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Research paper

Two hub genes of bipolar disorder, a bioinformatics study based on the GEO database

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ABSTRACT

Bipolar disorder is a mood illness that affects many people. It has a high recurrence frequency and will cause significant damage to the patient's social function. At present, the pathogenesis of BD is not clear. The National Center for Biotechnology Information (NCBI) established and maintained the Gene Expression Omnibus (GEO) database, a gene expression database. For bioinformatics analysis, researchers can obtain expression data from the internet. At present, the samples of the dataset used in the research of BD are mostly from brain tissue, and the data containing blood samples are rarely used. GEO databases (GSE46416, GSE5388, and GSE5389) were used to retrieve public data, and utilizing the online tool GEO2R, differentially expressed genes (DEGs) were retrieved. The common DEGs between the samples of patients with BD and the samples of the normal population were screened by Venn diagrams. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were used to perform functional annotation and pathway enrichment analysis of DEGs. A protein-protein interaction network (PPI) was built to investigate hub genes on this basis. There were 117 up-regulated DEGs and 38 down-regulated DEGs discovered, with two hub genes [SRC, CDKN1A] among the up-regulated DEGs. These two hub genes were also highly enriched in the oxytocin signaling pathway, proteoglycans in cancer and bladder cancer, according to KEGG analysis. The results of the receiver operating characteristic curve (ROC) of SRC and CDKN1A in the three datasets strongly suggested that SRC and CDKN1A were potential diagnostic markers of BD. The results strongly suggest that SRC and CDKN1A are related to the pathogenesis of BD.

1. Introduction

A prevalent mood disorder affecting more than 1 % of the world's population is Bipolar disorder (BD). Bipolar disorder has a lifetime incidence of 2.4 % and an annual prevalence of 1.5 %, according to epidemiological research. The impact of the disease itself on patients has caused a large family and social burden all over the world (Carvalho et al., 2020). And another study shows that BD affects around 4 % of the population in the United States (Merikangas et al., 2007). BD can lead to pathological emotional fluctuations, increase the risk of suicide, and cause cognitive damage, and some physical diseases also have significant comorbidity with BD (Plans et al., 2019; Millan et al., 2012; Crump et al., 2013). Although patients with BD are quite common in the clinic, the diagnosis of this disease mainly depends on typical clinical symptoms, including alternating manic /mild manic and depressive episodes, the specific pathogenesis of BD is still not clear. There are many hypotheses about the pathogenesis of BD, but more and more studies show that genetic variation plays an important role in the pathogenesis of BD (McGuffin et al., 2003; Kraemer, 2012; Segura et al., 2019).

The bioinformatics methodology is frequently applied in the diagnosis and treatment of diseases. Series matrix files of many diseases can be uniformly stored in the network database for researchers to use. GEO database (http://www.ncbi.nlm.nih.gov/geo) is an authoritative online database whitch contains a variety of disease datasets (Edgar et al.,

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Table 1
Statistical data for GSE5388,GSE5389 and GSE46416.

Dataset ID	BD	Control	Platform	Sample type	Gene counts (upregulation)	Gene counts (downregulation)
GSE5388	30	31	GPL96	human prefrontal cortex (BA46)	1175	1287
GES5389	10	11	GPL96	dorsolateral prefrontal cortex	1944	1385
GSE46416	22	10	GPL11028	blood	3705	1201

2002). And GEO2R(http://www.ncbi.nlm.nih.gov/ GEO /geo2r/) in GEO allows researchers to analyze the gene expression of patients and healthy people in the database online (Barrett et al., 2013). However, it is rare to use the database to study mental diseases, and the existing studies about BD mostly use the datasets of brain tissue samples (You et al., 2020; Liu et al., 2019). However, the use of datasets of blood samples is not common. This research aims to analyze and find the potential hub genes of BD through three datasets containing brain tissue and blood samples, then take these hub genes as the potential diagnostic markers of BD. SRC and CDKN1A, two hub genes intimately associated with BD, were examined and identified by the comprehensive bioinformatics methodology used in this study. The AUC in the ROC suggests that they are valuable in helping the diagnosis of BD. The results of this experiment will provide new ideas for the diagnosis of BD and the application of bioinformatics methodology in mental diseases.

2. Materials and methods

2.1. Source and filtering of datasets

The GEO database served as the source for the gene expression datasets explored in this study. There are three datasets included in our research, GSE5388 and GSE5389 are microarrays based on GPL96 [HG-U133A] Affymetrix Human Genome U133A Array. 61 postmortem dorsolateral prefrontal brain samples, comprising 30 BD cases and 31 healthy samples, were included in GSE5388. 10 BD samples and 11 healthy samples were among the 21 orbitofrontal cortex samples in GSE5389. GSE46416 is a microarray based on GPL11028 [HuEx-1_0-st] Affymetrix Human Exon 1.0 ST Array, containing blood samples including 22 BD samples and 10 healthy samples. The above three datasets are all from the GEO database, all of which are included in a unified standard and contain data on bipolar disorder and healthy controls. Therefore, the three datasets are comparable. However, due to the different microarrays in the three datasets, this study adopted the method of screening differential genes separately and then intersecting them to avoid the impact of differences caused by different microarrays

