No	No	No
NR3C1	chr5:142781532	cg18998365	0.006	0.005	1.19	0.234	No	No	No
NR3C1	chr5:142782415	cg17617527	0.001	0.001	1.09	0.275	No	No	No
NR3C1	chr5:142783385	cg18019515	-0.001	0.001	-1.01	0.312	No	No	No
NR3C1	chr5:142783639	cg15645634	-0.001	0.001	-0.90	0.368	No	No	No
NR3C1	chr5:142784323	cg06968181	-0.002	0.002	-0.88	0.379	No	No	No
NR3C1	chr5:142729913	cg03857453	-0.002	0.003	-0.76	0.448	No	No	No
NR3C1	chr5:142776274	cg27107893	-0.004	0.006	-0.75	0.456	No	No	No
NR3C1	chr5:142783569	cg17860381	0.000	0.001	-0.66	0.510	No	No	No
NR3C1	chr5:142784382	cg18849621	0.002	0.002	0.63	0.530	No	No	No
NR3C1	chr5:142780693	cg08845721	0.001	0.003	0.48	0.632	No	No	No
NR3C1	chr5:142781498	cg07733851	0.002	0.005	0.47	0.640	No	No	No
NR3C1	chr5:142740314	cg18484679	-0.001	0.003	-0.45	0.651	No	No	No
NR3C1	chr5:142782072	cg06521673	0.001	0.001	0.45	0.652	No	No	No
NR3C1	chr5:142757312	cg25535999	-0.001	0.002	-0.42	0.671	No	No	No
NR3C1	chr5:142784462	cg16335926	0.000	0.001	0.32	0.747	No	No	No
NR3C1	chr5:142783621	cg15910486	0.000	0.001	0.32	0.751	No	No	No
NR3C1	chr5:142692961	cg19457823	0.002	0.005	0.32	0.752	No	No	No
NR3C1	chr5:142781723	cg27122725	0.002	0.006	0.30	0.761	No	No	No
NR3C1	chr5:142783383	cg11152298	0.000	0.002	-0.30	0.761	No	No	No
NR3C1	chr5:142784522	cg10847032	0.000	0.001	-0.27	0.784	No	No	No
NR3C1	chr5:142784721	cg21702128	0.001	0.003	0.24	0.807	No	No	No
NR3C1	chr5:142783843	cg18068240	0.000	0.001	0.23	0.815	No	No	No
NR3C1	chr5:142779552	cg06613263	0.000	0.003	0.18	0.857	No	No	No

NR3C1	chr5:142783379	cg00629244	0.000	0.000	-0.09	0.930	No	No	No
NR3C1	chr5:142783607	cg04111177	0.000	0.002	-0.06	0.955	No	No	No
NR3C1	chr5:142757011	cg16586394	0.000	0.002	0.00	0.997	No	No	No
NR3C1	chr5:142782791	cg20753294	-0.001	0.003	-0.27	0.791	No	No	No
NR3C1	chr5:142782827	cg18146873	0.000	0.002	0.20	0.840	No	No	No
OXTR	chr3:8810077	cg12695586	0.004	0.003	1.42	0.158	No	No	No
OXTR	chr3:8810549	cg03987506	-0.006	0.004	-1.38	0.168	No	No	No
OXTR	chr3:8810139	cg19619174	-0.002	0.002	-1.22	0.223	No	No	No
OXTR	chr3:8811543	cg00247334	0.004	0.004	0.99	0.326	No	No	No
OXTR	chr3:8811601	cg17036624	0.006	0.007	0.93	0.356	No	No	No
OXTR	chr3:8811437	cg25140571	0.004	0.006	0.71	0.479	No	No	No
OXTR	chr3:8808259	cg00385883	-0.001	0.002	-0.70	0.483	No	No	No
OXTR	chr3:8811758	cg14483142	0.003	0.005	0.69	0.494	No	No	No
OXTR	chr3:8809306	cg15317815	0.004	0.007	0.53	0.600	No	No	No
OXTR	chr3:8806317	cg11589699	0.001	0.002	0.52	0.603	No	No	No
OXTR	chr3:8809715	cg27501759	0.001	0.001	0.43	0.669	No	No	No
OXTR	chr3:8809501	cg04523291	-0.002	0.006	-0.36	0.722	No	No	No
OXTR	chr3:8810592	cg00078085	-0.001	0.005	-0.11	0.911	No	No	No
OXTR	chr3:8809536	cg02192228	0.000	0.005	-0.01	0.990	No	No	No
OXTR	chr3:8811279	cg23391006	0.001	0.002	0.77	0.445	No	No	No
OXTR	chr3:8811004	cg17285225	0.000	0.001	-0.31	0.753	No	No	No
OXTR	chr3:8811092	cg09353063	0.000	0.002	-0.23	0.822	No	No	No
OXTR	chr3:8810980	cg08535600	0.000	0.003	0.15	0.883	No	No	No
SLC6A4	chr17:28564094	cg06841846	0.005	0.002	2.75	0.006	No	No	Yes
SLC6A4	chr17:28563089	cg26741280	-0.004	0.002	-1.97	0.051	No	No	No
SLC6A4	chr17:28563119	cg27569822	0.002	0.001	1.90	0.059	No	No	No
SLC6A4	chr17:28524160	cg20592995	-0.003	0.002	-1.27	0.207	No	No	No
SLC6A4	chr17:28559497	cg26126367	-0.002	0.002	-1.16	0.248	No	No	No
SLC6A4	chr17:28562142	cg05951817	0.003	0.006	0.58	0.561	No	No	No
SLC6A4	chr17:28562220	cg22584138	-0.004	0.007	-0.57	0.571	No	No	No
SLC6A4	chr17:28548496	cg24984698	-0.001	0.002	-0.49	0.622	No	No	No
SLC6A4	chr17:28562474	cg03363743	-0.002	0.004	-0.44	0.659	No	No	No
SLC6A4	chr17:28563054	cg25725890	-0.001	0.002	-0.43	0.667	No	No	No
SLC6A4	chr17:28563300	cg18584905	0.001	0.003	0.31	0.755	No	No	No
SLC6A4	chr17:28549806	cg01330016	0.000	0.002	-0.07	0.945	No	No	No
SLC6A4	chr17:28562685	cg14692377	0.000	0.002	-0.31	0.757	No	No	No
SLC6A4	chr17:28562813	cg05016953	0.000	0.001	-0.30	0.761	No	No	No

Note. Chr = chromosome; sign = significance. Gene-wide significance was calculated as 0.05/n probes within the gene. The gene-wide thresholds were <0.001 for *BDNF* (74 probes), <0.001 for *NR3C1* (40 probes), 0.003 for *OXTR* (18 probes), 0.004 for *SLC6A4* (14 probes).

