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Microarray Analysis of the Major Depressive Disorder mRNA Profile Data

Lishu Gao[1], Yue Gao[2] ✉, Enping Xu[3], and Jian Xie[1]

[1]Department of Clinical Psychology, Hangzhou First People's Hospital, Hangzhou, Zhejiang, PR China
[2]Department of Gerontology, Hangzhou First People's Hospital, Hangzhou, Zhejiang, PR China
[3]Department of Pathology, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, PR China

Objective Major depressive disorder (MDD) is a common mood disorder associated with several psychophysiological changes like disturbances of sleep, appetite, or sexual desire, and it affects the patients' life seriously. We aimed to explore a genetic method to investigate the mechanism of MDD.

Methods The mRNA expression profile (GSE53987) of MDD was downloaded from Gene Expression Omnibus database, including 105 samples of three brain regions in post-mortem tissue suffered from MDD and unaffected controls. Differentially expressed genes (DEGs) in MDD were identified using the Limma package in R. Gene Ontology functions and Kyoto Enrichment of Genes and Genomes pathways of the selected DEGs were enriched using Database for Annotation, Visualization and Integrated Discovery. Protein-protein interactive network of DEGs was constructed using the Cytoscape software.

Results Totally, 241 DEGs in MDD-hip group, 218 DEGs in MDD-pfc group, and 327 DEGs in MDD-str group were identified. Also, different kinds of biological processes of DEGs in each group were enriched. Besides, glycan biosynthesis of DEGs in MDD-str group, RIG-I-like receptor signaling and pyrimidine metabolism of DEGs in the MDD-hip group were enriched, respectively. Moreover, several DEGs like *PTK2*, *TDG* and *CETN2* in MDD-str group, *DCT*, *AR* and *GNRHR* in MDD-pfc group, and *AKT1* and *IRAK1* in MDD-hip group were selected from PPI network.

Conclusion Our data suggests that the brain striatum tissue may be greatly affected by MDD, and DEGs like *PTK2*, *GALNT2* and *GALNT2* in striatum, *AR* in prefrontal cortex and *IRAK1* and *IL12A* in hippocampus may provide novel therapeutic basis for MDD treatment.
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Key Words Differentially expressed genes, Function enrichment, Major depressive disorder, Pathway enrichment.

INTRODUCTION

Depression is a heterogeneous mental disorder that is characterized by mood depression, retardative thinking and bradypragia, and it does not remit when the external cause of sadness emotion dissipates.[1] Major depressive disorder (MDD) is mainly accompanied with the bad mood, inappetence, despair and suicidal behavior, which brings a tremendous influence on both patients and society.[2,3] MDD has an increasing trend year by year with the accessorial work and life pressure.[4] The mechanism of depression is complicated while the medicine treatment on MDD patients is poor, therefore, there is an urgent need to explore several effective treatment methods on MDD.

Previous studies have demonstrated that variety factors participated in the MDD development, such as genetic factor, biological chemistry, psychology, society and environment.[5] The development of MDD could promote some inflammatory cytokines and the level of pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α was higher in MDD cells.[6] It has been reported that hypothalamus-pituitary gland-thyroid (HPT) was associated with MDD.[7] Also, Schutter proved that the stimulation of hypothalamus-pituitary gland-adrenal gland axis (HPA) were a symbol of MDD, and the diurnal blood pressure variation of HPA and adrenal glucocorticoids was abnormal in MDD patients.[8] Be-

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✉ **Correspondence:** Yue Gao, MM
Department of Gerontology, Hangzhou First People's Hospital, HuanSha road 261 Hangzhou, Zhejiang 310006, PR China
Tel: +86-571-85358828, **Fax:** +86-571-85358828, **E-mail:** yuer980821@sina.com

sides, the level of adtevak 5-hydroxytryptamine (5-HT) and the serum total cholesterol (CHO) in MDD patients was significantly lower than in normal people.[9] In Ronald's study, 5-HT plays a role in neural remodeling, and the decreased neuronal synapses in brain regions that regulate mood and cognition were related to MDD.[10] In addition, some studies proved that phosphoinositide signal transduction pathway system was abnormal in MDD patients,[11] and protein kinase C (PKC) was failed in regulating the 5-HT to reuptake the antidepressant moderator 5-HT_2R.[12]

Despite many studies have found that MDD was associated with the nervous, endocrine and immune, it was till hard to clarify the mechanisms of MDD formation. Thus, studies at the genetic level would offer a deeper insight into the pathogenesis of MDD. Maura reported the number of hippocampal granule neuron was associated with MDD.[13] Also, the increasing volume of dorsolateral prefrontal cortex could affect the antidepressant effects of sertraline.[14] Additionally, sustained fronto-striatal connectivity was associated with the positive effect in MDD.[15] Therefore, understanding the genetic basis of MDD will allow disease prediction and risk stratification.

