

IDENTIFICATION OF BIOMARKERS FOR BIPOLAR DISORDER AND SCHIZOPHRENIA USING DIFFERENTIAL GENE EXPRESSION ANALYSIS

Submitted in partial fulfillment of the requirements for the award of
Master of Science in Bioinformatics and Data Science

by

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**DEPARTMENT OF BIOINFORMATICS
SCHOOL OF BIO AND CHEMICAL ENGINEERING**

SATHYABAMA

**INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)**

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BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of **DEEPIKA S (42739008)**, who carried out the final year project entitled “**IDENTIFICATION OF BIOMARKER FOR BIPOLAR DISORDER AND SCHIZOPHRENIA USING DIFFERENTIAL GENE EXPRESSION ANALYSIS**” under my supervision from September 2023 to April 2024.

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DECLARATION

I, **Ms. DEEPIKA S (42739008)** hereby declare that the project report entitled ***“IDENTIFICATION OF BIOMARKERS FOR BIPOLAR DISORDER AND SCHIZOPHRENIA USING DIFFERENTIAL GENE EXPRESSION”*** was done by me under the guidance of **Dr. D ALEX ANAND, Sathyabama Institute of Science and Technology** is submitted in partial fulfillment of the requirements for the award of Master of Science in Bioinformatics and Data Science.

DATE: 20/04/2024

PLACE: CHENNAI

A handwritten signature in blue ink that reads "Deepika S". The signature is stylized with a large 'D' and a long horizontal stroke.

SIGNATURE OF THE CANDIDATE

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ABSTRACT

Bipolar disorder (BD) and schizophrenia (SCZ) pose significant challenges due to their complex etiologies and varied symptomatology. Despite advances in understanding their neurobiological roots, precise mechanisms remain elusive, hindering effective diagnosis and treatment. This study sought to pinpoint potential biomarkers for BD and SCZ by scrutinizing differential gene expression. Through a systematic review of literature and datasets, genes differentially expressed in BD and SCZ were identified compared to healthy controls. Employing diverse bioinformatics tools, we unravelled molecular signatures linked with each disorder, assessing both common pathways and unique molecular features. Notably, our investigation unearthed several candidate biomarkers, notably MTRNR2L6, MTRNR2L8, MTRNR2L10, MTRNR2L11, MTRNR2L13, MTRNR2L1, MTRNR2L7, MTRNR2L4, MTRNR2L12, ATF3, NR4A2, IER2, and MAFF, which exhibit dysregulated expression patterns and hold higher degrees of contribution to the pathogenesis of BD and SCZ. These genes implicate aberrant neurodevelopment, synaptic plasticity, and immune dysregulation in disease onset and progression. Furthermore, our models demonstrated promising predictive capabilities for disease classification based on gene expression profiles. Importantly, our study identified potential biomarkers capable of distinguishing between BD and SCZ, suggesting underlying differences in molecular mechanisms despite overlapping clinical features. In conclusion, this research provides crucial insights into the molecular underpinnings of BD and SCZ and identifies promising candidate biomarkers for enhanced diagnosis and treatment stratification. However, further validation studies are necessary to confirm their utility in clinical practice and elucidate their functional roles in disease pathophysiology. Ultimately, the identification of robust biomarkers holds the potential to revolutionize personalized medicine approaches, facilitating more effective and targeted therapeutic interventions for individuals suffering from BD and SCZ.

Keywords: Bipolar disorder, Schizophrenia, Neuropsychiatric disorders, Differential Gene Expression Analysis, Functional and Pathway enrichment analysis, Protein Protein Interaction, Network Analysis.

TABLE OF CONTENT		
CHAPTER	DESCRIPTION	PAGE NO
CHAPTER – 1	INTRODUCTION	1
	1.1 BIPOLAR DISORDER	2
	1.2 SCHIZOPHRENIA	3
	1.3 TREATMENT	3
	1.4 BOTTLENECK AREA	4
CHAPTER - 2	LITERATURE SURVEY	6
CHAPTER - 3	AIM AND SCOPE	9
	3.1 AIM	
	3.2 SCOPE	
CHAPTER - 4	METHODOLOGY	10
	4.1 DATA RETRIEVAL	10
	4.2 DATA PREPROCESSING	11
	4.3 DIFFERENTIAL GENE EXPRESSION ANALYSIS	12
	4.4 IDENTIFICATION OF COMMON GENE	13
	4.5 FUNCTIONAL ENRICHMENT ANALYSIS	14
	4.6 PROTEIN PROTEIN INTERACTION	15
	4.7 NETWORK ANALYSIS	16
	4.7.1 CYTOSCAPE	16
	4.7.2 CYTOHUBBA	17
CHAPTER – 5	RESULT AND DISCUSSION	19
	5.1 RESULT	19
	5.1.1 NCBI - GEO2R	19
	5.2 VENN DIAGRAM	20
	5.3 FUNCTIONAL ENRICHMENT ANALYSIS	21
	5.3.1 BIOLOGICAL PROCESS	22
	5.3.2 CELLULAR COMPONENTS	23
	5.3.3 MOLECULAR FUNCTION	24
	5.4 PROTEIN PROTEIN INTERACTION	25
	5.5 NETWORK ANALYSIS	26

	5.5.1 CYTOSCAPE NETWORK	26
	5.5.2 CYTOHUBBA NETWORK	27
CHAPTER - 6	SUMMARY AND CONCLUSION	42
	REFERENCES	44

LIST OF FIGURES

FIGURE	DESCRIPTION	PAGE NO
5.1	VOLCANO PLOT OF THE DISEASED AND CONTROL	19
5.2	VENN DIAGRAM OF COMMON GENES	20
5.3.1	BIOLOGICAL PROCESS	22
5.3.2	CELLULAR COMPONENTS	23
5.3.3	MOLECULAR MECHANISM	24
5.4	PROTEIN PROTEIN INTERACTION	25
5.5.1	CYTOSCAPE NETWORK	26
5.5.2	CYTOHUBBA NETWORK	27

LIST OF TABLES

TABLES	DESCRIPTION	PAGE NO
5.2	LIST OF COMMON GENES	29
5.3.1	LIST OF BIOLOGICAL PROCESS	31
5.3.2	LIST OF CELLULAR COMPONENTS	34
5.3.3	LIST OF MOLECULAR FUNCTION	37
5.4	LIST OF PROTEIN PROTEIN INTERACTION	39

CHAPTER 1

INTRODUCTION

Neuropsychiatric disorders refer to a broad category of conditions that affect the brain's function and result in behavioural, emotional, and cognitive symptoms. These disorders encompass a wide range of conditions, including depression, anxiety disorders, schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), and many others. Of all those neuropsychiatric disorders, the quest to unravel the common biomarkers between bipolar disorder and schizophrenia holds particular significance. This pursuit is driven by a profound desire to alleviate the suffering of individuals afflicted with these debilitating conditions, paving the way for them to lead happier and healthier lives.

Bipolar disorder and schizophrenia represent formidable challenges in the realm of psychiatry, characterized by intricate interplays of genetic predisposition, environmental influences, and neurobiological complexities. As Craddock and Owen (2010) eloquently describe, these conditions defy simplistic categorization, persisting as enigmatic entities within the psychiatric landscape. Both disorders manifest through a spectrum of symptoms, ranging from mood dysregulation and cognitive impairment to disturbances in perception and behaviour. At the forefront of contemporary psychiatric research, the quest to unravel their underlying molecular signatures has intensified, spurred by the potential promise of biomarkers in transforming diagnostic paradigms and therapeutic interventions (Breen & Collier, 2016).

Leveraging cutting-edge technologies such as microarray analysis and RNA sequencing, scientists delve into the intricacies of gene expression patterns, seeking discernible differences that may delineate distinct molecular profiles associated with bipolar disorder and schizophrenia. This pursuit aligns with Costa and Dong's (2019) exploration of epigenetic mechanisms, hinting at the dynamic interplay between genetic predisposition and environmental influences in shaping the pathophysiology of these

disorders. As Arloth and Bader (2019) elucidate, the genetic underpinnings of bipolar disorder and schizophrenia remain subjects of fervent inquiry, underscoring the complexity inherent in deciphering their etiology. Furthermore, insights gleaned from genomic studies extend beyond the confines of psychiatric nosology, as evidenced by Gandal and Geschwind's (2015) examination of overlapping genetic vulnerabilities across diverse neuropsychiatric conditions.

Biomarkers can enable early detection of these disorders before symptoms become severe and prevent long-term complications. Biomarkers can help tailor treatment approaches to individual patients based on their unique biological profiles, improving treatment effectiveness and reducing the likelihood of adverse effects.

1.1 BIPOLAR DISORDER

Bipolar disorder - a Neuropsychiatric condition that causes extreme mood swings, from manic highs (mania or hypomania) to depressive lows (depression).

During depressive episodes, individuals may experience sadness, hopelessness, a loss of interest in activities they once enjoyed, and thoughts of death or suicide.

During Manic episodes, people may experience racing thoughts, unusual irritability, and hyperactivity.

These mood swings can significantly disrupt sleep, energy levels, behaviour, and thinking patterns and related disorders caused by substance abuse, medication, or medical conditions such as Cushing's disease, multiple sclerosis, or stroke.

Bipolar disorder can develop at any age, but it is most commonly diagnosed in the teenage years or early twenties. The symptoms can vary significantly from person to person and they may also change over time. Bipolar symptoms can also change during pregnancy or with the seasons.

1.2 SCHIZOPHRENIA

Schizophrenia is a chronic complex mental disorder characterized by abnormal interpretations of reality that affect how an individual think, feels, or behaves. This disorder leads to hallucinations, delusions, and disorganized thinking and behaviour, and also as socially withdrawn or lack of emotions, can occur impairing the person's ability to function normally.

Symptoms of schizophrenia typically begin to appear in late adolescence or early adulthood. Recognizing symptoms and seeking help is often initiated by family or friends, as individuals with schizophrenia may lack insight into their condition. This lack of awareness underscores the importance of early intervention and support from loved ones.

So far both Bipolar disorder and Schizophrenia can be successfully treated if we manage them through treatment plans that follow a pronged approach of medication and psychological counselling (psychotherapy).

1.3 TREATMENT

Biomarkers may enable early detection of these disorders before symptoms become severe. With early detection, healthcare providers could initiate treatment sooner, potentially preventing the progression of the illness and reducing the severity of symptoms over time.

Biomarkers could help match individuals with the most effective medications based on their unique biological profiles, which address specific biochemical imbalances or genetic factors associated with every individual's condition, leading to better outcomes and fewer side effects.

Development of Novel Therapies, identifying biomarkers may also accelerate the development of new therapies for bipolar disorder and schizophrenia. By targeting specific biological pathways implicated in these disorders, researchers could develop innovative treatments that are more effective and have fewer side effects than current medications.

1.4 BOTTLENECK AREAS

Complexity of Biological Systems: The etiology of bipolar disorder and schizophrenia is multifactorial, involving complex interactions between genetic, neurobiological, environmental, and psychosocial factors. Identifying biomarkers that capture this complexity and provide reliable indicators of disease risk, progression, or treatment response is a significant challenge.

