ORIGINAL ARTICLE

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Identification and Analyses of Crucial Genes Associated with Pathogenesis of Major Depressive Disorder

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ABSTRACT

Background: Major depressive disorder is a debilitating mental condition that causes severe disability leading to a high fatality rate. No valid blood-based biomarkers for major depressive disorder are currently available. The purpose of this research is to investigate gene biomarkers and pathways that may be linked to major depressive disorder pathogenesis.

Methods: Two microarray databases were retrieved from Gene Expression Omnibus for screening of candidate differentially expressed genes. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses were performed followed by protein–protein interaction network of differentially expressed genes.

Results: About 1181 differentially expressed genes were identified from the microarray databases. Gene Ontology analyses indicated that these differentially expressed genes were significantly enriched in mRNA splicing via spliceosome, neutrophil degranulation, peptide antigen assembly with MHC class II protein complex, and immunoglobulin production-mediated immune response. The most enriched Kyoto Encyclopedia of Genes and Genomes pathway terms of the 10 significant were Hematopoietic cell lineage. About 20 genes were identified as hub genes after pathway analyses, mostly involved in colorectal cancer and the composition of ribosomes and protein processing, including KRAS, CD86, RPL9, RPL3, and RPL18.

Conclusion: New candidate genes have been identified using bioinformatic approaches that suggest their involvement in the pathogenesis of major depressive disorder and serve as potential genetic diagnostic markers as well as new therapeutic targets.

ARTICLE HISTORY

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INTRODUCTION

Major depressive disorder (MDD), featured by a low mood, dwindling interest, poor cognitive function, and vegetative symptoms, has a global lifetime prevalence of 14.6% and an annual prevalence of 5.5%.[1] Major depressive disorder has been referred to as the "common cold of mental disease" at times, although such an analogy obscured the serious effects of MDD on both individuals and societies.[2] Major depressive disorder remains a mental illness with a significantly high level of disability and mortality.[3] likely related to the mutual influence of genetic and environmental factors. According to the World Health Organization (WHO), the population affected by MDD to varying degrees accounts for 16% of the global population.[4]

Despite the high prevalence and incidence, MDD is currently diagnosed based on subjective symptom assessments.[5] In light of the lack of objective criteria, easier and targeted diagnostic evaluation tools are needed. Gobs of researches indicated that a biomarker is a detectable sign of a certain biological condition.[6] Therefore, an elucidation of the pathogenesis of MDD will help the development of possible biomarkers and prognostic indicators, which are of significant importance for the accurate diagnosis or treatment of MDD.

In recent years, illness biomedical research has made extensive use of the combination of gene chip technology and bioinformatics methodologies to demonstrate a thorough understanding of the molecular mechanisms of many diseases. Furthermore, microarray is a promising and widely used technology for large-scale gene expression profiling. To identify possible biomarkers, we used bioinformatics techniques in conjunction with microarray datasets in this work. Besides, so as to reduce the situation that the reliability of the results is impaired due to the small sample size, we selected two microarray datasets to

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expand the sample size. This research will shed more light on the pathophysiology of MDD development at the molecular level, as well as investigate potential molecular targets for new interventional strategies via a comprehensive analysis of Gene Expression Omnibus (GEO) data.

MATERIAL AND METHODS

Data Collection

The flowchart of the dataset selection was described in Figure 1. The data and information included in this study were retrieved from Public Website. The authors were not involved in animal or human experiments as described in the original datasets. The study protocols involved in the relevant datasets were approved by the Ethics Committee of Gunma University (Permit number: 899) and the Medical Ethics Committee of Freyer University Medical Center. Written informed consent was obtained from all participants.

Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) of National Center for Biotechnology Information (NCBI) is an international public depository that contains next-generation sequencing, microarray, and diverse high-throughput functional genomic data sets. In this project, 2 genetic expression datasets, including GSE76826 and GSE19738, were retrieved from GEO and used to identify the candidate genes in MDD specimens. The data type of both datasets was the array expression profile and the species were Homo sapiens.

