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Epigenetic signatures of maternal-fetal health: insights from cord blood and placenta

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ABSTRACT

The placenta is vital for fetal growth, and its methylation patterns reflect placental function, affecting the fetus and providing insights into disease origins. While cord blood methylation is convenient for assessing the fetal environment, methylation profiles vary by tissue due to variance in cell populations, function, and life stage. As tissue differences extensively contribute to the DNA methylation patterns, using surrogate samples such as cord blood may result in inconsistent findings. In this study, we aim to quantify the correlation of *cytosine-phosphate-guanine dinucleotides (CpGs) between paired cord blood and placenta* samples. Using the Infinium Human Methylation 450 K BeadChip, we compared methylation patterns in cord blood mononuclear cells (CBMC; $n = 54$), the maternally-facing side of placental tissue (MP; $n = 68$), and the fetal-facing side of placental tissue (FP; $n = 67$). Methylation patterns from the FP (6,021 CpGs) were significantly correlated with CBMC compared to the MP (2,862 CpGs). These CpGs were related to the biological (mitotic cell) process and molecular function (ribonucleoprotein complex binding). Our findings quantified CpG site correlation between cord blood and placenta, providing a valuable reference for future studies on placental health that rely on cord blood methylation in the absence of placental biospecimens.

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Introduction

Epigenetic modifications, such as alterations in 5' DNA methylation (DNAm) are key indicators of gene–environment interactions influencing phenotypes [1]. DNAm changes are crucial for understanding potential gene expression alterations without altering nucleotide sequences [2]. Advances in high-throughput assays, linkage with reference genomes, and their reversible nature in response to lifestyle and environmental factors have led to the application of epigenomics in understanding molecular pathways of various phenotypes [3–5]. The placenta is a critical organ that connects the fetus to the mother and promotes fetal growth and development, where epigenetic changes are among the prominent mediators between maternal environmental stressors and fetal developmental disorders [6].

During fetal development, most methylation of imprinted genes is erased and reestablished during gametogenesis, and reestablished postfertilization; thus, maternal environmental insults can affect the mother (F0), developing fetus (F1), and the fetus's germ cells (F2) [7]. This provides a unique opportunity to study the placental epigenome at birth as a potential marker for the developmental origins of health and diseases [8,9]. While some studies have examined cord blood methylation to

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understand fetal development, the maternal–fetal interface and its associated placental DNA methylation have received less attention [8,10]. Among human studies examining placental DNA methylation, some have analyzed tissue from the fetal-facing side of the placenta [11–13], or from the maternally-facing side [14]. Others have used pooled samples from both sides [15–17], or analyzed them separately [18–20], to understand fetal health. However, there is no consensus on the use of the maternal or fetal-facing side of placenta tissue for DNA methylation experiments. The placenta comprises both maternal and fetal cells, leading to tissue-specific epigenetic variations between the maternal versus the fetal components, due to differences in cell proportions, function, and developmental stages [21]. Our goal is to facilitate the interpretation of DNA methylation findings in cord blood mononuclear cells (CBMC – due to their relevance to maternal environmental insults) and their relevance to placental methylation. This study aimed to assess DNA methylation (DNAm) concordance between cord blood mononuclear cells (CBMC), the maternally-facing side of the placenta (MP), and the fetal-facing side of the placenta (FP).

Methods

We enrolled 75 pregnant women between 2014 and 2017, who planned to deliver their child at the University of Cincinnati Medical Center, Cincinnati, Ohio. This study was originally initiated to understand the impact of maternal environmental insults on fetal development. The Institutional Review Board at the University of Cincinnati reviewed and approved the research protocol. We enrolled pregnant women aged between 18 and 45 years, without medical history of diabetes, thyroid disorders, cardiovascular, renal or hepatic conditions, malignancies, or severe maternal/fetal complications, and having provided informed consent to participate. In this cross-sectional study, we collected 10 mL of cord blood in collection tubes coated with EDTA and placenta tissue from the maternal and fetal-facing sides right after delivery.