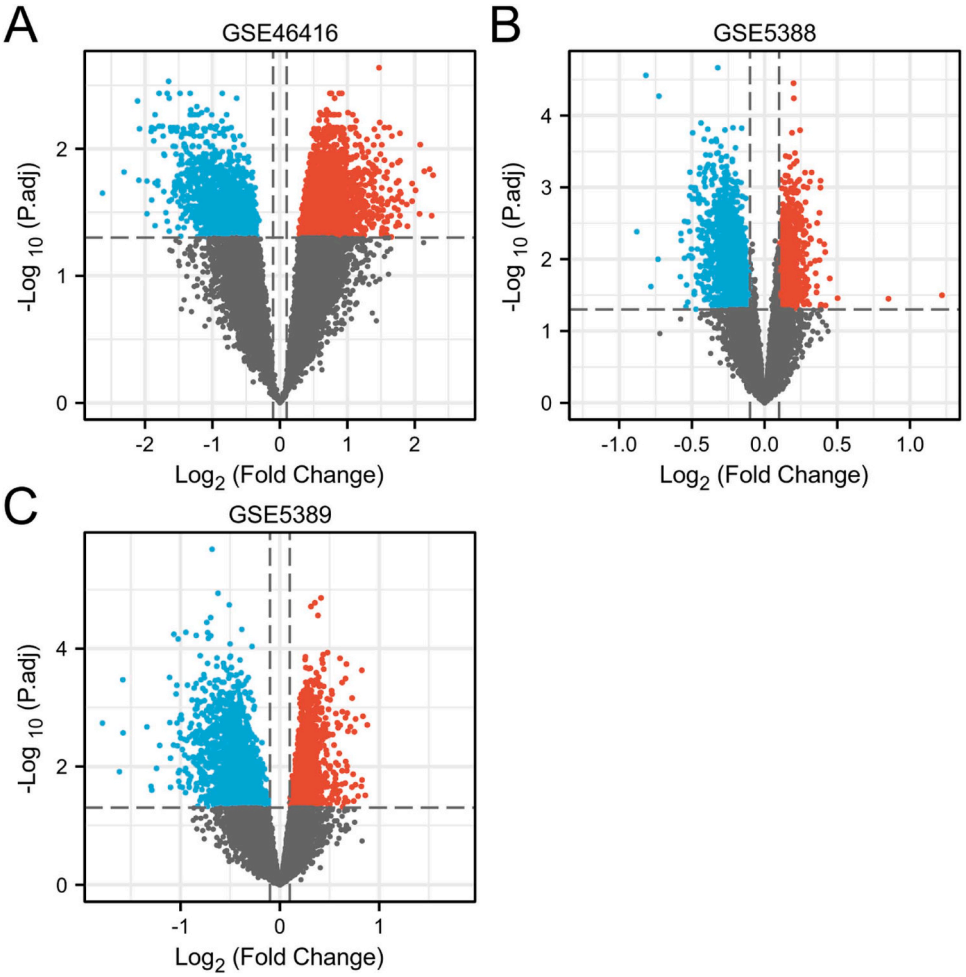

Fig. 1. DEGs between BD patients and healthy controls.

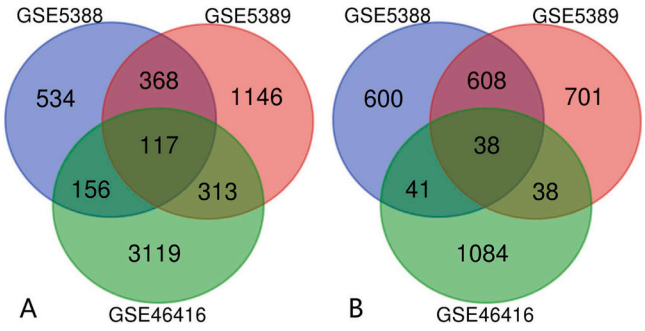

Fig. 2. Venn diagram of DEGs from 3 GEO datasets. A. up-regulated genes. B. down-regulated genes.

on the results.

2.2. Differentially expressed genes

To analyze the DEGs among all samples, the GEO2R analysis program was used online. We intentionally defined P <0.05 and |log FC= >0.1 as the inclusion criterion for DEGs in order to prevent missing more valuable DEGs. DEGs with log FC <0 were seen as being down-regulated, whilst DEGs with log FC >0 were regarded as being up-regulated. Three datasets, GSE46416, GSE5388, and GSE5389, were evaluated by GEO2R, and the online plotting tool was used to create maps of the three datasets' volcanoes (https://www.xiantao.love/products). In volcano maps, the fold change (log-scaled) is represented on the X-axis, while the P-value is represented on the Y-axis (log-scaled). Each symbol denotes a distinct gene. Red symbols indicate genes that are up-regulated, whereas green symbols indicate genes that are down-regulated. The Venn diagram online tool was then used to find the intersection of DEGs (http://bioinformatics.psb.ugent.be/webtools/Venn/).

2.3. GO and KEGG enrichment analysis

By utilizing the DAVID(6.8) (https://david.ncifcrf) database, GO annotation and KEGG enrichment analysis of the DEGs were carried out. GO has three levels of analysis: molecular function (MF), cellular component (CC), and biological process (BP). A widespread database used to investigate illnesses, chemicals, medications, biological processes, and genomes is called KEGG. When DEG met P <0.05 in the above two analyses, it had statistical significance in this study. Weshengxin, a free online application for data processing and visualization (http://www.bioinformatics.com.cn), was used to create the bubble diagram.

2.4. Protein-protein interaction (PPI) network and hub genes

The network of PPI data was built using a database named STRING (https://string-db. org/). Then, using Cytoscape software, a network of PPI was visualized. Finally use the CytoHubba plug-in, take the number of degrees as the standard, to select the top 10 genes as hub genes.