Recently, Hideo et al.[16] also used the mRNA GSE53987 microarrays to investigate the transcription immaturity of prefrontal cortex in patients with schizophrenia, and they found that transcriptomic immaturity of prefrontal cortex may be an endophenotype of schizophrenia. However, the study did not attempt to investigate the differentially expressed genes (DEGs) or pathways in three kinds brain tissues (hippocampus, prefrontal cortex and striatum) involved in the MDD. In this study, we used microarray analysis[17] to screen the DEGs in MDD samples from three human brain tissues compared to the health-control samples based on the same profile data. Comprehensive bioinformatics analysis was used to enrich the significant functions and pathways of DEGs and to construct the protein-protein interactive (PPI) network to provide a deeper insight into the biological mechanisms of MDD. This approach was beneficial for predicting the hub genes and significant pathways that are most likely associated with MDD and identify the molecular mechanisms that could serve as novel therapeutic basis for MDD.

METHODS

Affymetrix microarray data and data preprocessing

The microarray and other forms of high flux data produced by the scientific community were archived and freely released from the Gene Expression Omnibus (GEO)[18] database of National Center for Biotechnology Information (NCBI),[19] which is the biggest completely public storage. We extracted the mRNA expression profiles (GSE53987) from the GEO database based on the GPL570 (HG-U133_Plus_2) Affymetrix Human Genome U133 plus 2.0 Array. The study contains a total of 205 samples of human brain regions in post-mortem tissue suffered from schizophrenia, bipolar disorder or MDD and unaffected controls (n=19 from each group). We selected 105 samples in the post-mortem brain tissues matched with MDD, which including 18 health-hippocampus (control-hip) samples and 17 MDD-hip samples, 19 health-prefrontal cortex (control-pfc) samples and 17 MDD-pfc samples, and 18 health-striatum (control-str) samples and 16 MDD-str samples.

Probes that mapped with the gene names labeled in annotation platform were performed in log2 transformation. Quantile method[20] was used to normalize the data from shewed normal distribution to the approximate normal distribution. The mRNA expression values were calculated based on the probe information.

Screening of DEGs in each group

The total 105 samples used in this study were separated into three groups based on the three kinds brain tissues, MDD-hip vs. control-hip, MDD-pfc vs. control-pfc and MDD-str vs. control-str. Limma package in R language[21] was used to select the DEGs of the MDD-samples and control samples in each group. The p-value<0.01 was chosen as the cut-off criterion.

Gene ontology analysis and pathway enrichment analysis

Gene ontology (GO) analysis has become a commonly used approach for functional studies of large-scale genomic or transcription data.[22] The Kyoto Enrichment of Genes and Genomes (KEGG) pathway database contains information of how molecules or genes are networked, which is complementary to most of the existing molecular biology databases containing the information of individual genes.[23] Database for Annota-

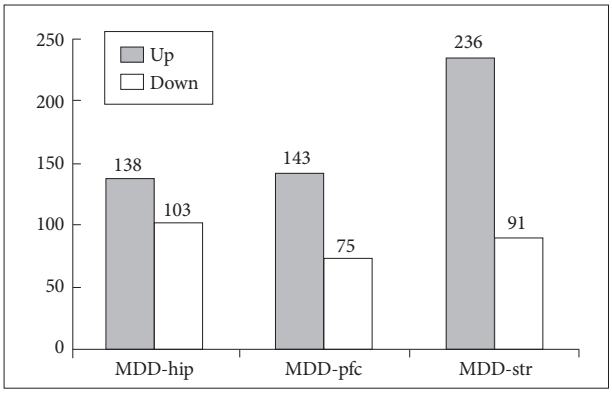

Figure 1. The screening DEGs in each group. hip: hippocampus, MDD: major depressive disorder, pfc: prefrontal cortex, str: striatum, DEG: defferentially expressed gene.