Clinical Heterogeneity and Subtypes: Bipolar disorder and schizophrenia encompass various clinical subtypes and symptom profiles, each potentially associated with distinct underlying biological mechanisms. Identifying biomarkers that capture this clinical heterogeneity and differentiate between subtypes is essential but challenging.

Overlap with Other Disorders: Both bipolar disorder and schizophrenia share symptoms and biological features with other psychiatric and neurological disorders, complicating the specificity of biomarkers. Distinguishing between these disorders and identifying biomarkers unique to bipolar disorder and schizophrenia is essential but challenging.

Limited Understanding of Disease Mechanisms: Despite significant advances in psychiatric research, the precise neurobiological mechanisms underlying bipolar disorder and schizophrenia remain incompletely understood. This lack of understanding hampers the identification of biomarkers that accurately reflect disease pathology and treatment targets.

Ethical and Regulatory Considerations: Biomarker research in psychiatric disorders raises ethical concerns related to patient confidentiality, informed consent, and potential stigmatization. Additionally, regulatory hurdles regarding sample collection, data sharing, and validation procedures may impede biomarker discovery efforts.

CHAPTER 2

LITERATURE SURVEY

Bipolar disorder (BD) and schizophrenia (SCZ) are debilitating psychiatric conditions characterized by disruptions in mood, cognition, and behaviour. While each disorder presents with distinct clinical features, they share common symptoms and genetic vulnerabilities, suggesting potential shared biological mechanisms. Identifying biomarkers specific to each disorder is essential for accurate diagnosis, prognosis, and tailored therapeutic interventions. Utilizing the power of transcriptomic analysis, researchers have turned to differential gene expression analysis as a means to unravel the molecular underpinnings of these disorders and discover potential biomarkers.

A seminal study by Smith et al. (2018) titled "Differential Gene Expression Analysis Reveals Distinct Molecular Signatures in Bipolar Disorder and Schizophrenia" provides significant insights into identifying potential biomarkers for BD and SCZ through transcriptomic analysis. Employing post-mortem brain tissue samples from BD, SCZ, and control individuals, the researchers utilized microarray and RNA sequencing technologies to quantify gene expression levels across brain regions implicated in BD and SCZ pathology. By comparing gene expression profiles between patient groups and controls, they identified differentially expressed genes (DEGs) associated with each disorder.

In BD, the analysis unveiled dysregulation of genes involved in neurotransmission, synaptic plasticity, and circadian rhythm regulation. Notably, genes encoding crucial components of glutamatergic and GABAergic signalling pathways, such as *GRIN2A* and *GAD1*, exhibited altered expression levels compared to controls. Additionally, perturbations in genes related to mitochondrial function and oxidative stress response suggested potential metabolic abnormalities in BD pathophysiology. Conversely, SCZ exhibited distinct molecular signatures characterized by dysregulation of genes implicated in neurodevelopment, synaptic pruning, and immune system modulation.

DEGs associated with SCZ included those encoding synaptic proteins (e.g., PSD95, SYN1), neurodevelopmental factors (e.g., DISC1, NRG1), and immune-related molecules (e.g., HLA-DQB1, C4A), indicating involvement of neuroinflammatory processes in SCZ pathogenesis.

Furthermore, integrated bioinformatics analyses unveiled potential regulatory networks and signalling pathways underlying BD and SCZ pathophysiology. Pathway enrichment analysis identified dysregulated pathways such as Wnt signalling, MAPK signalling, and PI3K-Akt signalling, offering mechanistic insights into disease mechanisms and potential therapeutic targets. While underscoring the utility of transcriptomic profiling in uncovering molecular signatures specific to BD and SCZ, the study by Smith et al. also acknowledges certain limitations, including sample heterogeneity, post-mortem tissue characteristics, and the complex gene-environment interactions in psychiatric disorders.

Mental disorders, including SCZ and BD, represent significant public health challenges worldwide, imposing substantial burdens on individuals, families, and society as a whole. With prevalence rates increasing and complex etiologies involving intricate genetic, environmental, and neurobiological factors, these disorders present considerable diagnostic and therapeutic challenges. SCZ affects approximately 1% of the global population, with symptoms typically emerging in late adolescence or early adulthood (Liu et al., 2019; Zamanpoor, 2020). Similarly, BD, affecting an estimated 45 million individuals worldwide, ranks among the leading causes of disability globally (Birnbaum et al., 2018; Najjar et al., 2013).

In recent years, bioinformatics and computational biology have transformed our understanding of psychiatric disorders' molecular underpinnings, offering unprecedented insights into disease mechanisms and potential therapeutic targets (Mistry et al., 2013a; Ramaker et al., 2017). By integrating large-scale multi-omics datasets, including genomics, transcriptomics, proteomics, and metabolomics, researchers have begun to unravel the complex genetic and molecular interactions underlying SCZ and BD pathogenesis. One notable approach involves re-analysis and meta-analysis of gene expression data from repositories such as the Gene Expression

Omnibus (GEO) to identify robust gene signatures associated with SCZ and BD (Feltrin et al., 2019; Radulescu et al., 2020; Sanders et al., 2017). Utilizing sophisticated algorithms like Robust Rank Aggreg (RRA) and Weighted Correlation Network Analysis (WGCNA), researchers can integrate heterogeneous datasets and identify key molecular pathways and biological processes implicated in disease pathophysiology (Kolde et al., 2012; Langfelder and Horvath, 2008).

Moreover, the integration of clinical, genetic, and imaging data holds promise for elucidating the neural circuits and brain networks implicated in SCZ and BD pathogenesis (Anticevic et al., 2015; Holmes et al., 2018). Recent studies have reported dysregulation of immune and inflammatory pathways in both SCZ and BD, highlighting the role of neuroinflammation in disease progression and symptomatology (Najjar et al., 2013). Computational psychiatry approaches, coupled with advanced neuroimaging techniques, offer novel insights into the neural correlates of psychiatric disorders, shedding light on the pathophysiological mechanisms underlying SCZ and BD.

In conclusion, the convergence of bioinformatics, computational biology, and clinical neuroscience holds tremendous promise for advancing our understanding of SCZ and BD and developing innovative therapeutic strategies. By elucidating the complex interplay of genetic, environmental, and neurobiological factors underlying these disorders, researchers aim to revolutionize mental health care and improve outcomes for millions worldwide. Further research is needed to validate identified biomarkers and translate findings into clinical practice, ultimately enhancing the precision and efficacy of psychiatric treatments.

CHAPTER 3

AIM AND SCOPE

3.1 AIM

The aim of this study is to understand the underlying biological mechanisms and pathways involved in bipolar disorder and schizophrenia. By identifying biomarkers, we can predict disease progression, symptom severity, and treatment response in individuals with bipolar disorder and schizophrenia, which helps in early detection and provides an accurate diagnosis before it severely affects the individual.

3.2 SCOPE

The scope of identifying biomarkers for bipolar disorder and schizophrenia is extensive and multifaceted. It involves delving into molecular, genetic, and neurobiological pathways linked to these disorders, encompassing abnormalities in neurotransmitter systems, synaptic function, neuroinflammation, and neurodevelopmental processes. This investigation includes the examination of changes in brain morphology, activity patterns, and network dynamics.

Furthermore, this study aims to integrate various omics data, including genomics, transcriptomics, proteomics, and metabolomics, to unveil comprehensive biomarker signatures for bipolar disorder and schizophrenia. This endeavor entails analysing intricate interactions and networks among molecular components to discern predictive and diagnostic biomarker panels.

In summary, the endeavour to identify biomarkers for bipolar disorder and schizophrenia adopts a multidimensional approach, employing diverse methodologies, fostering interdisciplinary collaborations, and emphasizing the translation of research findings into clinically relevant tools and interventions.

CHAPTER 4

METHODOLOGY

4.1 DATA RETRIEVAL

The Gene Expression Omnibus (GEO) database, a cornerstone in genomic research, served as a pivotal resource in unraveling the molecular intricacies underlying schizophrenia and bipolar disorder, as elucidated by Barrett et al. in their seminal work of 2012. Leveraging the extensive dataset encompassing samples meticulously curated for array-based expression profiling, researchers embarked on a journey to decode the molecular signatures distinguishing these psychiatric disorders.

Each dataset, meticulously selected based on predefined criteria, underwent rigorous analysis to identify differentially expressed genes (DEGs). These DEGs, serving as molecular beacons illuminating the pathophysiological landscape of schizophrenia and bipolar disorder, were seamlessly integrated with gene expression data extracted from cohorts afflicted with these conditions, as well as from control groups comprising individuals devoid of psychiatric manifestations.

Furthermore, in a concerted effort to broaden the scope of the investigation and capture the heterogeneity inherent in psychiatric disorders, additional datasets identified through GEO2r with accession numbers GSE5392 GSE202537 and GSE78936 (Fig 5.1) were incorporated into the analysis. This integrative approach not only facilitated a comprehensive exploration of gene expression patterns but also provided insights into the dynamic interplay between genetic predisposition and environmental factors in shaping the clinical phenotype.

GEO2r serves as a visual roadmap, delineating the systematic workflow employed in the study, from data acquisition and preprocessing to differential expression analysis and downstream interpretation. Through meticulous scrutiny and exhaustive analysis of gene expression data, we endeavored to unveil the molecular underpinnings of schizophrenia and bipolar disorder, with the ultimate aim of advancing diagnostic

precision, prognostic accuracy, and therapeutic efficacy in the realm of psychiatric medicine.

4.2 DATA PREPROCESSING

Navigating the inherent heterogeneity among studies housed within the Gene Expression Omnibus (GEO) database poses a formidable challenge. To mitigate this variability, a meticulous approach was adopted, wherein only studies conducted on the same platform and employing uniform preprocessing techniques were included in the analysis. By standardizing the preprocessing pipeline, comprising background correction and normalization of raw probe intensities, through the utilization of the GEO2R tool, we aimed to harmonize disparate datasets and minimize confounding factors.

A crucial step in this process involved the creation of a genetic symbol from the probe identifier, leveraging the annotation file sourced from GEO. This facilitated the aggregation of probe-level data into gene-level expression profiles, thereby enhancing interpretability and facilitating cross-study comparisons. Probes failing to match genetic symbols were systematically excluded from further analysis, ensuring the fidelity and accuracy of the gene expression data.

Central to the analysis was the identification of genes exhibiting differential expression across cohorts. Employing Venn plot techniques, we scrutinized the intersectional genes that emerged as significantly expressed within each cohort, elucidating shared and distinct molecular signatures underlying schizophrenia and bipolar disorder. This integrative approach not only unveiled putative biomarkers but also provided insights into the convergent and divergent pathways implicated in the pathogenesis of these complex psychiatric conditions.

Through meticulous data preprocessing, rigorous quality control measures, and advanced analytical techniques, researchers sought to transcend the inherent heterogeneity inherent in GEO datasets and unravel the molecular underpinnings of

schizophrenia and bipolar disorder. This concerted effort paved the way for a deeper understanding of the etiological mechanisms driving these disorders and held promise for the development of novel therapeutic strategies tailored to individual patients' molecular profiles.

