Screening of the key genes and signaling pathways for schizophrenia using bioinformatics and next generation sequencing data analysis

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ABSTRACT

Schizophrenia is thought to be the most prevalent chronic psychiatric disorder. Researchers have identified numerous proteins associated with the occurrence and development of schizophrenia. This study aimed to identify potential core genes and pathways involved in schizophrenia through exhaustive bioinformatics and next generation sequencing (NGS) data analyses using GSE106589 NGS data of neural progenitor cells and neurons obtained from healthy controls and patients with schizophrenia. The NGS data were downloaded from the Gene Expression Omnibus database. NGS data was processed by the DESeq2 package in R software, and the differentially expressed genes (DEGs) were identified. Gene ontology (GO) enrichment analysis and REACTOME pathway enrichment analysis were carried out to identify potential biological functions and pathways of the DEGs. Protein-protein interaction network, module, micro-RNA (miRNA)-hub gene regulatory network, transcription factor (TF)-hub gene regulatory network, and drug-hub gene interaction network analysis were performed to identify the hub genes, miRNA, TFs, and drug molecules. Potential hub genes were analyzed using receiver operating characteristic curves in the R package. In this investigation, an overall 955 DEGs were identified: 478 genes were remarkably upregulated and 477 genes were distinctly downregulated. These genes were enriched for GO terms and pathways mainly involved in the multicellular organismal process, G protein-coupled receptor ligand binding, regulation of cellular processes, and amine ligand-binding receptors. *MYC*, *FN1*, *CDKN2A*, *EEF1G*, *CAV1*, *ONECUT1*, *SYK*, *MAPK13*, *TFAP2A*, and *BTK* were considered the potential hub genes. The MiRNA-hub gene regulatory network, TF-hub gene regulatory network, and drug-hub gene interaction network were constructed successfully and predicted key miRNAs, TFs, and drug molecules for schizophrenia diagnosis and treatment. On the whole, the findings of this investigation enhance our understanding of the potential molecular mechanisms of schizophrenia and provide potential targets for further investigation.

Introduction

Schizophrenia is a chronic brain disease in which there is an imbalance in serial neurotransmitters, such as dopamine and glutamate.[1] Schizophrenia affects around 1% of the world's population and causes a severe health burden.[2] The main features of the progression of schizophrenia are delusions, hallucinations, thought disorders, anhedonia, avolition, social withdrawal, poverty of thought, and cognitive dysfunction.[3] Schizophrenia, one of the major components of the heterogeneous psychiatric disorder, is closely associated with a variety of diseases such as cardiovascular diseases,[4] neurodegenerative diseases,[5] infections,[6] obesity,[7] diabetes mellitus,[8] and hypertension.[9] Although there are extensive studies on the molecular mechanism in schizophrenia progression, the causes of schizophrenia are still not clear. The occurrence and progression of schizophrenia are correlated with multiple factors from the point of view of science and research, for instance, genetic and environmental factors.[10] The causes and the underlying molecular mechanisms, discovering molecular biomarkers for early diagnosis, prevention, and personalized therapy, are critically important and highly demanded.

In recent years, several biomarkers have been found to be associated with changes in neuron structure and function in schizophrenia patients.[11] With the advancement of the next generation sequencing (NGS) technology and bioinformatics techniques, the ability of humans to understand diseases from the root has greatly improved, and more and more disease-related risk genes have been identified. Many NGS studies have shown that mRNAs and protein encodes play essential roles in the pathogenesis of schizophrenia. They influence disease manifestation, advancement, and prognosis through their interactions and regulation of signaling pathways. For example, investigations have shown that *GLT8D1* and *CSNK2B*,[12] *PPP3CC*,[13] *DTNBP1*,[14] *CSMD1*, *C10orf26*, *CACNA1C* and *TCF4*,[15] and *ZNF804A* expression are altered in schizophrenia patients;[16]they can be used as biomarkers for the diagnosis of schizophrenia. Interestingly, signaling pathways include the Akt signaling pathway,[17] Wnt signaling pathway,[18] MAPK-and cAMP-associated signaling pathways,[19] NF-κB signaling pathway,[20] and PI3K signaling pathway were observed in schizophrenia.[21] However, our ability to understand the molecular basis of schizophrenia remains limited. In this regard, it is necessary to address the association of genes and signaling pathways in candidate genomes with schizophrenia development.

