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Deciphering the Molecular Landscape of Schizophrenia: A Multi-Brain-Region Bioinformatics Analysis Identifies Key Hub Genes and miRNA Regulatory Networks

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Abstract

Schizophrenia is a complex neuropsychiatric disorder characterized by aberrant brain function and structural alterations. Elucidating the molecular mechanisms underlying SZ is essential for the development of targeted diagnostic and therapeutic approaches. In this study, we conducted a comprehensive bioinformatics analysis of gene expression data from three distinct brain regions: Brodmann Area 46, the Hippocampus, and the Associative Striatum—using the GEO database (GSE53987). Differentially expressed genes (DEGs) were identified with filtering criteria (P-value < 0.05, |log FC| > 0.2), revealing 163 common DEGs across all regions. Gene Ontology (GO) and KEGG pathway analyses highlighted enrichment in processes related to detoxification of copper ion, cellular zinc ion homeostasis, stress response to copper ion, zinc ion homeostasis, and detoxification of inorganic compound, and several signaling pathways, including Mineral absorption, HIF−1 signaling pathway, PI3K−Akt signaling pathway, Adipocytokine signaling pathway. A protein-protein interaction (PPI) network identified two hub genes(STAT3 and CDKN1A), which showed significant diagnostic potential, with ROC analysis yielding AUC values consistently above 0.7 across three brain regions. Additionally, miRNA-gene regulatory networks were constructed for the hub genes, revealing six key miRNAs, (hsa-miR-6825-5p, hsa-miR-665, hsa-miR-6886-3p, hsa-miR-106a-5p, hsa-miR-3135b and hsa-miR-17-5p), that may modulate SZ pathogenesis. Our findings offer valuable insights into the molecular mechanisms of SZ and identify potential biomarkers for early diagnosis and therapeutic intervention.

Keyword: Schizophrenia, miRNA, Bioinformatics Analysis, GEO

1.Introduction

Schizophrenia (SZ) is a severe psychiatric disorder that affects between 0.25 and 0.33 percent of the population (Solmi et al., 2023). It is one of the twenty leading causes of disability(Li et al., 2023), with life expectancy reduced by around 15 years(Hjorthøj et al., 2017)and the risk of death by suicide was higher for people with SZ than for the general population(Lyu & Zhang, 2021). Despite extensive research, the exact molecular mechanisms of SZ remain unclear, and current diagnosis primarily relies on clinical symptoms , often leading to delayed detection (Westhoff et al., 2021).

Brodmann Area 46, situated in the prefrontal cortex, is critical for executive functions, including working memory, attention, and cognitive flexibility. Dysfunction in this region is strongly associated with cognitive deficits related to SZ. Neuroimaging and postmortem studies have revealed reduced gray matter volume and altered gene expression in this region among SZ patients, indicating disrupted prefrontal cortex functioning(Ketharanathan et al., 2024). Additionally, deficits in working memory, a core cognitive impairment in SZ, have been associated with hypoactivity in Brodmann Area 46(Lett et al., 2014). The hippocampus, a critical structure for memory consolidation and spatial navigation, exhibits volume reductions and functional abnormalities in SZ. Hippocampal hyperactivity has been proposed as a key mechanism underlying the cognitive deficits and psychotic symptoms in SZ

patients(Lanz et al., 2019).The striatum, particularly the associative subregion, is involved in motor planning, reinforcement learning, and reward processing(Park et al., 2024). Dopamine dysregulation in the dorsal striatum has been identified as a hallmark of SZ, contributing to positive symptoms such as hallucinations and delusions(Sekiguchi et al., 2019).