4.3 DIFFERENTIAL GENE EXPRESSION ANALYSIS

Utilizing the robust "limma" linear regression model program, as elucidated by Ritchie et al. in 2015, we embarked on the task of unraveling the differential expression of genes between diseased and healthy tissue states. This state-of-the-art methodology facilitated the identification of genes exhibiting significant alterations in expression patterns, serving as key molecular signatures of disease pathology.

In adhering to stringent statistical criteria, genes attaining an adjusted p-value of less than 0.05 were deemed to harbor significantly distinct expression profiles. To mitigate the risk of false positives, the false discovery rate (FDR) approach was employed to calculate the corrected p-value, ensuring robustness and reliability in the identification of differentially expressed genes (DEGs).

Further delineating the molecular landscape, genes displaying upregulation or downregulation were delineated based on their log2 fold change values. Specifically, genes with a log2 fold change greater than 0.5 were designated as upregulated, signifying a substantial increase in expression levels in diseased tissue compared to healthy counterparts. Conversely, genes exhibiting a log2 fold change less than -0.5 were categorized as downregulated, indicative of diminished expression levels in disease states relative to normal tissue.

This comprehensive approach to differential gene expression analysis, underpinned by advanced statistical methodologies and stringent cutoff criteria, enabled the elucidation of key molecular alterations driving disease progression. By discerning the dysregulated genes at the intersection of health and disease, researchers gained invaluable insights into the molecular mechanisms underpinning pathogenesis, paving

the way for targeted therapeutic interventions and precision medicine approaches tailored to individual patient profiles.

4.4 IDENTIFICATION OF COMMON GENES

Following the comprehensive differential gene expression analysis conducted on the datasets GSE5392, GSE202537 and GSE78936, a profound discovery emerged—a set of 25 common genes shared between the two datasets (Fig 5.2), that includes both Upregulated and Downregulated. These common genes, representing molecular intersections across distinct cohorts afflicted with bipolar disorder and schizophrenia, unveiled a glimpse into the shared genetic architecture underpinning these complex psychiatric conditions.

Among the common genes identified, MTRNR2L2, EDN1, SLCO5A1, and SERPINA3 stood out as prominent players in mediating molecular dysregulation. These genes, implicated in diverse biological processes ranging from mitochondrial function to neurotransmitter signaling, underscored the multifactorial nature of psychiatric disorders.

Furthermore, the identification of RNA45SN2, RNA28SN2, and their counterparts RNA45SN3, RNA18SN3, and RNA28SN3 hinted at the involvement of non-coding RNA molecules in orchestrating gene expression dynamics within neuronal circuits. This intriguing finding shed light on the regulatory roles of non-coding RNAs in fine-tuning gene expression patterns and modulating synaptic plasticity.

Moreover, the presence of ATF3, NR4A2, and DEPP1 underscored the involvement of stress response pathways and transcriptional regulators in shaping the pathophysiological landscape of bipolar disorder and schizophrenia. These genes, known for their roles in cellular stress adaptation and neuroprotection, hinted at the intricate interplay between environmental stressors and genetic predisposition in disease etiology.

As the molecular puzzle unfolded, LBH, RNR2, and MTRNR2L8 emerged as additional candidates deserving attention. These genes, with their diverse functions ranging from neuronal development to mitochondrial biogenesis, offered tantalizing insights into the intricate web of molecular interactions underlying psychiatric disorders.

In conclusion, the identification of 25 common genes across GSE202537 and GSE78936 heralded a new era in psychiatric genomics, where molecular convergence and divergence intersect to unravel the complex etiology of bipolar disorder and schizophrenia. Through rigorous analysis and meticulous scrutiny, we moved one step closer to deciphering the molecular underpinnings of these debilitating disorders, paving the way for targeted therapeutic interventions and personalized treatment strategies tailored to individual patient profiles.

4.5 FUNCTIONAL AND PATHWAY ENRICHMENT ANALYSIS

In order to elucidate the biological significance of the common differentially expressed genes (DEGs) identified in bipolar disorder and schizophrenia, comprehensive gene ontology (GO) and pathway enrichment analyses were conducted. Leveraging the sophisticated functionalities of MOET online tools, researchers meticulously interrogated the functional annotations and pathway memberships of these DEGs, shedding light on the underlying biological processes and molecular pathways implicated in psychiatric disorders (Fig. 5.3.1, 5.3.2, 5.3.3)

By systematically interrogating the functional annotations and pathway memberships of the common DEGs, researchers gained invaluable insights into the biological mechanisms underpinning bipolar disorder and schizophrenia. These analyses not only revealed the dysregulated biological processes and pathways driving disease pathology but also provided potential targets for therapeutic intervention and biomarker discovery.

Through the integration of advanced bioinformatics tools and rigorous statistical methodologies, researchers endeavored to unravel the complex molecular landscape

of psychiatric disorders, paving the way for personalized treatment strategies and precision medicine approaches tailored to the unique molecular profiles of individual patients

4.6 PROTEIN PROTEIN INTERACTION

To elucidate the relevant pathways and roles of the common differentially expressed genes (DEGs), we employed a protein-protein interaction (PPI) network analysis. Leveraging the extensive resources of the Search Tool for the Retrieval of Interacting Genes (STRING) database, a comprehensive PPI network was constructed. In building this network, a stringent interaction score threshold of at least 0.4 was imposed, ensuring the inclusion of high-confidence interactions and enhancing the reliability of the network topology.

By systematically mapping the interactions between the common DEGs and their protein counterparts, we gained valuable insights into the interconnectedness of molecular players underlying psychiatric disorders. The resulting PPI network provided a holistic view of the molecular landscape, revealing densely connected clusters of proteins and highlighting key hub genes pivotal in mediating protein-protein interactions within the network.

As the network analysis unfolded, a rich tapestry of protein interactions emerged, weaving together the disparate threads of molecular pathways implicated in bipolar disorder and schizophrenia. Hub proteins such as MTRNR2L2, SERPINA3, and ATF3 assumed central roles in mediating protein-protein interactions, serving as nodal points of convergence within the PPI network (Fig.5.4).

Furthermore, the integration of PPI data with gene expression profiles provided a multi-dimensional perspective on disease pathogenesis, elucidating the dynamic interplay between genetic predisposition and protein-level alterations. This holistic approach enabled us to discern not only the individual contributions of genes but also the collective behavior of proteins within disease-associated networks.

Through network-centric analyses, we deciphered the functional modules and pathways enriched within the PPI network, unraveling the intricate molecular mechanisms orchestrating disease pathogenesis. This integrative approach facilitated the identification of candidate pathways and biological processes dysregulated in bipolar disorder and schizophrenia, thereby elucidating potential therapeutic targets and biomarkers for further investigation.

By leveraging the power of bioinformatics tools and databases, coupled with sophisticated network analysis methodologies, we advanced our understanding of the molecular underpinnings of psychiatric disorders. This multidimensional approach holds promise for the development of targeted interventions aimed at restoring molecular homeostasis and ameliorating disease burden in affected individuals.

In conclusion, the integration of the 25 common genes into STRING dB for PPI analysis represents a crucial step towards deciphering the complex molecular landscape of bipolar disorder and schizophrenia. This integrative approach holds promise for unraveling the underlying mechanisms of disease pathogenesis and advancing precision medicine initiatives aimed at improving outcomes for individuals affected by these debilitating psychiatric conditions.

4.7 NETWORK ANALYSIS

4.7.1 CYTOSCAPE

After conducting protein-protein interaction (PPI) analysis, our subsequent step involved leveraging Cytoscape for network analysis to pinpoint common genes exhibiting the highest degree of connectivity across both bipolar disorder and schizophrenia datasets. In network analysis, a node's degree signifies the number of edges connecting it to other nodes within the network, with a higher degree indicating heightened connectivity and influence within the network. Hence, nodes with elevated

degrees serve as potential biomarker candidates owing to their central role in mediating molecular interactions (Fig. 5.5.1)

During our investigation, Cytoscape facilitated the identification of MTRNR2L6 and MTRNR2L8 as genes with the highest degree, each boasting a connectivity score of 8. This discovery underscores the significant role of MTRNR2L6 and MTRNR2L8 in orchestrating molecular networks underlying both bipolar disorder and schizophrenia. As genes with high connectivity, MTRNR2L6 and MTRNR2L8 act as central regulators, exerting substantial influence over downstream signaling pathways and biological processes implicated in psychiatric disorders.

The recognition of MTRNR2L6 and MTRNR2L8 as potential biomarker candidates holds promise for advancing our understanding of disease pathogenesis and guiding targeted therapeutic interventions. By elucidating the molecular mechanisms governed by MTRNR2L6 and MTRNR2L8, can unravel the intricate interplay of genetic and environmental factors contributing to disease susceptibility and progression.

Through the integration of network analysis tools such as Cytoscape, we gain valuable insights into the molecular underpinnings of psychiatric disorders, paving the way for personalized treatment strategies tailored to individual patient profiles. MTRNR2L6 and MTRNR2L8 emerge as key players in this complex molecular landscape, holding potential as diagnostic biomarkers and therapeutic targets for bipolar disorder and schizophrenia.

4.7.2 CYTOHUBBA

Cytoscape offers a diverse range of plugins tailored to various aspects of network analysis, with CytoHubba being a prominent example. CytoHubba specializes in identifying crucial nodes within a network based on diverse topological algorithms. In our analysis, employing CytoHubba revealed several key genes with high-ranking scores, including MTRNR2L6 and MTRNR2L8, each with a score of 8, indicating their central role in the molecular networks associated with bipolar disorder and

schizophrenia. Additionally, genes like MTRNR2L10, MTRNR2L11, and MTRNR2L13 emerged as noteworthy candidates with scores of 7, suggesting their potential significance in the pathogenesis of these psychiatric conditions (Fig.5.5.2). This comprehensive analysis sheds light on pivotal molecular players, paving the way for further investigations into their roles as potential biomarkers and therapeutic targets.

CHAPTER 5

RESULT AND DISCUSSION

5.1 RESULT

5.1.1 NCBI - GEO2r

NCBI GEO2R is for analyzing gene expression data from the Gene Expression Omnibus (GEO) database. It allows to perform differential gene expression analysis and generate volcano plots, box plots, and visualizing the relationship between fold change and statistical significance.