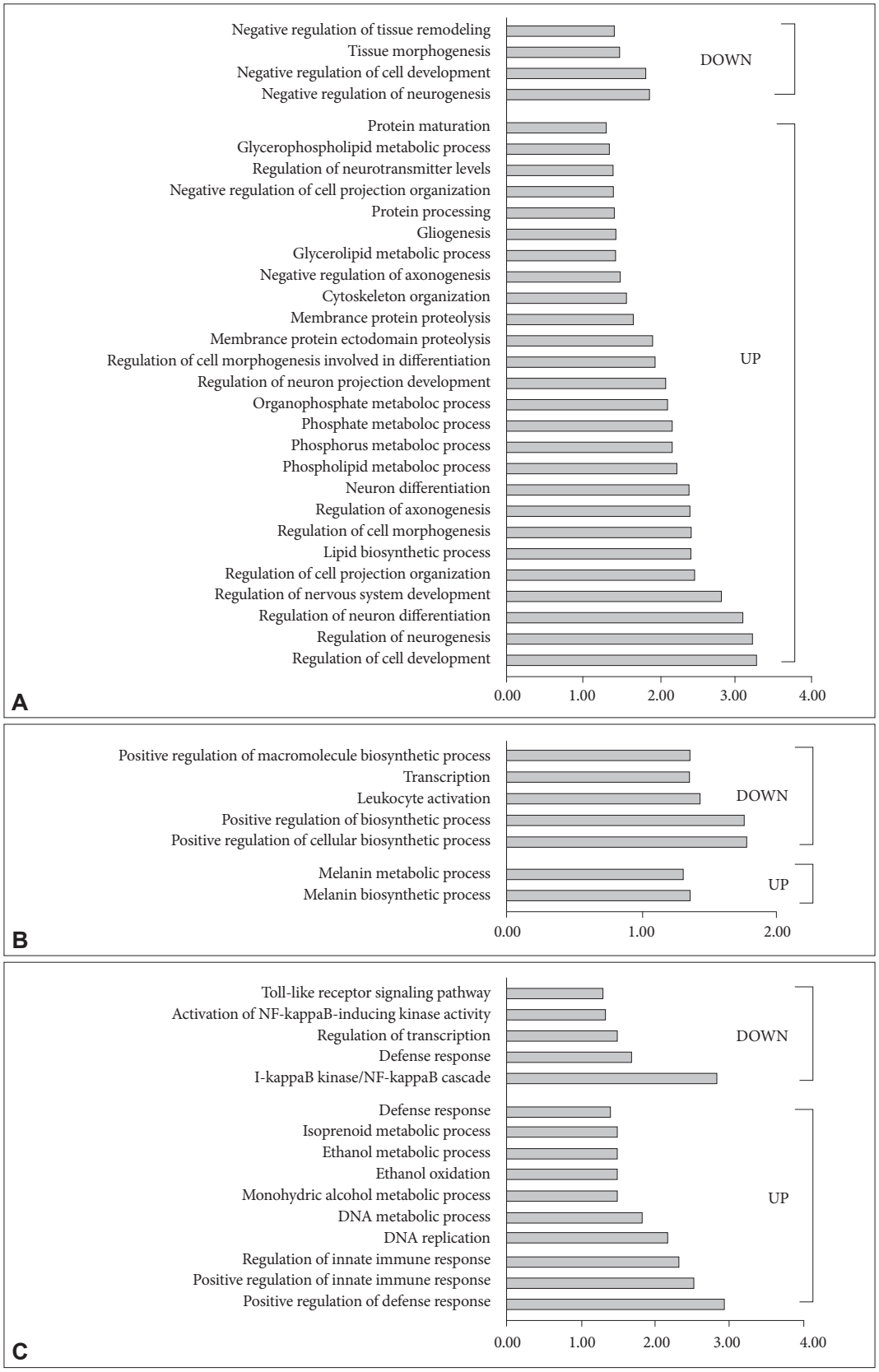

Figure 2. The GO-BP terms of DEGs in each group. A: GO-BP terms of DEGs in MDD-str group. B: GO-BP terms of DEGs in MDD-pfc group. C: GO-BP terms of DEGs in MDD-hip group. GO-BP: gene ontology-biological process, DEG: differentially expressed gene, MDD: major depressive disorder.