Gene expression analysis provides a powerful approach for uncovering the molecular basis of SZ, identifying potential biomarkers for early diagnosis, and guiding therapeutic strategies. Bioinformatics is an emerging subject that is already widely used for early diagnosis and predicting the prognosis of cancer patients(Wang & Liotta, 2011). This new approach has been used broadly in the study of various cancers(Heidari et al., 2025; Li et al., 2025; Ye et al., 2025) and has also played a role in the identification of a few new biomarkers for non-oncology diseases(do Nascimento et al., 2025; Fan et al., 2025; Xie et al., 2025).Microarray technology is widely used to screen for genomic-level differential alterations and can be utilized for predicting schizophrenia development. Li et al identified 15 key genes (SLC1A3, AQP4, GJA1, ALDH1L1, SOX9, SLC4A4, EGR1, NOTCH2, PVALB, ID4, ABCG2, METTL7A, ARC, F3 and EMX2) in SZ by performing multiple bioinformatics analysis algorithms (Z. Li et al., 2022). WU et al demonstrated that CCL3, IL1B, CXCL8, CXCL10 and miR-34a-5p may be biomarkers that play crucial roles in the underlying mechanisms of early-onset SZ immune-related pathways(Don & Hammond, 1985). Chen et al found genes(CCL8, PSMD1, AVPR1B and SEMG1) might regulate peripheral immune cells in early-onset SZ(Chen et al., 2024). The first identified microRNAs(miRNA) were discovered in the nematode species Caenorhabditis elegans (C. elegans) approximately three decades ago(Lee et al., 1993). With the advancement of scientific research, it has been discovered that microRNAs (miRNAs) are widely present in both invertebrates and vertebrates(Lagos-Quintana et al., 2001). Given that miRNAs regulate the expression of more than one-third of the human genome, their influence on gene expression and cellular functions is profound(Ardekani & Naeini, 2010). Growing evidence suggests that miRNAs contribute significantly to the complicated etiology and pathogenesis in SZ(Li et al., 2024; Zaki et al., 2024; Zhang et al., 2023). Accordingly, in our study, we downloaded datasets of three different brain regions from common mRNA microarray datasets from Gene Expression Omnibus (GEO) and performed them to identify DEGs between normal and SZ of three different brain regions. Subsequently, enrichment analysis of GO terms and KEGG pathways, as well as PPI network analysis, were conducted to elucidate the underlying molecular mechanisms involved in the pathogenesis of SZ. Lastly, miRNA gene regulatory networks were construct for predicting potential microRNAs (miRNAs) associated with hub genes with the use of Cytoscape and miRNAWALK. In summary, there were 163 DEGs, 2 hub genes and 6 potential miRNAs that were identified as potential target biomarkers for SZ.

2.Materials and Methods

2.1 Source and Filtering of Datasets

The gene expression dataset employed in this study were obtained from the Gene Expression Omnibus (GEO) database(http://www.ncbi.nlm.nih.gov/geo). The dataset GSE53987(Lanz et al., 2019), based on GPL570 (Affymetrix Human Genome U133A Plus 2.0 Array), included 34 postmortem Brodmann Area 46 brain samples, with 15 SZ cases and 19 healthy controls. Additionally, 33 hippocampal samples were included, comprising 15 and 18 SZ cases. 36 associative Striatum samples, 18 disease samples and 18 healthy samples were incorporated. All data originated from the same microarray platform, thereby ensuring strong comparability among the three brain regions.There were no statistically significant differences in age and gender between the disease groups and healthy control groups across the three brain regions(Table 1).

Table 1: Demographic characteristics.The differences in age between groups were assessed using the Independent Samples t-test, whereas the differences in gender distribution were analyzed using the Chi-square test.A p-value less than 0.05 was considered statistically significant.

Region / Demographic	Brodmann Area 46	Hippocampus	Associative Striatum
Disease Group Age (Mean ± SD)	45.67 ± 8.56	45.67 ± 8.56	45.28 ± 8.24
Control Group Age (Mean ± SD)	48.68 ± 11.95	48.33 ± 11.98	48.61 ± 11.12
Disease Group Male(n)	7	9	10

Disease Group Female(n)	8	6	8
Control Group Male(n)	10	9	10
Control Group Female(n)	9	9	8
Age p-value	0.41	0.65	0.55
Sex p-value	0.65	0.55	1

2.2 Differentially Expressed Genes (DEGs)

Differentially expressed genes (DEGs) across the three brain regions were identified using the online tool of GEO2R. Criteria of P-value < 0.05 and |log FC| > 0.2 were applied to identify the DEGs. DEGs with log FC < 0 were considered down-regulated, whereas those with log FC > 0 were regarded as up-regulated. Volcano plots for DEGs in Brodmann Area 46, the Hippocampus, and the Associative Striatum were generated using the same online tool. The tool was employed to create a Venn diagram to identify common DEGs across the three brain regions.
(https://www.xiantao.love/products).In volcano maps, the fold change (log-scaled) was represented on the X-axis, while the P-value was represented on the Y-axis (log-scaled). Each symbol represent a distinct gene. Red symbols indicated up-regulated genes, while blue symbols indicated down-regulated genes.

2.3 Gene Ontology (GO) and KEGG Pathway Analysis

GO and KEGG pathway analysis were conducted using the same tool(https://www.xiantao.love/products). GO terms were classified into three categories: molecular function (MF), cellular component (CC), and biological process (BP).(Pomaznoy et al., 2018). The KEGG pathway analysis identified significant pathways related to SZ pathology(Kanehisa et al., 2017), with statistical significance defined as P-value < 0.05.