2.5. Diagnostic value of hub genes

The ROC curve is created using the online mapping tool (https://www.xiantao.love/products), and it is useful for assessing the diagnostic value of hub genes for BD prediction.

3. Results

3.1. Identification of DEGs

In our study, the criteria of P< 0.05 and | log FC | > 0.1 were used to analyze the differential expression across three datasets (GSE46416, GSE5388, and GSE5389). A total of 2462 DEGs were detected by GSE5388, of which 1175 genes were up-regulated and 1287 genes were

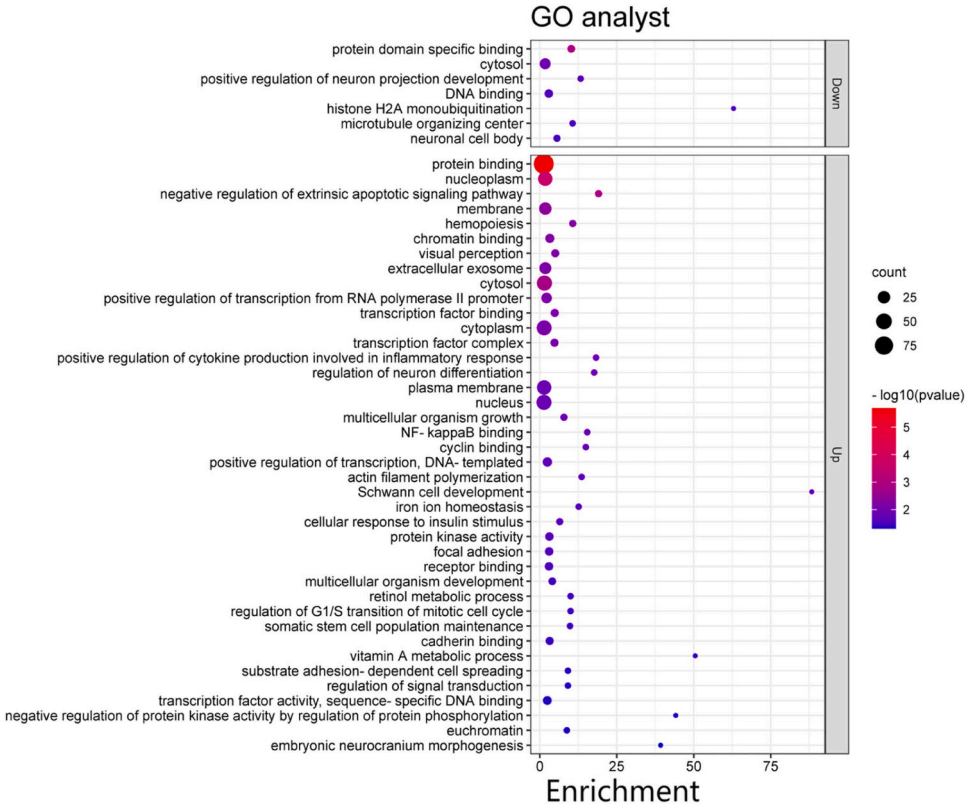

Fig. 3. Significant GO terms of upregulated DEGs and downregulated DEGs.

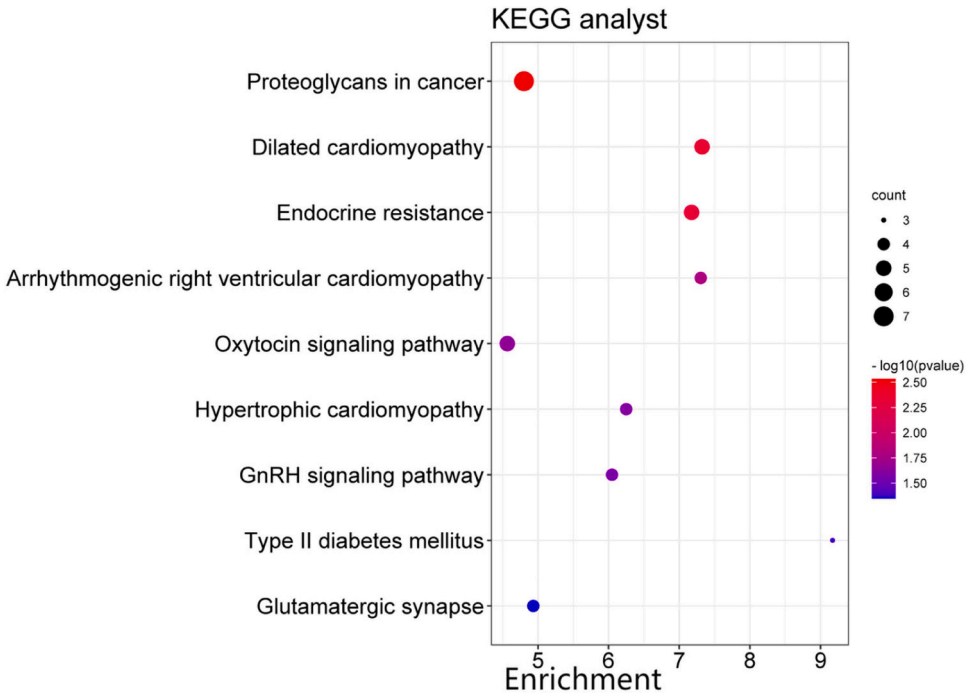

Fig. 4. Significant KEGG pathways of up-regulated DEGs.

