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ABOUT COVER

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AIMS AND SCOPE

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WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, *etc*.

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ORIGINAL ARTICLE

Basic Study

Identification and characterization of noncoding RNAs-associated competing endogenous RNA networks in major depressive disorder

Zhi-Li Zou, Yu Ye, Bo Zhou, Yuan Zhang

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Abstract

BACKGROUND

Major depressive disorder (MDD) is a common and serious mental illness. Many novel genes in MDD have been characterized by high-throughput methods such as microarrays or sequencing. Recently, noncoding RNAs (ncRNAs) were suggested to be involved in the complicated environmental-genetic regulatory network of MDD occurrence; however, the interplay among RNA species, including protein-coding RNAs and ncRNAs, in MDD remains unclear.

AIM

To investigate the RNA expression datasets downloaded from a public database and construct a network based on differentially expressed long noncoding RNA (lncRNAs), microRNAs (miRNAs), and mRNAs between MDD and controls.

METHODS

Gene expression data were searched in NCBI Gene Expression Omnibus using the search term "major depressive disorder." Six array datasets from humans were related to the search term: GSE19738, GSE32280, GSE38206, GSE52790, GSE76826, and GSE81152. These datasets were processed for initial assessment and subjected to quality control and differential expression analysis. Differentially expressed lncRNAs, miRNAs, and mRNAs were determined, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were performed, and protein-protein interaction network was generated. The results were analyzed for

their association with MDD.

RESULTS

After analysis, 3 miRNAs, 12 lncRNAs, and 33 mRNAs were identified in the competing endogenous RNA network. Two of these miRNAs were earlier shown to be involved in psychiatric disorders, and differentially expressed mRNAs were found to be highly enriched in pathways related to neurogenesis and neuroplasticity as per Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses. The expression of hub gene fatty acid 2-hydroxylase was enriched, and the encoded protein was found to be involved in myelin formation, indicating that neurological development and signal transduction are involved in MDD pathogenesis.

CONCLUSION

The present study presents candidate ncRNAs involved in the neurogenesis and neuroplasticity pathways related to MDD.

Key Words: Major depressive disorder; Noncoding RNA; Competing endogenous RNA; Bioinformatics; Data mining

Core Tip: Competing endogenous RNAs (ceRNAs) are novel regulatory molecules involved in a wide range of biological processes and diseases. This study explored the potential ceRNA networks (ceRNETs) involved in the pathogenesis of major depressive disorder (MDD) using bioinformatics data mining. A ceRNET comprising 3 miRNAs, 12 lncRNAs, and 33 mRNAs was constructed based on two public datasets obtained from the Gene Expression Omnibus database. Elucidating the correlation of the ceRNET with MDD opens new avenues to discover specific diagnostic biomarkers for MDD and expands our knowledge about this disease.

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INTRODUCTION

Major depressive disorder (MDD), characterized by persistent and intense feelings of sadness for extended periods, is one of the most common causes of morbidity and mortality worldwide[1], yearly affecting approximately 5% of adults worldwide[2]. The exact cause of MDD remains unknown; however, the occurrence of MDD is widely believed to involve crosstalk between genetic, environmental, social, and developmental vulnerabilities and resilience factors[2,3]. Numerous risk factors for MDD have been identified from three major perspectives: medical, social, and substance[4,5]. Available treatment options primarily include pharmacotherapy, psychotherapy, and lifestyle changes. However, prevention and treatment of this disease remain difficult because of varying presentations, unpredictable course and prognosis, and variable responses to treatment[6]. Therefore, further studies are needed to determine the biological mechanisms underlying MDD to develop better patient therapies.

The increasing popularity of high-throughput microarray technologies has facilitated the identification of genome variations in MDD, improving the understanding of its pathogenesis and development, and revealing promising biomarkers. Gao *et al*[7] identified 241 differentially expressed genes (DEGs) in the hippocampus (hip), 218 DEGs in the prefrontal cortex (pfc), and 327 DEGs in the striatum (str) from patients with MDD. These DEGs were enriched in glycan biosynthesis, RIG-I-like receptor signaling, and pyrimidine metabolism pathways, which significantly contribute to MDD pathogenesis. Additionally, the DEGs AR, PTK2, IRAK1, IL12A, GALNT12, GALNT2, CD19, and PTDSS2 were identified as novel therapeutic targets[7,8]. Moreover, Segman *et al*[9] found 73 DEGs between patients with postpartum major depression and controls using peripheral blood cells; the immune response, transcriptional effects on cell proliferation, and DNA replication and repair were significantly enriched in these patients. Although novel genes have been discovered and well-studied, genetic predisposition to MDD only partly explains the occurrence of this illness. With the development of epigenetic theory and technology, non-coding RNAs (ncRNAs) have been identified to help explain the interaction between genetics and the environment. Li *et al*[10] found an inverse relationship between serum brain-derived neurotrophic factor (BDNF) levels and miR-132/miR-182 levels in depression, supporting the

notion that miR-182 is a putative regulatory microRNA (miRNA) of BDNF. Zhou *et al*[11] found that miRNAs act as key regulators of synaptic plasticity in MDD pathogenesis. Liu *et al*[12] detected four long non-coding ribonucleic acids (lncRNAs) related to the expression of mRNAs associated with MDD. Although ncRNAs have been proposed to play important roles in MDD, the regulatory network among RNA species remains unclear.

The competing endogenous RNA (ceRNA) network proposed by Salmena *et al*[13] has been verified in an increasing number of studies. This complicated post-transcriptional regulatory network plays a critical role in the progression and pathogenesis of various illnesses, including cancer. However, to date, no ceRNA network has been proposed for MDD. Here, we investigated RNA expression datasets downloaded from the Gene Expression Omnibus (GEO) database and constructed a network based on differentially expressed lncRNAs, miRNAs, and mRNAs between MDD and controls. This network was used to mine for functional ncRNAs that may contribute to the epigenetic mechanism underlying MDD pathogenesis and may be useful as potential therapeutic targets and biomarkers for MDD.

MATERIALS AND METHODS

Data resources and preprocessing

Gene expression data were searched in NCBI GEO using the search term "major depressive disorder". Six array datasets from humans were related to the search term: GSE19738 (expression profiling by array, n = 42; MDD, 21; control, 21), GSE32280 (expression profiling by array, n = 24; MDD, 8; subsyndromal symptomatic depression, SSD, 8; control, 8), GSE38206 (expression profiling by array, n = 18; MDD, 9; control, 9), GSE52790 (expression profiling by array and ncRNA profiling by array, n = 22; MDD, 10; control, 12), GSE76826 (expression profiling by array, n = 22; MDD, 10; control, 12), and GSE81152 (ncRNA profiling by array, n = 50; MDD, 31; control, 19). These datasets were processed for initial assessment; if they met the requirements, they were subjected to quality control and differential expression analysis.

Identification of differentially expressed lncRNAs, miRNAs, and mRNAs

The differentially expressed mRNAs, lncRNAs, or miRNAs were determined based on the threshold criteria of $|\log2 \text{(fold-change)}| \geq 1$ and an adjusted P value < 0.05 using the R limma package (version 3.40.6). The differentially expressed lncRNAs (DE_lncRNAs) obtained from GSE76826 were entered into the miRcode database (http://www.mircode.org/) that provides an integrated, searchable map of putative target sites of miRNAs, to predict the interactions of DE_lncRNAs and DE_miRNAs. Only DE_lncRNAs for which miRNAs were successfully predicted were selected for ceRNA network construction. The miRNAs obtained were overlapped with differentially expressed miRNAs obtained from GSE81152, and the overlapping miRNAs were identified as a differentially expressed miRNA (DE_miRNA). The name of the DE_miRNA was entered into the miRDB (http://mirdb.org/) and TargetScan (http://www.targetscan.org/vert_72/) databases, both of which are online databases used to predict miRNA targets. The mRNAs obtained above were overlapped with differentially expressed RNAs identified from GSE76826. The DE_lncRNAs, DE_miRNAs, and DE_mRNAs obtained in the manner described above were used for ceRNA network construction.

DE_lncRNA/DE_miRNA/DE_mRNA network construction

Cytoscape 3.4.0 was used to visualize the DE_lncRNA/DE_miRNA/DE_mRNA network construction.

Gene Ontology function and Kyoto Encyclopedia of Genes and Genome pathway enrichment analysis

To help identify the potential biological functions of these genes in the MDD ceRNA network, Gene Ontology (GO) functional and Kyoto Encyclopedia of Genes and Genome (KEGG) pathway enrichment analyses were performed using the clusterProfiler package in R. GO terms have three categories; biological process, cellular compartment, and molecular function. $P \leq 0.05$ indicated a significant difference in GO terms and KEGG pathways.

Construction of the protein interaction network

The protein interaction (PPI) network was constructed to evaluate the interactions among genes. The DE_mRNAs were selected to construct a PPI network based on Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) ver.11.0 (https://string-db.org/). In the PPI network, a node represents a gene; the undirected link between two nodes is an edge, representing the interaction between two genes, and the degree of a node corresponds to the number of interactions of a gene with other genes in the network.

RESULTS

Quality control and differential expression analysis

The workflow of the analysis is shown in Figure 1. Because the GSE19738 dataset lacks documents to annotate gene symbols and the GSE32280 dataset uses peripheral blood mononuclear cells rather than whole blood, both these datasets were excluded from analysis at the first stage. Next, sample-level quality control was performed using principal component analysis to ensure that the cases and controls were well-separated and to identify sample outliers. After removing the outliers, there were 10 controls and 8 MDD cases in GSE52790, 12 controls and 9 MDD cases in GSE76826, and 10 controls and 23 MDD cases in GSE81152. The four remaining datasets, GSE32280, GSE52790, GSE76826, and GSE81152, were utilized to identify differentially expressed mRNAs, lncRNAs, and miRNAs using the limma R package with the threshold set to an adjusted P value < 0.05 and $|\log2 \text{(fold-change)}| \geq 1$. A hierarchical cluster heatmap showing the expression patterns of the DEGs between MDD and controls is shown in Figure 2. As no DEGs were found in GSE32280, this dataset was excluded from subsequent analysis. A total of 125, 373, and 54 DEGs were identified in the GSE52790, GSE76826, and GSE81152 datasets, respectively. There were 112 upregulated and 13 downregulated genes among the 125 DEGs in GSE52790, 109 upregulated genes (including 89 mRNAs and 10 lncRNAs) and 264 downregulated genes (including 198 mRNAs and 66 LncRNAs) in the 373 DEGs of GSE76826, and 51 upregulated and 3 downregulated genes in the 54 DEGs of GSE81152.

Construction of a ceRNA network for MDD

To better understand the effect of lncRNAs on mRNAs mediated by combinations with miRNAs in MDD, we constructed a ceRNA network based on the GSE76826 and GSE81152 data. Eighty-six differentially expressed lncRNAs from GSE76826 were retrieved and entered into the miRcode database to predict the potential interacting miRNAs. Eighty-four miRNAs (645 LncRNA-miRNA pairs) were identified in the miRcode database. Next, we overlapped these 84 miRNAs to the differentially expressed miRNAs identified in GSE81152, generating 3 shared miRNAs (the corresponding lncRNAs were reduced to 12) (Table 1). Thereafter, we entered these 3 miRNAs into the miRDB and TargetScan databases to identify their potential target mRNAs and combined the results from these two databases to achieve high true-positive coverage. A total of 1,868 mRNAs was generated from the two databases; when the 287 differentially expressed mRNAs identified from GSE76826 were overlapped, 33 shared mRNAs were identified (Table 2). Finally, we assembled all identified ceRNA pairs to generate an mRNA-miRNA-lncRNA network in MDD (Figure 3).

Gene set enrichment analysis

Enrichment analysis indicated that the 33 differentially expressed mRNAs were significantly associated with the GO terms for 887 biological process, 105 molecular function, and 55 cell component terms. For the KEGG pathways, the only significant pathway was the mammalian target of rapamycin (mTOR) signaling pathway. Table 3 and Figure 4 list the top 10 most significant biological processes, molecular functions, and cellular components from the GO terms.

PPI network construction

A total of 33 DEG mRNAs were entered into the STRING database to build a PPI network. Gene nodes with the highest W values in the network were *ACVR1C*, *ELOVL4*, *fatty acid 2-hydroxylase* (*FA2H*), *INHBB*, *NIPAL4*, and *UGT8* (Figure 5).

DISCUSSION

Considerable progress has been made in understanding the pathophysiology of MDD; however, no single model or mechanism can fully explain all aspects of the disease[6]. MDD is believed to involve the following: Reduced levels of monoamines, changes in the hypothalamic-pituitary-adrenal axis, inflammation, limited neurogenesis, changes in brain structure and function, heredity factors, environmental milieu, and epigenetics[6]. Epigenetics, a field focusing on gene-environment interactions, has gained attention over the past decades. The recent application of microarray-based genome-wide expression analysis has enabled the identification of MDD-associated genes, including novel ncRNAs. Although numerous studies have demonstrated that ncRNAs play important roles in MDD pathogenesis, the mechanisms of how these genes regulate MDD have not been well-characterized[14, 15]. Thus, we performed ceRNA network analysis by data mining to determine the potential regulatory mechanisms of MDD.

Multiple GO terms were identified in enrichment analysis, reflecting the complexity of the disorder. We observed that protein-coding genes in the network were highly correlated with cellular growth and developmental differentiation, including the activin receptor signaling pathway, peripheral nervous system development, G protein-coupled receptor internalization, receptor-ligand activity, hormone

Table 1 The twenty differentially expressed long noncoding RNAs and differentially expressed_microRNA pairs identified in this study

lncRNA	miRNA
STAG3L4	hsa-miR-4465
MTERFD2	hsa-miR-4465
TCL6	hsa-miR-4465
MDS2	hsa-miR-4465
LINC00202	hsa-miR-4465
LINC00402	hsa-miR-4465
TCL6	hsa-miR-137
ANKRD36BP2	hsa-miR-137
LINC00202	hsa-miR-137
LINC00402	hsa-miR-137
MIR600HG	hsa-miR-137
MTERFD2	hsa-miR-125b-5p
HCG4	hsa-miR-125b-5p
TCL6	hsa-miR-125b-5p
UBE2Q2P2	hsa-miR-125b-5p
TREML2P1	hsa-miR-125b-5p
KIAA0125	hsa-miR-125b-5p
ANKRD36BP2	hsa-miR-125b-5p
LINC00202	hsa-miR-125b-5p
MIR600HG	hsa-miR-125b-5p

lncRNA: Long noncoding RNA; miRNA: microRNA.

activity, growth factor activity, and cellular growth. The term "signaling by activins" in our results is consistent with previous studies showing that activin can modulate depression and anxiety-related behavior[16-21]. Activins are members of the transforming growth factor-β superfamily that are expressed in various tissues, including neuronal cells, and are involved in proliferation, differentiation, metabolism, homeostasis, apoptosis, immune response, and tissue repair. Postnatal neurogenesis, which leads to the production of new neurons in the adult brain, can influence the replacement of damaged neurons, stress responses, memory formation, and depression, among others[22]. Previous studies have reported that the activin activity in the adult forebrain influences locomotor activity, anxiety-related behavior, and hippocampal neurogenesis, which is also associated with age-related cognitive decline [23]. Additionally, consistent with our results, utilizing a genome-wide association study, Smeeth *et al* [23] suggested a complex relationship among reproductive hormones, hippocampal neurogenesis, and depression. Based on transcriptome array results analysis of Chinese patients with MDD, Liu *et al*[12] reported the enrichment of differentially expressed coding genes in the signal transduction pathway and basic metabolic process associated with neurodevelopmental disease[12,13]. Our KEGG results also showed that the mTOR signaling pathway is a part of the regulatory network of MDD. This agrees with previous studies which showed that the mTOR signaling pathway, which senses and integrates diverse extracellular stimuli to promote cellular growth or limit catabolic processes, contributes to normal neuronal growth and is associated with neurogenesis[24]. Notably, the mTOR signaling pathway has become an important target for treating depression using drugs such as ketamine[25,26].