In this investigation, we screened out the differentially expressed genes (DEGs), between normal control and schizophrenia patients in both neural progenitor cells and neurons from NGS data of Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/) .[22] The key pathways and biomarkers were identified from analysis of gene ontology (GO), REACTOME pathways, protein-protein interaction (PPI) networks, modules, micro-RNA (miRNA)-hub gene regulatory network, transcription factor (TF)-hub gene regulatory network, drug-hub gene interaction network, and receiver operating characteristic (ROC) curve analysis tools that offer a new clue to uncover the novel molecular pathogenesis and therapeutic targets of schizophrenia.

Materials and Methods

Next generation sequencing data source

NGS dataset GSE106589 was downloaded from GEO.[23] GSE106589 containing 46 cases of schizophrenia and 33 normal control cases were obtained from the GPL16791 Illumina HiSeq 2500 (Homo sapiens) platform. All cases were of human source.

Identification of differentially expressed genes

The differential expression analysis on mRNA was performed using the DESeq2 package in R software.[24] The DEGs between schizophrenia and normal control were identified using a p-value of <0.05 and |fold change| >0.69 for upregulated genes and |fold change| <-0.51 for downregulated genes as the cutoff for screening. The volcano map and heatmap of the DEGs were respectively generated using the ggplot2 and gplot packages in R software.

Gene ontology and pathway enrichment analyses of differentially expressed genes

GO functional annotation (http://www.geneontology.org) includes biological processes (BP), cellular component (CC), and molecular function (MF), which can be used to clarify the potential biological functions of the enriched genes.[25] Pathway enrichment analysis can be used to identify the main biochemical metabolic pathways and signal transduction pathways involved in enriched genes. GO and REACTOME (https://reactome.org/) pathway enrichment analysis of the DEGs were performed using the g:Profiler (http://biit.cs.ut.ee/gprofiler/).[26,27] A p-value of ≤0.05 was used as the cutoff for screening.

Construction of the protein-protein interaction network and module analysis

The International Molecular Exchange Consortium (IMEx) (https://www.imexconsortium.org/),[28] the most commonly used online tool for PPI network analysis in the biomedical field, was used to develop the PPI network of DEGs. Finally, the PPI network was visualized using the Cytoscape software (V3.10.1; http://cytoscape.org/).[29] The network analyzer plug-in was used to calculate node degree, betweenness, stress, and closeness of hub genes in the PPI network.[30-33] The PEWCC of Cytoscape was carried out to module analyze and visualize the result of PPI network and the key modules with the highest score were selected for visualization display.[34]

Construction of the micro-RNA-hub gene regulatory network

miRNA-hub gene was predicted by the miRNet database (https://www.mirnet.ca/).[35] The miRNAs of interaction in databases (TarBase, miRTarBase, miRecords, miRanda (S mansoni only), miR2Disease, HMDD, PhenomiR, SM2miR, PharmacomiR, EpimiR, starBase, TransmiR, ADmiRE and TAM 2) were as the predicted miRNA that might regulate schizophrenia. The miRNA-hub gene network was visualized by cytoscape software.[29]

Construction of the transcription factor-hub gene regulatory network

TF-hub gene was predicted by the NetworkAnalyst database (https://www.networkanalyst.ca/).[36] The TFs of interaction in database (Jasper) were as the predicted TF that might regulate schizophrenia. The TF- hub gene network was visualized by cytoscape software.[29]

Construction of the drug-hub gene interactions network

The NetworkAnalyst database (https://www.networkanalyst.ca/) is an online database for identifying drug- hub gene interaction by integrating the data from DrugBank.[36] The hub genes were imported into the database to search for potential drugs. The drug-hub gene interactions network was visualized by the cytoscape software.[29]

Receiver operating characteristic curve analysis

ROC curve analysis, which yields indicators of certainty such as the area under the curve (AUC), provides the crucial principle and explanation for distinguishing between the specificity and sensitivity of diagnostic performance of hub genes. We used the pROC package of R software to conduct our ROC curve analysis.[37]

Results

Identification of differentially expressed genes

The NGS dataset GSE106589 was downloaded from the GEO database, and 955 schizophrenia-related DEGs were obtained by a differential analysis, of which 478 were highly expressed ($p<0.05$, $|\text{fold change}| >0.69$) and 477 were poorly expressed ($p<0.05$, $|\text{fold change}| <-0.51$) (*Supplementary Table 1*). To visualize the DEGs, we constructed a volcano plot (*Supplementary Figure 1*) and heatmap (*Supplementary Figure 2*).