GSE76826 were from Miyata et al[7] composed of the micro-array dataset utilizing GPL17077 Agilent 039494 SurePrint G3 Human GE v2 8x60K Micro-array 039381. Among a total of 32 specimens of peripheral blood cells, 10 were from MDD patients, 10 were from MDD patients in remission, and the remaining 12 were from healthy volunteers (controls). The microarray dataset GSE19738 was provided by Spijker[8] via GPL6848 Agilent-012391 Whole Human Genome Oligo Micro-array G4112A, composed of 67 samples including 33 MDD and 34 healthy controls.

Filtering for Differential Genes

GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) is a web-based interactive tool that compares normal and patient samples to determine DEGs.[9] To select genes associated with MDD, the DEGs between MDD groups and normal control groups from 2 datasets were identified via GEO2R, |log FC| (an absolute LOG2 values in gene expression fold change)>0.6 and P value < .05 were determined as the cut-off criteria for screening differential genes.

MAIN POINTS

- KRAS, which belongs to the rat sarcoma viral oncogene homolog (RAS) gene family and commonly mutated in colorectal cancer, was among the top three genes with the highest association among the major depressive disorder.
- It was likely that hematopoietic cell lineage might play a prominent role in the etiopathogenesis of major depressive disorder.
- Our Gene Ontology enrichment analysis in the present study further confirmed the importance of immune response and RNA splicing in the pathogenesis of major depressive disorder.

Gene Ontology Functional and Kyoto Encyclopedia of Genes and Genomes Pathway Enrichment Analysis of Differentially Expressed Genes

Gene Ontology is an extensively utilized biological information tool, which contains 3 subcategories of structural annotation of genes and gene products, namely BP (biological process), cellular components (CC), and molecular function (MF).[10] Kyoto Encyclopedia of Genes and Genomes is a collection of databases that help researchers understand and model the higher-order functional behavior of cells and organisms using genomic data.[11] The DAVID database (https://david.ncifcrf.gov/), which is an online tool website that provides a series of comprehensive function annotations, was utilized to complete GO and KEGG studies to better comprehend the biological meaning of DEGs. P value < .05 was considered as the cut-off criterion.

Modular Selection and the Establishment of a Protein-Protein Interaction Network

With the purpose of systematically analyzing the biological functions of the pooled DEGs, the Search Tool for the Retrieval of Interacting Genes (STRING, https://cn.string-db.org/), a database with web-tools that gives information on protein–protein interactions and predicted interactions, was utilized to establish the PPI net after the GO and KEGG analysis.[12] Besides, the statistical significance of interaction effects with composite scores greater than 0.4 was determined. The MCODE (Molecular Complex Detection) plug-in in Cytoscape was employed to extract the main interaction sub-network.

Hub Gene Selection Analysis

Subsequently, The Cytoscape cytohubba plug-in selected and arranged the top 20 hub genes with the greatest connectivity followed by the construction of the PPI network. The results of selection were visualized by Cytoscape, the higher the correlation scoring the redder the color on the graph. In addition, pathway and functional enrichment analysis were subsequently performed for all 20 hub genes using DAVID. P-value less than 0.05 was set as a criterion for statistical significance.

RESULTS

Determination of Differentially Expressed Genes in Major Depressive Disorder

Two micro-array datasets (GSE76826 and GSE19738) that both contain genetic information of MDD patients and

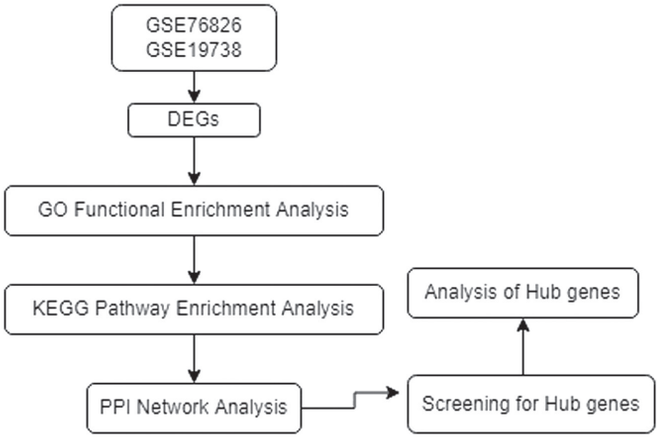

Figure 1. Schematic diagram of the methods applied in this study.

normal controls were selected to download from GEO website, and eventually 1181 DEGs of 2 datasets were identified and analyzed by GEO2R. Among them, 339 genes were upregulated, and 842 genes were downregulated.