The use of ncRNAs as biomarkers of psychological disorders is gaining momentum. In the ceRNA network developed in this study, there were 12 lncRNAs, 3 miRNAs, and 33 mRNAs specific to MDD. Consistent with our results, hsa-mir-137, as a brain-enriched miRNA, was earlier confirmed as a gene related to MDD, bipolar disorder, schizophrenia, and Parkinson's disease susceptibility[27-30], whose underlying mechanisms regulate synaptic plasticity. Moreover, Zhao *et al*[31] detected significantly lower hsa-miR-137 Levels in the brain and peripheral blood in post-stroke depression rats, and Kim *et al* [32] found that it can be used as a diagnostic marker for methamphetamine withdrawal syndrome. Similarly, hsa-miR-125b-5p in the peripheral blood is highly expressed in Alzheimer's disease compared with that in controls.

Table 2 The forty-three differentially expressed_mRNAs and differentially expressed microRNA pairs identified in this study

miRNA	mRNA
hsa-miR-4465	FAM98B
hsa-miR-4465	ADM
hsa-miR-4465	INHBB
hsa-miR-4465	FA2H
hsa-miR-4465	HOXA9
hsa-miR-4465	GRB10
hsa-miR-4465	UGT8
hsa-miR-4465	ACVR1C
hsa-miR-4465	COL19A1
hsa-miR-4465	TTC28
hsa-miR-4465	HAS3
hsa-miR-4465	SLC22A23
hsa-miR-4465	ADAM23
hsa-miR-4465	NACC2
hsa-miR-4465	SH3PXD2A
hsa-miR-4465	CELSR1
hsa-miR-4465	PLEKHG1
hsa-miR-4465	ZSWIM5
hsa-miR-137	AKAP2
hsa-miR-137	HLF
hsa-miR-137	FGF9
hsa-miR-137	GLIS2
hsa-miR-137	SIPA1L2
hsa-miR-137	WNT7A
hsa-miR-137	NRG1
hsa-miR-137	ADAM23
hsa-miR-137	LRRC4
hsa-miR-137	SLC22A23
hsa-miR-137	COL19A1
hsa-miR-137	TTC28
hsa-miR-137	APLN
hsa-miR-137	NACC2
hsa-miR-137	BACH2
hsa-miR-137	ACVR1C
hsa-miR-125b-5p	NIPAL4
hsa-miR-125b-5p	NR6A1
hsa-miR-125b-5p	ZSWIM5
hsa-miR-125b-5p	GALNT14
hsa-miR-125b-5p	GRB10
hsa-miR-125b-5p	ELOVL4
hsa-miR-125b-5p	ACVR1C

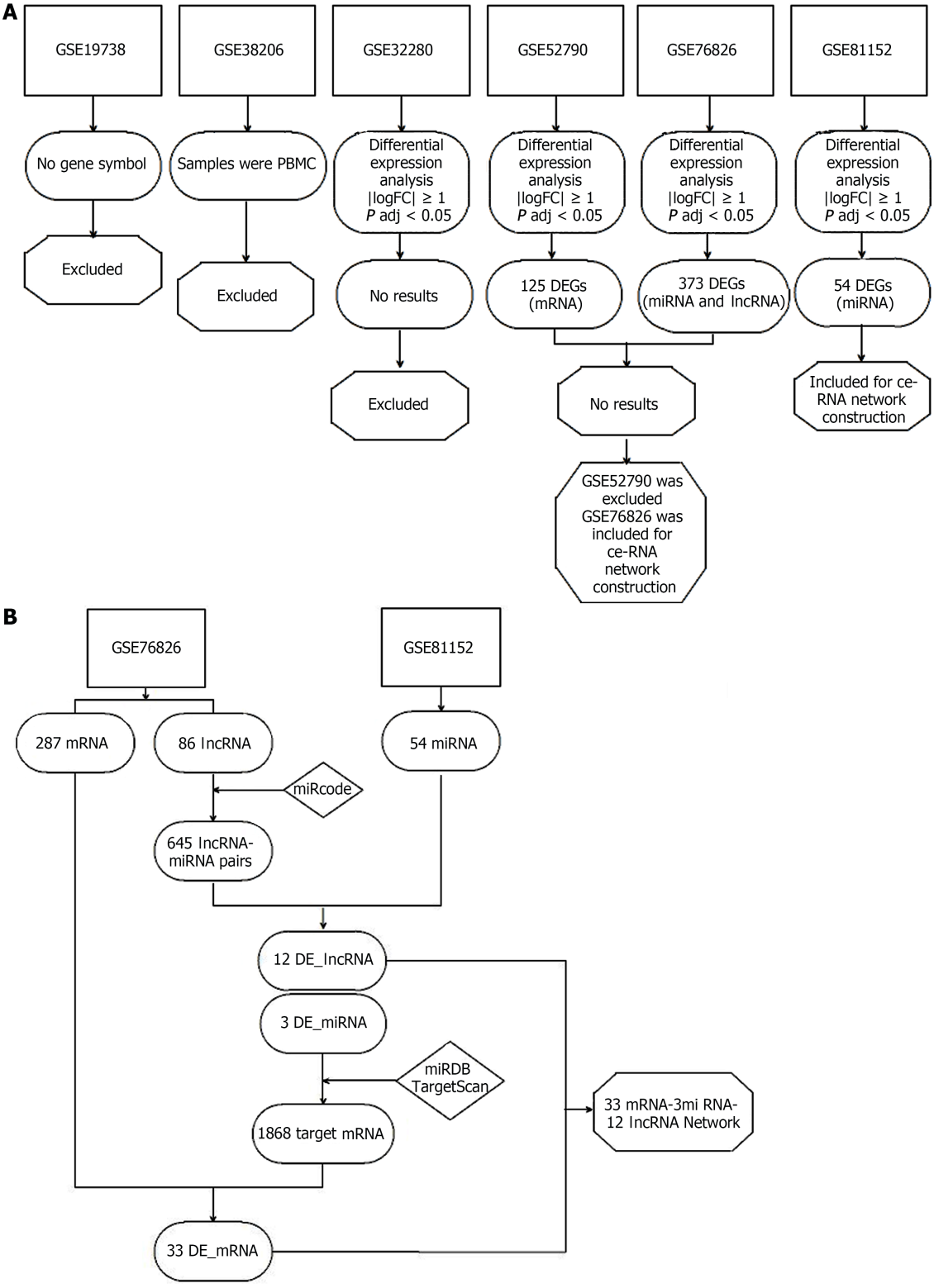
hsa-miR-125b-5p	RALGPS2
hsa-miR-125b-5p	GLIS2

FA2H: Fatty acid 2-hydroxylase.

Table 3 The significant Gene Ontology terms identified in this study

Category	Term description	Count of genes	*P* value
Biology process	Activin receptor signaling pathway	3	5.54E-05
Biology process	Peripheral nervous system development	3	0.000292
Biology process	G protein-coupled receptor internalization	2	0.0003
Biology process	Desensitization of G protein-coupled receptor signaling pathway	2	0.000487
Biology process	Negative adaptation of signaling pathway	2	0.000487
Biology process	Positive regulation of vascular endothelial growth factor receptor signaling pathway	2	0.000487
Biology process	Adaptation of signaling pathway	2	0.000597
Biology process	Uterus development	2	0.000656
Biology process	Sphingolipid biosynthetic process	3	0.000679
Biology process	Reproductive structure development	5	0.00078
Cellular component	Glutamatergic synapse	4	0.002395
Cellular component	Schaffer collateral-CA1 synapse	2	0.00786
Cellular component	Cul2-RING ubiquitin ligase complex	1	0.024149
Cellular component	Integral component of synaptic membrane	2	0.025933
Cellular component	Intrinsic component of synaptic membrane	2	0.029786
Cellular component	Extracellular matrix	3	0.044750
Cellular component	Podosome	1	0.047732
Cellular component	Excitatory synapse	1	0.075303
Cellular component	Integral component of postsynaptic density membrane	1	0.079823
Cellular component	Intrinsic component of postsynaptic density membrane	1	0.084321
Molecular function	Receptor ligand activity	6	0.000191
Molecular function	Hormone activity	3	0.001352
Molecular function	UDP-glycosyltransferase activity	3	0.002314
Molecular function	Guanyl-nucleotide exchange factor activity	4	0.002772
Molecular function	Growth factor activity	3	0.003326
Molecular function	Transferase activity, transferring hexosyl groups	3	0.006074
Molecular function	Phosphatidylinositol-4,5-bisphosphate 3-kinase activity	2	0.006746
Molecular function	Cytokine activity	3	0.007189
Molecular function	Phosphatidylinositol bisphosphate kinase activity	2	0.007334
Molecular function	Transcription factor activity, RNA polymerase II proximal promoter sequence-specific DNA binding	4	0.008356

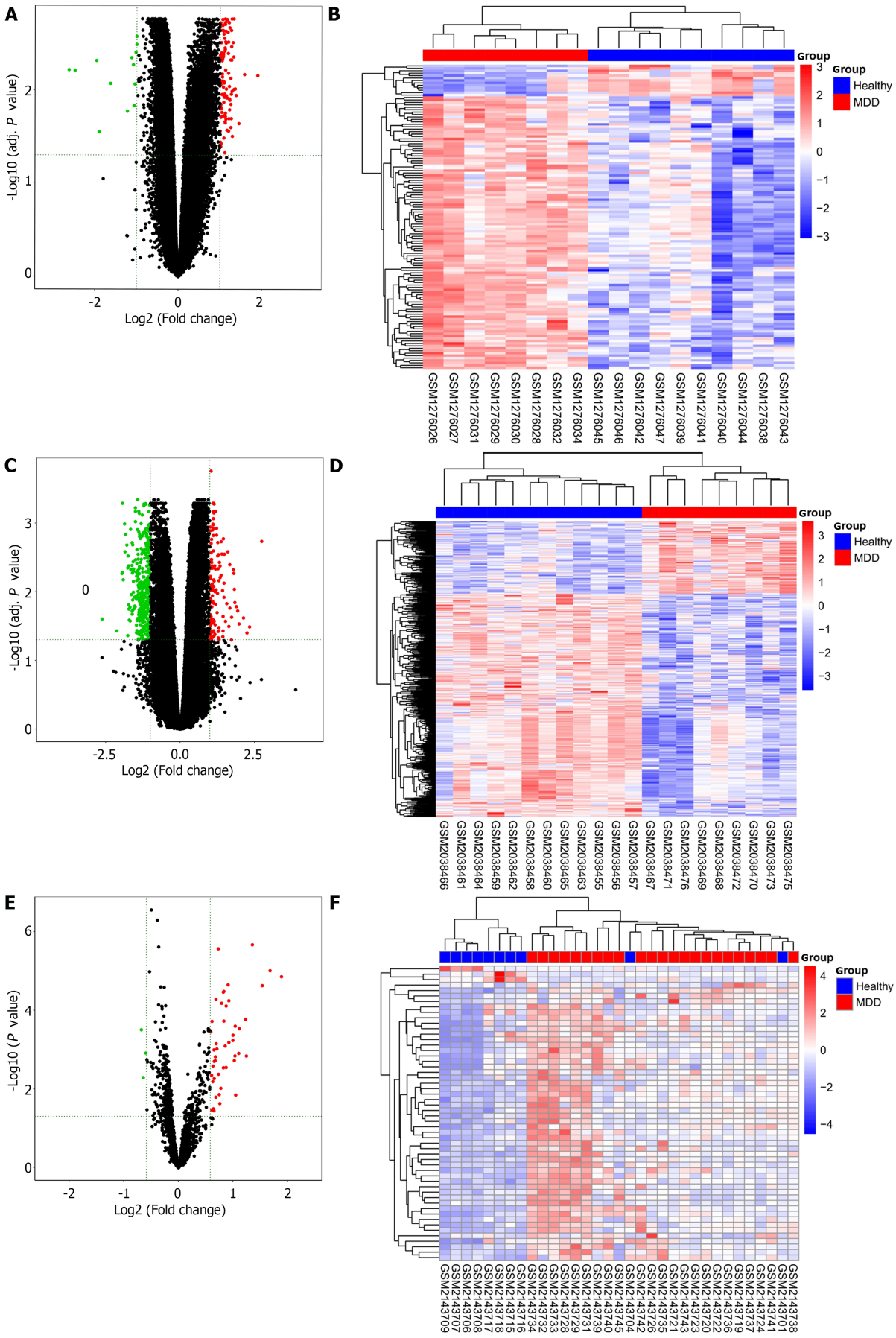
In addition to genetic components, different epigenetic mechanisms play an important role in the occurrence and development of MDD. A previous study revealed that the non-protein-coding RNA repressor of NFAT, human accelerated region 1, transcribed antisense of rheelin, and B-secretase-1 are associated with cognitive function, potentially contributing to MDD, and the lncRNA BDNF-AS was reportedly related to synaptic plasticity and potentially associated with MDD[33-36]. In a recent study, Abedpoor and colleagues reported that the lncRNA network could play an indispensable role in regulating depression-like behaviors in mice[37]. Furthermore, two studies reported lower RMRP expression in a mouse model of depression and MDD relative to normal subject samples[14]. In another



DOI: 10.5498/wjp.v13.i2.36

Figure 1 Flowchart of the study. A: Step 1, dataset screening; B: Step 2, competing endogenous RNA network construction. DEGs: Differentially Expressed Genes; mRNA: Messenger RNA; miRNA: MicroRNA; lncRNA: Long non-coding RNA; ceRNA: Competing endogenous RNAs; miRcode: http://www.mircode.org/; miRDB: http://mirdb.org/; TargetScan: http://www.targetscan.org/vert_72/; DE_mRNA: Differentially expressed mRNA; DE_lncRNA: Differentially expressed lncRNA; DE_miRNA: Differentially expressed miRNA.

study, Issler *et al*[38] observed that LINC00473 was downregulated in the prefrontal cortex of depressed females. Collectively, these results suggest that lncRNAs are potential diagnostic and prognostic biomarkers. Our results revealed 12 different lncRNAs involved in the MDD ceRNA network, suggesting the existence of a regulatory network in MDD.



DOI: 10.5498/wjp.v13.i2.36

Figure 2 Difference and cluster analyses. A: Volcanic maps of differentially expressed genes in GSE52790; B: Cluster analysis heatmap of the expression patterns of the differentially expressed genes in GSE52790; C: Volcanic maps of differentially expressed genes in GSE76826; D: Cluster analysis heatmap of the

expression patterns of the differentially expressed genes in GSE76826; E: Volcanic maps of differentially expressed genes in GSE81152; F: Cluster analysis heatmap of the expression patterns of the differentially expressed genes in GSE81152. Red indicates upregulated genes; green indicates downregulated genes.

