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Postpartum Depression: Once and for All?

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Postpartum depression (PPD) is moderate to severe depression in a woman after she has given birth. It may occur soon after delivery or up to a year later. The time after childbirth, which is supposed to be one of the happiest periods of life, turns to be a sad, painful, and even dramatically so, in the women's life. Moreover, it potentially harms not only the depressive women but also the newborn child [1] and the entire family [2,3]. Sometimes the damage is irreversible [4-7].

There are a lot of unknowns regarding postpartum depression. In spite the fact that the number of studies in the field of PPD is growing in the last decade, the etiology and pathogenesis of the disease are still unclear.

The existing data revealed different psychosocial and physiological correlates. The former includes a history of depression or anxiety during pregnancy, stressful life events or changes during pregnancy, inadequate social support, a history of psychiatric disorders, possible nicotine use [7]. The latter include decreased noradrenaline or serotonin blood level [8] and it's decreased activity in the brain [9], decreased Omega-3 fatty acids [10,11] or 25(OH) Vitamin D [12], fluctuating oxytocin [13] and IL-1beta levels [14,15], abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) [16-20] and others for the PPD development.

A special attention is paid to the role of genetic factors in the etiology of postpartum depression. Several studies have attempted to characterize the specific expressional modifications in patients with mood disorders in general [21-23] and PPD in particular [15,20] and to develop biomarkers for this depressive state. Spijker et al. [21] identified a set of genes whose expressional pattern is strongly correlated with major depressive disorder (MDD). Another study demonstrates altered expression of genes related to inflammatory, apoptotic, and oxidative stress in post-mortem human brain tissue samples (BR 10 area) in MDD [23].

During decade, the involvement the epigenetic factors in the development of perinatal depression has been evaluated [24,25]. For example, Champagne FA in his review provides evidence that epigenetic mechanisms are capable of mediating the inheritance of specific traits across generation including psychiatric disorders such as depression [24]. Guintivano et al. [25] put in data that the DNA methylation associated with PPD risk correlated significantly with estradiol treatment-induced DNA methylation change in blood obtained during the antenatal period of pregnant mood disorder patients [25].

In our recent study, we focused on the possible genetic correlates and causes of PPD [26]. We investigated gene expression in the euthymic women with a history of postpartum depression without any clinical signs of the disease at the onset of the study. We hypothesized that stable modifications in gene expression might be involved in PPD development. That is why it was important to see the expression profile at a "calm time" and not during the stressful time of labor and delivery which can lead to dramatic but temporary changes in genes expression.

In our study, we used microarray technology [27]. The results demonstrated the extremely significant difference in gene expression signature (352 highly differentially expressed genes) in the women with a history of postpartum depression as compared to the control women without any previous psychiatric disorders. The ontology and pathway analysis of these genes discovered five pathways which apparently relate to PPD: Phosphatidylinositol signaling system, Systemic lupus erythematosus, Long-term potentiating, long-term depression, and Pathogenic Escherichia coli infection. It is of interest that according to the number of genes in the input list associated with particular annotation term, the aforementioned pathways related to neuropsychiatric disorders such as Alzheimer's

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disease, Parkinson's disease, Huntington's Chorea or inflammatory autoimmune diseases such as Systemic Lupus Erythematosus (SLE) that are known to be comorbid with depression. Moreover, according to the database screening, all five pathways relate to mood disorders in general and, in particular, to depression.