Kyoto Encyclopedia of Genes and Genomes Analysis and Gene Ontology Analysis of Differentially Expressed Genes

DAVID was utilized to analyze the GO and KEGG pathway enrichment of screened DEGs. The GO results revealed that BPs(biological process) variations were primarily sponged in mRNA splicing via spliceosome, neutrophil degranulation, membrane organization and immunoglobulin production mediated immune response, antigen processing and presentation, peptide antigen assembly with MHC class II protein complex. Changes in CCs (cellular components) were substantially enriched in the cytosol, nucleoplasm, integral component of plasmatic membranes, nuclei, and exocellular exosomes. Variations in MFs (molecular function) for the DEGs were sponged predominantly in protein binding, RNA binding, MHC class II receptor activity, ubiquitin protein ligase binding, MHC class II protein complex binding. The results of the enrichment of GO function are represented in the following tables and graphs respectively (Table 1, Figure 2).

On the other hand, the most enriched KEGG pathway terms were hematogenous cell lineage, Intestinal immunity network for the generation of IgA, Graft-versus-host illness, primary immunodeficiency, viral myocarditis, phagosome, antigen processing, presentation, and so on. Figure 3 shows the findings of the KEGG enrichment analysis (Figure 3).

Protein-Protein Interaction Network Enstablishment and Modulae Analyses

For systematically analyzing the integrated biological networks of the DEG, a PPI network of DEGs including 98 nodes and 232 edges was created from the STRING database and visualized using Cytoscape. (Figure 4) Subnetwork analysis was performed using the MCODE clustering algorithm and four essential modules with a relatively high degree of significance in the regulatory network were selected (Figure 5).

Hub Gene Selection and Analysis

As identified by the PPI network using the cytoHubba plugin, hub genes may be important in the development of MDD. Twenty genes were identified as hub genes, including *KRAS*, *CD86*, *RPL9*, *RPL3*, *RPL18*, *GNAS*, *COX4I1*, *RRP1B*, *CD24*, *KCNG1*, *RAB5A*, *EEF1D*, *RPS21*, *MRPL20*, *SAG*, *FGR*, *NF2*, *SNRPC*, *PPP2R5C*, *BCAT1*, and they were all shown in Figure 5. We used functional analysis and pathway enrichment analysis to investigate the biological classification of hub genes (Table 2). Gene Ontology analysis results demonstrated that BPs alterations of hub genes were clearly enriched in translation, cytoplasm translation, SRP (signal recognition particle)-reliant cotranslation protein that targets membranes, nonsense-mediated decay, nuclear-transcribed mRNA katabolic processes, virus transcription, immune response-modulating cellular surface acceptor signal paths, translational initiation, rRNA processing, modulation of long-term neuron synapsis plasticity, and ribosomal large subunit assembly. Cellular components changes of hub genes were significantly enriched in ribosome, cytosol, cytosolic ribosome, cytosolic large ribosomal subunit, ruffle, membrane, focal adhesion, membrane raft, and polysomal ribosome. Changes in the molecular functions of hub genes were predominantly enriched in a structural constituent of ribosome, RNA binding, protein binding, rRNA binding, and GTPase activity. Furthermore, according to KEGG analyses, the hub genes were primarily sponged in ribosome, coronavirus disease—COVID-19, thermogenesis, and vasopressin-regulated water reabsorption.

DISCUSSION

Major depressive disorder is a serious public health problem worldwide.[13] However, as of now, the clinical diagnosis of MDD is based on questionnaires and clinical interviews to collect subjective experiences and perceptions.[14] Growing number of studies indicated that prospectively investigating biological predictors could be especially useful in comprehending the etiology of MDD to improve diagnosis, treatment outcomes, and prevention of recurrence.[15] Therefore, the purpose of this study was to help identify diagnostic biomarkers of MDD, using 2 GEO micro-array data sets to acquire DEGs and hub genes. Among 1181 DEGs and 20 hub genes identified from MDD and control specimens, additional GO, KEGG, and PPI network analyses revealed a significant association between MDD with immune responses.