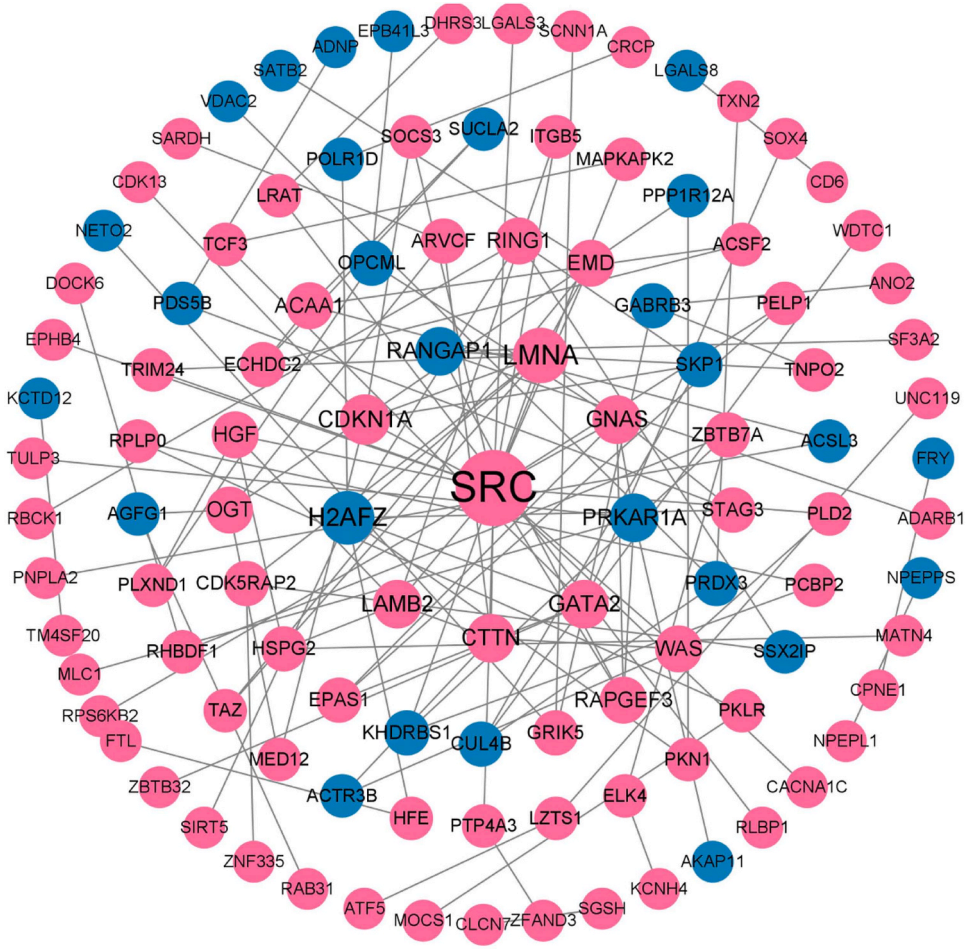

Fig. 5. Network of protein-protein interactions. Genes that have been up- or down-regulated are shown by red and blue nodes, respectively. The larger the node, the more important it is.