ST5. Gene ontology in-house results with MissMethyl validation

ID	Name	nGenesinPathway	nTestListinPathway	P:GenesinTestList	OR	P:GeneSize	Beta:GeneSize
GO:0014701	junctional sarcoplasmic reticulum membrane	10	3	2.75E-22	1.02	0.588	4.72E-06
GO:0015278	calcium-release channel activity	17	4	1.54E-20	1.02	0.000	4.89E-05
GO:0033017	sarcoplasmic reticulum membrane	35	5	3.89E-17	1.03	0.804	4.05E-06
GO:0003309	type B pancreatic cell differentiation	16	3	5.23E-14	1.02	0.483	7.75E-06
GO:0005024	transforming growth factor beta-activated receptor activity	17	3	8.86E-14	1.02	0.633	-5.44E-06
GO:0004675	transmembrane receptor protein serine/threonine kinase activity	17	3	8.86E-14	1.02	0.633	-5.44E-06
GO:0014897	striated muscle hypertrophy	17	3	5.81E-12	1.02	0.001	3.84E-05
GO:0003300	cardiac muscle hypertrophy	17	3	5.81E-12	1.02	0.001	3.84E-05
GO:0046332	SMAD binding	61	6	1.85E-11	1.03	0.000	1.11E-04
GO:0060316	positive regulation of ryanodine-sensitive calcium-release channel activity	10	2	3.11E-11	1.01	0.282	-9.39E-06
GO:0042554	superoxide anion generation	11	2	1.81E-10	1.01	0.148	-1.33E-05
GO:0032863	activation of Rac GTPase activity	10	2	1.87E-10	1.01	0.461	6.43E-06
GO:0018107	peptidyl-threonine phosphorylation	38	4	2.75E-10	1.03	0.647	7.78E-06
GO:0050919	negative chemotaxis	10	2	1.05E-09	1.01	0.010	2.24E-05
GO:0007164	establishment of tissue polarity	12	2	6.27E-09	1.01	0.625	4.68E-06
GO:0001736	establishment of planar polarity	12	2	6.27E-09	1.01	0.625	4.68E-06
GO:0032855	positive regulation of Rac GTPase activity	28	3	1.84E-08	1.02	0.904	-1.76E-06
GO:0000042	protein targeting to Golgi	15	2	2.09E-08	1.01	0.009	-2.81E-05
GO:0019068	virion assembly	14	2	2.33E-08	1.01	0.245	-1.20E-05

GO:0033598	mammary gland epithelial cell proliferation	13	2	2.97E-08	1.01	0.536	6.16E-06
GO:0090129	positive regulation of synapse maturation	12	2	4.10E-08	1.01	0.007	2.56E-05
GO:0090178	regulation of establishment of planar polarity involved in neural tube closure	13	2	4.67E-08	1.01	0.248	1.15E-05
GO:0090179	planar cell polarity pathway involved in neural tube closure	13	2	4.67E-08	1.01	0.248	1.15E-05
GO:0032856	activation of Ras GTPase activity	30	3	6.25E-08	1.02	0.902	-1.86E-06
GO:0048841	regulation of axon extension involved in axon guidance	13	2	6.90E-08	1.01	0.103	1.62E-05
GO:0060487	lung epithelial cell differentiation	27	3	7.49E-08	1.02	0.019	3.36E-05
GO:0085029	extracellular matrix assembly	11	2	9.57E-08	1.01	0.000	5.14E-05
GO:0002068	glandular epithelial cell development	14	2	1.31E-07	1.01	0.355	9.55E-06
GO:0021781	glial cell fate commitment	15	2	4.79E-07	1.01	0.222	1.31E-05
GO:0048596	embryonic camera-type eye morphogenesis	28	3	5.13E-07	1.02	0.000	5.83E-05
GO:0086019	cell-cell signaling involved in cardiac conduction	14	2	5.54E-07	1.01	0.006	2.86E-05
GO:0032008	positive regulation of TOR signaling	14	2	7.75E-07	1.01	0.001	3.32E-05
GO:0000118	histone deacetylase complex	47	4	7.75E-07	1.02	0.000	8.98E-05
GO:0032320	positive regulation of Ras GTPase activity	110	6	2.69E-06	1.03	0.001	9.92E-05
GO:0007178	transmembrane receptor protein serine/threonine kinase signaling pathway	183	8	2.81E-06	1.04	0.002	1.13E-04
GO:0051270	regulation of cellular component movement	537	16	3.19E-06	1.07	0.000	2.86E-04
GO:0016209	antioxidant activity	67	4	3.42E-06	1.02	0.494	-1.54E-05
GO:0032148	activation of protein kinase B activity	17	2	6.37E-06	1.01	0.015	2.77E-05
GO:0045995	regulation of embryonic development	89	5	9.58E-06	1.03	0.003	7.64E-05
GO:0002088	lens development in camera-type eye	63	4	1.21E-05	1.02	0.018	5.17E-05

GO:0060603	mammary gland duct morphogenesis	37	3	1.38E-05	1.02	0.003	4.93E-05
GO:0006352	DNA-templated transcription	209	8	2.06E-05	1.04	0.007	1.08E-04
GO:0001654	eye development	292	10	2.19E-05	1.05	0.000	1.63E-04
GO:0002690	positive regulation of leukocyte chemotaxis	54	3	3.13E-05	1.02	0.012	-5.10E-05
GO:0035088	establishment or maintenance of apical/basal cell polarity	21	2	3.26E-05	1.01	0.230	1.52E-05
GO:0061245	establishment or maintenance of bipolar cell polarity	21	2	3.26E-05	1.01	0.230	1.52E-05
GO:0045778	positive regulation of ossification	44	3	4.23E-05	1.02	0.141	2.69E-05
GO:0050918	positive chemotaxis	24	2	5.36E-05	1.01	0.866	-2.29E-06
GO:0048365	Rac GTPase binding	22	2	5.77E-05	1.01	0.178	1.75E-05
GO:0032292	peripheral nervous system axon ensheathment	21	2	7.00E-05	1.01	0.015	3.08E-05
GO:0022011	myelination in peripheral nervous system	21	2	7.00E-05	1.01	0.015	3.08E-05
GO:2000026	regulation of multicellular organismal development	1236	27	8.43E-05	1.09	0.000	7.68E-04
GO:0001105	RNA polymerase II transcription coactivator activity	23	2	1.14E-04	1.01	0.079	2.33E-05
GO:0001709	cell fate determination	43	3	1.33E-04	1.02	0.000	6.83E-05
GO:0017016	Ras GTPase binding	151	6	1.33E-04	1.03	0.014	8.29E-05
GO:2001235	positive regulation of apoptotic signaling pathway	120	5	1.57E-04	1.03	0.194	3.92E-05
GO:0016055	Wnt signaling pathway	227	8	1.60E-04	1.04	0.000	1.70E-04
GO:0006935	chemotaxis	560	15	1.61E-04	1.06	0.000	4.05E-04
GO:0042330	taxis	560	15	1.61E-04	1.06	0.000	4.05E-04
GO:0001843	neural tube closure	74	4	2.71E-04	1.02	0.000	1.02E-04
GO:0001936	regulation of endothelial cell proliferation	85	4	3.13E-04	1.02	0.047	5.05E-05