2.4 Protein-Protein Interaction (PPI) Network and Hub Genes

PPI networks were constructed using the STRING database (http://string-db.org)(Franceschini et al., 2013) and visualized with Cytoscape(3.9.0). Cytoscape is an open-source bioinformatics software platform used for visualizing molecular interaction networks and integrating these interactions with annotations and gene expression profiles(Smoot et al., 2011).CytoHubba, a plugin for Cytoscape, was used to identify hub genes based on the degree of connectivity. The Hub genes were selected based on a connectivity degree greater than 10.

2.5 Re-analysis of Hub Genes with GO and KEGG

To further elucidate the biological functions and associated pathways of the identified hub genes, GO and KEGG enrichment analysis were conducted again,with statistical significance defined as P-value < 0.05.

2.6 Diagnostic Value and selection of true Hub Genes

ROC curves were used to assess the diagnostic performance of the hub genes in distinguishing SZ cases from healthy controls across the three brain regions. The area under the curve (AUC) values were computed. The viable hub genes were identified by ensuring that AUC values in all three brain regions exceeded 70.

2.7 MiRNAs Related to Hub Genes

The miRNAs targeting the hub genes were predicted using the miRNAWalk tool （http://mirwalk.umm.uni-heidelberg.de/）,an online platform for visualization that helps to identify miRNA-gene interactions in Gene Regulatory Networks. For each hub gene, miRNAs were identified as having a degree cutoff = 0.95. A regulatory network was established in Cytoscape to illustrate the interactions between the hub genes and their corresponding miRNAs.

3.Results

3.1 Identification of Differentially Expressed Genes (DEGs)

In our study, the criteria of P.value< 0.05 and | log FC | > 0.2 were used to analyze the differential expression across three different brain regions (Brodmann Area 46, Hippocampus, and Associative Striatum). A total of 876 DEGs were identified for the Brodmann Area 46, with 644 up-regulated and 232 down-regulated genes. In the Hippocampus, 2996 DEGs were identified, consisting of 1264 up-regu-

lated and 1732 down-regulated genes. For the Associative Striatum, 1129 DEGs were found, with 443 up-regulated and 686 down-regulated genes. Volcano plots of the DEGs for each region were generated, with red symbols indicating up-regulated genes and blue symbols indicating down-regulated genes (Fig1.A,B,C). Venn diagram analysis revealed 163 common DEGs across all three regions, of which 118 were up-regulated and 45 were down-regulated (Fig2.A,B).

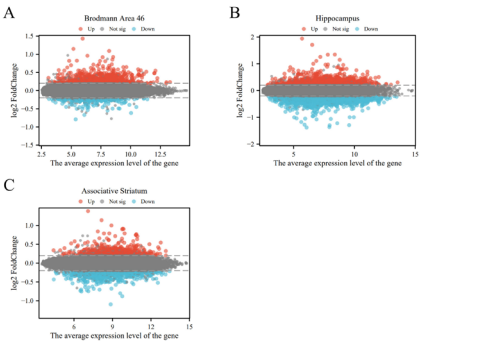

Figure 1:Volcano plots indicating differentially expressed genes (DEGs) among the control and SZ groups. (A–C) DEGs of the Brodmann Area 46, Hippocampus and Associative Striatum were shown, separately. Red data points denoted upregulated genes, while blue data points indicated downregulated genes. Genes that did not exhibit significant differences were shown in grey.

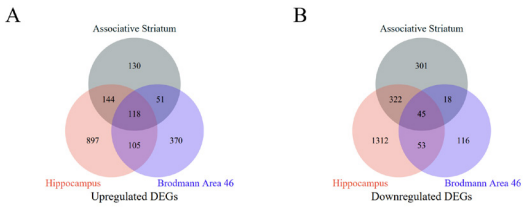

Figure 2:Venn diagrams were constructed to illustrate the overlapping DEGs among the three brain regions derived from the GSE53987 dataset. (A,B) Indicate the overlap of upregulated and downregulated genes in the Brodmann Area 46, Hippocampus and Associative Striatum, separately.

3.2 GO and KEGG Pathway Enrichment Analysis

To functionally identify the 163 DEGs, 47 different GO terms and 4 significant KEGG pathways were found using the inclusion threshold of P<0.05. GO analysis (Fig3.A) revealed significant enrichment in biological processes related to detoxification of copper ion, cellular zinc ion homeostasis, stress response to copper ion, zinc ion homeostasis, and detoxification of inorganic compound. Molecular function enrichment was observed in protein transporter activity, protein transmembrane transporter activity, growth factor binding, organic acid binding, and macromolecule transmembrane transporter activity. There were no enrichment in Cellular component.KEGG pathway analysis identified several pathways involved in SZ, including Mineral absorption, HIF−1 signaling pathway, PI3K−Akt signaling pathway, Adipocytokine signaling pathway(Fig3.B).