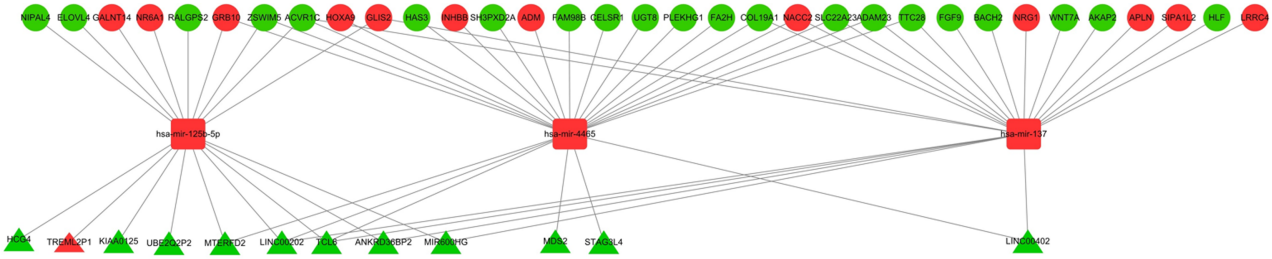


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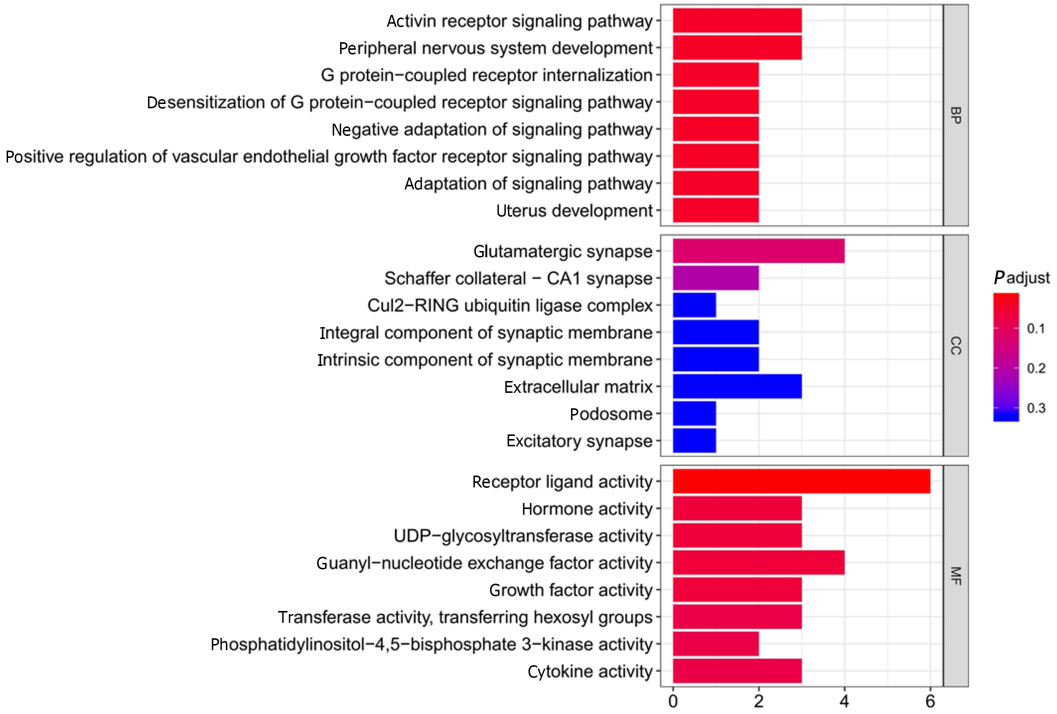
Figure 3 Major depressive disorder-associated enriched competing endogenous RNA network. Red and green indicate upregulated downregulated genes, respectively. The circles represent differentially expressed RNA (DE_RNA), triangles represent DE long noncoding RNA (DE_lncRNA), and rounded squares represent DE_microRNA.



DOI: 10.5498/wjp.v13.i2.36

Figure 4 Gene Ontology functional enrichment analysis.

In the present study, FA2H was highlighted in the PPI network. FA2H encoded by *FA2H* is highly expressed in the human brain and is involved in the formation of 2-hydroxy galactosylceramides and 2-hydroxy sulfatides in myelin[39,40]. The FA2H gene appears to be related to lipid metabolism and is one of the 10 candidate genes identified in an inherited neurologic disorder known as neurodegeneration with brain iron accumulation and is also involved in hereditary spastic paraplegia SPG35 and leukodystrophy[41,42]. Mutations in FA2H have been identified in autism spectrum disorders[43]. The function of FA2H does not appear to be limited to the brain since elevated FA2H expression has also been found in hepatocellular carcinoma and lung adenocarcinoma involving UGT8[44,45]. However, there have been no reports of FA2H in MDD and thus, this is the first study to suggest that FA2H is related to MDD. Considering its role in myelin formation, this gene may contribute to MDD pathogenesis *via* impacting neurological development and modulating signal transduction.

Elongation of very long-chain fatty acids-4 (ELOVL4) was another protein of interest identified in the PPI. This protein is essential for the synthesis of very long-chain polyunsaturated (VLC-PUFA) and saturated fatty acids (VLC-SFA) of chain lengths greater than 26 carbons[46]. The VLC-PUFAs play an important role in maintaining neural tissue homeostasis. Studies have suggested that dysregulated

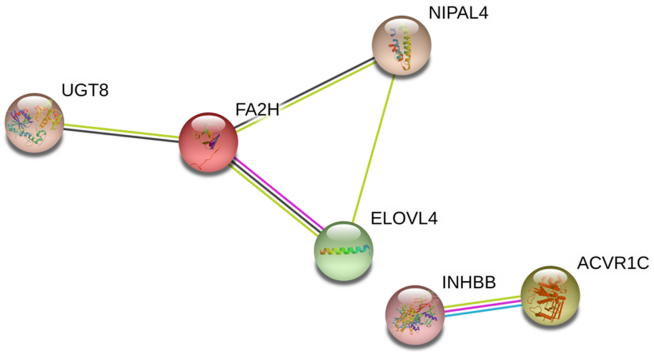


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Figure 5 Protein interaction network construction. FA2H: Fatty acid 2-hydroxylase.

ELOVL4 expression may be involved in the lipid alterations observed in neuroblastoma, and mutations in the ELOVL4 gene could cause several distinct neurodegenerative diseases, including stargardt-like macular dystrophy, spinocerebellar ataxia 34, and a neuro-ichthyotic syndrome with severe seizures and spasticity[47,48]. However, like FA2H, none of the studies so far have linked ELOVL4 and MDD, and therefore, future validation benchmark experiments are needed.

There were some limitations to our study. The potentially important genes associated with MDD lack gene expression and functional validation, and hence, further *in vivo* and *in vitro* studies are required. Furthermore, the two datasets were not from the same platform, which may have resulted in a few deviations. However, the present study provides novel insight into MDD pathogenesis.

CONCLUSION

To date, MDD diagnosis mainly depends on the patient's subjective expression, which may be misinterpreted by clinicians. Therefore, identification of a reliable biomarker that can be used to diagnose MDD and guide its treatment is imperative. In conclusion, the present study revealed that hsa-miR-4465, hsa-miR-137, and hsa-miR-125b-5p may be useful genetic biomarkers for MDD as they are potentially involved in the neurogenesis and neuroplasticity pathways in MDD. These results require further validation in future studies.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) is a common and serious mental illness. Many novel genes in MDD have been characterized by high-throughput methods such as microarrays or sequencing. Recently, noncoding RNAs (ncRNAs) were suggested to be involved in the complicated environmental-genetic regulatory network of MDD occurrence.

Research motivation

The interplay among RNA species, including protein-coding RNAs and ncRNAs, in MDD remains unclear.

Research objectives

To investigate the RNA expression datasets and construct a network based on differentially expressed long noncoding RNA (lncRNAs), miRNAs, and mRNAs between MDD and controls through data mining method.

Research methods

Gene expression data were searched and downloaded from NCBI Gene Expression Omnibus database. Six array datasets from humans were related to the search term: GSE19738, GSE32280, GSE38206, GSE52790, GSE76826, and GSE81152. These datasets were processed for initial assessment and subjected to quality control and differential expression analysis. Differentially expressed lncRNAs, miRNAs, and mRNAs were determined, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were performed, and protein-protein interaction network was generated. The results were analyzed for their association with MDD.

Research results

After analysis, 3 miRNAs, 12 lncRNAs, and 33 mRNAs were identified in the ceRNA network. Two of these miRNAs were earlier shown to be involved in psychiatric disorders, and differentially expressed mRNAs were found to be highly enriched in pathways related to neurogenesis and neuroplasticity as per Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses. The expression of hub gene fatty acid 2-hydroxylase was enriched, and the encoded protein was found to be involved in myelin formation, indicating that neurological development and signal transduction are involved in MDD pathogenesis.

Research conclusions

The present study presents candidate ncRNAs involved in the neurogenesis and neuroplasticity pathways related to MDD.

Research perspectives

Bioinformatic data mining method can be an cost-effective way to explore potential biomarkers for complicated diseases. However, benchmark experiment is needed in the future to validate the results.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Relationship between family cohesion/adaptability and postpartum depressive symptoms: A single-center retrospective study

Guo-Rong Zhang, Peng-Sheng Li, Yan-Bin Jia

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Abstract

BACKGROUND

Depression is the most common mental illness in postpartum mothers, and the etiology of postpartum depression remains poorly understood. Over the past several decades, studies have reported that postpartum depression is caused by multiple factors, such as genetic, psychological, pregnancy, and environmental factors, with the family environment being an important environmental factor. The theory of family cohesion and adaptability put forward by Olson is a classic model that describes the level of family function. However, to date, this model has not been examined regarding its applicability to patients with postpartum depression.

AIM

To investigate the relationship between family cohesion and adaptability and the risk of postpartum depressive symptoms.

METHODS

We retrospectively analyzed 1446 patients admitted to the postpartum healthcare clinic of the Affiliated Foshan Maternity and Child Healthcare Hospital from April 2021 to December 2021. Patients were grouped according to whether postpartum depression symptoms were reported (symptoms, n = 454; no symptoms, n = 992). All patients completed the Edinburgh Postpartum Depression Scale and the Chinese version of the Family Cohesion and Adaptability Assessment Scale II. Baseline and clinical data were compared between groups. Univariate regression analysis was used to investigate the association between different types of family cohesion and postpartum depressive symptoms and the association between different family adaptability types and postpartum

depressive symptoms.

RESULTS

After adjusting for age, education, occupation, gravidity, parity, and mode of delivery, disengaged [adjusted odds ratio (AOR) = 3.36, 95%CI: 1.91–5.91], and separated (AOR = 1.97, 95%CI: 1.34–2.90) family cohesion types showed a higher risk of postpartum depression than the connection type, whereas the enmeshed type (AOR = 0.38, 95%CI: 0.28–0.51) protected against postpartum depressive symptoms. Rigid (AOR = 4.41, 95%CI: 3.02–6.43) and structured families (AOR = 1.88, 95%CI: 1.34–2.63) had a higher risk of postpartum depressive symptoms than flexible families, whereas chaotic families (AOR = 0.35, 95%CI: 0.24–0.51) protected against postpartum depressive symptoms.

CONCLUSION

Family cohesion and adaptability are influencing factors for postpartum depressive symptoms, with higher family cohesion and adaptability being associated with a lower risk of postpartum depressive symptoms.

Key Words: Family cohesion; Adaptability; Postpartum depressive symptoms; Cross-sectional study

Core Tip: Postpartum depression is the most common mental illness in postpartum mothers; studies have reported that postpartum depression is caused by multiple factors. This study analyzed the family environments of 1446 postnatal women, showing that high family cohesion and adaptability prevented the development of postpartum depressive symptoms. Further, we observed a linear relationship between family cohesion, adaptability, and postpartum depressive symptoms, where higher family cohesion and adaptability scores were associated with a risk of postpartum depressive symptoms.

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INTRODUCTION

Postpartum depression is the most common mental illness in postpartum mothers. In high-income countries, more than 10% of postpartum women experience postpartum depression, and the prevalence is higher in low-income countries[1,2]. Postpartum depression is a leading cause of death for postpartum women, and numerous studies have suggested that postpartum depression in mothers affects the developmental processes of their children, including cognitive and language delays, behavioral problems, unsafe attachment, decreased academic performance, and increased risk of depression in adulthood[3,4]. Postpartum depression places heavy burdens on families and society. Therefore, early detection and intervention of postpartum depressive symptoms are crucial for prevention and treatment.

The etiology of postpartum depression remains poorly understood. Over the past several decades, studies have reported that postpartum depression is caused by multiple factors, such as genetic, psychological[5], pregnancy[6], and environmental factors[7-10]. Guan *et al*[11] found that a poor family environment contributes to the development of postpartum depression, and family communication, emotional responses, and other related factors influence the development of postpartum depression. A study conducted in Japan found that women who live with family members who have a high level of perception and participate in parenting have a low risk of postpartum depression[12]. In addition, Kızılırmak reported a significant negative correlation between Edinburgh Postnatal Depression Scale (EPDS) scores and the total scores for spousal, emotional, social, and physical support in postpartum women[13]. In terms of marital satisfaction, pregnant women who are unsatisfied with the quality of their marriage are more likely to suffer from postpartum depression[14]. A large retrospective study on the correlation between postpartum depression and domestic violence among Asian mothers found that women who experience domestic violence from their partners are at high risk of developing postpartum depression. Moreover, violence and intimidation by other family members are associated with the incidence of postpartum depression, and domestic violence increases the risk of suicidal ideation in patients with postpartum depression[15].

The theory of family cohesion and adaptability put forward by Olson is a classic model that describes the level of family function[16,17]. Family cohesion reflects the robustness of family members' emotional ties and refers to the ability of family members to support each other, unite, and overcome difficulties when dealing with family difficulties. Family adaptability reflects the flexibility of families to deal with changes and is based on the ability to change family power structures or roles in the process of family development. However, to date, this model has not been examined regarding families of patients with postpartum depression. In this study, we conducted a cross-sectional survey among postpartum women in China to explore the effects of family cohesion and adaptability on postpartum depressive symptoms and provide a reference for treatment.

MATERIALS AND METHODS

Participants

We retrospectively analyzed 1446 patients admitted to the postpartum healthcare clinic of the Affiliated Foshan Maternity and Child Healthcare Hospital from April 2021 to December 2021. According to whether postpartum depression symptoms were reported, patients were divided into a postpartum depression symptoms group and a no postpartum depression symptoms group. The inclusion criteria were: (1) Postpartum women of Han ethnicity (self-reported) in China aged 18–45 years; (2) no cognitive, intellectual, or behavior disorders; (3) voluntary participation in the study and ability to independently complete the questionnaires; (4) no serious complications during pregnancy and childbirth and no postpartum child death; and (5) an Apgar score of 8–10. The exclusion criteria were: (1) Postpartum women with major traumatic stress events in the last month, such as spouse death, divorce, and domestic violence; (2) severe or unstable somatic disease; and (3) previous diagnosis of schizophrenia, depression (including postpartum depression), bipolar disorder, obsessive-compulsive disorder, generalized anxiety disorder, panic attacks, or epilepsy.

Postpartum depressive symptoms

The EPDS was used to measure postpartum depressive symptoms. The EPDS was developed in 1987 and is used specifically for screening for postpartum depression. The scale has good reliability and validity. The total score of the scale ranges from 0 to 30, where a higher score indicates greater severity of depression. The Chinese version of the EPDS has been shown to have good reliability and validity [18]. In the Chinese version, the demarcation of depressive symptoms is divided into nine points.