We centrifuged the cord blood at 1500 g for 30 minutes to extract the buffy coat. The buffy coat was diluted with Dulbecco's Phosphate Buffered Saline (DPBS) without Ca2+ or Mg2+ [22], and then we transferred the diluted buffy coat onto the Ficoll gradient solution (Histopaque-1077, Sigma 10,771) and spun at 400 g for 30 minutes at room temperature. Upon centrifugation, we aspirated the upper layer (within 0.5 cm of the opaque interface) containing mononuclear cells. We then washed cord blood mononuclear cells (CBMC) by adding 10 mL of isotonic phosphate-buffered saline solution. Separated CBMCs were resuspended in DPBS, centrifuged to wash the cells, and then transferred to cryovials (20 µl aliquots). We stored CBMC biospecimens in 1.5 mL tubes upon removing supernatant at −80°C until processed for DNA methylation. We relied on mononuclear cells for the epigenetics experiment due to their sensitivity to the maternal environment and potential as a biomarker for birth outcomes [23].

We collected the placenta tissue biopsies by placing the placenta on an absorbent pad with the fetal side (or cord insertion) up. Then identified two locations on the tissue with fewer or no veins were identified to obtain two core placenta samples about 2 cm (width), 2 cm (height), and 3 cm deep. We then vertically dissected the placenta tissue into equal-sized samples, measuring 1–1.5 cm deep on each side. The tissue with amnion and chorion was considered as the fetal side of the placenta tissue. We then placed the tissue samples on gauze to absorb as much of the blood as possible and quickly transferred the placenta tissue samples into 2 ml sterile cryovials. The tissue samples for DNA methylation were stored in a −70°C freezer.

Among the 75 study participants, 54 samples were measured for CBMC methylation, 67 for the fetal side placenta, and 68 for the maternal side placenta. Samples with genomic DNA <2 µg per 100 µL were excluded from the epigenetic assay. DNA from the biospecimens was extracted using the DNeasy Blood and Tissue Kit with RNase A following the manufacturer's instructions. The DNA samples were then processed for the assay following the Illumina Infinium HD Assay Methylation Protocol Guide. Extracted DNA was randomly assigned to well plates with a chip to minimize potential batch effects. Bisulfate conversion of the DNA was performed using EZ DNA

Methylation Kit (Zymo Research, Irvine, CA), and the measurement of methylation patterns was performed using Infinium HumanMethylation450K BeadChip (Illumina, San Diego, CA), by the Genomics, Epigenomics and Sequencing Core at the University of Cincinnati. We pre-processed the raw methylation data using the minfi pipeline, performed quality control steps, and CpGs were annotated to genes as described previously [20].

We estimated pair-wise correlation of CpG site methylation intensities (beta-values) in CBMC and placenta tissues using the Spearman method [24]. These coefficients were presented in three combinations: CBMC-FP ($n = 54$), CBMC-MP ($n = 54$), and FP-MP ($n = 68$). We accounted for multiple tests using a 5% false discovery rate (Benjamini-Hochberg method) for statistical significance ($q < 0.05$) [25]. Using the statistically significantly correlated CpGs across the three combinations, we performed functional analysis using the gene ontology and KEGG databases and presented these results by clustering the pathways to parent terms [26–28]. For clustering the enriched pathways, we created a semantic similarity matrix using genome-wide annotation for the human database as a reference and using 0.7 as a threshold for the semantic similarity scores [29].

Results and discussion

Study participants were pregnant women with a median age of 29 years (IQR: 25–32), predominantly non-Hispanic Black (47%), and from low-income households (64%). The median gestational period was 39 weeks (IQR 38–39), and 58% of the newborns were male. This study includes newborns delivered at full term (gestational age ≥37 weeks). Among the study participants, 69% underwent a C-section and the remaining were vaginal deliveries. About 9% of participants experienced membrane rupture, 12% induced labor, and 13% augmented labor. We analyzed epigenomes from 54 cord blood samples, 67 FP, and 68 MP samples. We calculated the pair-wise correlation between CBMC-FP (406,617), CBMC-MP (403,555), and FP-MP (410,061) CpG sites.