Table 1. The KEGG pathway enrichment analysis of DEGs in each group

Groups	Pathway numbers	Pathway terms	p-value
MDD-hip up	2	RIG-I-like receptor signaling pathway	0.010545874
		Pyrimidine metabolism	0.022990395
MDD-str up	1	O-glycan biosynthesis	0.03587961

MDD: major depressive disorder, hip: hippocampus, str: striatum, KEGG: Kyoto Enrichment of Genes and Genomes, DEG: differentially expressed gene

tion, Visualization and Integrated Discovery (DAVID) bioinformatics resources consist of an integrated biological knowledgebase and analytic tools aimed at systematically extracting biological meaning from large gene or protein lists.[24]

We used the DAVID to enrich the functions and pathways of the DEGs in each group. The p-value<0.05 was chosen as the threshold.

PPI network construction

Varieties of cell physiological activities, and the reactions of cells to the external and internal environments were all connected by the protein interaction network.[25] Therefore, a further investigation on the protein interaction is necessary for recognizing and understanding the biological phenomena.[26] The PPI interactive network of DEGs in each group was constructed in the Search Tool for the Retrieval of Interacting Genes (STRING) database[27] using the cytoscape software.[28] The interactive pattern degree ≥0.4 was chosen as the threshold.

RESULTS

Screening of DEGs in each group

We obtained 34296 mRNA expression values (19745 gene expression values) after the profile data were normalized. Totally, 241 DEGs (138 up-regulated and 103 down-regulated) in MDD-hip group, 218 DEGs (143 up-regulated and 75 down-regulated) in MDD-pfc group, and 327 DEGs (236 up-regulated and 91 down-regulated) in MDD-str group were selected (Figure 1). The total DEGs in MDD-hip group were more than that in the other two kinds groups from the perspective of comparison within groups.

Function analysis of DEGs

To investigate the function changes of the screened DEGs in each group, we used DAVID to identify the significant GO categories in biological process. Thirty GO-BP terms in the MDD-str group that neuro development related and phosphorus metabolism associated biological processed were enriched, such as neuron differentiation, regulation of axonogenesis, negative regulation of cell development and regulation of neurogenesis (Figure 2A). Also, 7 GO terms in MDD-pfc group like positive regulation of macromolecule biosynthetic process, transcription and melanin metabolic process were enrich (Figure 2B). Besides, 15 GO terms like toll-like receptor signaling pathway, regulation of innate immune response and positive regulation of defense response in the MDD-hip group were enriched (Figure 2C).

Pathway analysis of DEGs

To gain further insights into the pathways of DEGs in each group, we used DAVID to identify the significant pathways. Only 3 pathways, 1 pathway "glycan biosynthesis" associated with the up-regulated DEGs like *GALNT6* (polypeptide N-acetylgalactosaminyltransferase 6), *GALNT2* and *GALNT12* in the MDD-str group and 2 pathways "RIG-I-like receptor signaling pathway" and "pyrimidine metabolism" in the MDD-hip group were enriched (Table 1). In addition, 4 up-regulated like *IFNE* (interferon, epsilon), *IL12A* (interleukin 12A), *NLRX1* (NLR family member X1) and *TFNK* were enriched in the RIG-I-like receptor signaling pathway while the other 4 down-regulated DEGs such as *POLR3G* [polymerase (RNA) III (DNA directed) polypeptide G], *NT5C1A* (5'-nucleotidase, cytosolic IA), *DHODH* (dihydroorotate dehydrogenase) and *POLR2B* [polymerase (RNA) II (DNA directed) polypeptide B] were enriched in the pyrimidine metabolism pathway.

PPI network construction

The PPI network of DEGs in MDD-hip, MDD-pfc and MDD-str group were annotated by calculating their interactive degrees with STRING database, respectively. The MDD-str PPI network were shown in Figure 3, and DEGs with the top 5 node degrees were *PTK2* (protein tyrosine kinase 2), *ANAPC5* (anaphase promoting complex subunit 5), *TDG* (thymine DNA glycosylase), *CETN2* (centrin, EF-hand protein 2), *SYNJ2* (synaptojanin 2). Also, the MDD-pfc PPI network were shown in Figure 4, and *DCT* (dopachrome tautomerase), *GNRHR* (gonadotropin-releasing hormone receptor), *AR* (androgen receptor), *SVIL* (supervilin), *ABCC2* (ATP-binding cassette, sub-family C) were the genes with the top 5 node degrees. In addition, *AKT1* (v-akt murine thymoma vrial oncogene homolog 1), *CHEK1* (checkpoint kinase 1), *MCM8* (minichromosome maintenance 8), *EGF* (epidermal growth factor), *IRAK1* (interleukin-1 receptor-associated kinase 1) were the genes with the top 5 node degrees in MDD-hip PPI network (Figure 5).