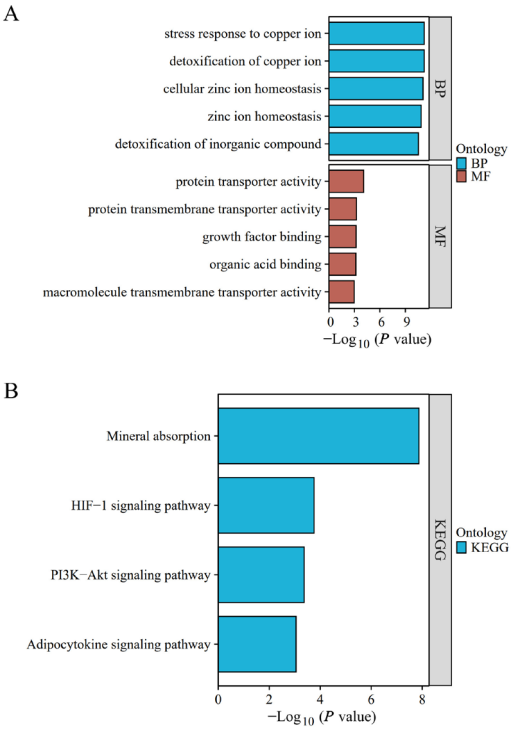

Figure 3: Function enrichment analysis of DEGs related to SZ. (A) Significant GO terms of DEGs. (B) KEGG enrichment analysis of DEGs.

3.3 PPI Network and Hub Gene Identification

The PPI network was constructed using the STRING database and visualized with Cytoscape. Fig4.A shows the PPI network, there were 148 nodes and 231 edges(confidence level= 0.4). The CytoHubba plugin could identify hub genes using the degree algorithm. In this study, the Degree algorithm was employed as the screening criterion. A higher number of edges indicated a greater importance of the genes within the network,as illustrated Fig4.B. Hub genes with a degree greater than 10 were identified, with a total of 8 hub genes(STAT3, SLC2A1, CDKN1A, IGF1R, FGF2, MCL1, PDK4, COL4A2).The 8 hub genes' degree scores were displayed in Fig. 4C. These hub genes were all up-regulation.

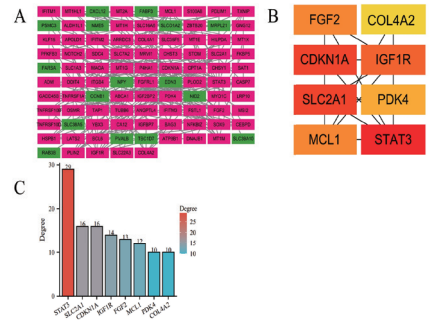

Figure 4: PPI networks of DEGs were constructed using Cytoscape. The red color indicatesd upregulated genes, while the green color diplayed downregulated genes (A). The densest connected region in the PPI network was identified using the Degree algorithm in cytoHubba (B). 8 hub genes were identified within the densest connected regions. The bar chart displayed the connectivity scores for each gene (C).

3.4 GO terms and KEGG enrichment analysis of Hub Genes

The GO analysis results (Fig. 5A and Table 2) showed that 8 hub genes were mainly enriched in cellular response to external stimulus, response to peptide hormone, response to nutrient levels, negative regulation of anoikis in BP. In CC, 8 hub genes were mainly enriched in caveola, plasma membrane raft, protein kinase complex, sarcolemma. In MF, 8 hub genes were mainly enriched in protein transporter activity, insulin receptor substrate binding, death domain binding, D–glucose transmembrane transporter activity.Fig.5B and Table 3 also show the findings of KEGG pathway analysis of the 8 hub genes, which were mostly enriched in HIF–1 signaling pathway, PI3K–Akt signaling pathway, Proteoglycans in cancer, Melanoma, EGFR tyrosine kinase inhibitor resistance.