Gene ontology and pathway enrichment analyses of differentially expressed genes

GO functional annotation and REACTOME pathway enrichment analysis were performed for the DEGs from the NGS dataset. The significant results are presented in *Supplementary Table 2*. In the BP group, the upregulated genes were mainly clustered in the multicellular organismal process and developmental process, and the downregulated genes were mainly clustered in the regulation of cellular process and biological regulation. For the CC group, the upregulated genes were primarily clustered in the cell periphery and cellular anatomical entity. The downregulated genes were primarily clustered in the cell periphery and plasma membrane. The upregulated genes in the MF group were mostly clustered in DNA-binding transcription activator activity, RNA polymerase II-specific and signaling receptor binding, and the downregulated genes were mostly clustered in double-stranded DNA binding and sequence-specific DNA binding. The top significantly enriched REACTOME pathways for the DEGs were also displayed by the g:Profiler online software and are presented in *Supplementary Table 3*. The upregulated genes were associated with G protein-coupled receptor (GPCR) ligand binding and extracellular matrix organization, while the downregulated genes were involved in amine lig-and-binding receptors and signaling by GPCR.

Construction of the protein-protein interaction network and module analysis

To investigate the molecular mechanism of schizophrenia from a systematic perspective, the PPI network was constructed to explore the relationship between proteins. The PPI network was constructed by IMEx for DEGs. There were 3647 nodes and 6307 edges in the visualization network using the Cytoscape (*Supplementary Figure 3*). The highest node degree, betweenness, stress, and closeness genes were *MYC*, *FN1*, *CDKN2A*, *EEF1G*, *CAV1*, *ONECUT1*, *SYK*, *MAPK13*, *TFAP2A* and *BTK*, and are listed in *Supplementary Table 4*. According to the degree of importance, we chose 2 significant modules from the PPI network complex for further analysis using Cytotype MCODE. Functional enrichment analysis showed that module 1 consisted of 54 nodes and 56 edges (*Supplementary Figure 4A*), which are mainly associated with cytokine signaling in immune system and multicellular organismal process, and that module 2 consisted of 99 nodes and 117 edges (*Supplementary Figure 4B*), which are mainly associated with regulation of cellular process and platelet activation, signaling and aggregation.

Construction of the micro-RNA-hub gene regulatory network

To explore the interactions between schizophrenia-related hub genes and miRNA, the miRNA-hub gene regulatory network containing 2191 nodes and 8938 edges was constructed (*Supplementary Figure 5*). Of all the nodes, 1937 nodes were miRNAs, while the other 254 nodes were hub genes. The top hub genes for miRNAs were *MYC* [modulated by 194 miRNAs (ex: hsa-mir-3157-5p)], *RUNX1* [modulated by 125 miRNAs (ex: hsa-mir-4530)], *CAV1* [modulated by 115 miRNAs (ex: hsa-mir-4796-3p)], *FN1* [modulated by 105 miRNAs (ex: hsa-mir-132-3p)], *CACNA1A* [modulated by 69 miRNAs (ex: hsa-mir-10b-5p)], *IRS4* [modulated by 134 miRNAs (ex: hsa-mir-769-3p)], *TFAP2A* [modulated by 100 miRNAs (ex: hsa-mir-4713-5p)], *HSPA2* [modulated by 45 miRNAs (ex: hsa-mir-155-5p)], *GDA* [modulated by 45 miRNAs (ex: hsa-mir-191-5p)] and *MAPK13* [modulated by 43 miRNAs (ex: hsa-mir-4516)], and are listed in *Supplementary Table 5*.

Construction of the transcription factor-hub gene regulatory network

To explore the interactions between schizophrenia-related hub genes and TF, the TF-hub gene regulatory network containing 334 nodes and 1972 edges was constructed (*Supplementary Figure 6*). Of all the nodes, 82 nodes were TFs, while the other 252 nodes were hub genes. The top hub genes for TFs were *STAT6* [modulated by 16 TFs (ex: *USF2*)], *CDKN2A* [modulated by 16 TFs (ex: *SRY*)], *CAV1* [modulated by 16 TFs (ex: *HOXA5*)], *FN1* [modulated by 14 TFs (ex: *RELA*)], *MAP1LC3A* [modulated by 14 TFs (ex: JUND)],

GDA [modulated by 13 TFs (ex: *GATA3*)], *SYK* [modulated by 13 TFs (ex: *FOXC1*)], *TFAP2A* [modulated by 13 TFs (ex: *PRDM1*)], *IRS4* [modulated by 11 TFs (ex: *PAX2*)] and *KHDRBS2* [modulated by 10 TFs (ex: *PDX1*)], and are listed in *Supplementary Table 5*.