Family adaptability and cohesion

Family cohesion and adaptability were measured using the Family Cohesion and Adaptability Scale (FACES II-CV). FACES II-CV was developed by Olson in 1982 and translated into Chinese by Fei *et al* [19]. The scale evaluates the cohesion and adaptability of families across a total of 30 items, which are scored on a 5-point Likert scale. A higher score indicates better family cohesion and adaptability. Family cohesion is divided into four types based on the total subscale score: disengaged (< 55.9), separated (55.9–63.9), connected (63.9–71.9), and enmeshed (> 71.9). Family adaptability is divided into four types: rigid (< 44.7), structured (44.7–50.9), flexible (50.9–57.1), and chaotic (> 57.1). We only used the section on actual family status, and Cronbach's alpha for this section was 0.93.

Covariates

Age[20], occupation[20], education[21], mode of delivery[22,23], gravidity, and parity[24] have previously been reported to be associated with postpartum depressive symptoms. Therefore, we included them as covariates in this study. The occupation was divided into "unit head", "professional and technical personnel", "clerks", "business and service personnel", "unemployed/housewife", and "other". Educational level was defined by participants' highest level of education, and responses included "junior high school or below", "senior high school", and "college or university". The mode of delivery was divided into "vaginal delivery" and "cesarean section".

Statistical analysis

The cohesion and adaptability of women with and without postpartum depressive symptoms are represented as mean ± SD and were compared using the Student's *t*-test. Age, occupation, educational level, mode of delivery, gravidity, and parity are described using frequency and rate and were compared using χ^2 tests. Logistic regression was performed to assess the association between postpartum depressive symptoms, family cohesion, and adaptability, and odds ratios (ORs) and 95%CIs were calculated. In model 1, the associations between family cohesion, adaptability, and postpartum depressive symptoms were assessed without adjusting for covariates. Subsequently, variables that were significant in the univariate analysis or those that have been reported in previous studies as confounding factors were adjusted for in model 2. A two-tailed $P < 0.05$ was considered significant. All analyses were performed using Statistical Analysis System software (version 9.2; SAS Institute, Inc.,

Cary, NC, USA).

RESULTS

Characteristics and postpartum depressive symptoms of participants

As shown in Table 1, the age range of participants was 19–49 years, with an average age of 30 ± 4.30 years. Postpartum depressive symptoms were reported in 454 postpartum women for a prevalence rate of 31.4%. There were no significant differences between women with and without postpartum depressive symptoms in age ($\chi^2 = 2.07$, $P = 0.354$), education level ($\chi^2 = 2.65$, $P = 0.448$), mode of delivery ($\chi^2 = 0.177$, $P = 0.674$), gravidity ($\chi^2 = 4.004$, $P = 0.261$), or parity ($\chi^2 = 6.107$, $P = 0.107$). However, there was a significant difference in occupation between the two groups ($\chi^2 = 11.26$, $P = 0.046$).

Family cohesion and adaptability of postpartum women

The total scores for family cohesion and adaptability were significantly lower in the postpartum depressive symptoms group than in the group without postpartum depressive symptoms ($P < 0.001$; Table 2).

Association between different types of family cohesion and postpartum depressive symptoms

As shown in Table 3, the results of the univariate regression analysis showed that different types of family cohesion were associated with postpartum depressive symptoms (model 1, $P < 0.001$). In model 2, after adjusting for age, educational level, occupation, gravidity, parity, and mode of delivery, the disengaged type [adjusted OR (AOR) = 3.36, 95%CI: 1.91–5.91] and separated type (AOR = 1.97, 95%C: 1.34–2.90) had a higher risk of postpartum depressive symptoms than the connection type, whereas the enmeshed type (AOR = 0.38, 95%CI: 0.28–0.51) was a protective factor of postpartum depressive symptoms.

Association between different family adaptability types and postpartum depressive symptoms

The results of the univariate regression analysis showed that different family adaptability types were associated with postpartum depressive symptoms (Table 4, model 1, $P < 0.001$). After adjusting for age, educational level, occupation, gravidity, parity, and mode of delivery, rigid (AOR = 4.41, 95%CI: 3.02–6.43) and structured families (AOR = 1.88, 95%CI: 1.34–2.63) had a higher risk of postpartum depressive symptoms than flexible families, whereas chaotic families (AOR = 0.35, 95%CI: 0.24–0.51) protected against postpartum depressive symptoms.

DISCUSSION

We found that the prevalence of postpartum depressive symptoms was 31.6%, which is consistent with previous studies[15]. This indicates that postpartum depressive symptoms are an important perinatal mental health problem among. Furthermore, the levels of family cohesion and adaptability in the postpartum depressive symptoms group were significantly lower than those in the non-postpartum depressive symptoms group, which suggested that, when families are in the transition period between pregnancy and birth, high levels of cohesion and adaptability can enable family members to join forces, adjust strategies, and jointly help the mother cope with the various difficulties involved in raising children and the increase in costs. This, in turn, reduces the psychological pressure on women and lowers the risk of postpartum depressive symptoms. Previous studies have similarly found that higher family cohesion and adaptability reduce the prevalence of psychological disorders. For example, a survey conducted in 100 patients with terminal illnesses admitted to a palliative care ward in South Korea found that higher family adaptability reduced anxiety and depression in patients, whereas higher family cohesion resulted in lower rates of depression[25]. In a study of family cohesion and adaptability in youth at high clinical risk for psychosis, the youth and their mothers were reported to have lower adaptability and cohesion than their healthy control counterparts[26]. Moreover, a study on anger traits and somatization in junior college students in Shanghai, China, found that a high level of family cohesion and adaptability played a protective role, reducing the effects of anger characteristics on physical symptoms. They suggested that intervention measures that combine family cohesion, adaptive training, and depression treatment may be effective for patients with a high level of anger characteristics [27]. Taken together, we suggest that, to prevent and treat postpartum depressive symptoms, mental health workers specializing in women's mental health should focus on improving maternal family cohesion and adaptability.

Olson's theory of families, called "The Circumplex Model", suggests that family cohesion and adaptability have a curvilinear relationship with psychological and behavioral disorders. Excessively high or low cohesion and adaptability in the family are considered dysfunctional, and moderate cohesion and adaptability in the family model are regarded as beneficial[16,28]. Inadequate cohesion

Table 1 Characteristics of participants with and without postpartum depressive symptoms (*n* = 1446)

Characteristics	With postpartum depressive symptoms (*n* = 454)		Without postpartum depressive symptoms (*n* = 992)		χ^2	*P* value
	n	Percent	*n*	Percent		
Age (yr)					2.07	0.354
18–28	181	39.9	365	36.8		
29–34	217	47.8	481	48.5		
Over 35	56	12.3	146	14.7		
Educational level					2.65	0.448
Junior high school or below	67	14.8	122	12.3		
Senior high school	90	19.8	208	21.0		
College	131	28.9	315	31.8		
University and above	166	36.6	347	35.0		
Occupation					11.26	0.046
Leadership	6	1.3	26	2.6		
Professional and technical personnel	82	18.1	222	22.4		
Clerks	96	21.1	225	22.7		
Business and service personnel	107	23.6	237	23.9		
Unemployed / housewife	150	33.0	262	26.4		
Others	13	2.9	20	2.0		
Mode of delivery					0.177	0.674
Vaginal delivery	239	52.6	534	53.8		
Cesarean section	215	47.4	458	46.2		
Gravidity					4.004	0.261
1	201	44.3	389	39.2		
2	141	31.1	354	35.7		
3	71	15.6	154	15.5		
≥ 4	41	9.0	95	9.6		
Parity					6.107	0.107
1	269	59.3	521	52.5		
2	159	35.0	412	41.5		
≥ 3	26	5.7	59	6.0		

Table 2 Family cohesion and adaptability scores of postpartum women (*n* = 1446) (mean ± SD)

FACES II-CV	With postpartum depressive symptoms (*n* = 454)	Without postpartum depressive symptoms (*n* = 992)	*t* value	*P* value
Cohesion	66.78 ± 9.88	74.03 ± 8.60	14.16	< 0.001
Adaptability	48.62 ± 8.48	55.11 ± 7.39	14.77	< 0.001

FACES II-CV: Family Cohesion and Adaptability Scale.

leads to alienation and poor communication among family members, whereas excessive cohesion leads to family members lacking a sense of boundary and self-space. Furthermore, families with insufficient adaptability have more rigid family rules and an inability to adapt to environmental changes, whereas an excessive level of adaptability leads to confusion around family rules and a lack of organizational

Table 3 Association between types of family cohesion and postpartum depression (*n* = 1446)

Types of family cohesion	*n*	Rate	Model 1			Model 2		
			COR	95%CI	*P* value	AOR	95%CI	*P* value
Connected	410	28.40%	1.00			1.00		
Disengaged	78	5.40%	3.82	2.27-6.43	< 0.001	3.36	1.91-5.91	< 0.001
Separated	180	12.40%	2.03	1.42-2.89	< 0.001	1.97	1.34-2.90	< 0.001
Enmeshed	778	53.80%	0.4	0.31-0.53	< 0.001	0.38	0.28-0.51	< 0.001

Model 1: Univariate regression model, without adjusting for covariates; Model 2: Multivariate regression model, adjusted for age, occupation, educational level, gravidity, parity, and delivery mode. COR: Crude odds ratio; AOR: Adjusted odds ratio.

Table 4 Relationship between types of family adaptability and postpartum depressive symptoms (*n* = 1446)

Type of family adaptability	*n*	Rate	Model 1			Model 2		
			COR	95%CI	*P* value	AOR	95%CI	*P* value
Flexible	282	19.5%	1.00			1.00		
Rigid	428	29.6%	4.07	2.91-5.70	< 0.001	4.41	3.02-6.43	< 0.001
Structured	526	36.4%	1.83	1.35-2.48	< 0.001	1.88	1.34-2.63	< 0.001
Chaotic	210	14.5%	0.37	0.26-0.52	< 0.001	0.35	0.24-0.51	< 0.001

Model 1: Uncorrected model: univariate regression model, uncorrected confounding factors; Model 2: Corrected model: multivariate regression model, adjusted for age, occupation, education, gravidity, parity, and mode delivery. COR: Crude odds ratio; AOR: Adjusted odds ratio.

guidance, which is not conducive to the physical or mental health development of family members[29]. However, this model has also been questioned and criticized by some scholars, and several studies have reported inconsistent results. In a study conducted in South Korea on the correlation between adolescent behavioral problems and family cohesion and adaptability, results showed that the relationship between family cohesion, adaptability, and adolescent behavioral problems was linear rather than curvilinear. The study found that higher scores of family cohesion and adaptability were associated with a lower incidence of adolescent behavioral problems[30]. In addition, in a study on the relationship between psychological stress and family cohesion and adaptability in infertile couples, results showed that the relationship between family cohesion, adaptability, and psychological stress was also linear rather than curvilinear. They found that higher scores of family cohesion and adaptability were associated with less psychological pressure in couples with infertility[31].

We observed a linear relationship between family cohesion, adaptability, and postpartum depressive symptoms, where higher family cohesion and adaptability scores were associated with a lower risk of postpartum depressive symptoms. We speculate that this difference is related to the specific physiological stage of the postpartum period. Postpartum women often have poor self-functioning and are dependent on their surrounding environment[32,33]. Moreover, pregnant women in China often follow the custom of "confinement"[34,35], where postpartum women are taken care of at home for one month after giving birth and are not permitted to do housework or leave the house. High levels of cohesion and adaptability enable family members to offer crucial help to pregnant women, reducing psychological pressure and preventing the development of postpartum depression. The present findings are in line with the abovementioned studies. The findings here of a linear relationship rather than a curvilinear relationship between family cohesion, adaptability, and psychological and behavioral disorders may be related to the study population. Previous studies reporting curvilinear relationships were mainly conducted in general populations[16,36], whereas those reporting linear relationships were mainly focused on specific groups, such as adolescents, couples with infertility, and postpartum women. These groups often have weaker self-functioning and high dependence on their external environment and require significant support from their families to meet their needs to maintain psychological balance and prevent psychological and behavioral problems.

Limitations

The sample size of the present study was large, and we controlled for potential confounding factors. For example, interviews were conducted in the hospital by trained nurses, and a scale specifically developed for speakers of Mandarin was used for assessment, which offered reliability of the results.

However, the study also had limitations. For example, this was a single-center study. Furthermore, we used the EPDS to assess depressive symptoms without using the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) interviews to confirm diagnoses of depression. Indeed, research has suggested that self-reporting methods produce higher EPDS scores[37]. In addition, although we adjusted for several confounding factors, we did not control for other factors related to postpartum depressive symptoms, such as breastfeeding[38-40], intimate partner violence[5,15], and marital relationships[41,42]. We aim to include these factors in future studies using a hierarchical approach.

CONCLUSION

The present research showed that high family cohesion and adaptability prevented the development of postpartum depressive symptoms. For familial treatment of postpartum depression, family therapists may need to consider the physical and mental characteristics, customs, and cultures of postpartum women and appropriately adjust and enhance family cohesion and adaptability as much as possible to help prevent pregnant women from developing postpartum depression.

ARTICLE HIGHLIGHTS

Research background

Postpartum depression is the most common mental illness of mothers after childbirth, and the family environment is an important environmental factor affecting postpartum depression. Olson's theory of family cohesion and adaptability is a classic model to describe the level of family function. However, this model has not been tested in families of patients with postpartum depression.

Research motivation

The main focus was to explore the relationship between family cohesion/adaptability and postpartum depression symptoms. The key problem to be solved was how to investigate family cohesion and adaptability and postpartum depression symptoms and how to study the relationship between them. This research has great significance for future explorations into reducing the risk of postpartum depression.

Research objectives

The purpose of this study was to explore the relationship between family cohesion and adaptability and the risk of postpartum depressive symptoms.

Research methods

The clinical data of 1446 postpartum women with and without depressive symptoms were analyzed retrospectively. The Edinburgh Postpartum Depression Scale and the Chinese version of the Family Cohesion and Adaptability Scale II were used to evaluate depressive symptoms and family cohesion, respectively. Univariate regression analysis was used to evaluate the correlation between family cohesion and postpartum depression symptoms.

Research results

The prevalence of depression in postpartum women was 31.4%, and the family cohesion scores of this population were low. Univariate regression analysis showed that the risk of postpartum depression in detached and separated families was higher than that in connected families, while cohesion was a protective factor for postpartum depression. In addition, rigid and structured families had a higher risk of postpartum depression than flexible families, while chaotic families could prevent postpartum depression.

Research conclusions

This study showed that the prevalence of depression in postpartum women was 31.4%, and the family cohesion scores of this group were low. The higher the scores of family cohesion and adaptability, the lower the risk of postpartum depressive symptoms. Disordered families and cohesive families can prevent postpartum depression.

Research perspectives

Future research should investigate differences in family cohesion and adaptability in different types of families and their influence on postpartum depression according to the age, education, and the annual income of postpartum women.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Development of a protocol for videoconferencing-based exposure and response prevention treatment of obsessive-compulsive disorder during the COVID-19 pandemic

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Abstract

BACKGROUND

The existing literature indicates that psychotherapeutic treatment, especially exposure and response prevention (ERP) is efficacious in treating obsessive-compulsive disorder (OCD). The coronavirus disease 2019 pandemic adversely impacted many patients with OCD and disrupted their usual treatment. Moreover, the pandemic forced a global switch to telemental health (TMH) services to maintain the standards and continuity of care. Consequently, clinicians are increasingly using TMH-based psychotherapeutic treatments to treat OCD. However, several challenges have made it difficult for them to implement these treatments in the changed circumstances imposed by the pandemic.