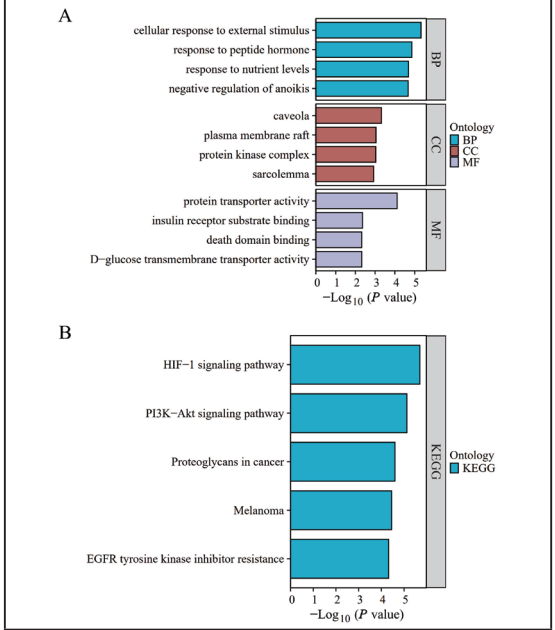

Figure 5: Functional enrichment analysis of 8 hub genes related to SZ. (A) Significant GO terms of hub genes. (B) KEGG enrichment analysis of hub genes.

Table 2 The results of GO analysis of hub genes.

ONTOLOGY	Description	pvalue	Gene symbol	Count
BP	cellular response to external stimulus	4.7566E-06	SLC2A1/CDKN1A/IGF1R/PDK4	4
BP	response to peptide hormone	1.3736E-05	STAT3/SLC2A1/IGF1R/PDK4	4
BP	response to nutrient levels	2.0283E-05	SLC2A1/CDKN1A/IGF1R/PDK4	4
BP	negative regulation of anoikis	2.1481E-05	MCL1/PDK4	2
CC	caveola	0.00047658	SLC2A1/IGF1R	2
CC	plasma membrane raft	0.00090236	SLC2A1/IGF1R	2
CC	protein kinase complex	0.00093435	CDKN1A/IGF1R	2
CC	sarcolemma	0.00120976	SLC2A1/IGF1R	2
MF	protein transporter activity	7.6352E-05	IGF1R/MCL1	2
MF	insulin receptor substrate binding	0.00433804	IGF1R	1
MF	D-glucose transmembrane transporter activity	0.00477093	SLC2A1	1
MF	death domain binding	0.00477093	MCL1	1

Table 3 The results of KEGG pathway analysis of hub genes.

ONTOLOGY	Description	pvalue	Gene symbol	Count
KEGG_PATHWAY	HIF-1 signaling pathway	2.0201E-06	STAT3/SLC2A1/CDKN1A/IGF1R	4
KEGG_PATHWAY	PI3K-Akt signaling pathway	7.493E-06	CDKN1A/IGF1R/FGF2/MCL1/COL4A2	5
KEGG_PATHWAY	Proteoglycans in cancer	2.4975E-05	STAT3/CDKN1A/IGF1R/FGF2	4
KEGG_PATHWAY	Melanoma	3.5688E-05	CDKN1A/IGF1R/FGF2	3
KEGG_PATHWAY	EGFR tyrosine kinase inhibitor resistance	4.7167E-05	STAT3/IGF1R/FGF2	3

3.5 Diagnostic Value of Hub Genes

ROC curves were used to assess expression levels in SZ samples to demonstrate the diagnostic usefulness of the 8 hub genes. For the Brodmann Area 46,the area under the curve (AUC) values for the 8 hub genes in SZ patients and healthy controls were 0.807 [95% CI, 0.652–0.962],0.618 [95% CI, 0.422–0.813], 0.716 [95% CI, 0.524–0.907],0.551 [95% CI, 0.352–0.750], 0.782 [95% CI, 0.625–0.940],0.537 [95% CI, 0.331–0.743], 0.653 [95% CI, 0.461–0.844],0.691 [95% CI, 0.497–0.886],as shown in Fig.6 (A-H).For the Hippocampus, the area under the curve (AUC) values for the 8 hub genes in SZ patients and healthy controls were 0.767 [95% CI, 0.601–0.933],1.0 [95% CI, 1.0–1.0], 0.830 [95% CI, 0.687–0.972],0.507 [95% CI, 0.291–0.724], 0.670 [95% CI, 0.467–0.873],0.563 [95% CI, 0.358–0.768], 0.750 [95% CI, 0.576–0.924],0.756 [95% CI, 0.580–0.932],as shown in Fig.7 (A-H).For the Associative Striatum, the area under the curve (AUC) values for the 8 hub genes in SZ patients and healthy controls were 0.752 [95% CI, 0.588–0.915],0.577 [95% CI, 0.382–0.772], 0.821 [95% CI, 0.682–0.960],0.657 [95% CI, 0.470–0.845], 0.691 [95% CI, 0.512–0.871],1.0[95% CI,1.0–1.0], 0.713 [95% CI, 0.539–0.887],0.645 [95% CI, 0.446–0.844],as shown in Fig.8 (A-H).