Table 1. Enrichment Results Table Showing of the Gene Ontology Function Annotations for Major Depressive Disorder

Term	Category	*P*
mRNA splicing, via spliceosome	Biological process	6.88372E-07
Neutrophil degranulation	Biological process	2.85009E-06
Antigen processing and presentation	Biological process	3.26710E-05
Peptide antigen assembly with MHC class II protein complex	Biological process	4.74226E-05
Membrane organization	Biological process	4.99295E-05
Immunoglobulin production mediated immune response	Biological process	6.56987E-05
Positive regulation of MAPK cascade	Biological process	0.000114469
Antigen processing and presentation of peptide or polysaccharide antigen	Biological process	0.000153957
Translation	Biological process	0.000337909
Signal transduction	Biological process	0.000571443
Cytosol	Cellular component	8.90672E-22
Nucleoplasm	Cellular component	3.46980E-10
Integral component of plasma membrane	Cellular component	1.12791E-08
Nucleus	Cellular component	1.58122E-08
Extracellular exosome	Cellular component	9.52022E-08
Extracellular region	Cellular component	1.70549E-07
Plasma membrane	Cellular component	2.42547E-07
Cytoplasmic stress granule	Cellular component	3.91995E-07
Extracellular space	Cellular component	5.32288E-07
Membrane	Cellular component	9.47558E-07
Protein binding	Molecular function	9.33196E-12
RNA binding	Molecular function	3.11809E-08
MHC class II receptor activity	Molecular function	0.000396622
Ubiquitin protein ligase binding	Molecular function	0.000531796
MHC class II protein complex binding	Molecular function	0.000931871
mRNA binding	Molecular function	0.001179954
Transferase activity	Molecular function	0.001258256
Protein domain-specific binding	Molecular function	0.001769213
Structural constituent of ribosome	Molecular function	0.001772385
Transmembrane signaling receptor activity	Molecular function	0.002095284

The initial GO analysis was performed on 1181 DEGs identified from GSE19738 and GSE76826 datasets, to investigate the causal links of MDD at the molecule level. The DEGs were mainly enriched in 3 main classifications. Immune response-related and mRNA splicing terms in the "BP" (biological process), cytosol and nucleoplasm terms in the "CC" (cellular component), and binding-related terms and MHC class II receptor activity in the "MF" (molecular function). The findings were consistent with observations reported by previous studies.[16] Jansen and his colleagues identified genes and their clusters significantly enriched with immune pathways associated with MDD etiology, by examining gene expression in 1848 peripheral blood samples from the Netherlands Study of Depression and Anxiety.[17] Verma et al[18] identified abnormal RNA splicing and stability as important factors of MDD. Data mining of our GO enrichment analysis in the present study further confirmed the importance of immune response and RNA splicing in the pathogenesis of MDD.

The additional KEGG analyses indicated the DEGs condensed in the primary immunodeficiency and intestinal immunity network for the IgA generation. The hematogenous cell lineage was also significantly enriched as revealed by the analyses. This finding was consistent with that from the previous study in the MDD indicating lineage parameters of red and white blood cells were affected, showing a general hematopoietic regulation or imbalance.[19] One explanation for such an association was that both innate and adaptive immune cells were derived from the hematopoietic stem cells and the MDD would affect the immune system at the cellular level.[20] Additional evidence suggested direct and rapid responses of hematogenous stem cells to immune signals revealed the explanation.[20] Thus, it was likely that hematopoietic cell lineage might play a prominent role in the etiopathogenesis of MDD.