AIM

To describe the formulation, implementation, feasibility, and usefulness of videoconferencing-based ERP (VC-ERP) treatment for OCD during the coronavirus disease 2019 pandemic.

METHODS

This prospective, observational study was conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (July 2020-June 2021). All patients with OCD were assessed using the home-based TMH services of the department. The VC-ERP protocol for OCD was the outcome of weekly Zoom meetings with a group of clinicians involved in administering the treatment. After a systematic evaluation of the available treatment options, an initial protocol for delivering VC-ERP was developed. Guidelines for clinicians and educational materials for patients and their families were prepared. The protocol was implemented among patients with OCD attending the TMH services, and their progress was monitored. The weekly meetings were used to upgrade the protocol

to meet the needs of all stakeholders. Feasibility and efficacy outcomes were examined.

RESULTS

All patients were diagnosed with OCD as a primary or a comorbid condition according to the International Classification of Diseases, 10th version criteria. Out of 115 patients who attended the services during the study period, 37 were excluded from the final analysis. Of the remaining 78 patients, VC-ERP was initiated in 43 patients. Six patients dropped out, and three were hospitalized for inpatient ERP. Eleven patients have completed the full VC-ERP treatment. One patient completed the psychoeducation part of the protocol. VC-ERP is ongoing in 22 patients. The protocol for VC-ERP treatment was developed and upgraded online. A large proportion of the eligible patients (n = 34/43; 79%) actively engaged in the VC-ERP treatment. Drop-out rates were low (n = 6/43; 14%). Satisfaction with the treatment was adequate among patients, caregivers, and clinicians. Apart from hospitalization in 3 patients, there were no other adverse events. Hybrid care and stepped care approaches could be incorporated into the VC-ERP protocol. Therefore, the feasibility of VC-ERP treatment in terms of operational viability, service utilization, service engagement, need for additional in-person services, frequency of adverse events, and user satisfaction was adequate. The VC-ERP treatment was found to be efficacious in the 11 patients who had completed the full treatment. Significant reductions in symptoms and maintenance of treatment gains on follow-up were observed.

CONCLUSION

This study provided preliminary evidence for the feasibility and usefulness of VC-ERP in the treatment of OCD. The results suggest that VC-ERP can be a useful option in resource-constrained settings.

Key Words: Videoconferencing; Exposure and response prevention; Obsessive-compulsive disorder; Telemedicine; COVID-19

Core Tip: The coronavirus disease 2019 pandemic adversely impacted many patients with obsessive-compulsive disorder (OCD), compelling clinicians to increasingly use telemental health-based options rather than conventional psychotherapeutic treatments for OCD. This study described the implementation of a videoconferencing-based exposure and response prevention treatment protocol developed by an online group of clinicians during the pandemic. On prospective follow-up, 34 patients had either completed or were undergoing the treatment. The preliminary results showed that videoconferencing-based exposure and response prevention was a feasible and efficacious mode of treatment and may be a useful option for OCD, even in low-resource settings.

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INTRODUCTION

The existing literature regarding the treatment of obsessive-compulsive disorder (OCD) indicates that exposure and response prevention (ERP) or cognitive behavior therapy (CBT) that includes ERP is more effective in treating OCD than any other control or active psychotherapeutic treatment[1-5]. Moreover, the evidence also suggests that ERP is more efficacious than medication treatment of OCD, and the gains from treatment last longer. Nevertheless, combined treatment with medications and psychotherapy is more effective for severe OCD and is commonly used in routine clinical practice. However, despite the availability of evidence-based and effective psychotherapeutic treatments, very few patients have ready access to them. The rates of treatment-seeking are low among patients due to poor awareness, stigma, and inadequate engagement. The provision of ERP is also hampered by the shortage of professionals trained in administering ERP and skepticism among clinicians about ERP. Other hurdles include the longer duration and greater costs of ERP and the need to travel long distances for treatment. It has been proposed that telemental health (TMH) treatments may help in overcoming many

of these limitations of conventional ERP[3,4,6-8].

TMH-based psychotherapy has been used to treat OCD for more than three decades[6-10]. The older forms of such TMH treatments for OCD included computerized CBT and telephone-based CBT with or without therapist support. These methods were followed by videoconferencing-based ERP (VC-ERP) or CBT, with the earliest trials of these interventions starting to appear by the 1990s. The latest development in this field has been the advent of online psychotherapeutic interventions including internet-based CBT, web-based self-help groups, virtual reality-based ERP, and smartphone-based interventions. The existing evidence shows that TMH-based ERP/CBT for OCD leads to significant symptom reduction and improved functioning[9,11-14]. Treatment gains are often maintained for several months[8,9,11-13]. These treatments are feasible, acceptable, and cost-effective[8,10,12,14,15]. There appears to be no difference in efficacy between the TMH-based and in-person treatments[6,9,11,13,14], but this is not a consistent finding[7,8,10,16]. However, the evidence for these findings is relatively scarce and hampered by methodological inadequacies among the constituent studies[7,8,11,13,14]. Moreover, there are concerns about technological obstacles such as connectivity, safety, privacy, and confidentiality[7,10,17]. Lastly, clinicians are particularly dissatisfied with the inadequate treatment alliance and dropouts in TMH treatments[6,9,16].

The onset of the coronavirus disease 2019 pandemic negatively affected many patients with OCD[18-21]. There was an increase in patients with new-onset OCD and exacerbation of symptoms in those already suffering from OCD. However, studies have differed in their estimation of the impact of the pandemic on OCD. It seems that around two-thirds of the patients have been unaffected, whereas about one-third of patients have worsened[22]. The delivery of in-person ERP was also adversely affected because of the disruption in mental health services during the pandemic. While some studies found that ERP services were curtailed or that clinicians found it difficult to adapt to the changed circumstances[19,23], others reported no difference between the pre-pandemic and post-pandemic phases[22]. Nevertheless, the forced switch to TMH-based services during the pandemic in several countries[24] has meant that many clinicians are using TMH-based rather than conventional ERP for OCD[22,23,25].

A major lacuna in the existing literature on TMH-based psychotherapy for OCD is that most of the studies have been conducted in Western countries[13,14]. This applies to studies of internet-based CBT, VC-ERP, and other online interventions. Only a few studies of these interventions from Japan[26,27], Korea[28], and the Middle East[29] could be identified. In general, research on the efficacy of TMH in the treatment of psychiatric disorders from developing countries is limited, and reviews of the subject have not included trials on TMH-based treatment of OCD[30-32]. Apart from the lack of evidence, cultural acceptability of TMH-based treatments, their efficacy, and engagement with these treatments are also quite different in these countries. The situation in India is similar. Though VC-based TMH services were used in India before the pandemic and there was an upsurge in these services during it, there were large gaps in the delivery of these services[33,34]. Controlled trials on TMH-based psychotherapy of OCD are not available. Therefore, a new beginning had to be made. This study described the formulation and implementation of VC-ERP treatment for OCD during the pandemic and its current status in terms of feasibility and usefulness.

MATERIALS AND METHODS

This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.

Setting

The VC-ERP protocol was developed in the psychiatric unit of a multi-specialty hospital in north India. Patients with OCD attending the unit were already being treated with in-person ERP mostly on an inpatient basis. Inpatient ERP was associated with good short-term outcomes, but the long-term outcomes were unclear because of the high dropout rate after discharge[35]. Similar outcomes for inpatient ERP had been reported from another Indian center[36]. The department had also been running a home-based TMH service on a smaller scale since September 2018. This service was used for VC-based follow-up of patients who had completed in-person ERP. Following the shutdown of the outpatient clinics in March 2020, the home-based TMH service was upgraded and scaled up to cater to all outpatients. The features of this service have been described elsewhere[37]. This expanded platform allowed the delivery of VC-ERP based on the treatment protocol for in-person ERP.

VC-ERP for OCD

The in-person ERP protocol was modified to allow it to be delivered through the VC platform using the Zoom software. The use of VC was supplemented by WhatsApp video calls and messaging, phone calls (landline or smartphones), and e-mail. Virtual prescriptions sent by WhatsApp messages were used to convey advice regarding investigations and medications. The use of multiple digital modes of patient-clinician communication was consonant with the hybrid model of care, which had been recommended particularly during the pandemic[38]. This improves the flexibility and versatility of TMH-based care

and maintains its continuity by switching between different modes when one of them fails.

The modified VC-ERP protocol was developed based on feedback from a weekly Zoom group of clinicians actively involved in VC-ERP treatment for OCD. The group consists mainly of trainee psychiatrists, (post-MD) senior residents, and a consultant psychiatrist. Apart from group supervision of the trainees administering the treatment, the activities undertaken by this group have included carrying out a detailed review of the literature on ERP for OCD, TMH-based treatment options, and VC-ERP for OCD. Standardized guidelines for VC-ERP were prepared, and clinicians adhered to these standards of care. Educational materials for patients and their families were also prepared. The final protocol for VC-ERP is shown in Tables 1 and 2.

Differences between VC and in-person ERP

The differences between ERP by VC or by in-person treatment and the difficulties encountered during VC-ERP were the primary focus of many group discussions. The consensus views on this aspect are included in Table 3. These considerations provided the basis for the modifications made in the VC-ERP treatment protocol.

Modifications in technique required for conducting VC-ERP

Introductory education sessions with the patients and their caregivers were felt to be essential to improve their understanding and motivation for ERP. Although detailed psychoeducation sessions were carried out as a part of the ERP later, during this phase the objective was to provide enough information to ensure patient and caregiver cooperation with the process of assessment[39]. The contents of the brief information leaflet used for this purpose are depicted in Table 2.

A structured procedure for assessment was used. The clinician-administered version of the Yale-Brown Obsessive Compulsive Scale (YBOCS) was used to screen for different obsessions/compulsions as well as to rate the severity of obsessive-compulsive symptoms. The YBOCS is the most commonly used instrument for this purpose because of its reliable psychometric properties[1,4,13]. Standardized procedures such as those by Hawton *et al*[40] were used to conduct the behavioral analysis in the ABC format (antecedents, behaviors, consequences). Subjective units of distress were used to rate the severity of behaviors and also construct an ascending hierarchy of problem behaviors. The construction of the hierarchy was a key step in the process of planning for VC-ERP. Inputs were actively solicited from patients and caregivers during this stage. They were asked to keep a daily record of symptoms for about a week to make the hierarchy as comprehensive as possible. Google sheets or WhatsApp messages that could be regularly updated were used for this purpose. The assessment process often took up to 2 wk, but a prolonged and comprehensive assessment had many advantages such as increasing awareness about symptoms among the patients and caregivers, reducing their distress, and acquainting them with the VC-ERP treatment to follow. Finally, the hierarchies made were continuously upgraded during treatment based on the new information provided by patients or caregivers. Therefore, the process of assessment continued throughout the treatment.

A five-step approach to VC-ERP was used. These five steps of ERP were based on standard protocols of ERP or CBT[1,39,41-43]. Benson's relaxation technique[44] was the preferred mode of teaching relaxation exercises. The only other modification was that "processing" was used instead of cognitive restructuring. Processing involved discussing the patients' experiences and understanding of ERP and how this matched their expectations of the treatment[13,42]. Processing also allowed for discussions on the reality of the patient's beliefs, explanations about neutralization strategies, and suggestions about using more adaptive coping strategies. Modifications to the other components of the ERP are summarized in Table 4.

Outcomes of VC-ERP

The main focus of this study was on the feasibility outcomes including operational viability, service utilization, service engagement, need for additional services, frequency of adverse events, and treatment satisfaction and treatment preferences among patients, caregivers, and clinicians. The information about treatment engagement and the dropout rate was obtained from the medical records of patients who were offered ERP and either consented or refused the treatment. For all other outcomes, only patients who had agreed to undertake ERP and those who had completed or were actively engaged in the treatment were included. Patients were not interviewed separately for this part. Rather, the information was obtained from their treatment records. Therefore, any patient with incomplete treatment records was excluded. For the efficacy outcomes, only the 11 patients who had completed the entire VC-ERP were considered. Pre- and post-treatment YBOCS scores were extracted from their records to determine the efficacy of VC-ERP treatment. Information about the maintenance of gains post-treatment over 13 mo was also extracted from the treatment records.

Statistical analysis

The sample was characterized by using frequencies, means, and standard deviations. Loss to follow-up at any time was considered a dropout. Pre- and post-treatment comparisons were carried out using the Wilcoxon signed rank test.

Table 1 The treatment protocol for videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Components	Details
Detailed assessment	Establishing the diagnosis based on history and mental state examination Relevant investigations. Formulating a management plan consisting of medications and psychosocial treatment. The decision to start ERP was made following this assessment
Introductory psychoeducation[1]	Brief introductory education sessions with patients and designated caregivers with the help of a two-page written information leaflet for them
Standardized assessments	(1) YBOCS screening (2) YBOCS rating (3) Standardized behavioral analysis, *e.g.*, by Hawton *et al*[40] (4) Construction of ascending hierarchy of symptoms (according to the subjective units of distress on a 0%-100% scale)
Five-step ERP[2]	Psychoeducation, symptom monitoring, relaxation exercises, exposure and response prevention, and processing
Conduct of VC sessions[3]	All VC-ERP sessions were conducted at home, supervised by the clinician, and attended by the caregiver. WhatsApp messages or phone calls were used to convey advice regarding details of sessions, investigations, and medications
Additional strategies	Incorporation of additional techniques, *e.g.*, thought stopping with ERP for those with predominant obsessions
Relapse prevention	Continued follow-up through VC with constant re-emphasis on all components of the ERP. Booster sessions, if required upon completion of the initial VC-ERP treatment
Caregiver involvement	A family member designated as the primary caregiver was involved in the entire process of the VC-ERP treatment. The caregiver conducted homework sessions
Hybrid care	Hybrid treatment had two components (1) Employing a combination of VC-ERP sessions at home and in-person ERP sessions at the outpatient department (2) Employing multiple modes of patient-clinician communication such as VC, mail, text messages, and phones to augment in-person care

[1]Details in Table 2.

[2]These five steps of exposure and response prevention (ERP) were based on standard protocols of ERP or cognitive behavior therapy[1,39,41-43]. Psychoeducation imparted more detailed information about obsessive-compulsive disorder (OCD) including a cognitive-behavioral model of OCD. Apart from providing basic information about OCD, it attempted to correct common misconceptions. Psychoeducation also involved providing a clear rationale for ERP, information about the components and procedure for ERP, conduct of videoconferencing-based ERP sessions, and how ERP was expected to help. Patients and caregivers were taught to objectively monitor symptoms, thoughts, and distress during sessions and during the course of treatment. Standard formats for monitoring during videoconferencing sessions were developed. Google sheets or text messages that could be regularly updated were exchanged between clinicians and patients. The clinician carried out his/her own assessments, and feedback about progress of treatment was provided to the patient. Relaxation exercises, preferably using Benson's relaxation technique[44] were taught. It involved muscle relaxation, deep breathing, and the use of relaxation as a coping strategy. It was used to reduce anxiety and improve motivation for treatment. Standard techniques of ERP were used with certain modifications as explained in Table 4. During processing, the patients' experience of the sessions was discussed to enhance their understanding of ERP, examining the reality of their beliefs, and discussing more adaptive ways of coping[13,42].