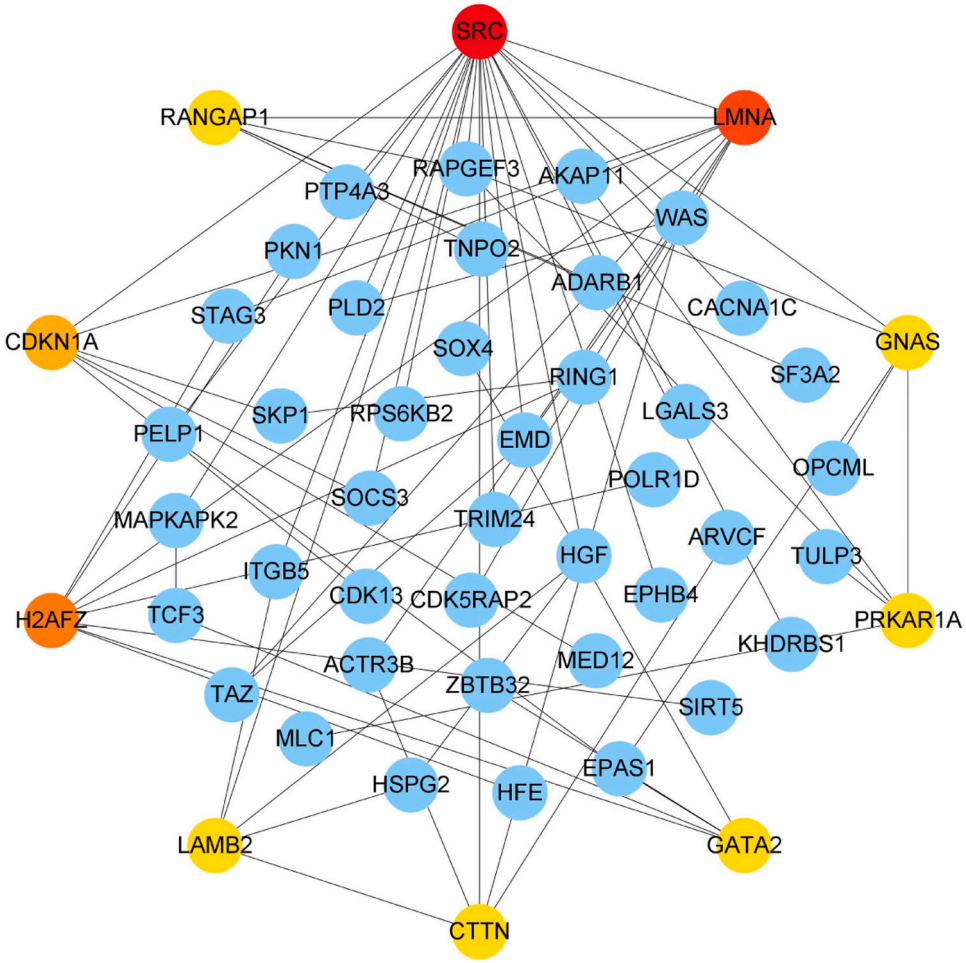

Fig. 6. Ten hub genes and extra DEG were used to form the PPI network. The colour of a gene affects how heavily it is distributed across the network.

down-regulated. 3329 DEGs were identified in GSE5389, including 1944 up-regulated genes and 1385 down-regulated genes. A total of 4096 DEGs were identified by GSE46416, of which 3705 were up-regulated and 1201 were down-regulate (Table 1).

The DEGs of three datasets of BD patients and healthy samples were shown using volcano plot analysis. DEGs were visible at every node in the volcano diagram.The blue nodes present the down-regulated DEGs, while the red nodes present the up-regulated DEGs. Fig. 1A, B, and C show volcano plots for GSE46416, GSE5388, and GSE5389.

Then, through the Venn diagram analysis, three intersection results are discovered. As shown in Fig. 2, there are 155 DEGs in these three datasets, of which 117 genes are up-regulated, and 38 genes are down-regulated.

3.2. GO analysis and KEGG pathway analysis of DEGs

To functionally identify the 155 DEGs, 47 different GO terms and 9 significant KEGG pathways were found using the inclusion threshold of $P<0.05$. In GO analysis, 117 up-regulated genes and 38 down-regulated genes were enriched and analyzed. The results are shown in Fig. 3. These genes might be involved in the etiology of BD physiologically.

The GO analysis results show that upregulated DEGs are mainly enriched in protein binding, cytosol, nucleus, cytoplasm, plasma membrane, and so on. The GO analysis's findings showed that the cytosol, DNA binding, protein domain specific binding, neuronal cell body, positive regulation of neuron projection development, microtubule organizing center, and histone H2A monoubiquitination are enriched with downregulated DEGs. The results showed that whether upregulated or down regulated, the DEGs were related to DNA, protein structure and neural development.

Table 2
Gene description and connectivity degree of 10 hub genes.

Name	Score	Type
SRC	42	Upregulation
LMNA	18	Upregulation
H2AFZ	16	Upregulation
CDKN1A	12	Upregulation
LAMB2	10	Upregulation
GATA2	10	Upregulation
GNAS	10	Upregulation
CTTN	10	Upregulation
RANGAP1	10	Upregulation
PRKAR1A	10	Upregulation

Fig. 4 also shows the findings of KEGG pathway analysis of the up-regulated DEGs, which were mostly enriched in Proteoglycans in cancer, Dilated cardiomyopathy, Endocrine resistance, Arrhythmogenic right ventricular cardiomyopathy, Oxytocin signaling pathway, Hypertrophic cardiomyopathy, GnRH signaling pathway, Type II diabetes mellitus, Glutamatergic synapse. But the down-regulation of DEGs did not analyze meaningful results.

3.3. PPI network and identification of hub genes

The PPI network was built by STRING and Cytoscape (3.9.0). Fig. 5 shows the PPI network, after removing 46 genes that are not associated

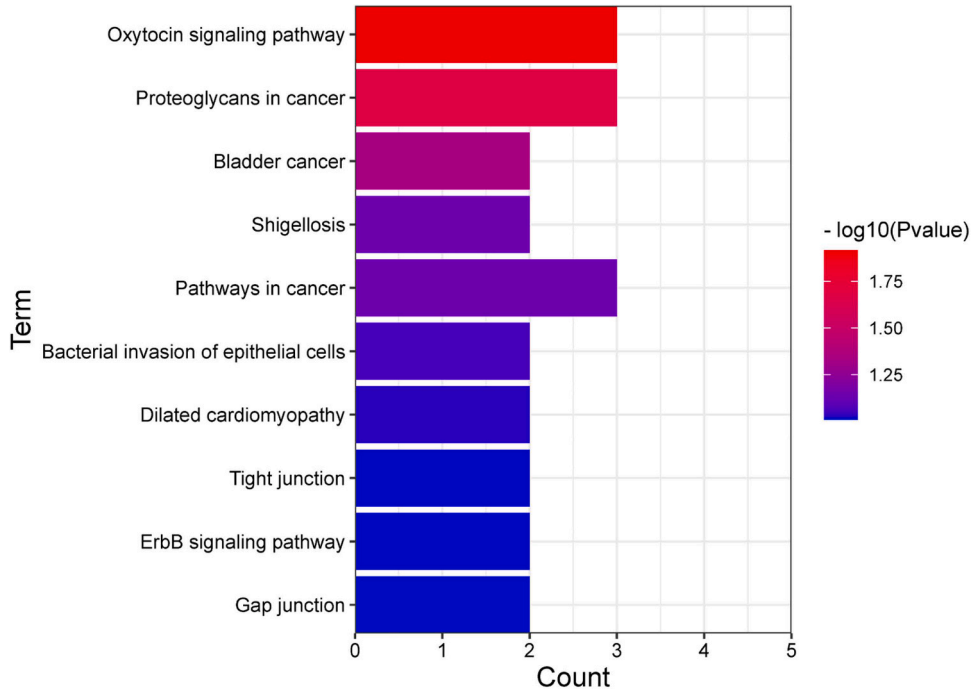

Fig. 7. Significant KEGG pathway of hub genes.