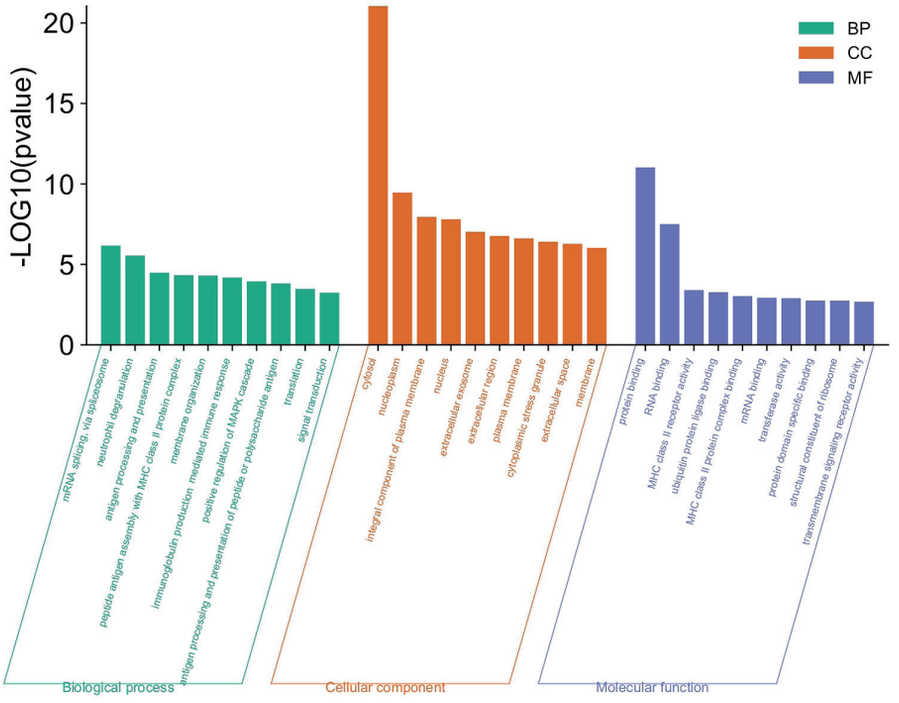

Figure 2. Enrichment bar chart showing distributional status of the GO annotations for MDD. BP, biological process; CC, cellular component; GO, Gene Ontology; MF, molecular function; MDD, major depressive disorder.

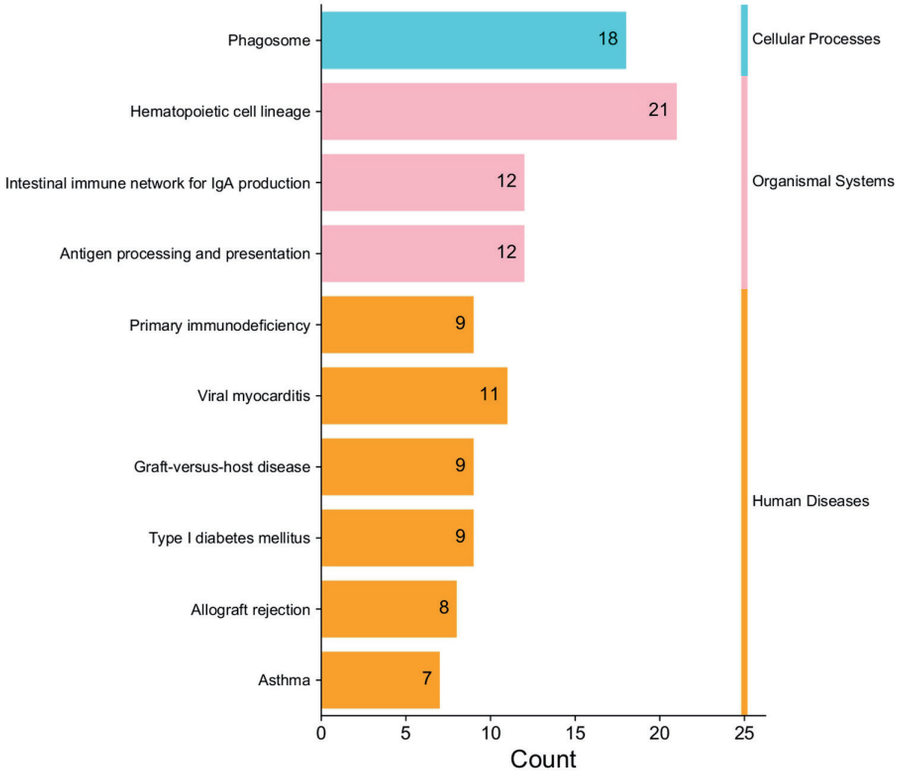

Figure 3. The top 10 KEGG pathways of DEGs. DEGs, differentially expressed genes; KEGG, Kyoto Encyclopedia of Genes and Genomes.