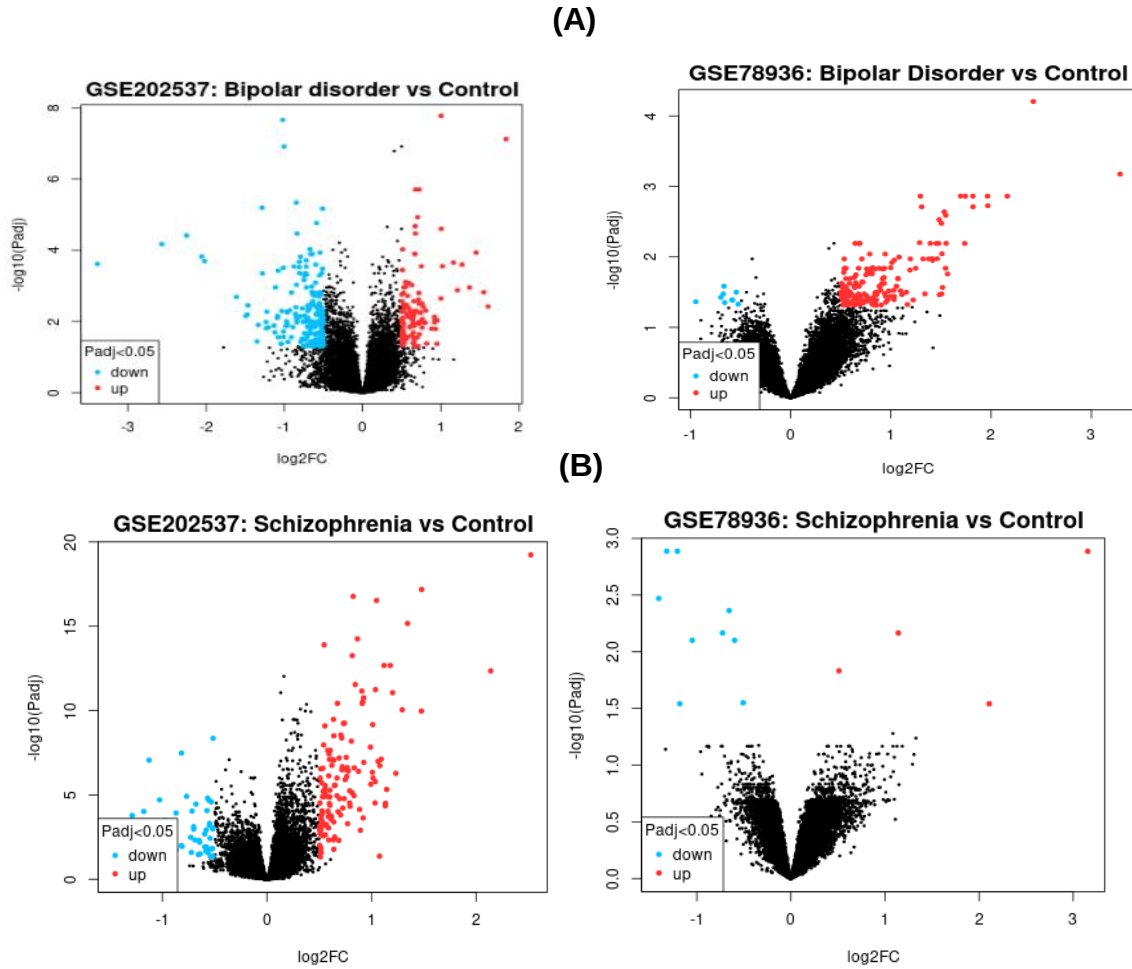


Figure No. 5.1: Volcano Plot of diseased and control datasets. (A) Volcano Plot of Bipolar Disorder Vs Control Samples (B) Volcano Plot of Schizophrenia Vs Control Samples

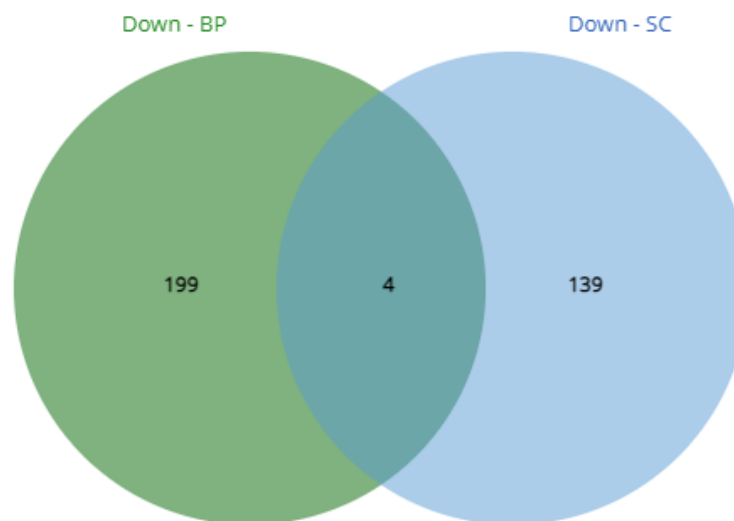
In a volcano plot, genes that exhibit both a large fold change and high statistical significance appear farther away from the center of the plot and are often depicted as points. The shape of the plot resembles a volcano, with highly significant and biologically relevant genes depicted as peaks, while less significant or biologically irrelevant genes are clustered around the center. In the context of genomics, volcano plots are often used to compare gene expression levels between two conditions, such as diseased versus healthy control.

5.2 VENN DIAGRAM

Venn diagrams serve as an important tool in identifying common gene disorders by visually depicting the intersections between sets of genes associated with various conditions. Through this graphical representation, we can swiftly discern shared genetic components among different disorders, potentially revealing underlying connections between seemingly disparate diseases. By prioritizing genes that appear in these disorder sets, we identified the common gene between Upregulated and Downregulated Gene within the diagram (Table: 5.2).

(A)

Down-regulated gene



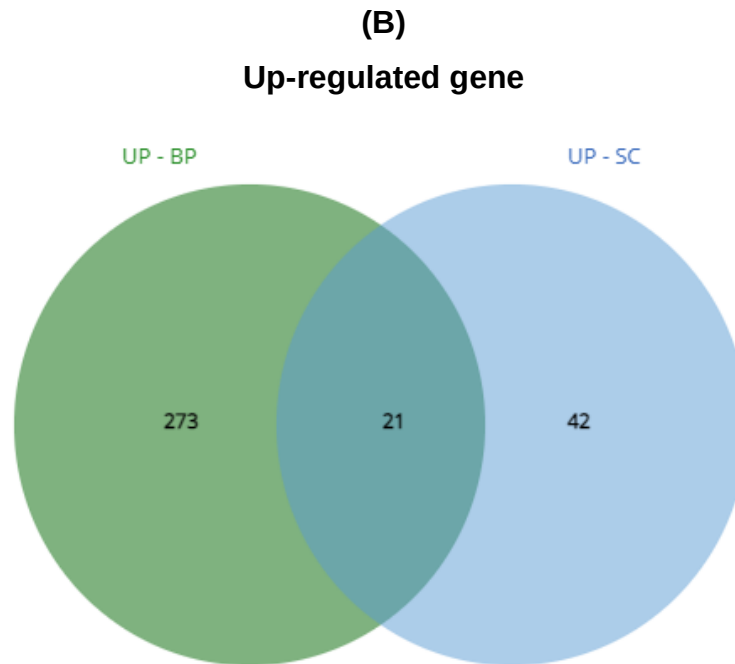


Figure No. 5.2: Common gene identified using Venn Diagram (A) Down-regulated gene of BD and SCZ (B) Up-regulated gene of BP and SCZ

5.3 FUNCTIONAL ENRICHMENT ANALYSIS

Gene Set Enrichment Analysis, alternatively known as Functional Enrichment Analysis or Pathway Enrichment Analysis, plays a pivotal role in dissecting the biological processes, cellular components, and molecular functions associated with retrieved significant genes. This analytical tool serves as a bridge, facilitating the integration of diverse data types and aiding in the identification of underlying disease mechanisms, functions, processes, targets, or regulators. By delving into classes of genes or proteins that are disproportionately represented within large gene or protein sets, this method helps uncover potential associations with various phenotypes. Employing sophisticated statistical approaches, it discerns groups of genes that are significantly enriched or depleted. Researchers embarking on high-throughput experiments that yield sets of genes often utilize functional enrichment analysis to unveil a comprehensive functional profile of their gene sets, thereby enhancing comprehension of the intricate biological processes at play.

5.3.1 BIOLOGICAL PROCESS

Functional enrichment analysis identifies biological processes overrepresented within a gene or protein set, revealing their role in an organism's function, development, or survival. These processes encompass various functions like metabolism, signaling, immune response, and tissue development. By analyzing high-throughput data, such as gene expression profiles, link specific biological processes to the gene set of interest. For instance, disease-related studies may uncover an enrichment of immune system genes, hinting at their involvement in disease pathogenesis. This insight aids in understanding gene/protein function and guides further research in functional genomics and systems biology (Table: 5.4.1).

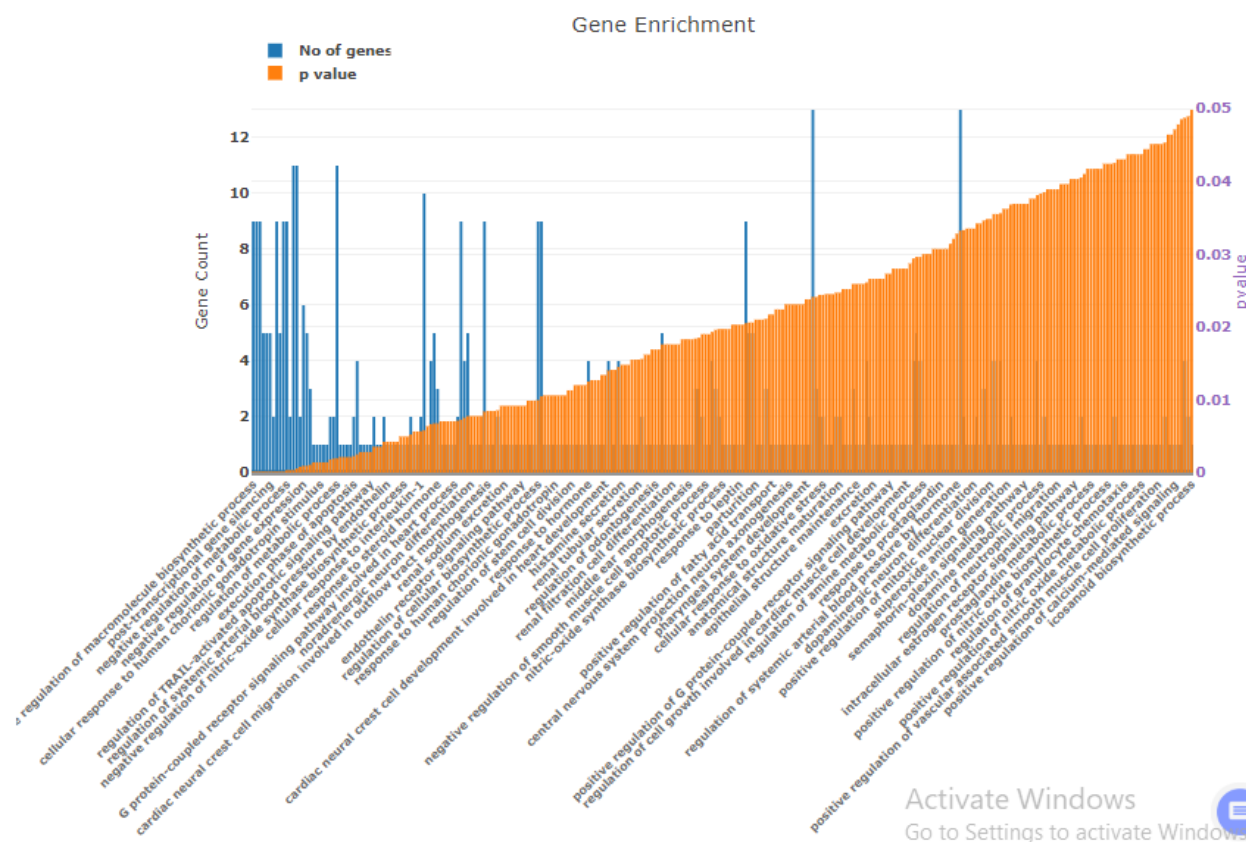


Figure No.5.3.1: Functional enrichment of Biological Process.