Construction of the drug-hub gene interaction network

The drug-hub gene interactions network showed the potential drugs that targeted the hub genes from the NetworkAnalyst database (*Supplementary Figure 7*). The drugs were predicted, and the detailed information was listed in *Supplementary Table 6*. Of these, 7 drugs (ex: Cabazitaxel) targeted *TUBA4A*; 3 drugs (ex: Becaplermin) targeted *A2M*; 1 drug (ex: Ocriplasmin) targeted *FN1*; 6 drugs (ex: Staurosporine) targeted *SYK*; 2 drugs (ex: XL418) targeted *BTK*; 2 drugs (ex: Lenalidomide) targeted *CDH5*.

Receiver operating characteristic curve analysis

The AUC values of the ten hub genes were evaluated by ROC curve analysis to examine their sensitivity and specificity for the diagnosis of schizophrenia. All ten hub genes (*MYC*, *FN1*, *CDKN2A*, *EEF1G*, *CAV1*, *ONECUT1*, *SYK*, *MAPK13*, *TFAP2A* and *BTK*) had AUC values more than 0.8, indicating that they have a strong diagnostic value for schizophrenia (*Supplementary Figure 8*).

Discussion

Although numerous relevant investigations of schizophrenia have been performed, early diagnosis, efficacy of treatment, and prognosis for schizophrenia remain poorly resolved. For diagnosis and treatment, it is necessary to further understand the molecular pathogenesis resulting in occurrence and advancement. Due to the advancement of NGS technology, genetic modifications due to disease progression can be detected, indicating gene targets for diagnosis, therapy, and prognosis of specific diseases.[38-39]

We firstly explored the DEGs in schizophrenia *versus* normal control using GSE106589. As a result, a total of 955 DEGs were identified. The expression of *HOTAIR*, *CCL11*, OLIG2, and *CRH* (corticotropin releasing hormone) might be associated with schizophrenia progression.[40-43] The abnormal expression of *HOTAIR* might be related to the progression of bipolar disorder.[44] The abnormal expression of *HOTAIR* contributes to the progression of Parkinson's disease.[45] *HOTAIR* (HOX transcript antisense RNA) and *CCL11* are master regulators that are activated in cardiovascular diseases.[46-47] *HOTAIR*, *SLC15A1*, and *CRH* genes might be related to the pathophysiology of obesity.[48-50] *HOTAIR*, *CCL11* and *CRH* expression is related to the patients with diabetes mellitus.[51-53] A study suggested that *HOXD10*, *CCL11*, *OLIG2* and *CRH* can promote Alzheimer's disease.[54-57] *CRH* is involved in growth and development of neurodegenerative diseases.[58] Research has shown that *CRH* plays an important role in the pathogenesis of hypertension.[59] Results suggest that these significant DEGs play a key role in the progression of schizophrenia.

GO and REACTOME pathway enrichment analyses were used to explore the molecular mechanisms of the enriched genes involved in the occurrence and development of schizophrenia. GPCR ligand binding, extracellular matrix organization, cytokine signaling in immune system, interferon signaling, signaling by GPCR, neuronal system and platelet activation, signaling and aggregation play an important role in the schizophrenia.[60-66]

Studies have revealed that *SIX1*, *VIP*, GATA6, *FRZB*, *CD40*, *WT1*, *PCDHGA3*, *TFAP2B*, *HFE*, *NKX2-5*, *IGFBP7*, *HLA-F*, *CCL2*, *COL1A2*, *RUNX1*, *TFF3*, *IRX4*, *NOS1*, *DKK2*, *IL18R1*, *ADAM12*, *NPPC*, *COL1A1*, *ABCG2*, *SIX2*, *CSRP1*, *MR1*, *NINJ2*, *ACE*, *TBX1*, *CTSC*, *DLX6*, *KCNE1*, *AZGP1*, *CYP1B1*, *PRRX1*, *CD34*, *A2M*, *CDKN2A*, *SERPINE1*, *CD44*, *FABP4*, *ITGB3*, *ALOX5AP*, *DAND5*, *SFRP4*, *RUNX2*, *TACR3*, *MYD88*, *CYBA*, *STAT6*, *FOXC1*, *FN1*, *TLR6*, *CAV1*, *RGS4*, *TPM2*, *TNFSF4*, *LOX*, *SMOC2*, *SPHK1*, *FOLH1*, *CYP2C8*, *CD163*, *DIRAS3*, *OSMR*, *POSTN*, *SELL*, *TMPRSS2*, *FLNC*, *CXCL16*, *APOBR*, *COL6A2*, *LTBP2*, *SPARCL1*, *FOSL2*, *ISL1*, *HTR2C*, *TNNT2*, *HGF*, IL33, *SYK*, *ADRB1*, *CMKLR1*, *SHOX2*, *MEG3*, *SCUBE1*, *CAT*, *LAMA3*, *COL15A1*, *DSC2*, *RSPO2*, *PCSK9*, *SCN5A*, *FOXF1*, *DACT2*, *LMOD2*, *CDH13*, *DSCAM*, *PCP4*, *ANG*, *GDF15*, RYR1, *IRGM*, *TRPC3*, *PDE2A*, *SCML4*, *SEMA3F*, *CUX2*, *ROBO4*, *DRD2*, *GP6*, *TRPM5*, *ABI3BP*, *ACAN* and *NPC1L1* play a key role in cardiovascular diseases.[67-181] Previous studies have reported that the *XCL1*, *HLA-DMB*, *CD40*, *HLA-DRA*, *RUNX1*, *IL18R1*, *NINJ2*, *ACE*, *CD44*, *IL4R*, *MYD88*, *WNT9B*, *CXCL16*, *CXCL13*, *RORB*, *GDF15*, *THEMIS*, *KCNH7*, *BTK* and *MOBP* (myelin associated oligodendrocyte basic protein) are key regulators of multiple sclerosis.[182-201]