DISCUSSION

MDD, which is a common mood disorder associated with several psychophysiological changes like disturbances of sleep, appetite, or sexual desire, and it affects the patients' life seriously, but the treatment on MDD was poor.[3] Therefore, it is an urgent necessity to investigate the mechanism of MDD and to develop an effective preventative strategy. In the present study, the mRNA expression profile GSE53987 from GEO database was used to analyze the possible functions of DEGs in three kinds of brain tissues between MDD and healthy samples. As a result, we screened 241 DEGs in MDD-hip group, 218 DEGs

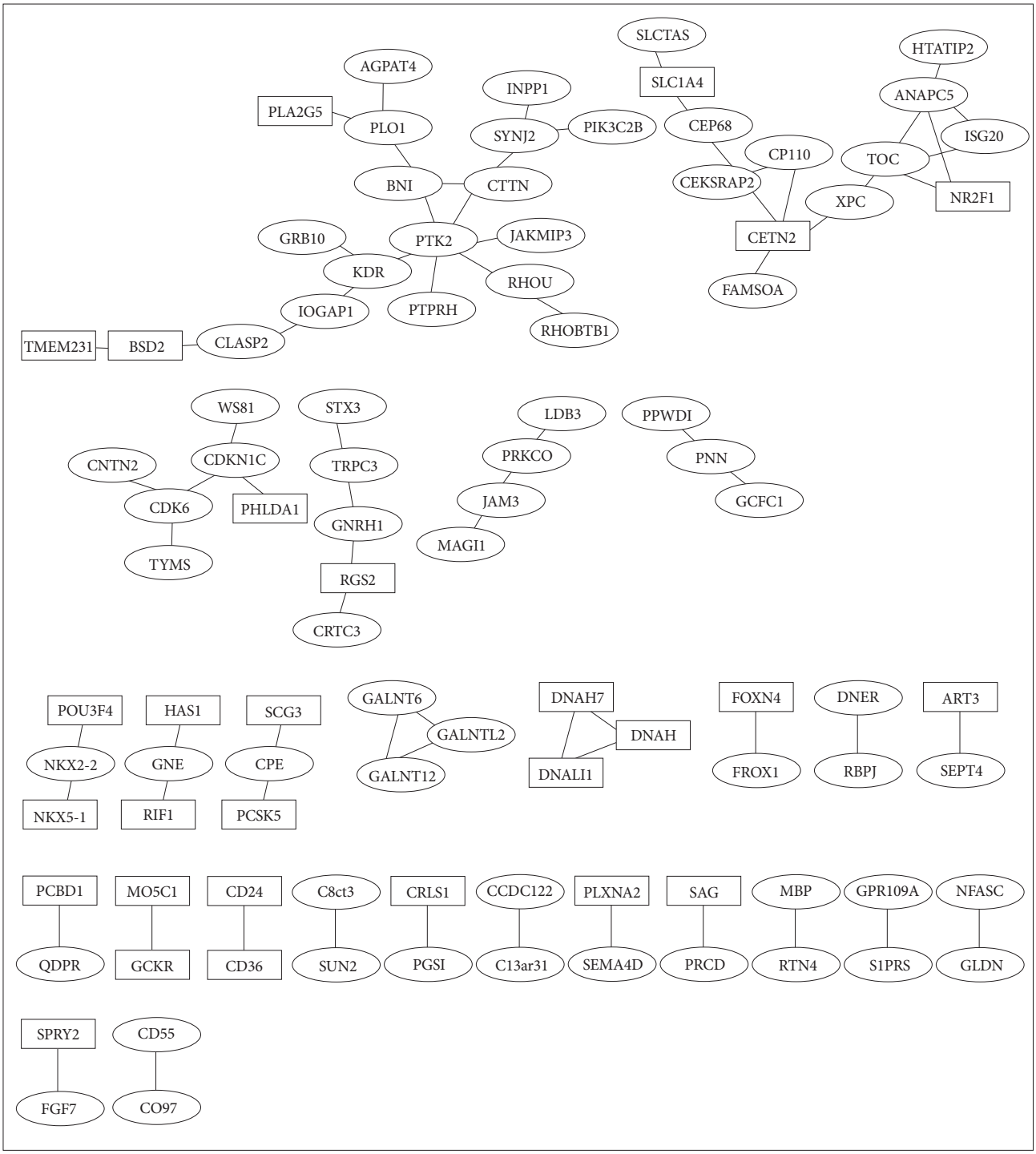

Figure 3. PPI network of DEGs in MDD-str group. Oval node stands for the up-regulated DEGs while rectangular node stands for the down-regulated DEGs. PPI: protein-protein interaction, DEG: differentially expressed gene, MDD: major depressive disorder.