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

Category	Term	Count	P-value	Genes
KEGG_PATHWAY	Oxytocin signaling pathway	3	0.012133	SRC, CDKN1A, GNAS
KEGG_PATHWAY	Proteoglycans in cancer	3	0.020982	SRC, CTTN, CDKN1A
KEGG_PATHWAY	Bladder cancer	2	0.046722	SRC, CDKN1A

with other genes, there are 109 nodes and 252 edges(confidence level= 0.4). Cytohubba is a plug-in in Cytoscape. The plug-in can screen hub genes through various algorithms. The screening rule used in this study is Degree, that is, according to the number of edges in the network diagram. The more the number of edges, the more important the genes are. As illustrated in Fig. 6, the top 10 genes were chosen based on the PPI network's degree of connectedness by CytoHubba. The 10 hub genes' complete gene descriptions and connectivity scores are included in Table 2. These hub genes are up-regulation.

3.4. Further screening of hub genes

From the first 10 hub genes, KEGG analysis was conducted again ($P<0.05$) to complete further screening of hub genes (Fig. 7). The findings revealed SRC and CDKN1A were both enriched in the oxytocin signaling pathway; proteoglycans in cancer and bladder cancer (Table 3).

3. Diagnostic evaluation of SRC and CDKN1A

ROC curves were used to assess expression levels in BD samples to demonstrate the diagnostic usefulness of SRC and CDKN1A. For the GSE46416 dataset, the area under the curve (AUC) values for SRC and CDKN1A in BD patients and healthy controls were 0.859 [95 % CI, 0.732–0.987],0.859 [95 % CI, 0.731–0.987], as shown in Fig. 8A.

The AUC values for SRC and CDKN1A computed for the GSE5388 were 0.655 [95 % CI, 0.517–0.793] and 0.658 [95 % CI, 0.519–0.797], as shown in Fig. 8B.

And the AUC values for SRC and CDKN1A reported for the GSE5389 were 0.773 [95 % confidence interval (CI), 0.547–0.998] and 0.900 [95 % confidence interval (CI), 0.769–1.000], as seen in Fig. 8C.

SRC and CDKN1A may be useful diagnostic biomarkers in the identification of bipolar illness (AUC:0.60–1.00). The AUC of these two hub genes in blood samples is greater than 0.8, so it can be considered that SRC and CDKN1A are more reliable and have stronger diagnostic significance in blood samples.

Fig. 9 displays the outcomes of using SRC and CDKN1A as combined indicators to assess their diagnostic usefulness. The AUC value for the hub gene combination in GSE46416 is 0.895 (95 %CI, 0.787–1.000) in Fig. 9A. The AUC value for GSE5388 is 0.654 (95 %CI, 0.549–0.818) in Fig. 9B. The AUC value for GSE5389 is 0.918 (95 % CI, 0.796–1.000) in Fig. 9C. The findings revealed that the AUC of joint indicators was higher than that of a single hub gene, suggesting that hub genes had higher diagnostic value when considered as a whole and were more supportive of the clinical assessment criteria for bipolar disorder.

4. Discussion

Although the biological basis of BD is still unclear, it is one of the top 20 causes of disability in the world, causing serious health damage to patients, and some patients are not ideal and easy to repeat treatment (Harrison et al., 2019). At present, the diagnosis of bipolar disorder mainly depends on symptomatology, but because BD overlaps with some symptoms of other mental diseases, it is easy to be misdiagnosed (Mitchell et al., 2010). Therefore, it is of far-reaching significance to find more accurate diagnostic indexes for BD, which is helpful to the diagnosis and targeted drug treatment of BD.

At present, bioinformatics prediction and computer technology have been widely used in all aspects of biomedical analysis (Zou et al., 2017). However, bioinformatics analysis for mental diseases is relatively rare. Through in-depth mining of BD data in the GEO database, this study not only uses the more common brain tissue expression data but also includes the expression data of blood samples, which is richer in sample types than previous studies. 155 DEGs were found in the three datasets, of which 117 were up-regulated and 38 were down-regulated, according to the findings. Two hub genes SRC and CDKN1A were screened out by