Recently, increasing evidence demonstrated that *HLA-DMB*, *VIP*, *GATA6*, *CD40*, *TFAP2B*, *HFE*, *IGFBP7*, *NPY2R*, *CCL2*, *AQP5*, *HLA-DMA*, *RUNX1*, *PPY*, *ASPA*, *NOS1*, *ADAM12*, *NPPC*, *COL1A1*, *IL1R1*, *ABCG2*, *ACE*, *CD34*, *HLA-DPA1*, *A2M*, *MEOX2*, *CDKN2A*, *SERPINE1*, *CD44*, *FABP4*, *ITGB3*, *ALOX5AP*, *SFRP4*, *ISM1*, *IL4R*, *RUNX2*, *CASP1*, *CCR4*, *MYD88*, *DRD3*, *STAT6*, *ANXA1*, *CAV1*, *RGS4*, *SPHK1*, *CYP2C8*, *CD163*, *DIRAS3*, *POSTN*, *SELL*, *TMPRSS2*, *CXCL16*, *FOSL2*, *ISL1*, *HGF* (hepatocyte growth factor), *ADRA2A*, *IL33*, *SYK*, *GCG*, *PTPRT*, *GRIK3*, *NR2E1*, *CMKLR1*, *ONECUT1*, *DEFB1*, *MNX1*, *MEG3*, *CAT*, *PCSK9*, *PLEK*, *EDA*, *KCNJ1*, *ANG*, *GDF15*, *TRPC3*, *RAG2*, *ROBO4*, *SLC2A4*, *DRD2*, *GP6*, *RASGRP1*, *TRPM5*, *NPC1L1*, *ALDH3A1* and *ADH1B* were altered expressed in diabetes mellitus.[202-281] Studies had shown that *VIP*, *HFE*, *IGFBP7*, *HOXC8*, *CCL2*, *GRHL3*, *NOS1*, *ADAM12*, *NINJ2*, *ACE*, *TBX1*, *HTR1B*, *CD34*, *HLA-DPA1*, *HTR7*, *FABP4*, *ITGB3*, *TACR3*, *MYD88*, *TGM2*, *DRD3*, *CAV1*, *RGS4*, *SLCO6A1*, *CD163*, *CACNA1A*, *HSPA1L*, *NALCN*, *HTR2C*, *CHRM1*, *LMX1A*, *SLITRK2*, *CCKBR*, *ADRA2A*, *IL33*, *IRS4*, *ADRA2C*, *GRIK3*, *NR2E1*, *MICB*, *MEG3*, *CAT*, *GPR78*, *PCSK9*, *SCN5A*, *NTNG2*, *CDH13*, *LGI1*, *SLC1A2*, *PDE2A*, *KCNH7*, *DRD2*, *GPR143*, *RASGRP1* and *ACAN* were associated with schizophrenia.[282-335] *VIP*, *CD40*, *CCL2*, *DKK2*, *ACE*, *KCNN4*, *A2M*, *CDKN2A*, *MYD88*, *TLR6*, *ANXA1*, *SPHK1*, *CACNA1A*, *SLITRK2*, *IL33*, *CAT*, *GPR78*, *ANG*, *GDF15* and *ADH1B* might be a potential therapeutic targets for neurodegenerative diseases treatment.[336-355] At present, abnormal expression of *VIP*, *HFE*, *CCL2*, *HLA-DRA*, *TFF3*, *NOS1*, *NPPC*, *ACE*, *GSDMD*, *A2M*, *PLXNA4*, *CD44*, *CASP1*, *DRD3*, *UNC5C*, *CAV1*, *SPHK1*, *CD163*, *RPH3A*, *HGF*, *CCKBR*, *TNFSF9*, *MEG3*, *GPR78*, *NEUROG2*, *ANG*, *GDF15*, *UNC5A*,