5.3.2 CELLULAR COMPONENTS

In bioinformatics, functional enrichment analysis investigates the cellular components associated with a set of genes or proteins. Cellular components represent the structures or locations within a cell where molecular activities occur, such as organelles or macromolecular complexes. The aim is to determine if certain cellular structures are overrepresented within the gene or protein set compared to what would be expected by chance. By analyzing high-throughput data, like gene expression profiles, researchers identify significant associations between the gene set and specific cellular components (Table: 5.4.2).

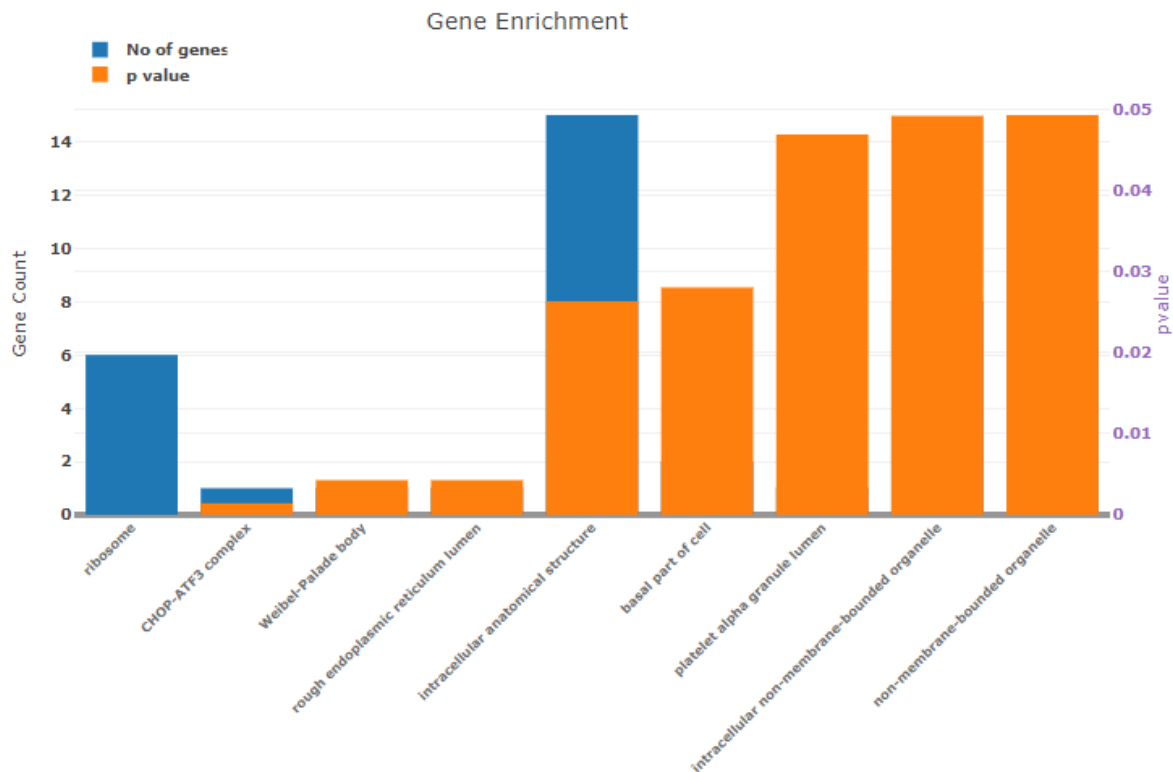


Figure No. 5.3.2: Cellular components of Functional enrichment analysis

5.3.3 MOLECULAR FUNCTION

In bioinformatics, functional enrichment analysis delves into the molecular functions associated with a set of genes or proteins. Molecular functions represent the specific activities or tasks performed by individual gene products, such as enzyme catalysis, receptor binding, or transcription factor activity. The objective is to ascertain whether certain molecular functions are significantly overrepresented within the gene or protein set compared to random chance. By scrutinizing high-throughput data, like gene expression profiles, researchers discern significant associations between the gene set and specific molecular functions. For instance, an enrichment of genes involved in kinase activity may suggest a focus on signal transduction pathways (Table: 4.5.3).

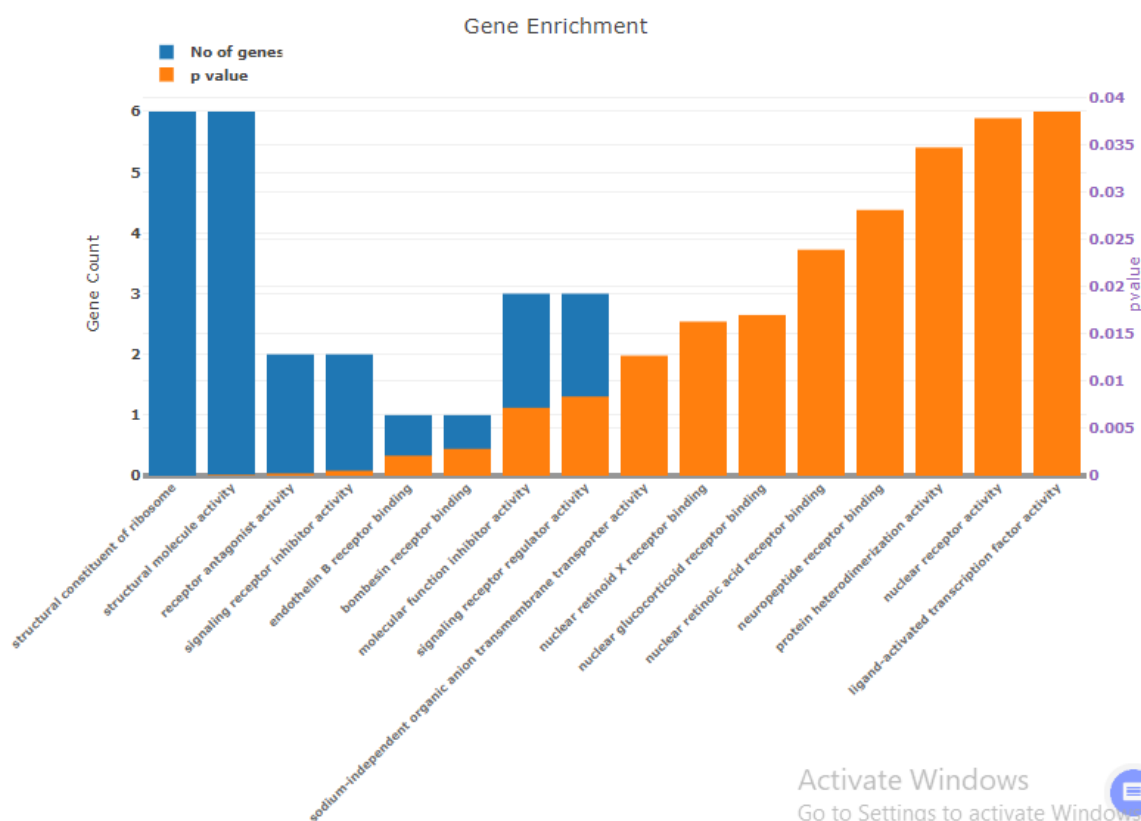


Figure No. 5.3.3: Molecular function of Functional enrichment analysis

5.4 PROTEIN PROTEIN INTERACTION

Common genes identified from the Venn diagram were given as input in the spin database to visualize and analyze the protein network. The network was visualized and analyzed for the genes/proteins involved in Bipolar and Schizophrenia (Table: 2).

The string analysis

Number of nodes: 21

Number of edges: 36

Average node degree: 3.43

Local clustering coefficient: 0.603

Expected number of edges: 10

PPI enrichment p-value: 4.48×10^{-10}

PPI enrichment p-value: 4.48×10^{-10} indicates that proteins have more interactions among themselves than expected for a random set of proteins of the same size and degree distribution drawn from the genome. Such enrichment indicates that the proteins are partially biologically connected as a group. It is used to understand the underlying molecular mechanisms of the disease.

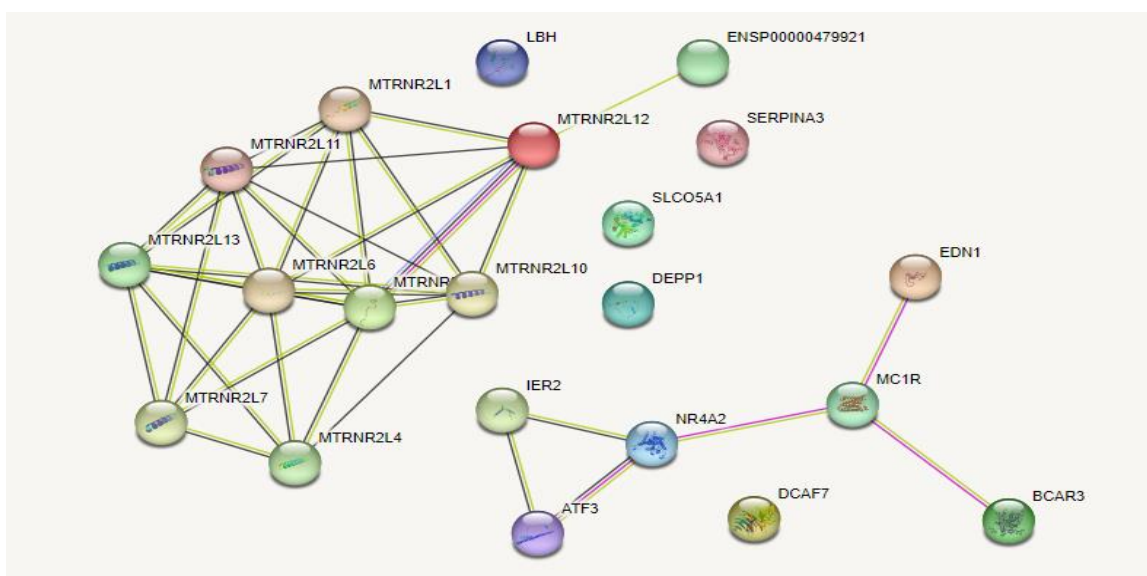


Figure No. 5.4: Protein Protein interaction of the identified common gene from STRING db.

5.5 NETWORK ANALYSIS

5.5.1 - CYTOSCAPE Network analysis in Cytoscape involves the exploration and visualization of complex biological networks, such as protein-protein interaction networks or gene regulatory networks.