GO:0071889	14-3-3 protein binding	18	2	3.65E-04	1.01	0.000	9.33E-05
GO:2000145	regulation of cell motility	477	12	5.45E-04	1.05	0.000	2.12E-04
GO:0008544	epidermis development	241	7	5.66E-04	1.03	0.646	1.96E-05
GO:0071277	cellular response to calcium ion	33	2	6.22E-04	1.01	0.539	-9.74E-06
GO:0042753	positive regulation of circadian rhythm	10	1	6.61E-04	1.01	0.254	-9.98E-06
GO:0030546	receptor activator activity	28	2	7.25E-04	1.01	0.042	2.98E-05
GO:0045080	positive regulation of chemokine biosynthetic process	10	1	7.30E-04	1.01	0.341	-8.32E-06
GO:0040020	regulation of meiosis	30	2	7.31E-04	1.01	0.297	1.58E-05
GO:0016888	endodeoxyribonuclease activity	10	1	7.64E-04	1.01	0.388	-7.55E-06
GO:2000379	positive regulation of reactive oxygen species metabolic process	32	2	7.72E-04	1.01	0.819	3.58E-06
GO:0040036	regulation of fibroblast growth factor receptor signaling pathway	27	2	7.79E-04	1.01	0.007	3.90E-05
GO:0016493	C-C chemokine receptor activity	11	1	7.98E-04	1.01	0.057	-1.74E-05
GO:0006623	protein targeting to vacuole	10	1	8.69E-04	1.01	0.538	-5.38E-06
GO:0072666	establishment of protein localization to vacuole	10	1	8.69E-04	1.01	0.538	-5.38E-06
GO:0006622	protein targeting to lysosome	10	1	8.69E-04	1.01	0.538	-5.38E-06
GO:0000979	RNA polymerase II core promoter sequence-specific DNA binding	29	2	9.05E-04	1.01	0.051	2.90E-05
GO:0004887	thyroid hormone receptor activity	10	1	9.44E-04	1.01	0.649	-3.98E-06
GO:0033692	cellular polysaccharide biosynthetic process	35	2	9.84E-04	1.01	0.590	-8.82E-06
GO:0046545	development of primary female sexual characteristics	104	4	9.94E-04	1.02	0.514	1.84E-05
GO:0032928	regulation of superoxide anion generation	10	1	9.94E-04	1.01	0.724	-3.09E-06
GO:0033962	cytoplasmic mRNA processing body assembly	10	1	1.05E-03	1.01	0.802	-2.19E-06

GO:0010935	regulation of macrophage cytokine production	10	1	1.06E-03	1.01	0.824	-1.94E-06
GO:0044292	dendrite terminus	10	1	1.17E-03	1.01	0.974	-2.81E-07
GO:0051865	protein autoubiquitination	34	2	1.30E-03	1.01	0.679	6.67E-06
GO:0043256	laminin complex	10	1	1.31E-03	1.01	0.840	1.76E-06
GO:0045292	mRNA cis splicing	11	1	1.37E-03	1.01	0.399	-7.73E-06
GO:0060638	mesenchymal-epithelial cell signaling	10	1	1.42E-03	1.01	0.717	3.16E-06
GO:0090009	primitive streak formation	10	1	1.57E-03	1.01	0.571	4.95E-06
GO:0008354	germ cell migration	11	1	1.62E-03	1.01	0.621	-4.54E-06
GO:0070234	positive regulation of T cell apoptotic process	11	1	1.77E-03	1.01	0.753	-2.88E-06
GO:0000578	embryonic axis specification	33	2	1.82E-03	1.01	0.131	2.39E-05
GO:0009566	fertilization	132	4	1.84E-03	1.02	0.048	-6.25E-05
GO:2000251	positive regulation of actin cytoskeleton reorganization	11	1	1.87E-03	1.01	0.839	-1.86E-06
GO:0005337	nucleoside transmembrane transporter activity	12	1	1.89E-03	1.01	0.247	-1.11E-05
GO:0033634	positive regulation of cell-cell adhesion mediated by integrin	10	1	1.91E-03	1.01	0.337	8.40E-06
GO:0006289	nucleotide-excision repair	75	3	1.91E-03	1.02	0.770	-6.98E-06
GO:0010640	regulation of platelet-derived growth factor receptor signaling pathway	11	1	2.02E-03	1.01	0.971	-3.29E-07
GO:0006895	Golgi to endosome transport	12	1	2.05E-03	1.01	0.318	-9.56E-06
GO:0097186	amelogenesis	11	1	2.28E-03	1.01	0.830	1.97E-06
GO:0019082	viral protein processing	12	1	2.31E-03	1.01	0.456	-7.14E-06
GO:0034045	pre-autophagosomal structure membrane	11	1	2.36E-03	1.01	0.776	2.61E-06
GO:0001921	positive regulation of receptor recycling	11	1	2.52E-03	1.01	0.672	3.88E-06

GO:0022038	corpus callosum development	10	1	2.53E-03	1.01	0.119	1.36E-05
GO:0050857	positive regulation of antigen receptor-mediated signaling pathway	12	1	2.62E-03	1.01	0.632	-4.59E-06
GO:0000109	nucleotide-excision repair complex	12	1	2.65E-03	1.01	0.651	-4.33E-06
GO:0034062	RNA polymerase activity	41	2	2.73E-03	1.01	0.586	-9.62E-06
GO:0003899	DNA-directed RNA polymerase activity	41	2	2.73E-03	1.01	0.586	-9.62E-06
GO:0010875	positive regulation of cholesterol efflux	11	1	2.79E-03	1.01	0.518	5.92E-06
GO:0032839	dendrite cytoplasm	12	1	2.85E-03	1.01	0.770	-2.80E-06
GO:0043252	sodium-independent organic anion transport	13	1	2.90E-03	1.01	0.258	-1.13E-05
GO:0000993	RNA polymerase II core binding	11	1	2.92E-03	1.01	0.457	6.82E-06
GO:0005247	voltage-gated chloride channel activity	12	1	3.23E-03	1.01	0.979	-2.50E-07
GO:0030971	receptor tyrosine kinase binding	38	2	3.51E-03	1.01	0.320	1.69E-05
GO:0045986	negative regulation of smooth muscle contraction	12	1	3.58E-03	1.01	0.841	1.92E-06
GO:0032677	regulation of interleukin-8 production	45	2	3.65E-03	1.01	0.277	-2.01E-05
GO:0035098	ESC/E(Z) complex	12	1	3.78E-03	1.01	0.749	3.07E-06
GO:0043981	histone H4-K5 acetylation	13	1	3.87E-03	1.01	0.615	-5.02E-06
GO:0043982	histone H4-K8 acetylation	13	1	3.87E-03	1.01	0.615	-5.02E-06
GO:0008276	protein methyltransferase activity	73	3	3.90E-03	1.01	0.101	3.87E-05
GO:0001711	endodermal cell fate commitment	13	1	4.03E-03	1.01	0.679	-4.13E-06
GO:0051205	protein insertion into membrane	12	1	4.57E-03	1.01	0.455	7.15E-06
GO:0030898	actin-dependent ATPase activity	11	1	4.88E-03	1.01	0.059	1.73E-05
GO:0008171	O-methyltransferase activity	14	1	5.00E-03	1.01	0.476	-7.36E-06