[3]More details in Table 4.

ERP: Exposure and response prevention; VC-ERP: Videoconferencing-based exposure and response prevention; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Ethical considerations

This observational study was a part of a larger study on home-based TMH services for all patients[37]. The protocol was approved by the institute's ethics committee. Due to the restrictions imposed by the pandemic, verbal informed consent over the phone was allowed. As explained above, data regarding outcomes were obtained only from patients who had verbally consented to undertake ERP and had actively engaged in the process of treatment. However, patients were not contacted or assessed separately to determine these outcomes. Rather, all data regarding outcomes were extracted from routine medical and treatment records. Patient identities have not been revealed. Therefore, written informed consent from patients was not obtained for information about treatment outcomes. All the methods followed the guidelines of the Declaration of Helsinki for medical research involving human subjects.

Table 2 Content of the brief introductory education session for videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Content
1 What is OCD? What are obsessions and compulsions in OCD?
2 How common is OCD?
3 How does the patient feel while experiencing the symptoms of OCD?
4 Why do patients develop OCD?
5 What are the types of treatment available?
6 What is the role of medications in treating OCD?
7 What is ERP and how does it work?
8 What is the need for ERP?
9 How will the VC-ERP sessions be conducted?
10 How long will the treatment take?

ERP: Exposure and response prevention; OCD; Obsessive-compulsive disorder; VC-ERP: Videoconferencing-based ERP for OCD.

Table 3 Problems with videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder and in-person and proposed solutions

	Difficulties with VC-ERP	Suggested solutions
Understanding and motivation of patients and caregivers	It was harder to explain the procedure to patients/caregivers. Motivation to engage in VC-ERP was often low. As a result, treatment engagement was variable	Early initiation of psychoeducation and the more frequent use of hybrid treatment
Difficulties faced during the assessment	The initial assessment took longer. Frequent interruptions due to poor network connectivity and the need to restart the process several times were common. Patients/caregivers often complained about the long period of assessment. Some patients became more anxious during the process	Educate patients/caregivers about the likely timeframes for assessment and treatment during the introductory psychoeducation sessions. Additional in-person sessions and administering benzodiazepines for short periods could help control anxiety
Conducting ERP sessions-patient-related and caregiver-related difficulties	These included variable cooperation, discomfort and hesitation, worry about confidentiality, indulging in neutralization strategies during sessions, preference for in-person visits, and problems with the timing and duration of the sessions	Shorter VC-ERP sessions (minimum of 30 min) and flexible scheduling of sessions (every 7-14 d). Ongoing education of patients and caregivers to ensure realistic expectations from VC-ERP
Conducting ERP sessions-clinician-related difficulties	Clinicians faced problems in sustaining their motivation, dealing with the additional burden of VC sessions and the need to adjust to a new medium	Training, supervision, and support for clinicians through regular group meetings
Technological difficulties	Poor connectivity, unavailability of proper equipment, user's unfamiliarity with technology, and time constraints	Modifications to the ERP procedure to make it more compatible with VC
Disadvantages	Group members conducting VC-ERP sessions rated it about three times as difficult compared to in-person ERP because of the problems encountered	A structured treatment package incorporating modifications in the treatment, ongoing education, and support for all users
Advantages	Group members agreed that VC-ERP had advantages such as greater access, convenience of carrying out sessions at home, and lesser likelihood of late disengagement if motivation could be ensured	The consensus was that though conducting VC-ERP may be more difficult than in-person ERP, the basic procedures and their implementation were similar

ERP: Exposure and response prevention; VC-ERP: Videoconferencing-based exposure and response prevention.

RESULTS

Participants

During the period of this study (July 2020-June 2021), the home-based TMH service was used to treat 3442 new and 12126 old patients. Of these, 115 new patients (3%) had a diagnosis of OCD as a primary or a comorbid condition according to the International Classification of Diseases, 10th version criteria. During subsequent follow-up, 1 patient whose diagnosis was changed from OCD to personality disorder was excluded; 28 patients had dropped out of treatment, and details regarding the status of 8 patients were not available. Therefore, 78 patients were included in the final analysis.

Table 4 Modifications in technique required for conducting videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

VC-ERP components	Modifications made to the VC-ERP
Detailed psychoeducation	Carried out using manuals in English and the local language for clinicians, patients, and caregivers. The content was simple, brief, and provided clear explanations. Psychoeducation sessions continued throughout the treatment
Monitoring of symptoms and progress	Simultaneous monitoring was carried out by the patients, caregivers, and clinicians through VC sessions, Google sheets, or WhatsApp messages that were regularly updated. Constant feedback about the progress of treatment was provided to the patient
Relaxation exercises	Benson's relaxation technique was preferred because of its brief and simple format. Autogenic training or modified Jacobson's progressive muscular relaxation exercises were taught if required. Written instructions in English and the local language and audio-visual aids for teaching were available for clinicians, patients, and caregivers
Duration of VC-ERP sessions	Though prolonged exposure is the goal because of its greater efficacy, it was quite difficult to have VC sessions of more than 30 min. Thus, the minimum duration was set at 30 min with the opportunity to prolong the sessions according to the patient's convenience
Frequency of VC-ERP sessions	The frequency of sessions varied from weekly sessions to one session every 10-14 d. Flexibility was essential in deciding the duration and frequency of sessions. Several other factors were considered, particularly patient/caregiver preferences, the stage of ERP, the severity of symptoms, and the availability of clinicians
Supervision of VC-ERP sessions	The patient's camera was not only focused on the patient but also covered a significant portion of the room so that clinician could detect any surreptitious compulsions or neutralizing acts. The camera was never switched off during the sessions
Engaging patients during the VC-ERP sessions	Clinicians, patients, and caregivers were all actively involved during the VC-ERP sessions. Every effort was made to minimize distractions. Neutralizing acts were noted and discussed later during processing. The clinician engaged with the patients at regular intervals to make sure that they were focusing on the treatment and to check the level of anxiety during sessions. However, constant talking was avoided because this might distract the patient
Ensuring patients' tolerance of anxiety	Patient comfort with the level of exposure and their ability to tolerate anxiety was of overriding importance. They were never forced to engage in something that made them uncomfortable during the ERP sessions. Rather, each step was undertaken after proper education and fully ensuring the patient's agreement and cooperation
The slower pace of VC-ERP	VC-ERP was expected to progress at a much slower pace than in-person ERP. This was explained to the patients and caregivers and usually did not present a problem
Privacy and confidentiality	Privacy was essential, and patients were informed about the people present in the room (*e.g.*, technicians) when the session was being conducted. The patient was only accompanied by the designated caregiver at home. Any recording was done only with the patient's explicit consent. All material relating to the treatment was stored securely
Safety	Patients were required to be accompanied by caregivers during the sessions. Anxiety levels were constantly monitored, and sessions were terminated if the patient was uncomfortable. If there were other concerns about the safety of the patient (*e.g.*, risk of self-harm or violence), closer monitoring was instituted for such highrisk situations. Caregivers were also educated to manage such high-risk situations. For persisting safety concerns including symptom exacerbations during VC-ERP, patients and family members were helped to attend outpatient or emergency services
Treatment of comorbidities	Other modalities such as medications or occasionally ECT were used to treat primary or secondary comorbidities. The VC-ERP was adapted to meet the needs of patients with comorbid symptoms. Techniques utilized included temporarily suspending the sessions when comorbid symptoms increased, offering increased support at this time using the VC platform, promoting greater involvement of caregivers, and combining VC sessions with in-person sessions
Using hybrid modes of treatment	Hybrid care involved conducting some of the initial ERP sessions on an in-person basis and the later sessions by utilizing VC. Similarly, for each new step of the hierarchy, the initial session was an in-person one followed by VC sessions. This often mitigated the problems of poor understanding and variable motivation noted in exclusive VC-ERP treatment. Requests from patients and caregivers for in-person sessions were catered to as far as possible
Self-exposure	In exceptional instances when caregivers were not available, therapist-guided self-exposure was tried. A greater level of patient motivation was required for self-exposure and the pace of ERP was slower

ERP: Exposure and response prevention; VC-ERP: Videoconferencing-based exposure and response prevention. ECT: Electroconvulsive therapy.

Patient profiles

Out of 78 patients, 38 were men and 40 were women. In general, patients seen during the pandemic were more likely to be older, married, better educated, and from higher-income families living near the hospital[37]. However, many patients were barely literate, impoverished, and from distant, rural locations. Three patients had late-onset OCD. Twenty-one patients had a comorbid psychiatric illness. OCD as a primary condition included the following comorbidities: single depressive episode (n = 6), recurrent depressive disorder (n = 4), dysthymia (n = 1), agoraphobia (n = 1), hypochondriasis (n = 1), and impulse control disorder (n = 1). OCD as a secondary comorbidity was present in schizophrenia (n = 3), bipolar disorder (n = 2), dementia (n = 1), and traumatic brain injury (n = 1). Most patients were on pharmacological treatment for OCD and comorbid conditions.

VC-based ERP for OCD: feasibility, acceptability, and efficacy

Tables 5 and 6 provide these details.

VC-ERP was considered in the majority of patients with OCD, but because of different reasons only about half of them (55%) started VC-ERP. Of the 43 patients who started VC-ERP, 6 dropped out early and 3 had to be hospitalized for inpatient ERP. Thus, a large proportion of the eligible patients (n = 33/43; 77%) had completed the full treatment (n = 11) or were currently undergoing VC-ERP (n = 22). One patient improved following the initial sessions and did not have to complete the entire treatment. Hybrid treatment was more commonly used by many of these patients (n = 20) once the outpatient services resumed. Most patients and caregivers considered this to be a better option and preferred hybrid care.

Feasibility outcomes among the 34 patients engaged in VC-ERP showed that it was possible to implement the treatment in usual clinical settings. Drop-out rates were low (n = 6/43; 14%). Apart from the 3 patients (9%) with severe OCD who did not respond to VC-ERP and required hospitalization, there were no other adverse events. The number of patients treated with VC-ERP in a year was more than those who had received inpatient ERP for a year during the pre-pandemic period. Satisfaction with the treatment was adequate among patients, caregivers, and clinicians. Therefore, the feasibility of VC-ERP treatment in terms of operational viability, service utilization, service engagement, need for additional in-person services, frequency of adverse events, and user satisfaction was adequate.

The 11 patients who completed the entire treatment had moderate levels of OCD for several years. VC-ERP led to significant reductions in the YBOCS scores on completion. Treatment gains have been maintained in these patients on follow-up for a year after completing the VC-ERP. More than half of them (54%) had comorbid conditions, but this did not affect their improvement with VC-ERP.

DISCUSSION

TMH-based services are efficacious and suitable alternatives to in-person care and have proved to be particularly useful during the pandemic. By promoting ready access to psychiatric care, they can remove several barriers associated with conventional services, enhance satisfaction among users, and empower the underserved population from remote areas[24,31,32].

The efficacy, advantages, and disadvantages of VC-based ERP for OCD

Several reviews[6-10] and meta-analyses[11,13] of TMH-based treatments for OCD have found that VC-based treatment is useful, but they have only included a few trials of VC-ERP for OCD. Similarly, meta-analyses[25,45,46] and reviews[17,47-50] that have found VC-based treatments to be effective for psychiatric disorders have included a limited number of VC-ERP studies of OCD. This is not surprising because there are only three randomized-controlled trials (RCTs) of VC-ERP in OCD[51-53]. A fourth RCT of VC treatment for anxiety and mood disorders included 4 patients with OCD[54]. These RCTs have shown that VC-ERP is more efficacious than neutral or active control treatments and equal in efficacy to in-person ERP. Treatment gains are maintained for several months, and VC-ERP had a more positive impact on the treatment alliance and patient engagement. Open trials have similarly shown that VC-ERP is an effective, feasible, acceptable, and cost-saving treatment, which can be used to supplement in-person ERP[27,55-58]. However, the RCTs have small sample sizes and are of brief duration. Therefore, without properly conducted RCTs with non-inferiority or equivalence designs, the current evidence in favor of VC-ERP for OCD cannot be considered adequate[59].

Like other TMH-based treatments, VC-ERP has several advantages compared to in-person ERP[7,13,17,50,52]. It leads to wider dissemination of ERP and greater patient access to evidence-based ERP. Home-based ERP allows greater flexibility, greater involvement of family members in ERP, and more opportunities to address the negative attitudes or accommodations by the family. It can be cost-effective because it reduces travel costs and absence from work. Since patients receive treatment at home, the stigma associated with seeking psychiatric treatment is lessened. However, VC-ERP has its challenges. It is heavily dependent on external factors such as technological infrastructure, internet penetration and affordability, network connectivity, and the user's familiarity with technology. Patient and family motivation might be poor, forging effective treatment alliances may be difficult, and supervision and monitoring may not be optimal[50,52,56].

VC-based ERP for OCD vs internet-based CBT

Currently, there seems to be a greater emphasis on delivering online or internet-based ERP or CBT for OCD particularly in high-income countries[9]. The two types of treatment have their advantages and disadvantages. Internet-based CBT has a broader evidence base and the number of trials including RCTs is much more than those of VC-ERP[10,11-14]. Its efficacy is comparable to in-person CBT. Internet-based CBT is particularly useful as an initial option for mild or moderate OCD. Moreover, it is more readily accessible and offers a wider choice of techniques and varying levels of clinician assistance. The treatment is efficacious and cost-effective even with low levels of clinician support[15]. Moreover, greater levels of clinician support can help minimize dropouts, and treatment gains are usually

Table 5 Details of videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Patients	Number	Comments/details
Patients with OCD attending the home-based TMH services during the study-period	115	This was 3% of all new outpatients and represented an increase in the number of such patients compared to the period before the pandemic
Patients available for analysis	78	ERP not considered (n = 17; 15%); improved with medications and did not require ERP (n = 2); refused ERP (n = 3); VC-ERP yet to be initiated (n = 13)
Patients in whom VC-ERP was initiated/early dropouts	43	Six patients dropped out from VC-ERP treatment. (Dropout rate 14%)
Improvement after initial treatment	1	One patient improved after initial psychoeducation and regular relaxation exercises and was not required to complete the entire VC-ERP treatment
Transition to hybrid care	20	Hybrid care became easier once the outpatient services resumed in December 2021
Transition to inpatient ERP	3	VC-ERP was followed by inpatient-based ERP because of severe OCD and non-response to VC-ERP.
Patients who have undergone/are undergoing VC-ERP	33	VC-ERP has been completed in 11 patients and is ongoing in 22 patients

ERP: Exposure and response prevention; OCD: Obsessive-compulsive disorder; VC-ERP: Videoconferencing-based exposure and response prevention; TMH: Telemental health.

Table 6 Efficacy of videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Age	Sex	Marital status	Residence	Comorbidity	Duration of OCD	Baseline YBOCS score	YBOCS score at completion
Mean: 31.27 (SD: 9.65) yr, range: 22-56 yr	Men: 9; Women: 2	Single: 8; Married: 3	Urban: 9; Rural: 2	OCD primary disorder: 7 (depressive disorder: 2); OCD secondary disorder: 4 (schizophrenia: 3; bipolar disorder: 1)	Mean: 6.90 (SD: 6.48) yr, range: 1-25 yr	Mean: 25.45 (SD: 5.63), range: 17-36	Mean: 4.27 (SD: 4.22)[1], range: 0-13

[1]Significant reduction in Yale-Brown Obsessive-Compulsive Scale scores; Z = 2.936; P < 0.01 (using the Wilcoxon signed rank test).
OCD: Obsessive-compulsive disorder; YBOCS: Yale-Brown Obsessive-Compulsive Scale; SD: Standard deviation.

enduring.