In these three brain regions, only STAT3 and CDKN1A maintained stable AUC values (greater than 0.7). Therefore, STAT3 and CDKN1A may be useful diagnostic biomarkers in the identification of SZ and were ultimately determined as the hub genes in this study.

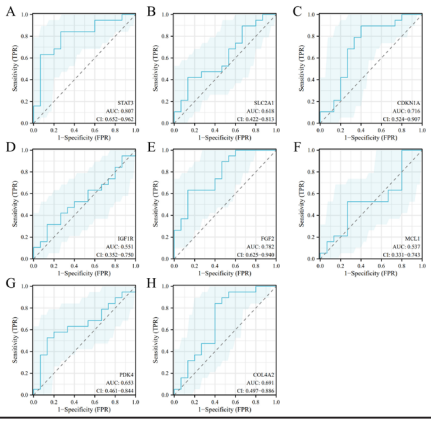

Figure 6: ROC curves and AUC values for 8 hub genes in the Brodmann Area 46.

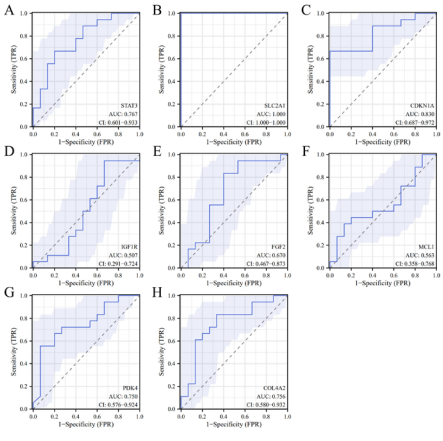

Figure 7: ROC curves and AUC values for 8 hub genes in the Hippocampus.

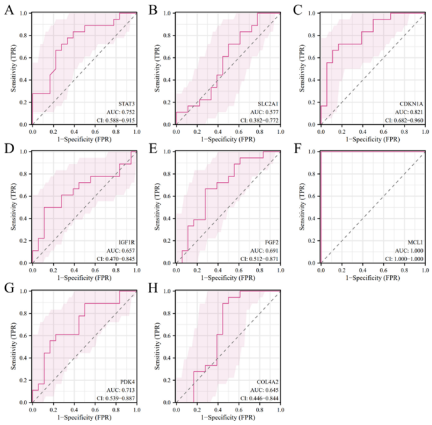

Figure 8: ROC curves and AUC values for 8 hub genes in the Associative Striatum.

3.6 MiRNAs-Hub Genes Regulatory Network

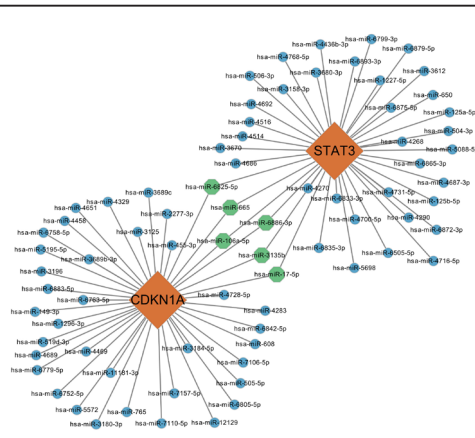

Figure 9: 2 hub genes in the integrated miRNA-DEGs network. The yellow diamond shape indicated the 2 hub genes. The blue circles displayed miRNAs with low connective properties to the hub genes. Green hexagons indicated miRNAs with high connective properties to the hub genes.

MiRNAs performed multiple roles in regulating gene expression. Based on the miRNAWALK database, Cytoscape was used to construct miRNAs-hub genes regulatory networks to identify miRNAs aimed at hub genes. Finally, 2 hub genes (STAT3 and CDKN1A) and their correspondent regulatory miRNAs molecules were shown in Fig.9. Among the 2 hub genes, stat3 and CDKN1A were common targets of 6 miRNAs (hsa-miR-6825-5p, hsa-miR-665, hsa-miR-6886-3p, hsa-miR-106a-5p, hsa-miR-3135b and hsa-miR-17-5p).