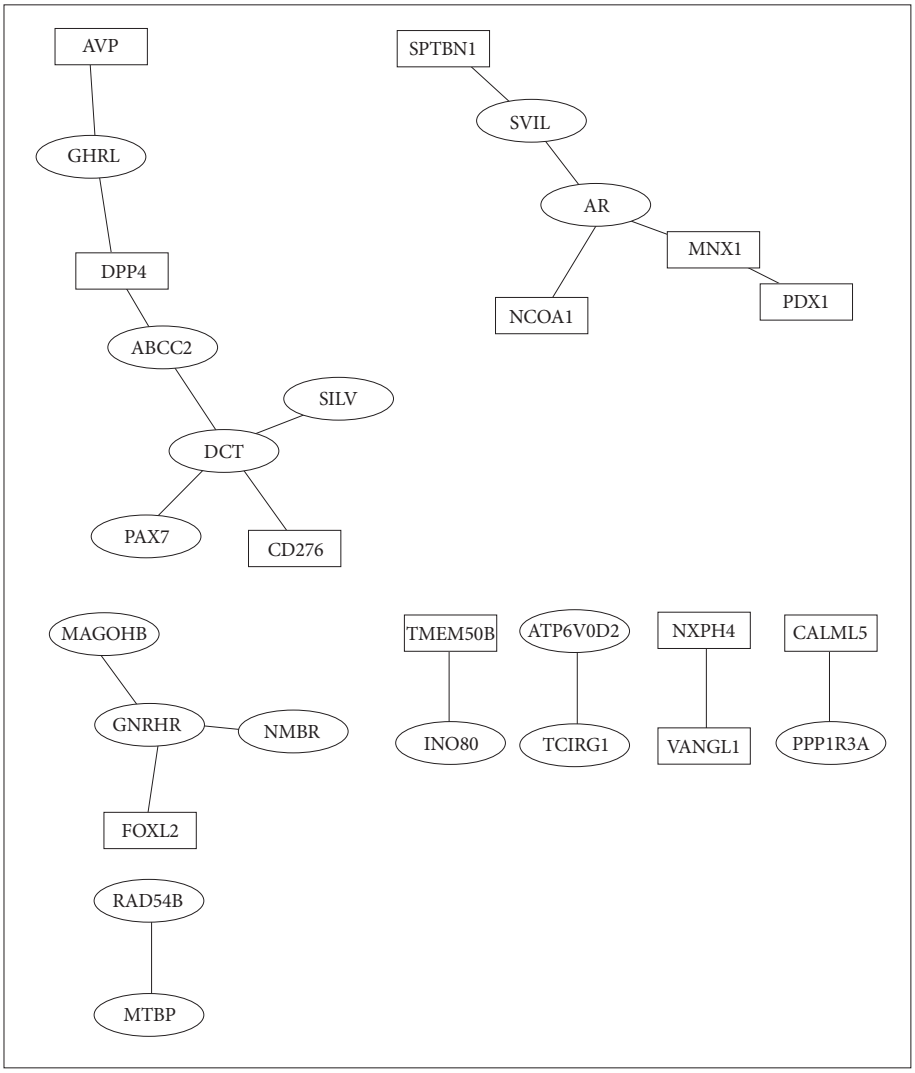

Figure 4. PPI network of DEGs in MDD-pfc group. Oval node stands for the up-regulated DEGs while rectangular node stands for the down-regulated DEGs. PPI: protein-protein interaction, DEG: differentially expressed gene, MDD: major depressive disorder.

in MDD-pfc group and 327 DEGs in MDD-str group. Also, different kinds of biological processes of DEGs in each group were enriched. Additionally, glycan biosynthesis pathway of DEGs in MDD-str group while RIG-I-like receptor signaling pathway and pyrimidine metabolism of DEGs in the MDD-hip group were enriched, respectively. In addition, several DEGs such as *PTK2*, *TDG* and *CETN2* in MDD-str group, *DCT*, *AR* and *GNRHR* in MDD-pfc group and *AKT1* and *IRAK1* in MDD-hip group were selected from their PPI network.