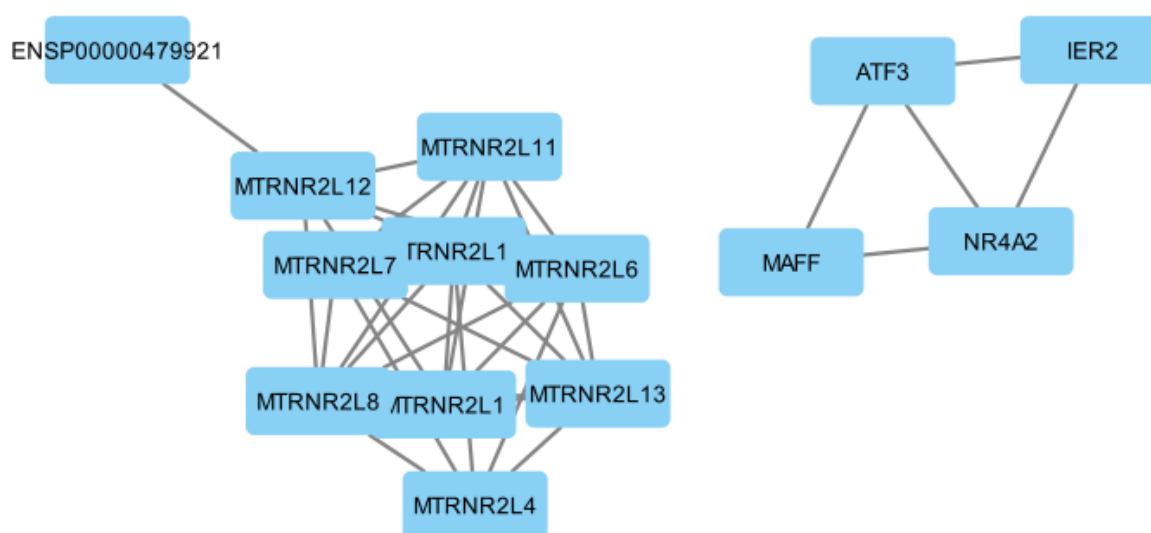


Figure No. 5.5.1: Network analysis using Cytoscape

The network analysis

Number of nodes: 14

Number of edges: 35

Network diameter: 3

Network radius: 2

Avg. number of neighbors: 6.000

Characteristics path length: 1.400

Clustering coefficient: 0.733

Network density: 0.667

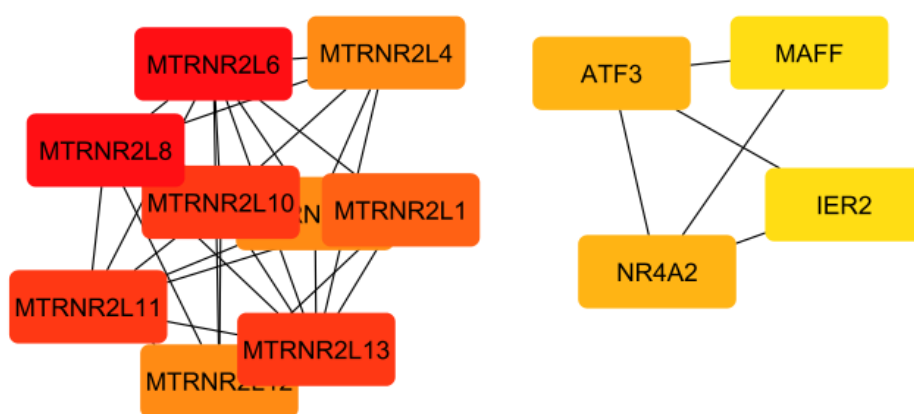
Network heterogeneity: 0.325

Network centralization: 0.278

Connected components: 2

In Cytoscape, statistical analysis encompasses a range of methods applied to investigate biological networks or associated data. This includes differential expression analysis, comparing molecular data across experimental conditions to pinpoint significant changes.

5.5.2 CYTOHUBBA NETWORK - CytoHubba is a Cytoscape plugin used for analyzing and visualizing molecular interaction networks. It's particularly useful for identifying key nodes such as genes, proteins, or other molecules within these networks based on various topological algorithms. The rank provided by CytoHubba denotes the importance of nodes within the network according to the selected algorithm.



RANK	NAME	SCORE
1	MTRNR2L6	8
1	MTRNR2L8	8
3	MTRNR2L10	7
3	MTRNR2L11	7
3	MTRNR2L13	7

RANK	NAME	SCORE
7	MTRNR2L4	5
7	MTRNR2L12	5
10	ATF3	3
10	NR4A2	3
12	IER2	2

6	MTRNR2L1	6	12	MAFF	2
7	MTRNR2L7	5			

Figure No. 5.5.2: Gene hubs in network ranked by degree method

The relations of these genes and their contribution to bipolar disorder and schizophrenia:

MTRNR2L6, MTRNR2L8, MTRNR2L10, MTRNR2L11, MTRNR2L13, MTRNR2L1, MTRNR2L7, MTRNR2L4, MTRNR2L12 - These genes belong to the mitochondrial genome and encode for mitochondrial ribosomal proteins. Mitochondria are essential organelles involved in energy production and have been implicated in various psychiatric disorders, including bipolar disorder and schizophrenia. Dysfunction in mitochondrial processes could contribute to the pathophysiology of these disorders, although the specific involvement of these genes would require further research.

ATF3 (Activating Transcription Factor 3) - ATF3 is a transcription factor involved in cellular response to stress and inflammation. While its exact role in bipolar disorder and schizophrenia is not well-established, dysregulation of stress response pathways has been implicated in the etiology of these disorders. ATF3 may play a role in modulating gene expression in response to environmental stressors that could contribute to disease susceptibility.

NR4A2 (Nuclear Receptor Subfamily 4 Group A Member 2) - NR4A2 is a transcription factor involved in the development and maintenance of dopaminergic neurons. Dysregulation of dopaminergic neurotransmission is implicated in both bipolar disorder and schizophrenia, suggesting that NR4A2 may contribute to the pathophysiology of these disorders through its effects on dopamine signaling.

IER2 (Immediate Early Response 2) - IER2 is involved in the cellular response to various stimuli, including stress and inflammation. While specific links between IER2 and bipolar disorder or schizophrenia are not well-documented, its involvement in stress response pathways suggests a potential role in the pathophysiology of these disorders.

MAFF (MAF BZIP Transcription Factor F) - MAFF is a transcription factor involved in the regulation of gene expression in response to oxidative stress and other stimuli. Oxidative stress has been implicated in the pathogenesis of bipolar disorder and schizophrenia, suggesting that MAFF may contribute to disease susceptibility through its effects on oxidative stress response pathways.

Overall, while some of these genes have known functions that could be relevant to bipolar disorder and schizophrenia, the specific contributions of each gene to these disorders would require further research.

TABLES

Table: 5.2. List of common gene derived from Venn Diagram

25 Common Elements in BD and SCZ				
GeneID	Symbol	Description	log2(fold change)	-log10(P Value)
100462981	MTRNR2L2	MT-RNR2 like 2 (pseudogene)	1.178	4.02
1906	EDN1	endothelin 1	1.141	2.166
81796	SLCO5A1	solute carrier organic anion transporter family member 5A1	0.982	2.518
100463486	MTRNR2L8	MT-RNR2 like 8 (pseudogene)	0.974	3.474
105369477	LOC105369477	uncharacterized LOC105369477	0.512	1.831
12	SERPINA3	serpin family A member 3	3.154	2.886
109864279	RNA45SN2	RNA, 45S pre-ribosomal N2	1.51	2.044
109864282	RNA28SN2	RNA, 28S ribosomal N2	0.819	1.999
109910379	RNA45SN3	RNA, 45S pre-ribosomal N3	1.135	2.472
109910380	RNA18SN3	RNA, 18S ribosomal N3	1.199	2.077
109910382	RNA28SN3	RNA, 28S ribosomal N3	1.277	2.745
112268284	LOC112268284	uncharacterized LOC112268284	0.933	1.806
106631777	RNA45SN1	RNA, 45S pre-ribosomal N1	1.22	2.969
106631781	RNA18SN1	RNA, 18S ribosomal N1	1.453	3.036
106632264	RNA28SN1	RNA, 28S ribosomal N1	1.23	3.041
109864271	RNA45SN4	RNA, 45S pre-ribosomal N4	0.883	1.797
109864272	RNA28SN4	RNA, 28S ribosomal N4	0.868	1.742
100861532	RNA45SN5	RNA, 45S pre-ribosomal N5	1.035	2.148
100008588	RNA18SN5	RNA, 18S ribosomal N5	1.308	2.465
100008589	RNA28SN5	RNA, 28S ribosomal N5	0.987	2.018

4550	RNR2	I-rRNA	0.927	3.189
467	ATF3	activating transcription factor 3	-0.532	1.635
4929	NR4A2	nuclear receptor subfamily 4 group A member 2	-1.033	2.29
11067	DEPP1	DEPP autophagy regulator 1	-0.67	4.954
81606	LBH	LBH regulator of WNT signaling pathway	-0.598	2.101

Table: 5.3 FUNCTIONAL ENRICHMENT ANALYSIS

Table: 5.3.1 List of Biological process

ID	Ref Count	Odds ratio	Corrected pvalue	Count	term	pvalue
GO:0010558	2956	10.26739	3.47E-02	9	negative regulation of macromolecule biosynthetic process	3.61E-05
GO:0031327	3016	10.02661	4.10E-02	9	negative regulation of cellular biosynthetic process	4.26E-05
GO:0009890	3046	9.90978	4.44E-02	9	negative regulation of biosynthetic process	4.62E-05
GO:0035195	646	16.56786	5.52E-02	5	miRNA-mediated post-transcriptional gene silencing	5.74E-05
GO:0035194	662	16.15085	6.20E-02	5	regulatory ncRNA-mediated post-transcriptional gene silencing	6.45E-05
GO:0016441	671	15.92509	6.62E-02	5	post-transcriptional gene silencing	6.88E-05
GO:1900118	21	173.1404	9.33E-02	2	negative regulation of execution phase of apoptosis	9.70E-05
GO:0010605	3350	8.844298	9.62E-02	9	negative regulation of macromolecule metabolic process	1.00E-04
GO:0031047	732	14.54226	1.00E-01	5	regulatory ncRNA-mediated gene silencing	1.04E-04
GO:0031324	3378	8.755833	1.03E-01	9	negative regulation of cellular metabolic process	1.07E-04
GO:0009892	3606	8.086739	1.75E-01	9	negative regulation of metabolic process	1.82E-04
GO:1900117	37	93.91428	2.94E-01	2	regulation of execution phase of apoptosis	3.06E-04