GO:0005916	fascia adherens	13	1	5.08E-03	1.01	0.912	1.10E-06
GO:0030502	negative regulation of bone mineralization	15	1	5.09E-03	1.01	0.166	-1.48E-05
GO:0045540	regulation of cholesterol biosynthetic process	13	1	5.11E-03	1.01	0.902	1.23E-06
GO:0010744	positive regulation of macrophage derived foam cell differentiation	15	1	5.11E-03	1.01	0.170	-1.47E-05
GO:0048387	negative regulation of retinoic acid receptor signaling pathway	14	1	5.63E-03	1.01	0.659	-4.56E-06
GO:0070528	protein kinase C signaling	11	1	5.82E-03	1.01	0.022	2.10E-05
GO:0019013	viral nucleocapsid	14	1	5.90E-03	1.01	0.742	-3.41E-06
GO:0045022	early endosome to late endosome transport	14	1	6.00E-03	1.01	0.770	-3.03E-06
GO:0001891	phagocytic cup	14	1	6.91E-03	1.01	0.968	4.18E-07
GO:0019198	transmembrane receptor protein phosphatase activity	20	2	7.07E-03	1.01	0.000	1.52E-04
GO:0005001	transmembrane receptor protein tyrosine phosphatase activity	20	2	7.07E-03	1.01	0.000	1.52E-04
GO:0046716	muscle cell cellular homeostasis	15	1	7.09E-03	1.01	0.543	-6.52E-06
GO:0021684	cerebellar granular layer formation	10	1	7.27E-03	1.01	0.000	3.44E-05
GO:0021707	cerebellar granule cell differentiation	10	1	7.27E-03	1.01	0.000	3.44E-05
GO:0006555	methionine metabolic process	14	1	7.31E-03	1.01	0.860	1.82E-06
GO:0006607	NLS-bearing protein import into nucleus	14	1	7.47E-03	1.01	0.822	2.33E-06
GO:0043524	negative regulation of neuron apoptotic process	122	4	7.80E-03	1.02	0.013	7.58E-05
GO:0015299	solute:hydrogen antiporter activity	14	1	8.66E-03	1.01	0.560	6.03E-06
GO:0000726	non-recombinational repair	15	1	8.78E-03	1.01	0.923	-1.03E-06
GO:0015238	drug transmembrane transporter activity	16	1	1.11E-02	1.01	0.867	-1.85E-06
GO:0030983	mismatched DNA binding	18	1	1.21E-02	1.01	0.275	-1.28E-05

GO:0032456	endocytic recycling	15	1	1.22E-02	1.01	0.475	7.64E-06
GO:0000314	organellar small ribosomal subunit	18	1	1.36E-02	1.01	0.432	-9.22E-06
GO:0005763	mitochondrial small ribosomal subunit	18	1	1.36E-02	1.01	0.432	-9.22E-06

Note. GO = gene ontology; n = number; OR = odd ratio; p = p-value. Cells highlighted in green were pathways which were validated by the MissMethyl method ($p < 0.05$)

ST6. mQLTs associated with the CpGs within the significant DNAm regions

Region	Location	CpG	Gene_UCSC_Ref	SNP affecting CpG DNAm
1	chr2:241458886-241460002	cg05371791	ANKMY1;ANKMY1	NA
1	chr2:241458886-241460002	cg06476685	ANKMY1;ANKMY1	rs10165759, rs4676426
1	chr2:241458886-241460002	cg03743720	ANKMY1;ANKMY1	rs10165759, rs4676426, rs4676425
1	chr2:241458886-241460002	cg24086040	ANKMY1;ANKMY1	rs3821348
1	chr2:241458886-241460002	cg08461339	ANKMY1;ANKMY1	rs3821348, rs11285932, rs4676426
1	chr2:241458886-241460002	cg24539848	ANKMY1;ANKMY1	rs4398270, rs13394744
1	chr2:241458886-241460002	cg16909733	ANKMY1;ANKMY1	rs4676426, rs4676349
1	chr2:241458886-241460002	cg08276645	ANKMY1;ANKMY1	rs7603521, rs4676430, rs4676426
2	chr6:30039027-30039600	cg00947782	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg02188185	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg03343571	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg05563515	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg06249604	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg07179033	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg07382347	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg08491487	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg09279736	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg10568066	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg10930308	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg12633154	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg13185413	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg13401893	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg13918754	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg15877520	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg16078649	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg18930910	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg20119745	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg20249327	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg23712018	RNF39;RNF39	NA
2	chr6:30039027-30039600	cg26730543	RNF39;RNF39	NA
3	chr6:33282879-33283184	cg03000593	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg05210804	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg07245868	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg07895437	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg08771019	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA

3	chr6:33282879-33283184	cg10134527	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg11917542	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg13027595	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg14096569	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg14309283	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg14473643	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg17055704	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg18144560	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg21330831	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg25954512	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg26646118	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
3	chr6:33282879-33283184	cg27168291	ZBTB22;TAPBP;TAPBP;TAPBP;ZBTB22	NA
4	chr2:21266727-21267334	cg00673290	APOB	rs17240441, rs577584
4	chr2:21266727-21267334	cg25123895	APOB	rs201371756, rs62122515
4	chr2:21266727-21267334	cg26112457	APOB	rs512535
4	chr2:21266727-21267334	cg03350299	APOB	rs515135, rs1367117
4	chr2:21266727-21267334	cg16723488	APOB	rs515135, rs17240441
4	chr2:21266727-21267334	cg07636176	APOB	rs60403635, rs7575840
4	chr2:21266727-21267334	cg15246511	APOB	rs60403635, rs7575840
4	chr2:21266727-21267334	cg24309555	APOB	rs6548010, rs515135
4	chr2:21266727-21267334	cg16306978	APOB	rs6548011, rs515135
4	chr2:21266727-21267334	cg25071744	APOB	rs6548011, rs515135
5	chr2:3642629-3642867	cg09974661	COLEC11;COLEC11	rs2071639
5	chr2:3642629-3642867	cg16430428	COLEC11;COLEC11	rs2071639
5	chr2:3642629-3642867	cg19867917	COLEC11;COLEC11	rs2071639
5	chr2:3642629-3642867	cg26615126	COLEC11;COLEC11	rs2071639
5	chr2:3642629-3642867	cg00835279	COLEC11;COLEC11;COLEC11;COLEC11	rs2071639
5	chr2:3642629-3642867	cg17872886	COLEC11;COLEC11;COLEC11;COLEC11	rs2071639
6	chr17:6797034-6797771	cg01758314	ALOX12P2	NA
6	chr17:6797034-6797771	cg07391831	ALOX12P2	NA
6	chr17:6797034-6797771	cg09705592	ALOX12P2	NA
6	chr17:6797034-6797771	cg16893174	ALOX12P2	NA
6	chr17:6797034-6797771	cg18007837	ALOX12P2	NA
6	chr17:6797034-6797771	cg26334670	ALOX12P2	NA
7	chr7:111368367-111368847	cg01567825	DOCK4	NA
7	chr7:111368367-111368847	cg09678349	DOCK4	NA
7	chr7:111368367-111368847	cg20959907	DOCK4	NA
7	chr7:111368367-111368847	cg21594400	DOCK4	NA