SLC1A2, *DRD2*, *GPR143*, *RASGRP1* and *MOBP* have been found in a Parkinson's disease.[356-387]

VIP, *CD40*, *WT1*, *HFE*, *TAC1*, *AQP5*, *WNT2B*, *RUNX1*, *NOS1*, *DKK2*, *ADAM12*, *ABCG2*, *NINJ2*, *ACE*, *PRKCB*, *A2M*, *MEOX2*, *CDKN2A*, *PLXNA4*, *SPINT1*, *SERPINE1*, *RGCC*, *CD44*, *CASP1*, *MYD88*, *DRD3*, *UNC5C*, *LOX*, *SPHK1*, *RPH3A*, *CXCL16*, *CASS4*, *IFITM3*, *COL25A1*, *SPARCL1*, *FOXG1*, *CHRM1*, *HSPA2*, *HGF*, *IL33*, *MEG3*, *RSPO2*, *PCSK9*, *PCSK9*, *RORB*, *ANGPT4*, *CDH13*, *PCP4*, *ANG*, *GDF15*, *OPRD1*, *PDE11A*, *TREML1*, *GP6*, *BTK*, *DSC1*, *LAMP5* and *ADH1B* were identified to be associated with Alzheimer's disease.[388-443]

VIP, *CD40*, *TFAP2B*, *NPY2R*, *CCL2*, *COL1A2*, *RUNX1*, *PPY*, *ASPA*, *TBX15*, *ADAM12*, *NPPC*, *COL1A1*, *ABCG2*, *STING1*, *NPY5R*, *ACE*, *HTR1B*, *PRKCB*, *NPR3*, *CYP1B1*, *CD34*, *A2M*, *CDKN2A*, *SERPINE1*, *CD44*, *FABP4*, *ALOX5AP*, *RUNX2*, *CASP1*, *MYD88*, *STAT6*, *TLR6*, *NPY1R*, *ANXA1*, *CAV1*, *RGS4*, *DOCK5*, *COBL*, *LOX*, *SPHK1*, *CD163*, *POSTN*, *TMPRSS2*, *CXCL16*, *IFITM3*, *ISL1*, *HTR2C*, *HSPA2*, *HGF*, *ADRA2A*, *IL33*, *GCG*, *PTPRT*, *ADRB1*, *NR2E1*, *CMKLR1*, *MEG3*, *SCUBE1*, *CAT*, *PCSK9*, *SCN5A*, *EDA*, *WNT10B*, *CDH13*, *GDF15*, *ACTN3*, *SLC2A4, DRD2*, *TRPM5*, *BMP8B*, *ACAN*, *NPC1L1* and *ADH1B* have been shown to be a biomarkers of obesity.[444-502]

VIP, *GATA6*, *CD40*, *WT1*, *HFE*, *IGFBP7*, *CCL2*, *AQP5*, *RUNX1*, *NOS1*, *XDH*, *ADAM12*, *NPPC*, *IL1R1*, *SIX2*, *ACE*, *CYP1B1*, *CD34*, *CDKN2A*, *EPHA6*, *CD44*, *FABP4*, *ITGB3*, *RUNX2*, *CASP1*, *MYD88*, *DRD3*, *STAT6*, *RCN3*, *FOXC1*, *TLR6*, *ANXA1*, *RAMP1*, *CAV1*, *LOX*, *SPHK1*, *CYP2C8*, *CD163*, *POSTN*, *TMPRSS2*, *RAB38*, *ECM2*, *CACNA1A*, *CAVIN2*, *CXCL16*, *COL6A2*, *SPARCL1*, *HGF*, *CCKBR*, *ADRA2A*, *IL33*, *CXCL13*, *CBLN2*, *ADRB1*, *CMKLR1*, *SCUBE1*, *CAT*, *PCSK9*, *FOXF1*, *CDH13*, *GDF15*, *TRPC3*, *GPR143*, *BTK*, *ACAN* and *ADH1B* have been found to be altered expression in hypertension.[503-562]