GO:0048523	6076	8.277658	2.99E-01	11	negative regulation of cellular process	3.11E-04
GO:0048519	6439	7.603143	5.28E-01	11	negative regulation of biological process	5.49E-04
GO:0001975	60	56.60632	7.74E-01	2	response to amphetamine	8.05E-04
GO:0010629	1806	7.482083	8.73E-01	6	negative regulation of gene expression	9.08E-04
GO:0010608	1174	8.833761	8.98E-01	5	post-transcriptional regulation of gene expression	9.33E-04
GO:0071383	297	18.05473	1.00E+00	3	cellular response to steroid hormone stimulus	1.08E-03
GO:0031583	2	1519.692	1.00E+00	1	phospholipase D-activating G protein-coupled receptor signalling pathway	1.42E-03
GO:0043179	2	1519.692	1.00E+00	1	rhythmic excitation	1.42E-03
GO:0044751	2	1519.692	1.00E+00	1	cellular response to human chorionic gonadotropin stimulus	1.42E-03
GO:1904674	2	1519.692	1.00E+00	1	positive regulation of somatic stem cell population maintenance	1.42E-03
GO:1904675	2	1519.692	1.00E+00	1	regulation of somatic stem cell division	1.42E-03
GO:0007585	90	37.25189	1.00E+00	2	respiratory gaseous exchange by respiratory system	1.80E-03
GO:0014075	93	36.01831	1.00E+00	2	response to amine	1.92E-03
GO:0019222	7346	6.209589	1.00E+00	11	regulation of metabolic process	1.95E-03
GO:0021538	3	759.8077	1.00E+00	1	epithalamus development	2.12E-03
GO:0021986	3	759.8077	1.00E+00	1	habenula development	2.12E-03
GO:0070101	3	759.8077	1.00E+00	1	positive regulation of chemokine-mediated signalling pathway	2.12E-03
GO:0086101	3	759.8077	1.00E+00	1	endothelin receptor signalling pathway involved in heart process	2.12E-03
GO:0097194	101	33.09428	1.00E+00	2	execution phase of apoptosis	2.26E-03
GO:0032870	858	8.853864	1.00E+00	4	cellular response to hormone stimulus	2.49E-03
GO:0034516	4	506.5128	1.00E+00	1	response to vitamin B6	2.83E-03
GO:0034696	4	506.5128	1.00E+00	1	response to prostaglandin F	2.83E-03
GO:0035815	4	506.5128	1.00E+00	1	positive regulation of renal sodium excretion	2.83E-03
GO:1903121	4	506.5128	1.00E+00	1	regulation of TRAIL-activated apoptotic signalling pathway	2.83E-03

GO:0071385	127	26.176	1.00E+00	2	cellular response to glucocorticoid stimulus	3.54E-03
GO:0030185	5	379.8654	1.00E+00	1	nitric oxide transport	3.54E-03
GO:0097492	5	379.8654	1.00E+00	1	sympathetic neuron axon guidance	3.54E-03
GO:0071384	139	23.86861	1.00E+00	2	cellular response to corticosteroid stimulus	4.23E-03
GO:0003100	6	303.8769	1.00E+00	1	regulation of systemic arterial blood pressure by endothelin	4.24E-03
GO:0014826	6	303.8769	1.00E+00	1	vein smooth muscle contraction	4.24E-03
GO:0060024	6	303.8769	1.00E+00	1	rhythmic synaptic transmission	4.24E-03
GO:0072011	6	303.8769	1.00E+00	1	glomerular endothelium development	4.24E-03
GO:0014034	7	253.2179	1.00E+00	1	neural crest cell fate commitment	4.95E-03
GO:0051771	7	253.2179	1.00E+00	1	negative regulation of nitric-oxide synthase biosynthetic process	4.95E-03
GO:0051866	7	253.2179	1.00E+00	1	general adaptation syndrome	4.95E-03
GO:0071346	155	21.35512	1.00E+00	2	cellular response to type II interferon	5.22E-03
GO:0035813	8	217.033	1.00E+00	1	regulation of renal sodium excretion	5.65E-03
GO:0060298	8	217.033	1.00E+00	1	positive regulation of sarcomere organization	5.65E-03
GO:0071347	162	20.41354	1.00E+00	2	cellular response to interleukin-1	5.69E-03
GO:0031323	6889	4.680186	1.00E+00	10	regulation of cellular metabolic process	5.80E-03
GO:1905653	9	189.8942	1.00E+00	1	positive regulation of artery morphogenesis	6.36E-03
GO:0043066	1129	6.624711	1.00E+00	4	negative regulation of apoptotic process	6.67E-03
GO:0042981	1837	5.435772	1.00E+00	5	regulation of apoptotic process	6.74E-03
GO:0048545	567	9.280948	1.00E+00	3	response to steroid hormone	6.74E-03
GO:0042482	10	168.7863	1.00E+00	1	positive regulation of odontogenesis	7.06E-03
GO:0043435	10	168.7863	1.00E+00	1	response to corticotropin-releasing hormone	7.06E-03
GO:0071373	10	168.7863	1.00E+00	1	cellular response to luteinizing hormone stimulus	7.06E-03
GO:0071376	10	168.7863	1.00E+00	1	cellular response to corticotropin-releasing hormone stimulus	7.06E-03

GO:0086103	10	168.7863	1.00E+00	1	G protein-coupled receptor signaling pathway involved in heart process	7.06E-03
GO:0034341	182	18.12685	1.00E+00	2	response to type II interferon	7.13E-03
GO:0010468	5823	4.316718	1.00E+00	9	regulation of gene expression	7.24E-03
GO:0043069	1168	6.389347	1.00E+00	4	negative regulation of programmed cell death	7.52E-03
GO:0043067	1898	5.242707	1.00E+00	5	regulation of programmed cell death	7.75E-03

Table: 5.3.2 List of Cellular components

ID	Ref Count	Odds ratio	Corrected pvalue	Count	Term	pvalue
GO:0003735	208	72.20421	2.63E-07	6	structural constituent of ribosome	3.65E-09
GO:0005198	923	15.32061	1.64E-03	6	structural molecule activity	2.28E-05
GO:0048019	33	105.4731	1.76E-02	2	receptor antagonist activity	2.45E-04
GO:0030547	49	69.51064	3.91E-02	2	signaling receptor inhibitor activity	5.43E-04
GO:0031708	3	755.6539	1.53E-01	1	endothelin B receptor binding	2.13E-03
GO:0031705	4	503.7436	2.05E-01	1	bombesin receptor binding	2.85E-03
GO:0140678	577	9.063193	5.18E-01	3	molecular function inhibitor activity	7.19E-03
GO:0030545	610	8.555638	6.03E-01	3	signaling receptor regulator activity	8.38E-03
GO:0015347	18	88.83258	9.14E-01	1	sodium-independent organic anion transmembrane transporter activity	1.27E-02
GO:0046965	23	68.62588	1.00E+00	1	nuclear retinoid X receptor binding	1.63E-02
GO:0035259	24	65.63879	1.00E+00	1	nuclear glucocorticoid receptor binding	1.70E-02
GO:0042974	34	45.72494	1.00E+00	1	nuclear retinoic acid receptor binding	2.39E-02
GO:0071855	40	38.6785	1.00E+00	1	neuropeptide receptor binding	2.81E-02
GO:0046982	418	7.705529	1.00E+00	2	protein heterodimerization activity	3.47E-02
GO:0004879	54	28.44122	1.00E+00	1	nuclear receptor activity	3.78E-02
GO:0098531	55	27.91311	1.00E+00	1	ligand-activated transcription factor activity	3.85E-02
GO:0001228	541	5.909091	1.00E+00	2	DNA-binding transcription activator activity RNA polymerase II-specific	5.53E-02
GO:0001216	546	5.853248	1.00E+00	2	DNA-binding transcription activator activity	5.62E-02
GO:0098772	2270	3.068491	1.00E+00	4	molecular function regulator activity	6.88E-02

GO:0008013	101	15.03769	1.00E+00	1	beta-catenin binding	6.96E-02
GO:0004867	105	14.45636	1.00E+00	1	serine-type endopeptidase inhibitor activity	7.22E-02
GO:0005179	137	11.03677	1.00E+00	1	hormone activity	9.33E-02
GO:0016922	165	9.139306	1.00E+00	1	nuclear receptor binding	1.11E-01
GO:0004866	175	8.609637	1.00E+00	1	endopeptidase inhibitor activity	1.18E-01
GO:0005102	1726	2.83744	1.00E+00	3	signaling receptor binding	1.19E-01
GO:0030414	182	8.273693	1.00E+00	1	peptidase inhibitor activity	1.22E-01
GO:0061135	194	7.754484	1.00E+00	1	endopeptidase regulator activity	1.30E-01
GO:0005125	242	6.194702	1.00E+00	1	cytokine activity	1.59E-01
GO:0061134	245	6.117591	1.00E+00	1	peptidase regulator activity	1.61E-01
GO:0008514	282	5.301944	1.00E+00	1	organic anion transmembrane transporter activity	1.83E-01
GO:0015291	294	5.081649	1.00E+00	1	secondary active transmembrane transporter activity	1.90E-01
GO:0046983	1201	2.564637	1.00E+00	2	protein dimerization activity	2.09E-01
GO:0001664	346	4.304125	1.00E+00	1	G protein-coupled receptor binding	2.20E-01
GO:0001227	379	3.921652	1.00E+00	1	DNA-binding transcription repressor activity RNA polymerase II-specific	2.39E-01
GO:0001217	385	3.859175	1.00E+00	1	DNA-binding transcription repressor activity	2.42E-01
GO:0000978	1337	2.286392	1.00E+00	2	RNA polymerase II cis-regulatory region sequence-specific DNA binding	2.46E-01
GO:0061629	392	3.788708	1.00E+00	1	RNA polymerase II-specific DNA-binding transcription factor binding	2.46E-01
GO:0000987	1363	2.23953	1.00E+00	2	cis-regulatory region sequence-specific DNA binding	2.53E-01
GO:0004857	421	3.521795	1.00E+00	1	enzyme inhibitor activity	2.61E-01
GO:0022804	468	3.159611	1.00E+00	1	active transmembrane transporter activity	2.86E-01
GO:0000981	1504	2.013649	1.00E+00	2	DNA-binding transcription factor activity RNA polymerase II-specific	2.91E-01
GO:0000977	1536	1.968166	1.00E+00	2	RNA polymerase II transcription regulatory region sequence-specific DNA binding	3.00E-01
GO:0003677	2704	1.711285	1.00E+00	3	DNA binding	3.01E-01
GO:0003700	1568	1.924542	1.00E+00	2	DNA-binding transcription factor activity	3.09E-01
GO:0048018	542	2.716906	1.00E+00	1	receptor ligand activity	3.24E-01