4.Discussion

Bioinformatics studies have significantly enriched the field of complex polygenic diseases, particularly in identifying genes associated with SZ, thus providing new insights into the pathogenesis of SZ. In this study, 163 DEGs were identified, consisting of 118 upregulated genes and 45 downregulated genes. The results of GO functional classification indicated that the DEGs were mainly enriched in detoxification of copper ion, cellular zinc ion homeostasis, stress response to copper ion, zinc ion homeostasis, and detoxification of inorganic compound. KEGG pathway analysis indicated that the DEGs were significantly enriched in Mineral absorption, HIF−1 signaling pathway, PI3K−Akt signaling pathway, Adipocytokine signaling pathway. In the PPI network of DEGs, 8 hub genes (STAT3, SLC2A1, CDKN1A, IGF1R, FGF2, MCL1, PDK4, COL4A2) had high degree of interaction. All of the 8 hub genes were upregulated in patients with SZ. GO term analysis showed that these 8 genes were highly enriched in cellular response to external stimulus, response to peptide hormone, response to nutrient levels, negative regulation of anoikis in BP, while KEGG pathway analysis were mainly enriched HIF−1 signaling pathway, PI3K−Akt signaling pathway, Proteoglycans in cancer, Melanoma, EGFR tyrosine kinase inhibitor resistance. Study has shown that one of the commonly used antipsychotic drugs, olanzapine, may induce metabolic disorders in SZ patients, potentially through alterations in signaling pathways such as PI3K/AKT(El-Shoura et al., 2024); In a study utilizing cuprizone-exposed mice as a SZ model, RNA sequencing of brain tissues was conducted and enrichment analysis of DEGs indicated that the PI3K-Akt signaling pathway may be implicated in cognitive impairment, with all enriched DEGs showing upregulation(Xu et al., 2024); A proteomics study investigating schizophrenia, bipolar disorder, and major depressive disorder found that the PI3K-Akt signaling pathway is a common biological pathway shared among these disorders(Fernandes et al., 2022); Research indicates that anoikis may contribute to neurodegeneration, particularly in Parkinson's disease. The PI3K/Akt pathway has been shown to reduce neuronal vulnerability, suggesting a potential protective role against neurodegeneration(Bao et al., 2024); A bioinformatics study identified anoikis-related genes in spinal cord injury and linked them to PI3K/Akt signaling, suggesting that anoikis regulation might play a role in neuroinflammation and neural survival((Yin et al., 2024)) .While direct links between anoikis and psychiatric disorders are scarce, studies highlight the involvement of the PI3K/Akt pathway in the pathogenesis of psychiatric conditions, including mood disorders and SZ.These findings suggest that the pathway could influence neuronal survival and apoptosis, indirectly affecting mental health.

ROC analysis of 8 hub genes across three brain regions identified STAT3 and CDKN1A as the most valuable, both with AUC > 70. STAT3(signal transducer and activator of transcription 3) encodes a STAT family protein activated by receptor-associated kinases in response to cytokines and growth factors (IFNs, EGF, IL5, IL6, HGF, LIF, BMP2, e.g.). Upon phosphorylation, it forms homo- or heterodimers, translocates to the nucleus, and regulates gene expression, playing a crucial role in cell growth and apoptosis. The small GTPase Rac1 modulates its activity, while PIAS3 acts as a specific inhibitor. Additionally, this gene is involved in host immune responses to viral and bacterial infections, and its mutations are linked to infantile-onset multisystem autoimmune disease and hyper-IgE syndrome(https://www.ncbi.nlm.nih.gov/gene/6774). Recent studies highlight STAT3 as a key regulator in the pathophysiology of SZ, primarily through its role in cytokine signaling, neuroimmune modulation, and gene transcription regulation. Such as ,the IL-6/STAT3 signaling axis has been implicated in SZ pathogenesis, where alterations in STAT3 phosphorylation have been observed in first-onset, drug-naïve SZ. Dysregulation of this pathway is associated with abnormal immune responses and neuroinflammation, both of which contribute to the disease's development(Lago et al., 2022). Moreover,

studies have demonstrated that STAT3 is involved in astrocyte reactivity and synaptic plasticity, which are critical for cognitive functions often impaired in SZ(Ceyzériat et al., 2016).Additionally, transcriptional analysis has identified STAT3 as a central hub gene involved in schizophrenia-related genetic networks (Reisinger et al., 2021).

CDKN1A (cyclin dependent kinase inhibitor 1A) encodes a cyclin-dependent kinase (CDK) inhibitor, regulating G1 phase cell cycle progression by inhibiting CDK2- and CDK4-cyclin complexes. Its expression is tightly controlled by p53, mediating p53-dependent G1 arrest in response to stress stimuli. The protein interacts with proliferating cell nuclear antigen (PCNA), modulating S-phase DNA replication and damage repair. It is specifically cleaved by CASP3-like proteases, leading to CDK2 activation and apoptosis execution (https://www.ncbi.nlm.nih.gov/gene/1026). Recent studies indicate that gestational exposure to antipsychotic drugs, such as haloperidol, can alter CDKN1A expression in the hippocampus, suggesting a potential link between prenatal environmental factors and schizophrenia susceptibility(Kumon et al., 2023). Moreover, bioinformatics analysis have identified CDKN1A as a core gene in SZ, with its expression significantly affected by antipsychotic treatment(-Kumon et al., 2023). Additionally, SZ patients frequently exhibit alterations in neuroimmune signaling, and CDKN1A has been identified as part of the genetic and pharmacological risk network for SZ and smoking behavior comorbidity(Ma et al., 2020). This emerging evidence suggests that CDKN1A is implicated in the pathogenesis of SZ.