Despite these advantages, there is no difference in efficacy between VC-ERP and internet-based treatments[13]. Indeed, some of the evidence seems to indicate that VC-ERP may be more efficacious than internet-based treatments[45,60]. Moreover, VC-ERP resembles the "gold-standard" in-person ERP more closely than internet-based ERP[13,16,17,45,46]. Since VC-ERP is conducted at home, it has the advantage of greater convenience, more chances of the behavioral gains generalizing to natural settings, increased involvement of the family, and a better insight into the patient's home environment[6,16,17,45,50]. Some reviews also suggest that VC-ERP is more suitable for those with severe OCD[8,9] and patients from remote locations[16,45-47,50], whereas internet-based treatments are more useful in milder OCD and for people with better access to the internet[8-10]. Lastly, the main advantage of VC-ERP seems to be the greater therapeutic contact it provides particularly in comparison to internet-based treatments with minimal therapist contact. There is considerable evidence to indicate that higher levels of therapeutic contact are associated with greater efficacy of TMH-based treatments for OCD[7,9,14,61,62].

The choice of VC-ERP in this study was influenced by these considerations along with the prior experience of in-person ERP in the department, the availability of a home-based platform for VC-ERP, and the unavailability of internet-based treatments.

Findings of the present study and its limitations

Being a preliminary report, this study had several obvious limitations. It was largely a descriptive account of the development and implementation of VC-ERP for OCD from a relatively under-resourced setting. The number of patients who had completed the treatment was very small, and all data related to the efficacy of VC-ERP are therefore prone to a high risk of bias. This risk is increased further because patients were not randomized to VC-ERP treatment, and there was no control group. A selection bias toward better-motivated patients is also possible. Since this was a naturalistic observational study, it was not possible to control for confounding factors such as the effect of pharmacological treatment or comorbid conditions.

Nevertheless, some of the findings were encouraging and could have some implications for further efforts in this area. The principal focus of this study was to describe the process of developing a protocol for VC-ERP treatment of OCD during the pandemic. Due to the restrictions imposed by the pandemic the entire process of development and subsequent implementation had to be carried out online. The primary aim of the study was to examine the operational viability and feasibility of conducting VC-ERP according to the treatment protocol developed in this study. The examination of these outcomes among 34 patients who had completed the treatment or were actively engaged in it indicated that the VC-ERP protocol was a feasible and viable means of treating OCD.

The VC-ERP treatment provided access to a larger number of patients who could benefit from ERP. Dropout rates were low and adverse events were relatively rare. The treatment was acceptable to patients, caregivers, and clinicians, and the levels of satisfaction were adequate. Since this was a naturalistic observation study among patients from routine care settings, these results can be generalized to other patients from similar clinical settings. Moreover, since the treatment was conducted in a low-resource setting of a developing country like India, these results could be particularly relevant for countries with similar resource constraints. Although the treatment was mostly conducted during the pandemic, the findings showed that it was feasible to implement the treatment even after the pandemic had subsided. Moreover, such naturalistic studies also fulfil the pressing need to conduct VC-ERP trials for OCD in real-world settings[9,16,60].

Its findings corresponded to the recent studies of OCD, which indicated that VC-ERP may be equally effective in routine treatment settings[22,63,64]. The use of hybrid treatment both in terms of multiple platforms for hosting VC-ERP and combining it with in-person care offers a greater degree of flexibility and has the potential for greater effectiveness[15,16,38,45,50]. Similarly, this study found that hybrid care was considered to be more advantageous and preferred by patients, caregivers, and clinicians. Another unexpected gain of the VC-ERP treatment was the opportunity to incorporate stepped care into the treatment protocol. Stepped care refers to the use of low-intensity treatments such as internet-based CBT for patients with less severe OCD with the option to transition to more intensive treatments if the illness is more severe. It has been advocated for a long time but is being re-emphasized because of the wide range of TMH-based treatments currently available for OCD[7,9,13,14,16]. In this study patients with milder OCD improved after the initial sessions, while many with more severe OCD moved on to hybrid care, and a few with the most severe illnesses could move on to inpatient ERP when VC-ERP failed. This was consistent with the stepped care approach.

The findings regarding the efficacy of VC-ERP among 11 patients who had completed the full treatment were very preliminary and had several limitations that have been listed above. Nevertheless, they did suggest that the VC-ERP treatment of this study was an effective means of managing OCD in terms of significant symptom reduction and maintenance of gains post-treatment. The extent of improvement was similar to other Indian studies of inpatient ERP for OCD[35,36]. However, the long-term outcome of VC-ERP was likely to be better because of the improved treatment engagement and follow-up with the treatment. These results were also in line with much of the existing evidence on the efficacy of VC-ERP from RCTs[51-54] and open trials[27,55-58]. Lastly, the findings suggested that VC-ERP treatment could be useful for a population with moderately severe OCD and high rates of comorbidity. Though most of the evidence appears to indicate that VC-ERP is ineffective in treating comorbid depression[7,11,22], some studies have shown that it is equally effective in those with comorbid conditions[22,64].

CONCLUSION

In conclusion, the present study has shown that despite many barriers it is possible to develop a structured form of VC-ERP for OCD that is feasible and acceptable to the users. The findings, though preliminary, suggest that VC-ERP could be a viable option for the treatment of OCD in low- and middle-income countries where the treatment gap for OCD is greater and TMH services are relatively underdeveloped. However, much more will need to be done to improve this treatment and prove its efficacy before it can be integrated into the wider system of mental healthcare in these countries.

ARTICLE HIGHLIGHTS

Research background

The existing literature indicates that exposure and response prevention (ERP) is efficacious in treating obsessive-compulsive disorder (OCD). However, despite the availability of such effective psychotherapeutic treatments, very few patients have ready access to them. Telemental health (TMH) treatments may help in overcoming these limitations of conventional ERP.

Research motivation

The coronavirus disease 2019 pandemic adversely impacted many patients with OCD, compelling clinicians to increasingly use telemental health-based options rather than conventional psychotherapeutic treatments for OCD. However, research on the efficacy of TMH in the treatment of psychiatric disorders from developing countries is limited, and trials on TMH-based treatment of OCD are rare. This study from India described the formulation and implementation of videoconferencing-based ERP (VC-ERP) treatment for OCD during the pandemic and its current status in terms of feasibility and usefulness.

Research objectives

To describe the formulation of a treatment-protocol for VC-ERP developed by an online group of clinicians, to describe the implementation of the protocol, and to examine the feasibility and usefulness of the VC-ERP treatment for OCD during the pandemic and after it.

Research methods

This prospective, observational study was conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (July 2020-June 2021). All patients with OCD were assessed using the home-based TMH services of the department. The VC-ERP protocol for OCD was the outcome of weekly Zoom meetings with a group of clinicians involved in administering the treatment. The protocol was implemented among patients with OCD attending the TMH services and upgraded to meet their needs. Feasibility and efficacy outcomes were examined.

Research results

One hundred and fifteen patients with OCD attended the TMH services during the study period; 37 of these were excluded. Of the remaining 78 patients, VC-ERP was initiated in 43 patients. Six patients dropped out, and 3 patients were hospitalized for inpatient ERP. Eleven patients have completed the full VC-ERP treatment. One patient improved following the initial sessions and did not have to complete the entire treatment. VC-ERP is ongoing in 22 patients. The feasibility of VC-ERP treatment in terms of operational viability, service utilization, service engagement, need for additional in-person services, frequency of adverse events, and user satisfaction was adequate. Significant reductions in symptoms and maintenance of treatment gains on follow-up were observed in 11 patients who completed the entire treatment.

Research conclusions

This study provided preliminary evidence for the feasibility and usefulness of VC-ERP in the treatment of OCD. It suggested that VC-ERP could be a viable option for the treatment of OCD in low- and middle-income countries with a greater treatment gap for OCD and underdeveloped TMH services.

Research perspectives

Further research is needed to improve the VC-ERP treatment and prove its efficacy before it can be integrated into the wider system of mental healthcare.

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FOOTNOTES

Author contributions: Kathiravan S and Chakrabarti S were involved in preparing the study protocol and conducting the review of the literature; Kathiravan S collected the data about patient treatment; Kathiravan S and Chakrabarti S were both involved in analyzing the data and preparing the manuscript; All authors have approved the final version of the manuscript for submission.

Institutional review board statement: This observational study was a part of a larger study on home-based TMH services for all patients[37]. The protocol was approved by the institute's ethics committee. Due to the restrictions imposed by the pandemic, verbal informed consent over the phone was allowed. Copies of the approval from the ethics committee have been uploaded.

Informed consent statement: This observational study was a part of a larger study on home-based TMH services for all patients[37]. The protocol was approved by the institute's ethics committee. Due to the restrictions imposed by the pandemic, verbal informed consent over the phone was allowed. As explained above, data regarding outcomes were

obtained only from patients who had verbally consented to undertake exposure and response prevention and had actively engaged in the process of treatment. However, patients were not contacted or assessed separately to determine these outcomes. Rather, all data regarding outcomes were extracted from routine medical and treatment records. Patient identities have not been revealed. Therefore, written informed consent from patients was not obtained for information about treatment outcomes. All the methods followed the guidelines of the Declaration of Helsinki for medical research involving human subjects.

Conflict-of-interest statement: None of the authors have any potential conflicts of interest to report. Details have been provided in the conflict-of-interest statement format.

Data sharing statement: Data regarding the study are available from the corresponding author (subhochd@yahoo.com) upon reasonable request.

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CASE REPORT

Major depressive disorder is correlated with the mitochondrial *ND1* T3394C mutation in two Han Chinese families: Two case reports

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Abstract

BACKGROUND

Major depressive disorder (MDD) is the most frequent reason of disabled people in the world, as reported by the World Health Organization. However, the diagnosis of MDD is mainly based on clinical symptoms.

CASE SUMMARY

The clinical, genetic, and molecular characteristics of two Chinese families with MDD are described in this study. There were variable ages of onset and severity in depression among the families. Both Chinese families had a very low prevalence of MDD. The mitochondrial genomes of these pedigrees were sequenced and indicated a homoplasmic T3394C (Y30H) mutation, with the polymorphism located at a highly conserved tyrosine at position 30 of *ND1*. The analysis also revealed unique sets of mitochondrial DNA (mtDNA) polymorphisms originating from haplogroups M9a3 and M9a.

CONCLUSION

This finding of the T3394C mutation in two unrelated depressed patients provides strong evidence that this mutation may have a part in the etiology of MDD. However, In these two Chinese families having the T3394C mutation, no functional mtDNA mutation was observed. Therefore, T3394C mutations are related with MDD, and the phenotypic manifestation of these mutations may be affected by changes in nuclear genes or environmental factors.

Key Words: Major depressive disorder; Mitochondrial DNA; *ND1*; Mutation; Haplogroup; Chinese; Case report

Core Tip: We characterized two Chinese families with suspected maternal transmission of major depressive disorder at the clinical, genetic, and molecular levels in the present study. Molecular investigation revealed that the T3394C mutation in the *ND1* gene was present in these Chinese families.

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INTRODUCTION

Major depressive disorder (MDD) is a frequent dangerous human disease, which severely impairs the normal life and work of patients and causes a heavy burden on their family and society. In 2008, the World Health Organization rated it as the third leading cause of worldwide disability, and by 2030, it is expected to lead the list[1]. Despite its high incidence and prevalence, clinical symptoms are the primary basis for a diagnosis of MDD, and there is little evidence at the molecular level[2]. In addition, current drug therapy for MDD is not effective, with only 27% of patients in remission after the first treatment and 67% in remission after four complete treatments[3]. These considerations imply that the currently available antidepressants that target the monoaminergic system are insufficient for therapeutic use. In evaluating new therapeutic approaches, specific biomarkers should be identified that objectively determine the pathology involved in MDD, and relevant molecular targets might be revealed[4].

Mitochondrial DNA (mtDNA) is a 16.6 kb circular molecule that is maternally transferred and found within the mitochondrion[5]. Mitochondria can be considered "power generators" because they transform oxygen, energy substrates (proteins, carbohydrates, and lipids), and other substances into adenosine triphosphate[6]. In major psychiatric diseases, significant changes in the mitochondrial count, shape and electron transport activity in neurons are accompanied by an increase in mitochondrial DNA polymorphism, deletion and mutation, suggesting that defects in the mitochondria might be a primary cause of MDD[7,8]. Munakata *et al*[9] sequenced the whole mitochondrial genome of white blood cells from a family in which a proband was suspected of maternal inheritance of borderline personality disorder, MDD, suicide and other psychiatric disorders. The patient was identified as having both MDD and epilepsy. Comparing the proband sequence to the standard human mtDNA sequence, the authors identified 34 base changes. From the mtDNA sequence, it is possible to detect comprehensive subhaplogroups, new mutations, and common single nucleotide polymorphisms. It is also possible to determine private mutations in mtDNA through resequencing, especially if they are homoplasmic, which contributes to the variance between individuals in mtDNA composition[10].

This study aimed to characterize clinical, genetic, and molecular characteristics of two Chinese families with possible maternally transmitted MDD. The T3394C mutation in the *ND1* gene in these Chinese families was identified through molecular analysis. We employed polymerase chain reaction (PCR) amplification of fragments covering the full mitochondrial genome and subsequent DNA sequence analysis to shed insight on the significance of the mitochondrial haplotype in the phenotypic expression of the T3394C mutation in two Chinese families.

CASE PRESENTATION

Chief complaints

We ascertained two Han Chinese families (Figure 1) through the Psychiatric Clinic of Ningbo Kangning Hospital, Zhejiang. The Ningbo Kangning Hospital Ethics Committee approved the protocol, and obtaining clinical assessments and collecting blood samples from all family members required informed consent. In-depth interviews were conducted with members of these pedigrees to discover family and personal medicinal records of major depressive disorder and other medical abnormalities. To check for mtDNA alterations, we collected 167 DNA samples from healthy Chinese people who served as controls.

In family NB011, as shown in Table 1, the proband (II-4) complained of depression and visited the Psychiatric Clinic at Ningbo Kangning Hospital at the age of 62. She struggled with MDD approximately 12 years prior. The Hamilton depression rating scale (HDRS) showed a score of 24 and no

Table 1 Summary of clinical molecular data for two probands carrying the *ND1* T3394C mutation

Subject	Gender	Age at testing (yr)	Age at onset (yr)	First episode	History of suicide attempt	HDRS	Level of depression	mtDNA haplogroup
NB011-II-4	F	62	50	N	N	21	Moderate	M9a3
NB054-III-4	M	20	12	N	Y	39	Severe	M9a

HDRS: Hamilton depression rating scale.