FRZB, *HLA-DRA*, *CD44*, *CASP1*, *LOX*, *ANG* and *RAG2* genes expression were found to be elevated in amyotrophic lateral sclerosis.[563-569] *IGFBP7*, *TFF3*, *ACE*, *ANXA1*, *EFEMP1*, *ANGPT4*, *GDF15* and *MOBP* expression are altered in the patients with dementia.[570-572] *NPY2R*, *CASP1*, *CHRM1* and *MEG3* have been proposed as novel biomarkers for Huntington disease.[573-576]

Some studies have shown that *SPOCD1*, *DRD3*, *DOCK5*, *SLCO6A1*, *HTR2C*, *OTX2*, *LMX1A*, *NR2E1*, *GPR78*, *RORB*, *NTNG2*, *PRR5-ARHGAP8*, *CACNA2D4*, *SLC1A2*, *CUX2*, *KCNH7* and *ACAN* plays a certain role in bipolar disorder.[577-588] The altered expression of *ABCG2*, *LAMC3*, *CACNA1A*, *COL6A2*, *SLC13A5*, *GABRA2*, *SCN5A*, *KCNQ5*, *SLC1A2*, *TRPC3*, *GABRA4*, *SLC6A11*, *KCNQ5* and *SLCO5A1* are associated with epilepsy.[589-601] In summary, DEGs involved in GO term and REACTOME pathway were more likely related to schizophrenia and might be important targets in schizophrenia therapy.

To explore the molecular pathogenesis of schizophrenia, we constructed PPI network and module analysis for systematic analysis. In order to further analyze the whole PPI network, the topological analysis was used to explain the importance of the hub genes in the network and the influence of the hub genes on the network. Previous studies had shown that the altered expression of *FN1*, *CDKN2A*, *CAV1*, *SYK* and *CD40* were closely related to the occurrence of cardiovascular diseases.[71,105,119,121,148] A study had shown that regulation of *CDKN2A*, *CAV1*, *ONECUT1*, *SYK*, *IL4R* and *CD40* promoted the diabetes mellitus.[148,205,226,233,241,260]

CDKN2A and *CD40* are involved in mediating the progression of neurodegenerative diseases.[337,343] Previous studies report the altered expression of *CDKN2A*, *BTK* and *CD40* in the nervious tissue obtained from Alzheimer's disease patients.[389,403,440] *CDKN2A*, *CAV1* and *CD40* are involved in the mediation of obesity.[226,445,472] The results showed that *CDKN2A*, *CAV1*, *BTK* and *CD40* were expressed in hypertension.[105,505,534,561] *CAV1* and *IRS4* expression is significantly regulated in schizophrenia patients.[303,317] Previous studies report that *CAV1* is involved in Parkinson's disease.[370] *BTK*, *IL4R* and *CD40* expression is associated with clinical and biochemical markers for multiple sclerosis.[184,191,200] We identified *MYC* (MYC proto-oncogene, bHLH transcription factor), *EEF1G*, *MAPK13*, *TFAP2A* and *SIRPB1* might serve as novel biomarkers for schizophrenia. The results suggested that these hub genes might play significant roles in schizophrenia. These findings indicate that hub genes might play a key role in the molecular pathogenesis of schizophrenia., and are key biomarkers linking schizophrenia.

To explore the molecular mechanism of schizophrenia, we constructed the schizophrenia related miRNA-hub gene regulatory network and TF-hub gene regulatory network. Moreover, we performed topological analysis and acquired hub genes, miRNAs and TFs with high topological features. *RUNX1*, *CAV1*, *FN1*, *STAT6*, *CDKN2A*, *SYK*, hsa-mir-769-3p, *HOXA5* [603], *JUND* (JunD proto-oncogene, AP-1 transcription factor subunit) and *FOXC1* were associated with cardiovascular diseases.[81,105,117,119,121,148,602-604]

RUNX1, hsa-mir-132-3p and *HOXA5* were important therapeutic targets of multiple sclerosis.[186,606,607] *RUNX1*, *CAV1*, *STAT6*, *CDKN2A*, *SYK*, hsa-mir-132-3p, hsa-mir-10b-5p, hsa-mir-155-5p, hsa-mir-191-5p, *SRY*, *PAX2* and *PDX1* were the potential molecular targets of the drugs for treating diabetes mellitus.[81,148,226,239,241,608-614]