Evidence highlights miRNAs as key post-transcriptional regulators in brain physiology and SZ pathology, with widespread dysregulation observed in both brain regions and serum of SZ patients(Banigan et al., 2013; Moreau et al., 2011; Santarelli et al., 2011). The results of our study suggest that several miRNAs, including hsa-miR-6825-5p, hsa-miR-665, hsa-miR-6886-3p, hsa-miR-106a-5p, hsa-miR-3135b and hsa-miR-17-5p, may play critical roles in SZ. Research indicate that Lnc-HOXB8-1:2 in exosomes derived from neuroendocrine differentiated CRC cells acted as a ceRNA competitively binding hsa-miR-6825-5p to upregulate CXCR3 expression and leading to TAM infiltration and M2 polarization, which promotes neuroendocrine differentiated CRC progression(X. Li et al., 2022). The regulatory functions of miR-665 in glioma cancer seem mainly focused on the HMG protein family. Overexpression of miR-665 in glioma cells inhibits tumor cell proliferation, migration, and invasion by targeting high mobility group box 1 and High Mobility Group AT-hook 1 protein, deactivating the Wnt/β-catenin pathway(Shen et al., 2021). CeRNA network identified hsa-miR-17-5p, hsa-miR-106a-5p and hsa-miR-2355-5p as potential diagnostic biomarkers for tuberculosis(Song et al., 2023).In multiple studies on Alzheimer's disease, both hsa-miR-106a-5p and hsa-miR-17-5p have been identified as hub genes associated with the condition. Evidence supports their correlation with the development of cognitive impairment(Frolov & Borisov, 1986; Gascón et al., 2024; Hashemi et al., 2023; Nguyen & Kim, 2022). A study on autism spectrum disorder (ASD) in the Han Chinese population revealed that hsa-miR-17-5p and hsa-miR-106a-5p are involved in neurodevelopment and the pathogenesis of autism(Wang et al., 2022; Wu et al., 2016).Surprisingly, a study investigating the ceRNA regulatory mechanisms in SZ discovered that in the Brodmann Area 10 brain region of SZ patients, hsa-miR-17-5p was identified as a competing endogenous RNA for long non-coding RNAs(Sabaie et al., 2022).hsa-miR-3135b has been identified as a potential biomarker for prediabetes in patients with alcohol dependence syndrome(Ramaswamy et al., 2025).Currently, there are no reported studies on the relevance of hsa-miR-6886-3p in the literature. Notably, in both oncological and neurological diseases, particularly those involving cognitive functions, hsa-miR-17-5p and hsa-miR-106a-5p have been frequently observed in numerous studies. This suggests that these two microRNAs play significant roles in the pathogenesis of various diseases. Their consistent presence also provides valuable insights for further research into the miRNA-mRNA regulatory networks in SZ.

This is no doubt that gene-miRNA regulatory networks act as an essential role in the SZ mechanism. This not only enhances the understanding of SZ, but also provides targets therapeutic strategies and predictions for SZ.This is limited in that microarray profiles were analyzed using bioinformatics analysis and not validated with primary experiments. Additionally,we do not explore the detailed mechanism for how hub genes and miRNAs modulated SZ.As a result,further validation of our findings with addi-

tional clinical samples and research is necessary in the future.

5.Conclusion

In conclusion, a total of 163 DEGs, 2 hub genes(STAT3 and CDKN1A) and 6 miRANs (hsa-miR-6825-5p, hsa-miR-665, hsa-miR-6886-3p, hsa-miR-106a-5p, hsa-miR-3135b and hsa-miR-17-5p) that may be involved in the progression or occurrence of SZ were identified in this study, which could be regarded as biomarkers of SZ. They have significant value in the diagnosis of schizophrenia.

Data availability statement

Publicly available dataset was analyzed in this study. This data can be found here: http://www.ncbi.nlm.nih.gov/geo.

Author contributions

Xu You: Data curation, Funding acquisition,Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft. Junbin Wang: Conceptualization, editing. Yimei Zhang, Huiyun Yin: Data curation. Wenjian Wei, Cui Zhao: Investigation,Data curation. Qiongmei Zhang, Haiyan Tian: Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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