Previous studies prove that MDD are associated with several different tissues of human brain regions. The small hippocampal volumes is correlated with the complex MDD in clinical and biological perspectives.[29] Positive emotion induced by the fronto-striatal circuitry tracks might benefit the MDD treatment.[15] Also, decreased medial prefrontal cortex was detected in the MDD patients compared to the healthy controls.[30] Our work showed that the total DEG numbers in MDD-str group was more than that in the other two groups, indicating that there may be more DEGs related to the MDD in striatum tissue. Thus, we speculated that the striatum tissue may be closely associated with MDD compared with the hippocampal tissue and prefrontal cortex tissue in human brain region.

AR, encoded by the *AR* gene, is a sterols receptor of the nuclear receptor superfamily and functions as a steroid-hormone activated transcription factor.[31] It has been discussed that testosterone is the main form of AR.[32] Studies have demonstrated that testosterone level declined in the male patients with MDD compared to the normal persons.[33,34] Besides, the mood disorder in postpartum and postmenopausal women was associated with the serum testosterone.[35] Both the serum cortisol and testosterone levels in MDD women were different than that in men with MDD.[36] Also, AR is produced in the brain region and is related to some neuropsychiatric disorders.[37] In this study, the *AR* gene in the prefrontal cortex brain region of the

postmortem tissue was up-regulated, implying that it might be crucial for the MDD development and could act as a biomarker for the MDD detection.

IRAK1 (encoded by *IRAK1* gene) is a key inherent immune signal regulating molecule of the IRAK kinase family, regulating the expression of inflammatory factors.[38] Lots of reactions could be regulated by IRAK1 via the signal pathways that are regulated by the toll-like receptor and IRAK1 receptor.[39] Also, IRAK1 could decrease the TNF-α expression to prevent the body tissue form damaging.[40] TNF-α demonstrates an important role in neuro-inflammation that leads to the anxiety symptom in MDD patients.[41,42] Neuro-inflammation played an important role in major depression because anxiety was a typical symptoms of MDD.[43] In this work *IRAK1* gene was down-reg-