The relationship among differential genes was evaluated using a constructed PPI network, and 20 hub genes were determined. Further study of these genes might facilitate the comprehension of the pathogenesis of MDD. Hence, GO and KEGG enrichments were carried out. The results were in general agreement with the results above of GO

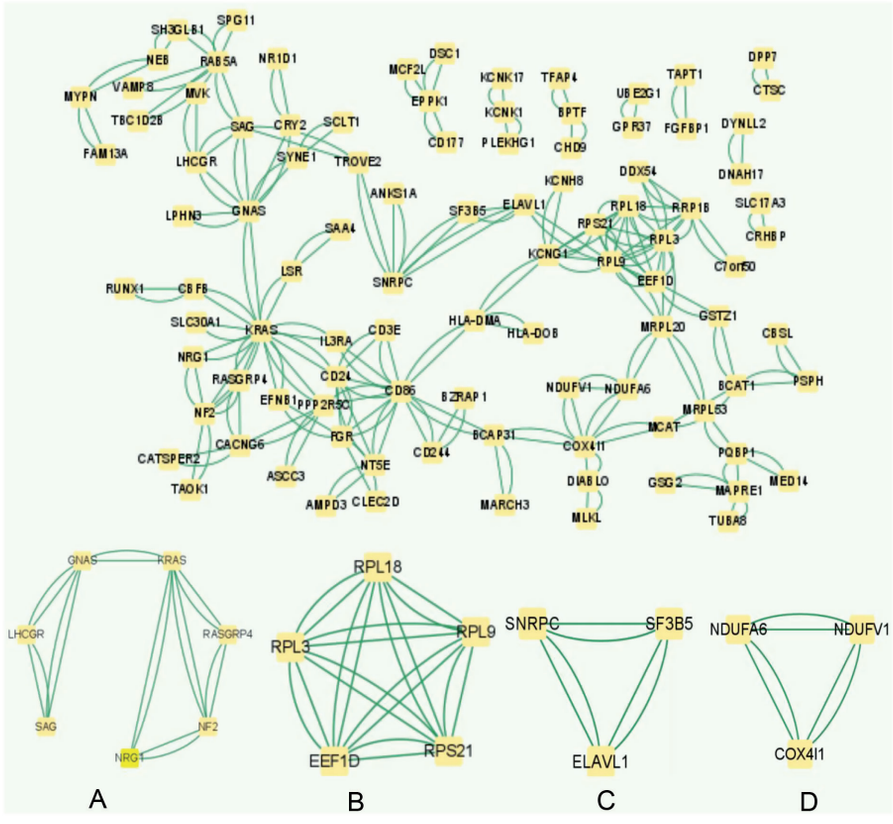

Figure 4. A PPI network including 98 nodes and 232 edges. The DEGs are represented by yellow nodes, while their interactions are shown by green edges: A, B, C, and D were 4 significant modules obtained from the PPI network. DEGs, differentially expressed genes; PPI, protein–protein interaction.

and KEGG analyses. One obvious finding among 20 hub genes was that some genes including *RPL9*, *RPL3*, *RPL18*, *RRP1B*, and *RPS2* are closely related to the composition of ribosomes and protein processing. The ribosomal genes have been directly linked to stress-mediating molecules including *ERBB3* and IL-6.[21] Moreover, ribosomal genes may reduce the sensitivity of the glucocorticoid receptor, resulting in hyperactivity of the HPA axis and hypercortisolism that might be involved in depression and stress vulnerability.[22] Interestingly, *KRAS* was among the top 3 genes with the highest association among the MDD, even though *KRAS* belongs to the rat sarcoma viral oncogene homolog (RAS) gene family, commonly mutated in colorectal cancer, without a clear link to the MDD.[23] Several lines of molecular biology evidence suggested that RAS proto-oncogene might be involved in the synthesis of serotonin and dopamine,[24] 2 major neurotransmitters involved in the pathogenesis as well as serving as the targets for the pharmacotherapy of MDD.[25-27] A recent epidemiological study has indicated high susceptibility to depression among individuals with high KRAS oncogene expression.[28] Given the high association between KARS/ribosomal-related genes and the pathogenesis of MDD, an early diagnosis of MDD might be developed based on these genes or gene products.

