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Bioinformatics analysis of gene expression profile in women with major depressive disorder

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Abstract

Introduction: Major depressive disorder (MDD) is a mental disorder occurring in women twice as much as men. In both sexes, the average age of people with MDD is roughly 25 years. Family, twin, and epidemiological studies all point to the multifactorial and polygenetic characteristics of the psychiatric traits of major depressive disorder. The present study aimed to screen genes related to the pathogenesis of major depressive disorder by bioinformatics.

Methods: Two hundred twenty-three different genes (DEGs) were expressed by comparing female patient samples with controls by TAC screening software using GSE98793 microarray data from the GEO database. Hub genes were screened via STRING and Cytoscape, followed by KEGG enrichment analysis.

Results: According to the obtained results, comparing female patients with control of 103 genes showed increased expression and 120 genes identified as decreased expression. The results of KEGG and panther pathway enrichment analysis comparing female patient samples with control showed that DEGs are mainly in the HIF-1 signaling pathway, FOXO signaling pathway, Th-17 cell differentiation pathway, pathway PI3K-Akt signaling, programmed cell death pathway (Ferptosis), and purine synthesis pathway were important. The results of this study revealed that IGF1R and ATM genes with increased expression and GMPS genes with decreased expression for women with this disease could also be beneficial for therapeutic purposes.

Conclusion: The key genes obtained by microarray analysis provide essential clues for revealing the molecular mechanism and could be suitable and new candidates for future studies on major depression as well as optimization of treatment methods.

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Extended Abstract

Introduction

Major depressive disorder (MDD) is a mental disorder occurring in women twice as much as men. In both sexes, the average age of people with MDD is about 25 years. Family, twin, and epidemiological studies all point to the multifactorial and polygenetic characteristics of the psychiatric traits of major depressive disorder. In recent years, many efforts have been made to identify biomarkers for diagnosing, preventing, and treating depression.

Bioinformatics is a new science that uses computers, computer software, and databases to try to answer biological questions, especially in the cellular and molecular fields, proteins, and genes. In this way, biological networks analysis is widely used to calculate and model intracellular interactions to identify cellular mechanisms. A biological network is any type of network that can depict a biological system. Biological networks can be used at three levels of the genome, transcriptome and proteome, to identify biological markers associated with various diseases. In the present study, expression data related to major depressive disorder were extracted and used to identify key genes of the disease, gene networks, and related metabolic pathways of major depressive disorder by bioinformatics.

Methods

By referring to the GEO database (http://www.ncbi.nlm.nih.gov/geo) and searching for the expression profile of MDD-related data, the data were extracted with the access number GSE98793 and the platform number GPL570 (Affymetrix Human Genome U133 Plus 2.0 Array) in CEL format. The DEGs were determined by using Affymetrix Transcriptome Analysis Console (TAC), following the software guidelines. The adjusted P-values (adj. P) and Benjamini and Hochberg false discovery rate were applied to balance between discoveries of statistically significant genes. Two hundred twenty-three different genes (DEGs) were expressed by comparing female patient samples with controls by TAC software. LogFC (fold change) >2 and adj. P-value <0.05 were considered statistically significant. In order to obtain the biological function and signaling pathways of DEGs, EnrichR (http://david.ncifcrf.gov) was used to GO annotation and KEGG pathways enrichment of DEGs. P<0.05 was considered statistically significant. The top 100 genes of DEGs were used for gene set enrichment analysis. EnrichR is a web-based gene function enrichment analysis software. It can provide a comprehensive set of functional annotation information of genes and proteins. GO annotation is a main bioinformatics tool to annotate genes and analyze the biological process of DEGs. KEGG is a database resource for understanding high-level functions and biological systems from large-scale molecular datasets generated by high-throughput experimental technologies.

The protein-protein interaction (PPI) network was constructed using the STRING (Search Tool for the Retrieval of Interacting Genes http://string-db.org) online database alongside Cytoscape software, followed by identifying hub genes.

The STRING database was used to obtain the predicted interactions to gain the interaction between DEGs. The STRING database constructed the PPI network of DEGs in the current study. The interaction with a combined score >0.7 was considered statistically significant. The visualization of the PPI network was used by Cytoscape software and Gephi. Besides, Cytoscape software (version 3.6.1), which can display molecular interaction networks, is an open-source bioinformatics software platform. Accordingly, protein-protein interaction networks of key hub genes were obtained from Gephi software.

Results

According to the obtained results, comparing female patients with control of 103 genes showed increased expression, and 120 genes identified as decreased expression. In women with depressive disorder, ATM, IGF1R, BCBP2, VHL, and EIF4G2 genes were highly expressed hub genes of a gene network, GMPS, PPP2R1A LCK, and HSP90AB1 gene was as hub genes of low-expressed genes network. The results of KEGG and panther pathway enrichment analysis comparing female patient samples with control showed that DEGs are mainly in the HIF-1 signaling pathway, FOXO signaling pathway, Th-17 cell differentiation pathway, pathway PI3K-Akt signaling, programmed cell death pathway (Ferptosis), and

purine synthesis pathway were important.

Conclusion

According to the specific study of women with depression with healthy women and finding different differential genes and different pathways in this group, it can be concluded that for women with this disease, IGFIR and ATM gene with increased expression and GMPS gene. IGF1R gene encodes the insulin-like growth factor receptor. Increased expression of insulin-like growth factors has a direct effect on the development of major depression. The ATM gene is involved in the p53 signaling pathway. Due to the function of this gene in apoptosis, it can be indirectly associated with depression. GMP signaling cascade is also expressed in the brain. The activity of this pathway is involved in learning and memory processes. Further studies have shown that the cGMP cascade in the brain acts as an antidepressant. The HIF signaling pathway is one of the pathways that were jointly identified through both KEGG and Panther databases in relation to the increase in gene expression in depressed women compared to healthy women in this study. In the future, this pathway can be studied with more confidence in depression in women for diagnostic and therapeutic purposes. Therefore, regarding the key genes obtained by microarray analysis and MDD DEGs and interpretation of their function, some genes showed significant differences in expression in people with depression compared to healthy individuals that their association with major depression has not been reported in previous studies. The results of this study showed that IGF1R and ATM genes with increased expression and GMPS genes with decreased expression for women with this disease could also be a good option for therapeutic purposes. These genes could be suitable and new candidates for future studies on major depression, as well as the optimization of treatment methods. The effective pathways identified in the present study were primarily involved in the brain pathways. In addition, dysfunction of one part of the brain causes depression. The key genes involved in this disease are influential in several diseases, which leads to people with this disease have an increased risk of developing other diseases. Bioinformatics examines the link between these genes, depression, and other diseases. Accordingly, these genes provide essential clues for revealing the molecular mechanism and could be suitable and new candidates for future studies on major depression, as well as the optimization of treatment methods.

Ethical Considerations

Compliance with ethical guidelines

The authors of this research declared that there are no data fabrications and falsifications or data manipulation in their submitted article, and all authors have observed the research ethics. The authors have cited any source in this study.

Authors' contributions

Farzaneh Esmaeili planned and designed the experiments, performed them out, analyzed the data, produced figures, and tables contributed literature review, authored and reviewed drafts of the article, and approved the final manuscript. Samaneh Zolghadri is the corresponding author that reviewed drafts of the article and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.