RUNX1, *CDKN2A*, *HSPA2*, hsa-mir-132-3p, hsa-mir-155-5p and *USF2* have been reported to be expressed in Alzheimer's disease.[395,403,423,610,615,616] *RUNX1*, *CAV1*, *STAT6*, *CDKN2A*, *HSPA2*, hsa-mir-10b-5p and *HOXA5* were related to the obesity.[226,449,468,472,485,617,618]

RUNX1, *CAV1*, *CACNA1A*, *STAT6*, *CDKN2A*, hsa-mir-4516, *SRY*, *FOXC1* and *PRDM1* might offer useful information for treating hypertension.[105,511,528,534,543,619-622]

CAV1, *CACNA1A*, *IRS4* and hsa-mir-155-5p expression have been found to be altered in patients with schizophrenia.[303,307,317,623] *CACNA1A*, *CDKN2A* and hsa-mir-132-3p were identified as potential targets of neurodegenerative diseases.[343,348,624] *CACNA1A* can be used as a potential biomarker for an epilepsy.[591] Increasing evidence demonstrated that *CAV1*, hsa-mir-132-3p, hsa-mir-4516 and *SRY* have a function in Parkinson's disease.[370,615,625,626] hsa-mir-10b-5p is involved in Huntington disease. hsa-mir-4516 is an emerging amyotrophic lateral sclerosis biomarker.[627,628]

In this investigation, *MYC*, *MAP1LC3A*, *TFAP2A*, *GDA*, *MAPK13*, *KHDRBS2*, hsa-mir-3157-5p, hsa-mir-4530, hsa-mir-4796-3p, hsa-mir-4713-5p, *RELA* and *REL* were identified as novel therapeutic targets that might be potential biomarkers for schizophrenia. This suggests that they all play a key role in the progression of schizophrenia. Finally, 21 candidate drugs were predicted. These drugs may serve as potential therapeutics to treat schizophrenia.

Conclusions

In conclusion, in the present investigation, we conducted a thorough bioinformatics and NGS data analysis of DEGs by GSE106589 data screening and identified several genes implicated in the development and progression of schizophrenia. A total of 955 genes were identified, of which *MYC*, *FN1*, *CDKN2A*, *EEF1G*, *CAV1*, *ONECUT1*, *SYK*, *MAPK13*, *TFAP2A* and *BTK* are probable core genes of schizophrenia. This investigation reveals a series of valuable genes for further research into the non-invasive diagnosis and targeted therapy of schizophrenia. However, bioinformatics and NGS data analyses merely indicate a general direction for further investigation. To confirm the functions of DEGs in schizophrenia, molecular biology experiments are required.

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Online supplementary material:

Supplementary Table 1. The statistical metrics for key differentially expressed genes.

Supplementary Table 2. The enriched gene ontology terms of the up and down regulated differentially expressed genes.

Supplementary Table 3. The enriched pathway terms of the up and down regulated differentially expressed genes.

Supplementary Table 4. Topology table for up and down regulated genes.

Supplementary Table 5. Micro-RNA-hub gene and transcript factor-hub gene topology table.

Supplemenary Table 6. Drug-hub gene topology table.

Supplementary Figure 1. Volcano plot of differentially expressed genes. Genes with a significant change of more than two-fold were selected. Green dot represented up regulated significant genes and red dot represented down regulated significant genes.

Supplementary Figure 2. Heat map of differentially expressed genes. Legend on the top left indicates log fold change of genes (A1 – A46 = schizophrenia samples; B1 – B33 = normal control samples).

Supplementary Figure 3. Protein-protein interaction network of differentially expressed genes. Up regulated genes are marked in parrot green; down regulated genes are marked in red.

Supplementary Figure 4. Modules selected from the protein-protein interaction (PPI) network. A) The most significant module was obtained from the PPI network with 54 nodes and 56 edges for upregulated genes; B) the most significant module was obtained from the PPI network with 99 nodes and 117 edges for downregulated genes. Upregulated genes are marked in parrot green; downregulated genes are marked in red.

Supplementary Figure 5. Hub gene – micro-RNA regulatory network. The blue color diamond nodes represent the key miRNAs; upregulated genes are marked in green; downregulated genes are marked in red.

Supplementary Figure 6. Hub gene – transcriptor factor (TF) regulatory network. The olive color triangle nodes represent the key TFs; upregulated genes are marked in green; downregulated genes are marked in red.

Supplementary Figure 7. Hub gene – drug interaction network. The blue color rectangle nodes represent the key drugs; upregulated genes are marked in green; downregulated genes are marked in red.

Supplementary Figure 8. Receiver operating characteristic curve analyses of hub genes.