About 1.5% of CpGs (6,021) are significantly correlated between CBMC and FP (q-value <0.05). The majority (99.5%) of these CpGs are positively correlated, with about 54% exhibiting moderate correlation ($r = 0.5–0.75$) strength (Figure S1, Table S1). Functional analysis of CpGs significantly correlated between CBMC and FP, were significantly enriched ($q < 0.2$) for biological process (mitotic cell process; GO:0000278 and GO:1903047) and molecular function (ribonucleoprotein complex binding; GO:0043021). About 0.7% of CpGs (2,862) are significantly correlated between CBMC and MP ($q < 0.05$). Among these CpGs, 72% were positively correlated with moderate correlation coefficients. Functional analysis of these CpGs did not result in significantly enriched pathways accounting for FDR correction. When using the raw p-values, we observed pathways involving the luminal side of the endoplasmic reticulum (GO:0071556, GO:0098553, GO:0098576) were enriched ($p < 1.56e-4$).

About 40% of CpGs (166,763) are significantly correlated between FP and MP (q-value <0.05). Functional analysis of statistically significant CpGs correlated between FP and MP, enriched for 341 pathways ($q < 0.05$) that involved 256 pathways representing biological processes, 43 – cellular components, and 42 – molecular functions (Table S2). These biological processes were reduced to parent pathways, such as nervous system development (parent GO:0007399; 28 sub-pathways), the establishment of localization (parent GO:0051234; 21 sub-pathways), and cellular component organization (parent GO:0016043; 16 sub-pathways). Molecular process pathways were reduced to the metal ion transporter activity (parent GO:0046873; 14 sub-pathways) and adenyl ribonucleotide binding (parent GO:0032559; 7 sub-pathways). Cellular process pathways were reduced to the extracellular region (parent GO:0005576; 6 sub-pathways) and cell periphery (parent GO:0071944; 6 pathways) (Figure 1).

We observed a cluster of CpGs that are moderately correlated between the FP-MP and the CBMC-FP pairs (Figure S2). A relatively higher number of CpGs in chromosome-1 were highly correlated between the three biospecimen pairs (Table S3). Twelve CpGs that are highly correlated ($r > 0.85$ and $q < 0.05$) across the three biospecimen pairs, among which six were annotated to *CAMMK1, KIAA1614, NBPF1*, *NINJ2* at the gene body region,