8	chr6:32145383-32146595	cg02973270	AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg06570818	AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg07482220	AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg09043226	AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg10023837	AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg11043450	AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg27370696	AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg08049198	AGPAT1;RNF5P1;RNF5	NA
8	chr6:32145383-32146595	cg18191873	AGPAT1;RNF5P1;RNF5	NA
8	chr6:32145383-32146595	cg18928683	AGPAT1;RNF5P1;RNF5	NA
8	chr6:32145383-32146595	cg23464264	AGPAT1;RNF5P1;RNF5	NA
8	chr6:32145383-32146595	cg25733934	AGPAT1;RNF5P1;RNF5	NA
8	chr6:32145383-32146595	cg24425483	RNF5;AGPAT1;RNF5;RNF5P1	NA
8	chr6:32145383-32146595	cg11995506	RNF5;AGPAT1;RNF5P1;RNF5	NA
8	chr6:32145383-32146595	cg01074928	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg02260340	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg03237964	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg03718284	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg08450897	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg09301199	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg13763617	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg14771938	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg20008357	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg22673001	RNF5P1;RNF5;AGPAT1	NA
8	chr6:32145383-32146595	cg01052103	RNF5P1;RNF5;AGPAT1;AGPAT1	NA
8	chr6:32145383-32146595	cg01466825	RNF5P1;RNF5;AGPAT1;AGPAT1	NA
8	chr6:32145383-32146595	cg15982308	RNF5P1;RNF5;AGPAT1;AGPAT1	NA
9	chr7:158749953-158751591	cg00538212		NA
9	chr7:158749953-158751591	cg00815399		NA
9	chr7:158749953-158751591	cg12744031		NA
9	chr7:158749953-158751591	cg00413089		rs35143397
9	chr7:158749953-158751591	cg10079374		rs35143397
9	chr7:158749953-158751591	cg11945929		rs35143397
9	chr7:158749953-158751591	cg12954512		rs35143397
9	chr7:158749953-158751591	cg13472359		rs61693740
10	chr6:33280149-33280436	cg01253676	TAPBP;TAPBP;TAPBP	NA
10	chr6:33280149-33280436	cg02863594	TAPBP;TAPBP;TAPBP	NA
10	chr6:33280149-33280436	cg11796996	TAPBP;TAPBP;TAPBP	NA

10	chr6:33280149-33280436	cg12589538	TAPBP;TAPBP;TAPBP	NA
10	chr6:33280149-33280436	cg13638257	TAPBP;TAPBP;TAPBP	NA
10	chr6:33280149-33280436	cg14419102	TAPBP;TAPBP;TAPBP	NA
10	chr6:33280149-33280436	cg18353226	TAPBP;TAPBP;TAPBP	NA
10	chr6:33280149-33280436	cg20998791	TAPBP;TAPBP;TAPBP	NA
10	chr6:33280149-33280436	cg26083458	TAPBP;TAPBP;TAPBP	NA
11	chr6:31867757-31868169	cg00058449	ZBTB12	NA
11	chr6:31867757-31868169	cg00805874	ZBTB12	NA
11	chr6:31867757-31868169	cg00889295	ZBTB12	NA
11	chr6:31867757-31868169	cg04603811	ZBTB12	NA
11	chr6:31867757-31868169	cg05680710	ZBTB12	NA
11	chr6:31867757-31868169	cg06636203	ZBTB12	NA
11	chr6:31867757-31868169	cg07249939	ZBTB12	NA
11	chr6:31867757-31868169	cg07910050	ZBTB12	NA
11	chr6:31867757-31868169	cg09788778	ZBTB12	NA
11	chr6:31867757-31868169	cg11645762	ZBTB12	NA
11	chr6:31867757-31868169	cg12484688	ZBTB12	NA
11	chr6:31867757-31868169	cg13127825	ZBTB12	NA
11	chr6:31867757-31868169	cg14562426	ZBTB12	NA
11	chr6:31867757-31868169	cg17243044	ZBTB12	NA
11	chr6:31867757-31868169	cg17766150	ZBTB12	NA
11	chr6:31867757-31868169	cg25013586	ZBTB12	NA
11	chr6:31867757-31868169	cg25110523	ZBTB12	NA
11	chr6:31867757-31868169	cg25470384	ZBTB12	NA
11	chr6:31867757-31868169	cg25861453	ZBTB12	NA
12	chr4:147164778-147165097	cg01539483	-	NA
12	chr4:147164778-147165097	cg04181032	-	NA
12	chr4:147164778-147165097	cg07701757	-	NA
12	chr4:147164778-147165097	cg07973709	-	NA
13	chr1:11714218-11714254	cg01420388	FBXO44;FBXO2;FBXO44;FBXO44;FBXO44	rs4478814
13	chr1:11714218-11714254	cg05796704	FBXO44;FBXO2;FBXO44;FBXO44;FBXO44	rs4478814
13	chr1:11714218-11714254	cg22697136	FBXO44;FBXO2;FBXO44;FBXO44;FBXO44	rs909934

Note. Chr = chromosome; DNAm = DNA methylation; NA = not available (mQTL not identified at the CpG site)

ST7. Associations between maternal sensitivity and DNA methylation at significant regions after adjustments for maternal education and psychopathology

		Restricted unadjusted model		Restricted adjusted model		
Location	**Gene(s)**	**estimate**	**SE**	**estimate**	**SE**	**% estimate change**
chr2:241458886-241460002	*ANKMY1*	-0.149	0.032	-0.149	0.033	0.00%
chr6:30039027-30039600	*RNF39*	-0.058	0.017	-0.059	0.018	1.72%
chr6:33282879-33283184	*ZBTB22; TAPBP*	-0.140	0.032	-0.132	0.033	-5.71%
chr2:21266727-21267334	*APOB*	-0.150	0.04	-0.119	0.041	-20.67%
chr2:3642629-3642867	*COLEC11*	-0.202	0.074	-0.196	0.076	-2.97%
chr17:6797034-6797771	*ALOX12P2*	-0.146	0.035	-0.146	0.036	0.00%
chr7:111368367-111368847	*DOCK4*	-0.576	0.071	-0.569	0.073	-1.22%
chr6:32145383-32146595	*RNF5P1; RNF5; AGPAT1*	0.007	0.004	0.004	0.004	-42.86%
chr7:158749953-158751591	*Non-annotated region*	0.079	0.028	0.087	0.028	10.13%
chr6:33280149-33280436	*TAPBP*	-0.133	0.039	-0.15	0.04	12.78%
chr6:31867757-31868169	*ZBTB12*	-0.012	0.005	-0.009	0.005	-25.00%
chr4:147164778-147165097	*Non-annotated*	0.444	0.079	0.451	0.081	1.58%
chr1:11714218-11714254	*FBXO44; FBXO2*	-0.051	0.021	-0.046	0.022	-9.80%

Note. Chr = chromosome; SE = standard error; % = percent

ST8. Associations between maternal sensitivity and DNA methylation at significant regions after adjustments for DNAm at birth

		Restricted unadjusted model		Restricted adjusted model		
Location		**estimate**	**SE**	**estimate**	**SE**	**% estimate change**
chr2:241458886-241460002	*ANKMY1*	-0.134	0.032	-0.079	0.027	-0.41
chr6:30039027-30039600	*RNF39*	-0.057	0.017	-0.002	0.013	-97.11
chr6:33282879-33283184	*ZBTB22; TAPBP*	-0.141	0.032	-0.111	0.032	-21.68
chr2:21266727-21267334	*APOB*	-0.156	0.040	-0.047	0.033	-69.66
chr2:3642629-3642867	*COLEC11*	-0.176	0.074	-0.070	0.050	-60.33
chr17:6797034-6797771	*ALOX12P2*	-0.173	0.034	-0.057	0.024	-67.02
chr7:111368367-111368847	*DOCK4*	-0.507	0.071	-0.284	0.059	-44.04
chr6:32145383-32146595	*RNF5P1; RNF5; AGPAT1*	0.007	0.004	0.001	0.004	-80.25
chr7:158749953-158751591	*Non-annotated region*	0.077	0.027	0.090	0.024	16.97
chr6:33280149-33280436	*TAPBP*	-0.177	0.039	-0.033	0.027	-81.17
chr6:31867757-31868169	*ZBTB12*	-0.011	0.005	-0.012	0.005	5.32
chr4:147164778-147165097	*Non-annotated*	0.419	0.080	0.227	0.063	-45.89
chr1:11714218-11714254	*FBXO44; FBXO2*	-0.055	0.021	-0.061	0.020	9.62