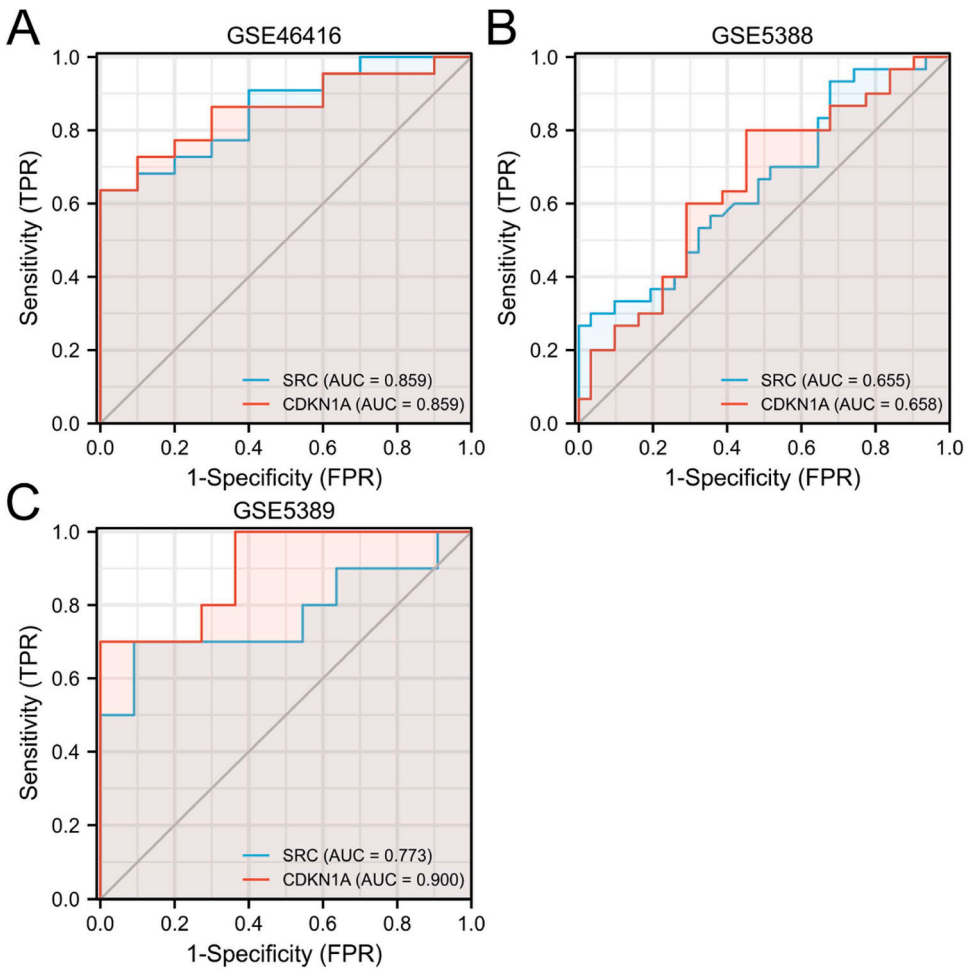

Fig. 8. ROC curves and AUC values for SRC and CDKN1A. A.GSE46416 B.GSE5388C.GSE5389.

systematic bioinformatics methodology analysis. The results of ROC strongly suggest that they have strong diagnostic significance for BD.

SRC is a proto-oncogene that plays a key role in cell morphology, motility, proliferation, and survival. It is responsible for the expression regulation of tyrosine-protein kinase (Roskoski, 2004). SRC is a key element of the Reelin signalling pathway and plays an indispensable role. Previous studies have shown that Reelin signalling pathway is involved in neuronal migration, dendritic growth, spinal development, and synaptic plasticity, which can eventually lead to a variety of human brain diseases, such as anencephaly, autism, schizophrenia, bipolar disorder, depression, mental retardation, Alzheimer's disease, and epilepsy (Jossin, 2020). Therefore, SRC may eventually lead to the occurrence and development of BD by participating in this pathway. This is consistent with the results obtained by bioinformatics methodology analysis in this study. Aripiprazole (ARP) is an atypical antipsychotic drug, which is widely used in the treatment of schizophrenia and bipolar disorder. Two previous studies have shown that SRC is one of the main targets of aripiprazole. Under the action of aripiprazole, the expression of SRC decreased significantly (Kim et al., 2018; Yoo et al., 2018). Lithium has also long been used to treat and prevent bipolar disorder. In another experiment, the researchers used mouse fibroblasts containing SRC as a model, and the normal phenotype of SRC-containing cells was impaired by lithium (Néel et al., 2009). In this study, SRC is highly expressed in the BD population. The inhibition of SRC by aripiprazole and lithium can partly explain its therapeutic effect on BD.

The results show that the position of SRC in the interaction network is the most critical, and it shows a large AUC (GSE46416, AUC: 0.859; GSE5388, AUC: 0.655 and GSE5389, AUC: 0.773) in the three array datasets. It is reasonable to believe that SRC may become a potential biomarker and therapeutic target for BD diagnosis with the help of integrated bioinformatics technology.

CDKN1A, known as cyclin-dependent kinase inhibitor 1 A, is located on human chromosome 6. This gene encodes a potent cyclin-dependent kinase inhibitor. The encoded protein binds to and inhibits the activity of cyclin-cyclin-dependent kinase2 or -cyclin-dependent kinase4 complexes, and thus functions as a regulator of cell cycle progression at G1. (https://www.ncbi.nlm.nih.gov/gene/1026). A previous GWAS study showed that CDKN1A was annotated as an active regulatory element in a tissue-specific manner, confirming its involvement in the regulatory network of lithium response in BD patients (Higgins et al., 2015). Quetiapine is an atypical antipsychotic drug, which is also used to treat patients with bipolar disorder. A study on quetiapine showed that CDKN1A was significantly down-regulated in oligodendrocyte precursor cells and neurons in cortical cell cultures treated with quetiapine (Kondo et al., 2013). In this study, the BD population also exhibits high levels of CDKN1A expression. This study's findings that quetiapine decreased CDKN1A expression can also be utilized to explain why the drug had a therapeutic impact on BD. In our previous studies on schizophrenia, we also found that this gene is closely related to the pathogenesis of schizophrenia. This may explain the similarities between the two diseases (Feng et al., 2022).