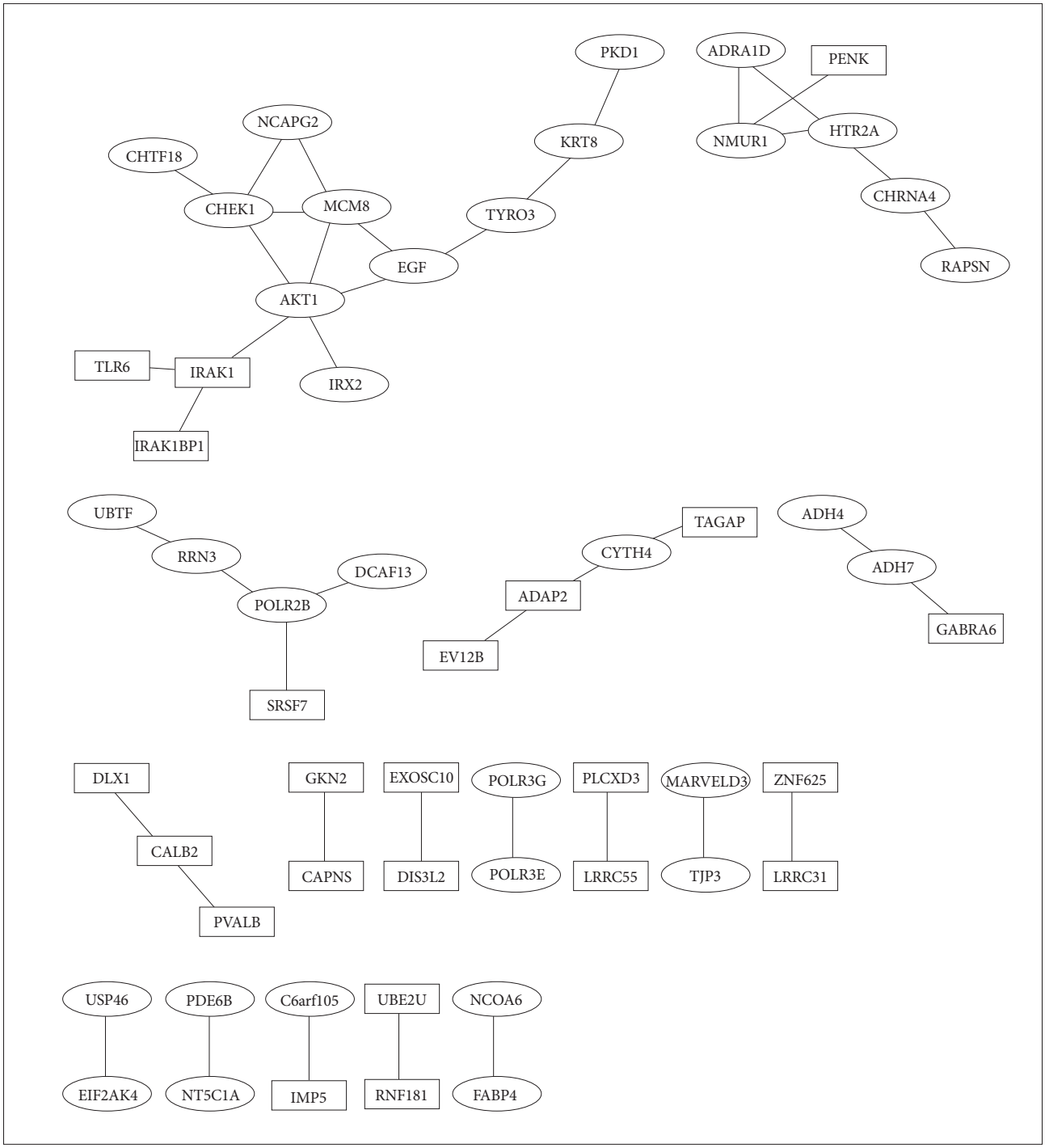

Figure 5. PPI network of DEGs in MDD-hip group. Oval node stands for the up-regulated DEGs while rectangular node stands for the down-regulated DEGs. PPI: protein-protein interaction, DEG: differentially expressed gene, MDD: major depressive disorder.

ulated in the MDD-hip, suggesting that it might be play a crucial role in MDD development in the hippocampus tissue of brain region.

Meanwhile, our findings showed that IL12A was up-regulated in MDD-hip via the RIG-I-like receptor signaling pathway, suggesting IL12A may be important to MDD. Kim *et al.* reported the plasma level of IL12A was higher in patients with schizophrenia.[44] Dysregulation of RLR signaling program may lead to the development of autoimmune diseases.[45] IL12 was a key factor in regulating the immune system.[46] Therefore, we speculated that *IL12A* may be a index for MDD progression regulated by the RIG-I-like receptor signaling pathway in brain hippocampus tissue.

Furthermore, PTK2 (encoded by *PTK2* gene), is a member of the focal adhesion kinase (FAK) subfamily of protein tyrosine kinases,[47] and has the ability to combine the cytoplasmic domain structure of the type I/II cytokines receptors, then to transfer the cytokine signals via the phosphorylation receptor subunits.[48] Otherwise, the role of PTK2 in MDD development has not been fully discussed. It has been proven tyrosine kinase A could be used as the neurochemical marker for the major depression in postmortem brains.[49] Therefore, tyrosine receptor kinase B might be associated with the depression treatment.[50] Our data showed that *PTK2* gene was up-regulated in the striatum brain region with MDD, we speculated that *PTK2* gene might act as a novel biomarker for the MDD diagnosis.

On the other hand, GALNT2, together with its paralog GALNT12, are two members of the GalNAc-transferases family that have distinct activities and initiation of O-glycosylation in cells.[51] Role of GALNT2 in MDD has not been fully discussed. However, Marucci et al.[52] suggested that GALNT2 was a mediator of intermediate glucose metabolism. Besides, previous study reveals that the glucose metabolism in regional brain was lower in patients suffered with MDD.[53] Our data displayed that the *GALNT2* and *GALNT2* were up-regulated in the MDD-str group, implying that *GALNT2* and *GALNT12* might play roles in preventing the MDD progression via the glucose metabolism pathway.

In conclusion, our present data suggests that the striatum brain region in postmortem tissue might be more affected by the MDD compared with the hippocampus and prefrontal cortex brain regions. *AR* and *PTK2* are up-regulated while *IRAK1*, *IL12A*, *GALNT12* and *GALNT2* are down-regulated in MDD, indicating that they may have different roles in MDD development, and they might provide novel therapeutic basis for MDD treatment.

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