Note. Chr = chromosome; SE = standard error; % = percent

ST9 Correlations of methylation values at birth with age 6 at significant regions

Location	Gene(s)	Min.	1st.Qu.	Median	Mean	3rd.Qu.	Max.
chr2:241458886-241460002	*ANKMY1*	0.36	0.52	0.60	0.59	0.68	0.78
chr6:30039027-30039600	*RNF39*	0.22	0.32	0.37	0.39	0.45	0.55
chr6:33282879-33283184	*ZBTB22; TAPBP*	0.22	0.45	0.56	0.51	0.60	0.81
chr2:21266727-21267334	*APOB*	0.57	0.69	0.72	0.71	0.75	0.78
chr2:3642629-3642867	*COLEC11*	0.63	0.72	0.77	0.76	0.82	0.83
chr17:6797034-6797771	*ALOX12P2*	0.51	0.58	0.67	0.64	0.71	0.75
chr7:111368367-111368847	*DOCK4*	0.48	0.52	0.57	0.59	0.63	0.72
chr6:32145383-32146595	*RNF5P1; RNF5; AGPAT1*	-0.01	0.12	0.15	0.16	0.21	0.32
chr7:158749953-158751591	*Non-annotated region*	0.48	0.89	0.93	0.86	0.94	0.94
chr6:33280149-33280436	*TAPBP*	0.46	0.52	0.56	0.60	0.63	0.81
chr6:31867757-31868169	*ZBTB12*	-0.03	0.07	0.11	0.11	0.17	0.23
chr4:147164778-147165097	*Non-annotated*	0.47	0.51	0.58	0.58	0.65	0.67
chr1:11714218-11714254	*FBXO44; FBXO2*	0.31	0.34	0.37	0.37	0.40	0.44

Note. Chr = chromosome; min. = minimum; 1st Qu. = 1st quartile; 3rd. Qu. = 3rd quartile; max = maximum

ST10. Gene ontology analysis based on the CpGs within the significant regions

ID	Name	OR	GenesinPathwayandTestList
GO:0019005	SCF ubiquitin ligase complex	1.18	FBXO2;FBXO44
GO:0030433	ER-associated ubiquitin-dependent protein catabolic process	1.18	FBXO2;RNF5
GO:0034379	very-low-density lipoprotein particle assembly	1.09	APOB
GO:0034383	low-density lipoprotein particle clearance	1.09	APOB
GO:0003841	1-acylglycerol-3-phosphate O-acyltransferase activity	1.09	AGPAT1
GO:0034374	low-density lipoprotein particle remodeling	1.09	APOB
GO:0006516	glycoprotein catabolic process	1.09	FBXO2
GO:0071379	cellular response to prostaglandin stimulus	1.09	APOB
GO:0031904	endosome lumen	1.09	APOB
GO:0016024	CDP-diacylglycerol biosynthetic process	1.09	AGPAT1
GO:0042627	chylomicron	1.09	APOB
GO:0017127	cholesterol transporter activity	1.09	APOB
GO:0034362	low-density lipoprotein particle	1.09	APOB
GO:0050750	low-density lipoprotein particle receptor binding	1.09	APOB
GO:0010885	regulation of cholesterol storage	1.09	APOB
GO:0045540	regulation of cholesterol biosynthetic process	1.09	APOB
GO:0010744	positive regulation of macrophage derived foam cell differentiation	1.09	APOB
GO:0042953	lipoprotein transport	1.09	APOB
GO:0030675	Rac GTPase activator activity	1.09	DOCK4
GO:0042887	amide transmembrane transporter activity	1.09	TAPBP
GO:0042288	MHC class I protein binding	1.08	TAPBP
GO:0005537	mannose binding	1.09	COLEC11
GO:0031146	SCF-dependent proteasomal ubiquitin-dependent protein catabolic process	1.09	FBXO2
GO:0071682	endocytic vesicle lumen	1.09	APOB
GO:0010884	positive regulation of lipid storage	1.09	APOB
GO:0019433	triglyceride catabolic process	1.09	APOB
GO:0001961	positive regulation of cytokine-mediated signaling pathway	1.09	AGPAT1
GO:0006641	triglyceride metabolic process	1.18	APOB;AGPAT1
GO:0048365	Rac GTPase binding	1.08	DOCK4
GO:0032420	stereocilium	1.08	DOCK4
GO:0006890	retrograde vesicle-mediated transport	1.08	TAPBP
GO:0033344	cholesterol efflux	1.09	APOB
GO:0042605	peptide antigen binding	1.08	TAPBP
GO:0070534	protein K63-linked ubiquitination	1.09	RNF5
GO:0001540	beta-amyloid binding	1.08	FBXO2

GO:0030669	clathrin-coated endocytic vesicle membrane	1.09	APOB
GO:0098553	lumenal side of endoplasmic reticulum membrane	1.08	TAPBP
GO:0098576	lumenal side of membrane	1.08	TAPBP
GO:0071556	integral component of lumenal side of endoplasmic reticulum membrane	1.08	TAPBP
GO:0032855	positive regulation of Rac GTPase activity	1.08	DOCK4
GO:0030163	protein catabolic process	1.36	FBXO2;FBXO44;APOB;RNF5
GO:0030317	sperm motility	1.09	APOB
GO:0030971	receptor tyrosine kinase binding	1.08	DOCK4
GO:0070936	protein K48-linked ubiquitination	1.08	RNF5
GO:0042277	peptide binding	1.17	FBXO2;TAPBP
GO:0048844	artery morphogenesis	1.08	APOB
GO:0030246	carbohydrate binding	1.17	FBXO2;COLEC11
GO:0005789	endoplasmic reticulum membrane	1.33	APOB;TAPBP;AGPAT1;RNF5
GO:0042158	lipoprotein biosynthetic process	1.08	APOB
GO:0001948	glycoprotein binding	1.08	FBXO2
GO:0015833	peptide transport	1.08	TAPBP
GO:0002479	antigen processing and presentation of exogenous peptide antigen via MHC class I	1.08	TAPBP
GO:0071356	cellular response to tumor necrosis factor	1.08	APOB
GO:0006518	peptide metabolic process	1.08	TAPBP
GO:0051082	unfolded protein binding	1.08	TAPBP
GO:0005581	collagen	1.08	COLEC11
GO:0030165	PDZ domain binding	1.08	DOCK4
GO:0042626	ATPase activity	1.08	TAPBP
GO:0044309	neuron spine	1.08	FBXO2
GO:0043197	dendritic spine	1.08	FBXO2
GO:0009791	post-embryonic development	1.08	APOB
GO:0017124	SH3 domain binding	1.08	DOCK4
GO:0060326	cell chemotaxis	1.08	DOCK4

Note. GO = gene ontology; OR = odd ratio; p = p-value. Pathways highlighted in green were validated by MissMethyl.