In this study, KEGG enrichment analysis suggests that CDKN1A participates in a variety of signal pathways, and it is closely related to other genes in the interaction network. Finally, CDKN1A also shows a large AUC (GSE46416, AUC: 0.859; GSE5388, AUC: 0.658 and GSE5389, AUC: 0.900) in the three array datasets. As a result, CDKN1A

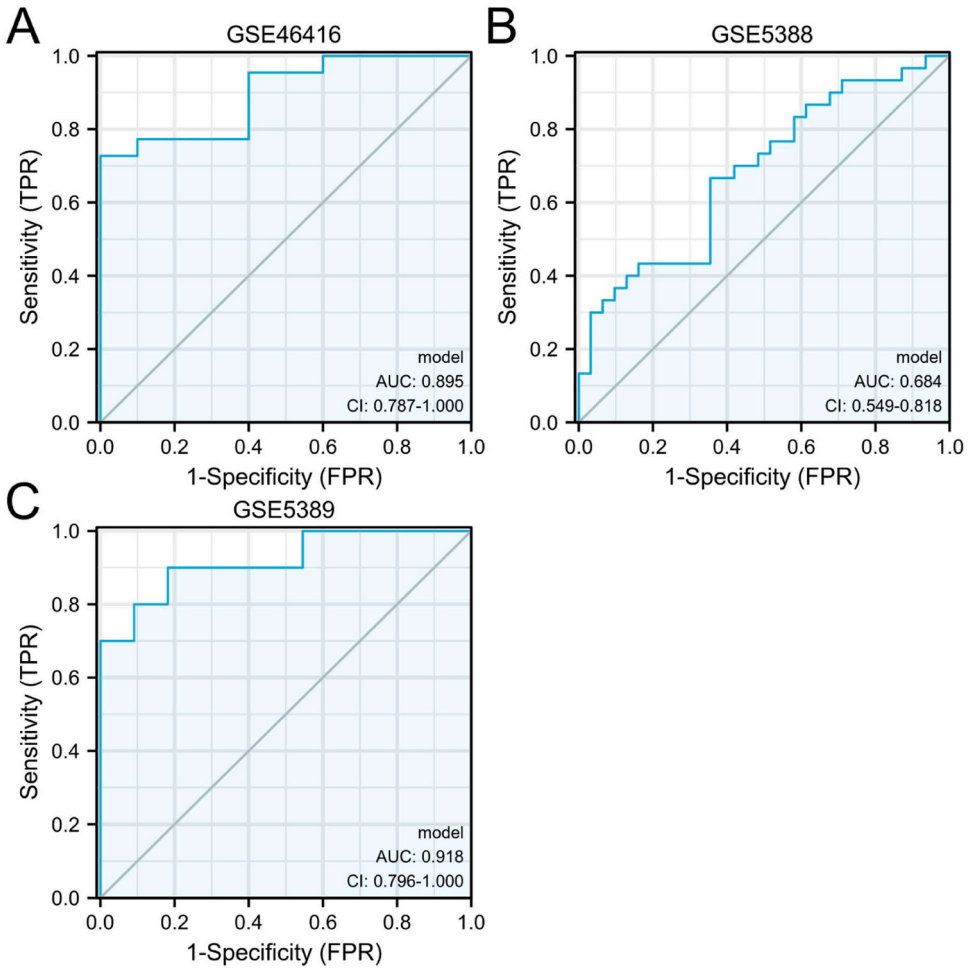

Fig. 9. Examination of joint indicators from three datasets for diagnostic purposes. (A) GSE46416; (B) GSE5388; (C) GSE5389.

has significant promise as a biomarker and as a therapeutic target for BD diagnosis. In the follow-up analysis, the results showed that the diagnostic value was higher when the two genes were used as joint indicators. This outcome might also offer a fresh perspective on how to accurately diagnose bipolar disorder in the future.

This study still has several shortcomings, though. First off, BD bioinformatics research using the GEO database is conducted strictly in accordance with established techniques for bioinformatic analysis of tumors or cancer. The research concepts are quite obvious in terms of methodology. Cancer and mental illness, on the other hand, are two distinct illnesses. If DEGs are chosen strictly according to tumor inclusion criteria, statistically, the DEG extraction in this study cannot be further analyzed. |log FC= is virtually usually restricted to 1 in a large number of literature on tumor bioinformatics analysis, which is a more statistically significant and convincing restriction that has been generally accepted by the scientific community. In this investigation, we attempted to obtain BD expression data from the GEO database on the same or various chip platforms. Only a tiny percentage of DEGs are filtered out when |log fold change (log FC) | is intentionally fixed between 0.2 and 1. We can acquire enough DEGs for subsequent GO and KEGG analysis if |log FC= is adjusted to 0.1.

Of fact, this might explain why just a few research have used bioinformatics to analyze psychiatric data from a single GEO collection. Second, despite the discovery of two differently expressed hub genes, no additional investigation was conducted because there are still some unknown relationships between genes and the lack of relevant biological models.

5. Conclusions

Two hub genes [SRC and CDKN1A] closely related to the occurrence of BD were discovered for the first time using the conventional Bioinformatics Method of cancer-related diseases. They have significant value in the diagnosis of bipolar disorder.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

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CRediT authorship contribution statement

Shunkang Feng: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **Yiru Fang:** Conceptualization, Funding acquisition, Writing – review & editing. **Hui Yu:** Data curation. **Xiaoxiao Wang:** Data curation. **Ping Sun:**

Conceptualization, Project administration.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2024.07.006.

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