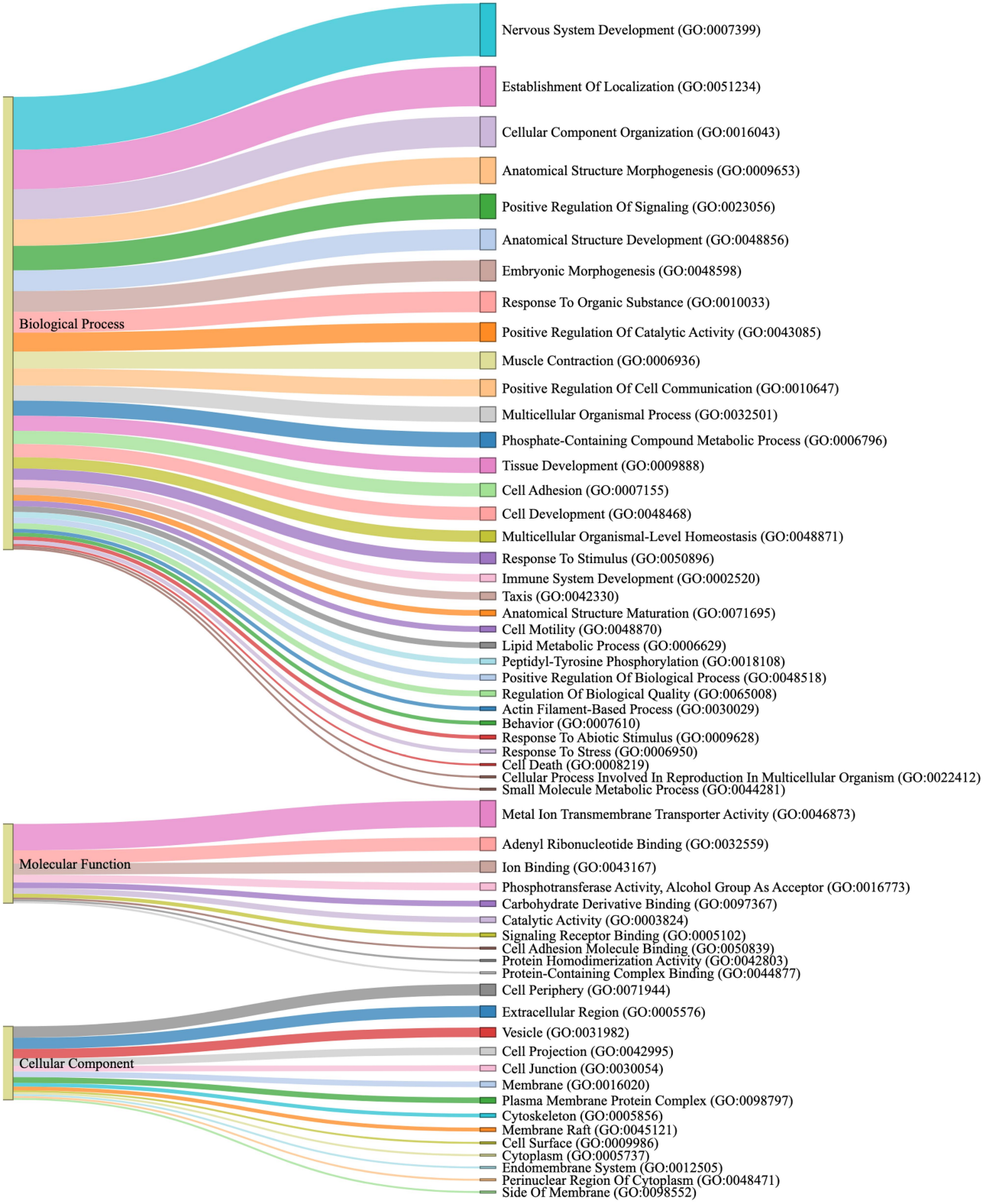

Figure 1. Summary of parent gene ontology terms statistically significantly ($q < 0.05$) associated with CpGs correlated between maternal and fetal sides of the placenta. The width of each section represents the number of sub-pathways clustered within the parent pathway term.

Table 1. CpGs commonly correlated across the sample pairs (CBMC-FP, CBMC-MP, FP-MP) [$n = 12$].

Gene	Corresponding CpGs
CAMKK1	cg15071166 (chr17)
KIAA1614	cg00864916 (chr1)
MRPL28	cg08923669 (chr16)
MRPS18A	cg04842962 (chr6)
NBPF1	cg26022684 (chr1)
NINJ2	cg26654770 (chr12)
Not Annotated	cg02622647 (chr17), cg10070864 (chr15), cg13473803 (chr10), cg15969227 (chr6), cg22337407 (chr1), cg25602718 (chr1)

These CpGs were filtered with r values of > 0.85 and q-value <0.05. List of CpGs mentioned in this table are Illumina IDs.

MRPL28 (5'UTR), and *MRPS18A* (1st Exon) (Table 1). Among these CpGs, cg04842962 (*MRPS18A*) and cg13473803 (not annotated) showed consistent hypomethylation, cg00864916 (*KIAA1614*), cg26022684 (*NBPF1*), and cg25602718 (not annotated) were hypermethylated, whereas the remaining CpGs exhibited diverging methylation patterns across participants (Figure S3).