Afterward, the 39 most prominent genes (with a maximal fold of difference in their expression, minimal p-value and possible physiological relationship to the depressive status) were submitted to the Real-Time PCR assay and additional statistical analysis. As a result, we identified nine genes whose alteration may be considered as potential markers for the postpartum depression. These genes are represented in **Table 1**. The results of the Real-Time PCR analysis support the suggestion that the pathways mentioned above could be involved in the PPD pathogenesis. For example, ARAP3 gene encodes a phosphoinositide binding protein and is critical for the phosphatidylinositol signaling system (PISS) [28,29]. The PISS linked either directly to the mood and neuropathic disorders or through its role in neural plasticity [30]. RIN1 gene is responsible for the RAS effector protein and may serve as an inhibitory modulator of neuronal plasticity, which when altered has been associated with mood disorders, as mentioned above [31,32]. Mutation in TBCD gene is associated with progressive encephalopathy and brain atrophy [33]. The six other genes from our list: NKG7, CD97, IGJ Hist1H3D, Hist1H4e and TRIM5 play an essential role the immune and inflammatory response [34-38]. For example, Hist1H3D and Hist1H4e were shown as important genes of the Systemic lupus erythematosus pathway; and TRIM5 innate immune signaling and this activity is amplified by retroviral infection and interaction with the capsid lattice [37]. The relationships between the described genes, pathways and diseases are summarized in the diagram below **(Figure 1)**.

Table 1. The list of genes with the most prominent difference in expression between the two experimental groups as revealed by a Volcano analysis (P-value of 0.05; ≥ 2-fold) and subsequent real-time PCR analysis.

No.	Gene name	Fold difference (log 2)	Gene description	RefSeq gene name
1	*CD97*	-1.863929174	*Homo sapiens CD97* molecule (*CD97*), transcript variant 1, mRNA	NM_078481
2	*NKG7*	-0.80865	*Homo sapiens* natural killer cell group 7 sequence (*NKG7*), mRNA	NM_005601
3	*RIN1*	-0.7935	*Homo sapiens Ras and Rab* interactor 1 (RIN1), mRNA	NM_004292
4	*ARAP3*	-0.768662705	*Homo sapiens* ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3 (*ARAP3*), mRNA	NM_022481
5	*HIST1H3D*	1.562908329	*Homo sapiens* histone cluster 1, *H3d* (*HIST1H3D*), mRNA	NM_003530
6	*HIST1H4E*	2.117464577	*Homo sapiens* histone cluster 1, *H4e* (*HIST1H4E*), mRNA	NM_003545
7	*IGJ*	1.653825396	*Homo sapiens* immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides (*IGJ*), mRNA	NM_144646
8	*TRIM58*	1.46963771	*Homo sapiens* tripartite motif-containing 58 (*TRIM58*), mRNA	NM_015431
9	*TBC1D8*	-1.023966069	*Homo sapiens* TBC1 domain family, member 8	

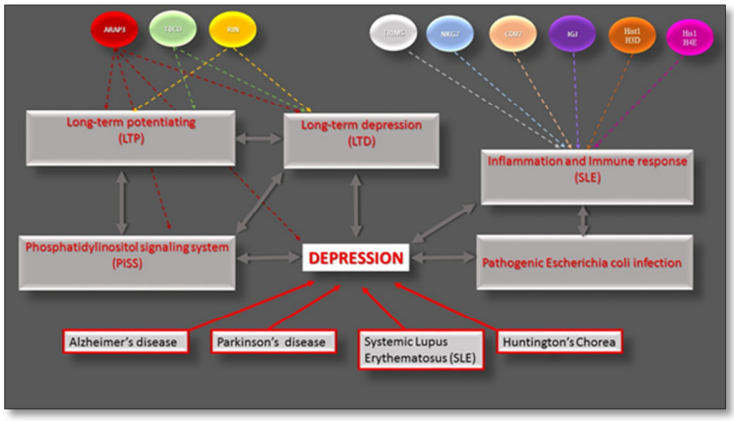

Figure 1. The relationships between the genes which could be possible candidates for PPD prediction (different colored ovals at the upper part of the diagram), the pathways (gray not framed rectangles) and the diseases (red).

The importance of these findings is obvious. First, understanding of the molecular events involved in the diseased is crucial for its successful treatment. Second, the aforementioned genes appear to be potential markers of predisposition to depression. Since the prediction of depression at the early stages of pregnancy and appropriate support of the women can prevent the development of the disease, it is critical not to underestimate the importance of the described above findings.

Another important question: are these expressional alterations specific for postpartum depression or do they occurring also in other types of depression. Answers to these questions await further research.

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