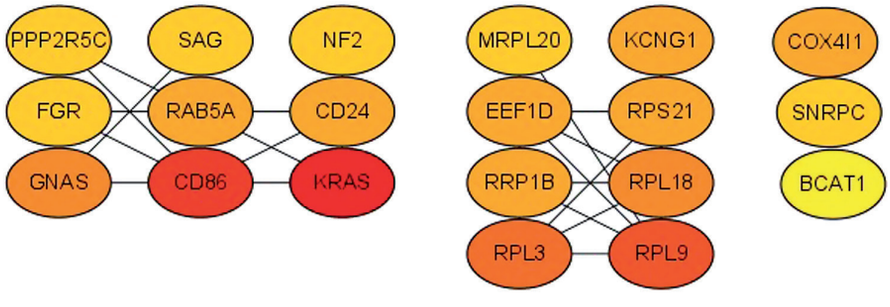

Figure 5. Twenty hub genes determined by cytoHubba plug-in. The redder the color, the higher the correlation score.

Table 2. Outcomes of Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Analyses of Core

Category	Term	Count
BP	Translation	5
BP	Cytoplasmic translation	4
BP	SRP-dependent cotranslational protein targeting membrane	4
BP	Viral transcription	4
BP	Nuclear-transcribed mRNA catabolic process, nonsense-mediated decay	4
BP	Translational initiation	4
BP	rRNA processing	4
BP	Immune response-regulating cell surface receptor signaling pathway	2
BP	Regulation of long-term neuronal synaptic plasticity	2
BP	Ribosomal large subunit assembly	2
CC	Ribosome	5
CC	Cytosol	15
CC	Cytosolic ribosome	4
CC	Cytosolic large ribosomal subunit	3
CC	Ruffle	3
CC	Membrane	8
CC	Focal adhesion	4
CC	Membrane raft	3
CC	Polysomal ribosome	2
MF	Structural constituent of ribosome	5
MF	RNA binding	7
MF	Protein binding	18
MF	rRNA binding	2
MF	GTPase activity	3
KEGG	Ribosome	5
KEGG	Coronavirus disease—COVID-19	4
KEGG	Thermogenesis	3
KEGG	Vasopressin-regulated water reabsorption	2

BP, biological process; CC, cellular component; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular function.

Our integrated bioinformatic analyses have revealed DEGs and hub genes as candidates for the early diagnoses of MDD. While GO and KEGG analyses indicated immune response, RNA splicing, and hematopoietic cell lineage involved in the pathogenesis of MDD, PPI network analysis suggested a role of ribosome-related genes. These findings may contribute to the development of new diagnostic and treatment strategies for MDD.

Limitations

This study had a few main limitations. First, although our bioinformatic analyses have identified candidate genes and pathways as potential biomarkers for early diagnosis of MDD, additional experimental assays are still needed to confirm and verify whether these genes and/or gene products are effective in vitro or in vivo. Notwithstanding, our findings were in general consistent with previous ones that might serve at least as a relative validation of our bioinformatic approach.[29,30] Second, the analyses were performed using data entirely derived from the peripheral blood cells. Some recent evidence suggested different patterns based on miRNA/mRNAs data from the brain tissues in the MDD.[31] Thus, a comprehensive analysis might be needed to verify our findings. Third, the genetic alterations mentioned in the text are only present in a subset of patients. Therefore, these alterations may only be present in certain subsets of patients with specific clinical and pathophysiological characteristics.

Ethics Committee Approval: The study protocols involved in the relevant datasets were approved by the Ethics Committee of Gunma University and the Medical Ethics Committee of Freyer University Medical Center (Permit number: 899).

Informed Consent: Written informed consent was obtained from the participants who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – L.J., M.A.; Design – L.J., M.Q.; Supervision – M.A., M.Q.; Resources – M.A., M.Q.; Materials – M.Q., L.J.; Data Collection and/or Processing – L.J.; Analysis and/or Interpretation – L.J., M.Q.; Literature Search – L.J.; Writing – L.J.; Critical Review – M.A., M.Q.

Declaration of Interests: The authors have no conflict of interest to declare.

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