Prior studies assessing correlations between cord blood and the placenta DNAm were limited to the inclusion of leukocytes and only one side of the placenta tissue [30,31]. Ma and colleagues reported 1,012 CpGs with correlation coefficients above 0.8 between whole blood and FP (169 paired samples). Carli et al. reported 714 CpGs with a correlation coefficient of 0.75 or above using cord blood buffy coat and FP (174 paired samples). Both studies utilized the HumanMethylation450 BeadChips (Illumina, Inc., CA, USA) for DNAm assays and preprocessed methylation data using the minfi pipeline.

Although we used the same assay and preprocessing pipeline, we observed fewer ($n = 228$) CpGs correlated ($r > 0.75$ and $q < 0.05$) between CBMC and FP compared to previous studies. Interestingly, CpGs annotated to six genes (*CAMKK1, KIAA1614, MRPL28, MRPS18A, NBPF1*, and *NINJ2*) were highly correlated between the three biospecimen pairs.

These six genes are protein-coding genes and play a role in ribosomal function (*MRPL28, MRPS18A*), enabling protein binding activity (*MRPL28, CAMKK1, KIAA1614, NBPF1, and NINJ2*) [32,33]. Notably, the MP (containing cells from maternal and fetal origins) carries predominantly maternal genes, while the FP (cells from fetal origin) expresses both maternal and paternal genes, including paternally imprinted genes that often have opposing growth regulatory functions. We acknowledge the limitations of our study, as we did not perform cell type validation for the biospecimens used in the methylation experiments. Additionally, given the complexity of placental tissue, our biospecimens (FP & MP) may be subject to cross-contamination, potentially including cells of both maternal and fetal origins [34]. The higher correlation of CpGs between FP-MP pairs needs to be interpreted in the light of potential cross-contamination of the placenta tissue. Future studies should investigate the relationship between DNAm and gene expression in FP-MP pairs and CBMC. One limitation of our study is the small sample size (54 samples). Larger studies using the Infinium BeadChip EPICv2 array would improve coverage [35].

Abbreviations

CAMKK1	Calcium/Calmodulin Dependent Protein Kinase Kinase 1
MRPL28	Mitochondrial Ribosomal Protein L28
MRPS18A	Mitochondrial Ribosomal Protein S18A
NINJ2	Ninjurin 2
NBPF1	Neuroblastoma breakpoint family Member-1.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Availability of data and materials

The HumanMethylation450K BeadChip data discussed in this publication have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE269983. Summary statistics of the correlation analysis are available in the supplementary material.

CRediT authorship contribution statement

Jagadeesh Puvvula: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Joseph Braun**: Writing – review & editing, Supervision, Conceptualization, Funding acquisition. **Emily DeFranco**: Writing – review & editing, Supervision, Conceptualization. **Shuk-Mei Ho**: Writing – review & editing, Supervision, Conceptualization, Funding acquisition. **Yuet-Kin Leung**: Writing – review & editing, Supervision, Conceptualization, Funding acquisition. **Shouxiong Huang**: Writing – review & editing, Supervision, Conceptualization. **Xiang Zhang**: Writing – review & editing, Supervision. **Ann Vuong**: Writing – review & editing, Conceptualization, Funding acquisition. **Stephani Kim**: Writing – review & editing, Conceptualization, Funding acquisition. **Zana Percy**: Writing – review & editing, Conceptualization, Funding acquisition. **Aimin Chen**: Writing – review & editing, Supervision, Conceptualization, Project administration, Funding acquisition.

Consent for publication

All authors approve the manuscript for publication.

Ethics approval and consent to participate

All procedures performed in this study involving human subjects were in compliance with the ethical standards of the Institutional Review Board at the University of Cincinnati.

Consent

Informed consent was obtained from all the subjects included in this study.

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