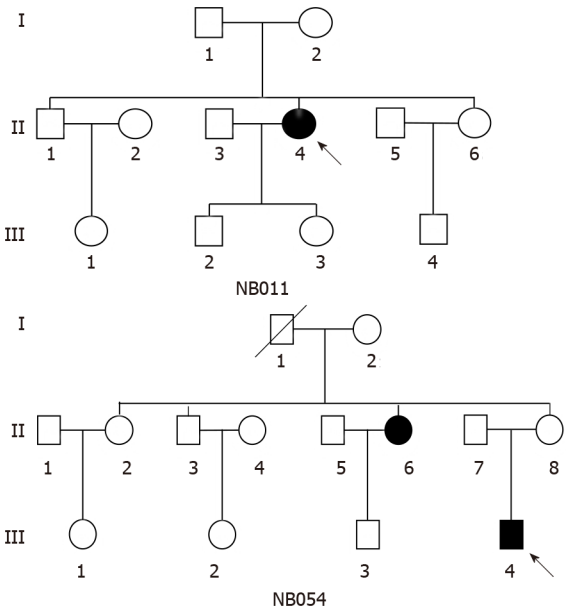

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Figure 1 Two Chinese pedigrees with major depressive disorder. Patients are indicated by filled symbols. The arrow denotes the probands.

history of suicide attempt. She exhibited the classic clinical features of MDD. The psychiatric examination found no other abnormalities. In addition, no further significant medical background was discovered. The family was from East China's Zhejiang Province. None of the remaining seven matrilineal relatives displayed MDD.

In the NB054 pedigree, the proband (III-4) visited the Psychiatric Clinic at Ningbo Kangning Hospital upon reaching the age of 20. He struggled with MDD 8 years prior. The HDRS showed a score of 39 and a history of suicide attempt. Thus, he had classic symptoms of clinical features of MDD. no further significant medical background was discovered. The family was also from Zhejiang Province in Eastern China. Clinical testing and additional research into II-6's family history confirmed that she had MDD. Other matrilineal relatives did not show signs of MDD.

History of present illness

In addition, there was no indication that any member of these families had an alternative recognized etiology for MDD.

History of past illness

Comprehensive family medical histories of these individuals showed no other clinical abnormalities existed in these people's families, such as diabetes, hearing loss, or vision problems.

Psychiatric examinations and evaluation by the Hamilton depression rating scale

The diagnosis of MDD for the probands was developed by utilizing structured clinical interviews[11] and was confirmed by a separate diagnostic examination conducted by a licensed psychiatrist. Depressive symptom intensity in patients with MDD was measured by the HDRS[12]. The probands with MDD got a minimum HDRS score of 17 on 17 items. The severity of MDD was determined by HDRS as follows: normal < 7; mild = 7-17; moderate = 17-24; severe > 24. The probands of MDD were not included if they had any of the following conditions according to DSM-IV: (1) Abuse of alcohol or drugs within the previous six months; (2) bipolar disorder; and (3) post-traumatic stress disorder or a history of an eating disorder within the previous month of study enrollment.

Laboratory examinations

Mitochondrial genome mutational analysis: Utilizing Puregene DNA Isolation Kits (Gentra Systems), genomic DNA was extracted from the subjects' entire blood. As previously stated, L- and H-strands oligonucleotide primer sets were used to amplify the whole mitochondrial genomes of the two probands by PCR in 24 overlapping fragments[13]. Each purified fragment was examined using direct sequencing on an ABI 3100 automated DNA sequencer utilizing a Big Dye Terminator Cycle sequencing reaction kit. Consensus Cambridge sequence was matched to these sequence findings (GenBank accession number: NC 012920)[14]. The Seqweb program GAP (GCG) was used for DNA and protein sequence alignments. Genomic DNA from Chinese controls were used as templates, we amplified segments spanning the required sites by PCR and sequenced the resulting PCR products to determine the allele frequency of the T3394C mutation in the *ND1* gene.

Phylogenetic analysis and haplogroup analyses: Homo sapiens[14], mouse[15], bovine[16], and Xenopus laevis[17] mitochondrial DNA sequences were utilized in the interspecific study. By comparing the four animals, the conservation was evaluated. The complete mtDNA sequences of the two Chinese probands with the T3394C mutation were allocated to the Asian mitochondrial haplogroups as per the nomenclature of mitochondrial haplogroups[18,19].

Mitochondrial DNA analysis: The mitochondrial genome of these probands for mutations was analyzed to determine the molecular basis of MDD. PCR was used to amplify the whole genome fragments of mitochondria that were then sequenced from the samples of these probands. Substances with MDD have been shown to carry a T-to-C transition at position 3394 (T3394C) in the *ND1* gene, which causes the amino acid tyrosine to be replaced by histidine (Y30H) at position 30[20]. Figure 2 shows that the tyrosine at ND1 position 30 is significantly preserved across 27 different species. Leber's hereditary optic neuropathy (LHON) has been linked to this mutation in 3 Chinese families[21] and 1 Finnish family[22], as well as metabolic diseases[23], and deafness[24] in 1 Chinese family. From a sample of 167 unrelated Chinese control people, we know that one (20-year-old man) carries the T3394C mutation based on allele frequency analysis.

Besides the identical T3394C mutation (Table 2), these individuals displayed unique mtDNA polymorphisms. Other nucleotide variations in these mitochondrial genomes include 12 documented variations in the D-loop, three recognized variations in the *12S rRNA* gene, 1 recognized variation in the *16S rRNA* gene, 14 recognized silent variants, and 11 (2 novel/9 known) nonsense mutations in the polypeptide-encoding genes. These nonsense mutations are T4216C (T304H) in the *ND1* gene; G4491A (V8I) in the *ND2* gene; A8701G (T59A), TG8728T (T68G), A8860G (T112A) and A9136G (I204V) in the *A6* gene; A10398G (T114A) in the *ND3* gene; A14417G (V86A) in the *ND6* gene; and C14766T (T7I) and A15326G (T194A) in the *Cytb* gene. There were 31 mutations that were carried by both probands. Phylogenetic analysis of these RNA and polypeptide variations and sequences from other taxa, such as mice[15], cattle[16], and Xenopus laevis[17], was used to assess these variants further. Nevertheless, with the exception of T3394C, none of these variations shown evolutionary conservation. The mtDNA sequence variants of two Chinese relatives were used to identify their haplogroup affiliation of each mtDNA using the nomenclature of mitochondrial haplogroups[18,19]. The mtDNA of pedigrees NB011 and NB054 correspond, respectively, to the Eastern Asian haplogroups M9a3 and M9a.

FINAL DIAGNOSIS

The described patients are all ultimately diagnosed with MDD.

DISCUSSION

In this investigation, the clinical, genetic, and molecular characteristics of two Chinese families with MDD were determined. MDD had a distinct clinical phenotype and solely existed in the maternal lineage in the two families, prompting us to speculate that mtDNA may be the molecular foundation of MDD. Complete mitochondrial genome sequence study of the two pedigrees revealed different mtDNA polymorphisms except for the same T3394C (Y30H) mutation in the *ND1* gene. The *ND1* gene is the central component of the 45 subunits of complex I, and the T3394C mutation caused a shift from tyrosine to histidine (Y30H) at position 30[25,26]. Actually, the hydroxyl group on Y30 of ND1 interacts electrostatically with the side chain of E4 and the carbonyl group on M1 of NDUFA1[26,27]. Consequently, the T3394C mutation may disturb the interactions among ND1 and NDUFA1, consequently affecting the structure and function of complex I[28]. Leber's optic neuropathy[21,22], metabolism disorders[23] and deafness[24] are only some of the additional clinical problems linked to the T3394C mutation.

Table 2 mtDNA mutations in two Chinese pedigrees with major depressive disorder

Gene	Positon	Replacement	Conservation[a] (H/B/M/X)	CRS[b]	NB011	NB054	Previously reported[c]
D-loop	73	A-G		A	G	G	Y
	146	T-C		T	C	C	Y
	153	A-G		A	G	G	Y
	263	A-G		A	G	G	Y
	309	C-CCT		C		CCT	Y
	310	T-C		T	TC	C	Y
	489	T-C		T	C	C	Y
	16223	C-T		C	T	T	Y
	16234	C-T		C	T	T	Y
	16291	C-T		C	T		Y
	16316	A-G		A	G	G	Y
	16362	T-C		T	C	C	Y
12S rRNA	750	A-G	A/A/A/-	A	G	G	Y
	1041	A-G	A/T/T/T	A	G	G	Y
	1438	A-G	A/A/A/G	A	G	G	Y
16S rRNA	2706	A-G	A/G/A/A	A	G	G	Y
ND1	3394	T-C (Tyr30His)	Y/Y/Y/Y	T	C	C	Y
	4216	T-C (Tyr304His)	Y/H/H/H	T	C		Y
ND2	4491	G-A (Val8Ile)	V/I/I/V	G	A	A	Y
	4769	A-G		A	G	G	Y
CO1	7028	C-T		C	T	T	Y
	7142	T-C		T	C		Y
CO2	7861	T-C		T	C		Y
ATP6	8701	A-G (Thr59Ala)	T/S/L/Q	A	G	G	Y
	8728	TG-T (Trp68Gly)	W/W/W/W	TG		T	N
	8860	A-G (Thr112Ala)	T/A/A/T	A	G	G	Y
	9136	A-G (Ile204Val)	I/F/F/I	A		G	N
CO3	9242	A-G		A	G		Y
	9540	T-C		T	C	C	Y
ND3	10398	A-G (Thr114Ala)	T/T/T/A	A	G	G	Y
	10400	C-T		C	T	T	Y
ND4	10873	T-C		T	C	C	Y
	11719	G-A		G	A	A	Y
ND5	12705	C-T		C	T	T	Y
ND6	14308	T-C		T	C	C	Y
	14417	A-G (Val86Ala)	V/K/W/S	A	G		Y
CYTB	14766	C-T (Thr7Ile)	T/S/T/S	C	T	T	Y
	14783	T-C		T	C	C	Y
	15043	G-A		G	A	A	Y
	15301	G-A		G	A	A	Y
	15326	A-G (Thr194Ala)	T/M/I/I	A	G	G	Y

[a]Conservation of amino acids for polypeptides or nucleotides for RNAs in human, bovine, mouse, and Xenopus laevis.
[b]Cambridge reference sequence (Andrews *et al*[14], 1999).
[c]See online mitochondrial genome databases http://www.mitomap.org and http://www.genpat.uu.se/mtDB/.
CRS: Cambridge reference sequence; H: Human; B: Bovine; M: Mouse; X: Xenopus laevis.

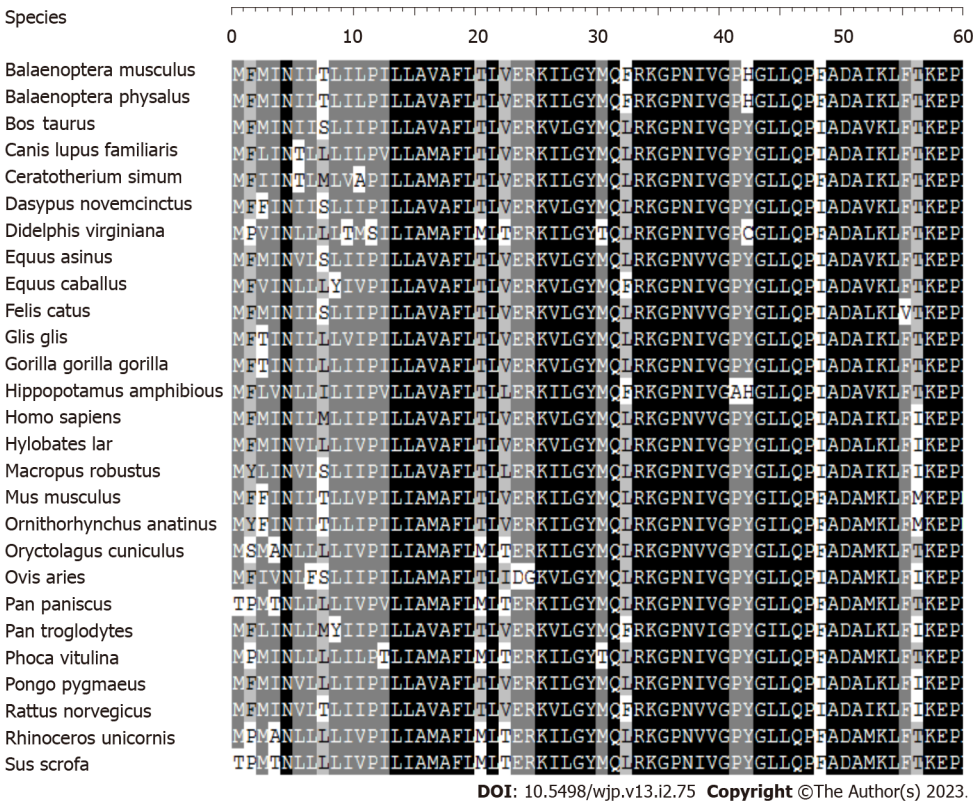

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Figure 2 Alignment of partial *ND1* polypeptides from different species. The arrow indicates the tyrosine at position 30 (Y30) at the N-terminus of the *ND1* polypeptide, corresponding to the T3394C mutation.

Although both families had typical clinical manifestations of major depressive disorder, there were differences in penetrance, age at onset, and severity. The penetrance of the two families was 8.3% and 14.3%, respectively. This relatively low penetrance of MDD in two Chinese families having the T3394C mutation and its presence in one out of 167 controls suggests that, similar to previous mutations[29,30], the T3394C mutation alone is inadequate to induce the clinical manifestation. Therefore, the T3394C mutation requires modifying variables, such as nuclear histories, additional external variables, and mitochondrial haplotypes for phenotypic expression. Particularly, it has been demonstrated that mitochondrial haplotypes alter the penetrance and expressivity of MDD linked with primary mtDNA mutations[31]. The mtDNA of pedigrees NB011 and NB054 correspond, respectively, to the Eastern Asian haplogroups M9a3 and M9a.

The homogenous mutation T3394C was found in MDD families with different genetic backgrounds. The minimal penetrance of MDD among families with this mutation suggests that the T3394C mutation is a molecular base for the pathogenesis of MDD, but the mutation alone is not sufficient to cause phenotypic expression of MDD. This suggests that other mediators played a synergistic role in the pathophysiology of these families. Furthermore, the whole mitochondrial genome of the two families did not carry other highly conserved and functional mutation sites, indicating that polymorphic sites related to mitochondrial haplomorphism may not have a significant impact in the pathophysiology of two MDD families with the T3394C mutation. Moreover, mtDNA epigenetics may be involved in the occurrence of MDD, but research on the role of mtDNA epigenetics in diseases and therapeutic targets is insufficient. Therefore, nuclear-modified genes or external variables have a function in the phenotypic expression of MDD related T3394C mutations in these Chinese individuals. In conclusion, the *ND1* T3394C mutation may be a mitochondrial gene mutation site associated with MDD.

CONCLUSION

This observation of the T3394C mutation in two genetically unrelated individuals who suffer from depression strongly indicates that the current mutation might contribute to developing MDD. However, in these two Chinese families having the T3394C mutation, no functional mtDNA mutation was found. Therefore, the phenotypic manifestation of T3394C mutations linked to MDD may be affected by nuclear changed genes or environmental factors.

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FOOTNOTES

Author contributions: Jing P participated in the conceptualization, methodology, data curation, original draft writing, visualization, and formal analysis; Mei X, Zhang YY, Zheng FJ, Luo XM, Liu LJ, and Yu HH contributed to data collection, writing of the original draft, review, and editing; Zhang XB contributed to the creation and design, aided in writing of the paper, and reviewed it carefully for significant intellectual content; All authors participated in the work, consented to its submission to the journal, and authorized the latest report.

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Informed consent statement: Written informed consent was obtained from the guardian for participation in this study.

Conflict-of-interest statement: The authors declare that no commercial or financial ties that might be considered as a potential conflict of interest existed during the conduct of the research.

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