ST11. BECon Brain-Blood Correlations

Region	Location	CpG	Genes	Cor.Blood.BA7	Cor.Blood.BA10	Cor.Blood.BA20	Cor.>.average
1	chr2:241458886-241460002	cg03743720	ANKMY1	0.28	0.4	0.16	No
1	chr2:241458886-241460002	cg05371791	ANKMY1	0.38	0.27	0.26	BA7
1	chr2:241458886-241460002	cg06476685	ANKMY1	0.34	0.36	0.12	No
1	chr2:241458886-241460002	cg08276645	ANKMY1	0.47	0.51	0.21	BA7, BA10
1	chr2:241458886-241460002	cg08461339	ANKMY1	0.19	0.22	-0.04	No
1	chr2:241458886-241460002	cg16909733	ANKMY1	0.49	0.33	0.22	BA7
1	chr2:241458886-241460002	cg24086040	ANKMY1	0.5	0.4	0.07	BA7
1	chr2:241458886-241460002	cg24539848	ANKMY1	0.22	-0.01	-0.15	No
2	chr6:30039027-30039600	cg00947782	RNF39	0.12	0.06	0.53	BA20
2	chr6:30039027-30039600	cg02188185	RNF39	-0.09	0.04	0	No
2	chr6:30039027-30039600	cg03343571	RNF39	0.69	0.28	0.68	BA7, BA20
2	chr6:30039027-30039600	cg05563515	RNF39	0.34	0.36	0.44	BA20
2	chr6:30039027-30039600	cg06249604	RNF39	0.22	0.27	0.68	BA20
2	chr6:30039027-30039600	cg07179033	RNF39	0.34	0.25	0.57	BA20
2	chr6:30039027-30039600	cg07382347	RNF39	0.28	0.2	0.76	BA20
2	chr6:30039027-30039600	cg08491487	RNF39	0.15	0.01	0.33	No
2	chr6:30039027-30039600	cg09279736	RNF39	0.39	0.37	0.69	BA7, BA20
2	chr6:30039027-30039600	cg10568066	RNF39	0.45	0.46	0.75	BA7, BA10, BA20
2	chr6:30039027-30039600	cg10930308	RNF39	0.24	0.46	0.51	BA10, BA20
2	chr6:30039027-30039600	cg12633154	RNF39	0.2	0.41	0.64	BA10, BA20
2	chr6:30039027-30039600	cg13185413	RNF39	0.42	0.26	0.59	BA7, BA20
2	chr6:30039027-30039600	cg13401893	RNF39	0.1	0.31	0.74	BA20
2	chr6:30039027-30039600	cg13918754	RNF39	0.24	-0.32	-0.03	No
2	chr6:30039027-30039600	cg15877520	RNF39	0.07	-0.28	0.41	BA20
2	chr6:30039027-30039600	cg16078649	RNF39	-0.2	0.37	0.59	BA20
2	chr6:30039027-30039600	cg18930910	RNF39	0.51	-0.18	0.5	BA7, BA20
2	chr6:30039027-30039600	cg20249327	RNF39	0.43	0.13	0.05	BA7
2	chr6:30039027-30039600	cg23712018	RNF39	0.09	0.04	0.61	BA20
2	chr6:30039027-30039600	cg26730543	RNF39	0.26	0.43	0.21	BA10

3	chr6:33282879-33283184	cg03000593	ZBTB22, TAPBP	-0.14	0.11	-0.25	No
3	chr6:33282879-33283184	cg05210804	ZBTB22, TAPBP	0.4	0.61	0.17	BA7, BA10
3	chr6:33282879-33283184	cg07245868	ZBTB22, TAPBP	0.34	0.15	-0.05	No
3	chr6:33282879-33283184	cg07895437	ZBTB22, TAPBP	0.54	0.6	0.17	BA7, BA10
3	chr6:33282879-33283184	cg08771019	ZBTB22, TAPBP	-0.04	0.47	0.12	BA10
3	chr6:33282879-33283184	cg10134527	ZBTB22, TAPBP	0.26	-0.14	-0.06	No
3	chr6:33282879-33283184	cg11917542	ZBTB22, TAPBP	-0.09	0.31	-0.27	No
3	chr6:33282879-33283184	cg13027595	ZBTB22, TAPBP	-0.21	-0.07	-0.24	No
3	chr6:33282879-33283184	cg14309283	ZBTB22, TAPBP	0.12	0.46	-0.09	BA10
3	chr6:33282879-33283184	cg14473643	ZBTB22, TAPBP	0.27	0.51	0.03	BA10
3	chr6:33282879-33283184	cg17055704	ZBTB22, TAPBP	0.54	0.51	0.04	BA7, BA10
3	chr6:33282879-33283184	cg18144560	ZBTB22, TAPBP	0.33	0.44	-0.02	BA10
3	chr6:33282879-33283184	cg25954512	ZBTB22, TAPBP	-0.06	-0.09	-0.22	No
3	chr6:33282879-33283184	cg26646118	ZBTB22, TAPBP	-0.15	0.14	-0.1	No
3	chr6:33282879-33283184	cg27168291	ZBTB22, TAPBP	0.24	0.04	-0.18	No
4	chr2:21266727-21267334	cg00673290	APOB	0.19	0.18	0.17	No
4	chr2:21266727-21267334	cg03350299	APOB	0.39	0.06	0.03	BA7
4	chr2:21266727-21267334	cg07636176	APOB	0.21	0.14	0.23	No
4	chr2:21266727-21267334	cg15246511	APOB	0.04	0.2	-0.18	No
4	chr2:21266727-21267334	cg16306978	APOB	0.09	-0.22	-0.14	No
4	chr2:21266727-21267334	cg16723488	APOB	0.31	-0.08	-0.04	No
4	chr2:21266727-21267334	cg24309555	APOB	0.59	0.09	-0.15	BA7
4	chr2:21266727-21267334	cg25071744	APOB	-0.19	0.03	-0.03	No
4	chr2:21266727-21267334	cg25123895	APOB	0.15	0.43	0.2	BA10
4	chr2:21266727-21267334	cg26112457	APOB	-0.07	-0.21	0.06	No
5	chr2:3642629-3642867	cg00835279	COLEC11	0.45	0.42	-0.02	BA7, BA10
5	chr2:3642629-3642867	cg09974661	COLEC11	0.49	0.41	0.23	BA7, BA10
5	chr2:3642629-3642867	cg16430428	COLEC11	0.45	0.26	-0.22	BA7
5	chr2:3642629-3642867	cg17872886	COLEC11	0.35	0.37	0.32	No
5	chr2:3642629-3642867	cg19867917	COLEC11	0.68	0.36	0.18	BA7
5	chr2:3642629-3642867	cg26615126	COLEC11	0.57	0.39	0.41	BA7, BA20
6	chr17:6797034-6797771	cg01758314	ALOX12P2	0.53	0.1	-0.03	BA7
6	chr17:6797034-6797771	cg07391831	ALOX12P2	-0.29	0.23	0.09	No
6	chr17:6797034-6797771	cg09705592	ALOX12P2	-0.05	-0.13	-0.01	No
6	chr17:6797034-6797771	cg16893174	ALOX12P2	-0.09	-0.21	0.02	No
6	chr17:6797034-6797771	cg18007837	ALOX12P2	-0.33	-0.39	0.29	No
6	chr17:6797034-6797771	cg26334670	ALOX12P2	0.46	-0.1	0.05	BA7
7	chr7:111368367-	cg01567825	DOCK4	-0.15	-0.45	-0.09	BA10

	111368847						
7	chr7:111368367-111368847	cg09678349	DOCK4	-0.31	-0.25	-0.15	No
7	chr7:111368367-111368847	cg20959907	DOCK4	-0.21	-0.39	-0.18	No
7	chr7:111368367-111368847	cg21594400	DOCK4	-0.36	-0.63	-0.3	BA10
8	chr6:32145383-32146595	cg01052103	AGPAT1, RNF5, RNF5P1, AGPAT1	-0.24	-0.17	-0.17	No
8	chr6:32145383-32146595	cg01074928	AGPAT1, RNF5, RNF5P1	-0.43	-0.14	-0.09	BA7
8	chr6:32145383-32146595	cg01466825	RNF5, RNF5P1, AGPAT1	0	-0.05	-0.06	No
8	chr6:32145383-32146595	cg02260340	RNF5, RNF5P1, AGPAT1	0.42	0.38	0.16	BA7
8	chr6:32145383-32146595	cg02973270	RNF5, RNF5P1, AGPAT1	0.17	-0.25	-0.31	No
8	chr6:32145383-32146595	cg03237964	AGPAT1, RNF5, RNF5P1	0.12	0.08	0.19	No
8	chr6:32145383-32146595	cg03718284	RNF5, RNF5P1, AGPAT1	0.33	-0.48	-0.62	BA10, BA20
8	chr6:32145383-32146595	cg06570818	RNF5, RNF5P1, AGPAT1	-0.14	0.11	0.14	No
8	chr6:32145383-32146595	cg07482220	RNF5, RNF5P1, AGPAT1	0.17	-0.36	-0.19	No
8	chr6:32145383-32146595	cg08049198	RNF5, RNF5P1, AGPAT1	-0.4	-0.11	0.01	BA7
8	chr6:32145383-32146595	cg08450897	RNF5, RNF5P1, AGPAT1	-0.09	-0.19	-0.36	BA20
8	chr6:32145383-32146595	cg09043226	RNF5, RNF5P1, AGPAT1	0.13	0.23	-0.06	No
8	chr6:32145383-32146595	cg09301199	RNF5, RNF5P1, AGPAT1	-0.27	0.03	-0.12	No
8	chr6:32145383-32146595	cg10023837	RNF5, RNF5P1, AGPAT1	-0.17	-0.01	0.19	No
8	chr6:32145383-32146595	cg11043450	RNF5, RNF5P1, AGPAT1	0.29	0.29	-0.13	No
8	chr6:32145383-32146595	cg11995506	RNF5, RNF5P1, AGPAT1	-0.24	0.04	-0.04	No
8	chr6:32145383-32146595	cg13763617	RNF5, RNF5P1, AGPAT1	-0.12	-0.58	-0.42	BA10, BA20
8	chr6:32145383-32146595	cg14771938	RNF5, RNF5P1, AGPAT1	0.44	-0.26	0.18	BA7
8	chr6:32145383-32146595	cg15982308	RNF5, RNF5P1, AGPAT1	-0.25	0.02	-0.2	No
8	chr6:32145383-32146595	cg18191873	RNF5, RNF5P1, AGPAT1	-0.5	0.09	0.06	BA7
8	chr6:32145383-32146595	cg18928683	RNF5, RNF5P1, AGPAT1	0.05	-0.37	-0.47	BA20
8	chr6:32145383-32146595	cg20008357	RNF5, RNF5P1, AGPAT1	0.62	0.48	0.65	BA7, BA10, BA20
8	chr6:32145383-32146595	cg22673001	AGPAT1, RNF5, RNF5P1	-0.16	-0.09	-0.37	BA20
8	chr6:32145383-32146595	cg23464264	RNF5, RNF5P1, AGPAT1	0.3	-0.38	-0.08	No
8	chr6:32145383-32146595	cg25733934	RNF5, RNF5P1, AGPAT1	-0.21	-0.22	0.05	No
8	chr6:32145383-32146595	cg27370696	RNF5, RNF5P1, AGPAT1	-0.42	-0.38	-0.45	BA7, BA20
9	chr7:158749953-158751591	cg00413089	None	0.64	0.42	0.51	BA7, BA10, BA20
9	chr7:158749953-158751591	cg00538212	None	0.35	0.16	0.47	BA20
9	chr7:158749953-	cg00815399	None	0.76	0.67	0.66	BA7, BA10,

	158751591						BA20
9	chr7:158749953-158751591	cg10079374	None	0.65	0.59	0.48	BA7, BA10, BA20
9	chr7:158749953-158751591	cg11945929	None	0.62	0.55	0.31	BA7, BA10
9	chr7:158749953-158751591	cg12744031	None	0.56	0.54	0.51	BA7, BA10, BA20
9	chr7:158749953-158751591	cg12954512	None	0.46	0.52	0.37	BA7, BA10, BA20
9	chr7:158749953-158751591	cg13472359	None	0.47	-0.18	-0.06	BA7
10	chr6:33280149-33280436	cg01253676	TAPBP	0.28	0.13	0.36	BA20
10	chr6:33280149-33280436	cg02863594	TAPBP	0.14	0.02	-0.12	No
10	chr6:33280149-33280436	cg11796996	TAPBP	0.21	0.18	0.06	No
10	chr6:33280149-33280436	cg12589538	TAPBP	0.01	0.23	0.34	BA20
10	chr6:33280149-33280436	cg13638257	TAPBP	-0.04	0.12	-0.08	No
10	chr6:33280149-33280436	cg14419102	TAPBP	0.26	0.19	0.14	No
10	chr6:33280149-33280436	cg18353226	TAPBP	-0.15	-0.22	0.09	No
10	chr6:33280149-33280436	cg20998791	TAPBP	0.14	0.16	0.24	No
10	chr6:33280149-33280436	cg26083458	TAPBP	0.54	0.13	0.15	BA7
11	chr6:31867757-31868169	cg00889295	ZBTB12	0.24	-0.28	0.37	BA20
11	chr6:31867757-31868169	cg05680710	ZBTB12	-0.01	0.11	0.21	No
11	chr6:31867757-31868169	cg07249939	ZBTB12	0.81	0.42	0.15	BA7, BA10
11	chr6:31867757-31868169	cg11645762	ZBTB12	0.39	0.4	0.22	BA7
11	chr6:31867757-31868169	cg14562426	ZBTB12	-0.07	-0.3	0.27	No
11	chr6:31867757-31868169	cg25110523	ZBTB12	0.14	0.13	0.06	No
12	chr4:147164778-147165097	cg01539483	None	0.09	-0.26	-0.01	No
12	chr4:147164778-147165097	cg04181032	None	0.27	0.22	0.18	No
12	chr4:147164778-147165097	cg07701757	None	0.03	-0.2	-0.17	No
12	chr4:147164778-147165097	cg07973709	None	-0.17	0.04	-0.27	No
13	chr1:11714218-11714254	cg01420388	FBXO2, FBXO44	0.21	0.09	-0.13	No
13	chr1:11714218-11714254	cg05796704	FBXO2, FBXO44	-0.03	-0.36	0.03	No
13	chr1:11714218-11714254	cg22697136	FBXO2, FBXO44	0.26	0.23	-0.07	No

Note. BA = Brodmann area; chr = chromosome; cor = correlation; > = greater than