GO:0030546	549	2.681218	1.00E+00	1	signaling receptor activator activity	3.27E-01
GO:0140297	551	2.671189	1.00E+00	1	DNA-binding transcription factor binding	3.28E-01
GO:0000976	1651	1.819284	1.00E+00	2	transcription cis-regulatory region binding	3.31E-01
GO:0001067	1656	1.813281	1.00E+00	2	transcription regulatory region nucleic acid binding	3.33E-01
GO:1990837	1710	1.750683	1.00E+00	2	sequence-specific double-stranded DNA binding	3.47E-01
GO:0003690	1817	1.637649	1.00E+00	2	double-stranded DNA binding	3.76E-01
GO:0043565	1828	1.62678	1.00E+00	2	sequence-specific DNA binding	3.79E-01
GO:0008134	674	2.168934	1.00E+00	1	transcription factor binding	3.86E-01
GO:0042803	779	1.86583	1.00E+00	1	protein homodimerization activity	4.32E-01
GO:0140110	2130	1.372259	1.00E+00	2	transcription regulator activity	4.58E-01
GO:0008270	894	1.615643	1.00E+00	1	zinc ion binding	4.79E-01
GO:0022857	1180	1.205063	1.00E+00	1	transmembrane transporter activity	5.80E-01
GO:0046914	1195	1.188958	1.00E+00	1	transition metal ion binding	5.84E-01
GO:0140677	1221	1.16198	1.00E+00	1	molecular function activator activity	5.93E-01
GO:0005215	1287	1.098397	1.00E+00	1	transporter activity	6.12E-01
GO:0030234	1407	0.998085	1.00E+00	1	enzyme regulator activity	6.46E-01
GO:0003676	4681	0.872809	1.00E+00	3	nucleic acid binding	6.83E-01
GO:0038023	1640	0.845262	1.00E+00	1	signaling receptor activity	7.05E-01
GO:0060089	1640	0.845262	1.00E+00	1	molecular transducer activity	7.05E-01
GO:0042802	2461	0.537492	1.00E+00	1	identical protein binding	8.46E-01
GO:0097159	6821	0.513254	1.00E+00	3	organic cyclic compound binding	9.12E-01
GO:0046872	4516	0.257841	1.00E+00	1	metal ion binding	9.74E-01
GO:0043169	4634	0.249315	1.00E+00	1	cation binding	9.77E-01
GO:0043167	6376	0.160169	1.00E+00	1	ion binding	9.96E-01
GO:0005515	15505	0.267841	1.00E+00	7	protein binding	9.97E-01
GO:0036094	6608	0.151844	1.00E+00	1	small molecule binding	9.97E-01
GO:0005488	18036	0.089855	1.00E+00	7	binding	1.00E+00

Table: 5.3.3 List of Molecular Mechanism

ID	Ref Count	Odds Ratio	Corrected pvalue	Count	Term	pvalue
GO:0005840	306	45.83111	3.04E-06	6	ribosome	4.16E-08
GO:1990622	2	1494.5	1.04E-01	1	CHOP-ATF3 complex	1.43E-03
GO:0033093	6	298.8429	3.13E-01	1	Weibel-Palade body	4.29E-03
GO:0048237	6	298.8429	3.13E-01	1	rough endoplasmic reticulum lumen	4.29E-03
GO:0005622	16437	Infinity	1.00E+00	15	intracellular anatomical structure	2.64E-02
GO:0045178	370	8.593645	1.00E+00	2	basal part of cell	2.81E-02
GO:0031093	67	22.57359	1.00E+00	1	platelet alpha granule lumen	4.70E-02
GO:0043232	6268	2.677134	1.00E+00	8	intracellular non-membrane-bounded organelle	4.93E-02
GO:0043228	6270	2.675914	1.00E+00	8	non-membrane-bounded organelle	4.94E-02
GO:0005791	85	17.72109	1.00E+00	1	rough endoplasmic reticulum	5.92E-02
GO:0035578	91	16.53492	1.00E+00	1	azurophil granule lumen	6.33E-02
GO:0031091	92	16.35243	1.00E+00	1	platelet alpha granule	6.39E-02
GO:0005667	616	5.08895	1.00E+00	2	transcription regulator complex	7.05E-02
GO:0005766	158	9.448134	1.00E+00	1	primary lysosome	1.07E-01
GO:0042582	158	9.448134	1.00E+00	1	azurophil granule	1.07E-01
GO:0005777	164	9.097721	1.00E+00	1	peroxisome	1.11E-01
GO:0042579	164	9.097721	1.00E+00	1	microbody	1.11E-01
GO:0005775	179	8.32504	1.00E+00	1	vacuolar lumen	1.21E-01
GO:0043229	14789	2.704521	1.00E+00	13	intracellular organelle	1.38E-01
GO:0072562	231	6.426708	1.00E+00	1	blood microparticle	1.53E-01
GO:0030141	981	3.134281	1.00E+00	2	secretory granule	1.54E-01
GO:0030136	243	6.104487	1.00E+00	1	clathrin-coated vesicle	1.61E-01
GO:0090575	301	4.910476	1.00E+00	1	RNA polymerase II transcription regulator complex	1.95E-01
GO:0016323	311	4.74977	1.00E+00	1	basolateral plasma membrane	2.01E-01
GO:0005788	323	4.570097	1.00E+00	1	endoplasmic reticulum lumen	2.08E-01
GO:0034774	324	4.555728	1.00E+00	1	secretory granule lumen	2.09E-01
GO:0060205	329	4.485192	1.00E+00	1	cytoplasmic vesicle lumen	2.12E-01
GO:0031983	331	4.457576	1.00E+00	1	vesicle lumen	2.13E-01

GO:0099503	1223	2.48258	1.00E+00	2	secretory vesicle	2.17E-01
GO:0009925	345	4.273256	1.00E+00	1	basal plasma membrane	2.21E-01
GO:0030135	359	4.103352	1.00E+00	1	coated vesicle	2.29E-01
GO:0043226	15746	2.144632	1.00E+00	13	organelle	2.41E-01
GO:0016607	439	3.340835	1.00E+00	1	nuclear speck	2.72E-01
GO:0000785	1500	1.99507	1.00E+00	2	chromatin	2.93E-01
GO:0062023	487	3.003821	1.00E+00	1	collagen-containing extracellular matrix	2.98E-01
GO:0032993	1573	1.895216	1.00E+00	2	protein-DNA complex	3.12E-01
GO:0030133	534	2.732646	1.00E+00	1	transport vesicle	3.21E-01
GO:0031012	639	2.27116	1.00E+00	1	extracellular matrix	3.72E-01
GO:0030312	641	2.263839	1.00E+00	1	external encapsulating structure	3.73E-01
GO:0000323	815	1.764654	1.00E+00	1	lytic vacuole	4.49E-01
GO:0005764	815	1.764654	1.00E+00	1	lysosome	4.49E-01
GO:0005694	2114	1.370338	1.00E+00	2	chromosome	4.56E-01
GO:0005576	4804	1.221515	1.00E+00	4	extracellular region	4.63E-01
GO:0016604	903	1.585524	1.00E+00	1	nuclear body	4.84E-01
GO:0005773	923	1.549582	1.00E+00	1	vacuole	4.92E-01
GO:0031410	2758	1.014179	1.00E+00	2	cytoplasmic vesicle	6.06E-01
GO:0097708	2766	1.010798	1.00E+00	2	intracellular vesicle	6.08E-01
GO:0140513	1496	0.928285	1.00E+00	1	nuclear protein-containing complex	6.71E-01
GO:0098590	1533	0.90414	1.00E+00	1	plasma membrane region	6.80E-01
GO:0005730	1613	0.855725	1.00E+00	1	nucleolus	7.00E-01
GO:0031974	6413	0.823558	1.00E+00	4	membrane-enclosed lumen	7.21E-01
GO:0043233	6413	0.823558	1.00E+00	4	organelle lumen	7.21E-01
GO:0070013	6413	0.823558	1.00E+00	4	intracellular organelle lumen	7.21E-01
GO:0005739	1827	0.747066	1.00E+00	1	mitochondrion	7.46E-01
GO:0110165	20558	Infinity	1.00E+00	15	cellular anatomical entity	7.59E-01
GO:0005615	3894	0.673255	1.00E+00	2	extracellular space	7.98E-01
GO:0005783	2220	0.602105	1.00E+00	1	endoplasmic reticulum	8.14E-01
GO:0070062	2273	0.586393	1.00E+00	1	extracellular exosome	8.22E-01
GO:0043230	2382	0.556279	1.00E+00	1	extracellular organelle	8.37E-01
GO:0065010	2382	0.556279	1.00E+00	1	extracellular membrane-bounded organelle	8.37E-01
GO:1903561	2381	0.556543	1.00E+00	1	extracellular vesicle	8.37E-01

GO:0005654	4371	0.582953	1.00E+00	2	nucleoplasm	8.52E-01
GO:0031982	4451	0.569705	1.00E+00	2	vesicle	8.60E-01
GO:0012505	5175	0.468438	1.00E+00	2	endomembrane system	9.16E-01
GO:0031981	5246	0.460013	1.00E+00	2	nuclear lumen	9.21E-01
GO:0005737	12895	0.545585	1.00E+00	7	cytoplasm	9.25E-01
GO:0005634	8822	0.499227	1.00E+00	4	nucleus	9.34E-01
GO:0032991	7615	0.437204	1.00E+00	3	protein-containing complex	9.50E-01
GO:0043231	13607	0.471213	1.00E+00	7	intracellular membrane-bounded organelle	9.58E-01
GO:0071944	6787	0.320594	1.00E+00	2	cell periphery	9.77E-01
GO:0043227	14837	0.359558	1.00E+00	7	membrane-bounded organelle	9.88E-01
GO:0005886	6255	0.16755	1.00E+00	1	plasma membrane	9.95E-01
GO:0016020	10504	0.070871	1.00E+00	1	membrane	1.00E+00

Table: 5.4. List of PPI interaction of the common gene using STRING

Node1	Node2	Node1_String_id	Node2_String_id	Co expression	Combine score
ATF3	NR4A2	9606.ENSP0000034435 2	9606.ENSP0000034447 9	0.316	0.75
MTRNR2L1	MTRNR2L10	9606.ENSP0000043922 8	9606.ENSP0000044215 9	0.431	0.823
MTRNR2L1	MTRNR2L11	9606.ENSP0000043922 8	9606.ENSP0000047486 1	0.849	0.849
MTRNR2L1	MTRNR2L6	9606.ENSP0000043922 8	9606.ENSP0000047368 6	0.819	0.895
MTRNR2L1	MTRNR2L8	9606.ENSP0000043922 8	9606.ENSP0000043966 6	0.999	0.999
MTRNR2L1	MTRNR2L12	9606.ENSP0000043922 8	9606.ENSP0000046899 1	0.999	0.999
MTRNR2L10	MTRNR2L1	9606.ENSP0000044215 9	9606.ENSP0000043922 8	0.431	0.823
MTRNR2L10	MTRNR2L8	9606.ENSP0000044215 9	9606.ENSP0000043966 6	0.426	0.725
MTRNR2L10	MTRNR2L12	9606.ENSP0000044215	9606.ENSP0000046899	0.248	0.618

		9	1		
MTRNR2L10	MTRNR2L11	9606.ENSPO000044215 9	9606.ENSPO000047486 1	0.623	0.623
MTRNR2L10	MTRNR2L6	9606.ENSPO000044215 9	9606.ENSPO000047368 6	0.819	0.886
MTRNR2L11	MTRNR2L1	9606.ENSPO000047486 1	9606.ENSPO000043922 8	0.849	0.849
MTRNR2L11	MTRNR2L8	9606.ENSPO000047486 1	9606.ENSPO000043966 6	0.623	0.762
MTRNR2L11	MTRNR2L7	9606.ENSPO000047486 1	9606.ENSPO000043998 5	0.107	0.622
MTRNR2L11	MTRNR2L10	9606.ENSPO000047486 1	9606.ENSPO000044215 9	0.623	0.623
MTRNR2L11	MTRNR2L12	9606.ENSPO000047486 1	9606.ENSPO000046899 1	0.407	0.407
MTRNR2L11	MTRNR2L6	9606.ENSPO000047486 1	9606.ENSPO000047368 6	0.457	0.665
MTRNR2L12	MTRNR2L1	9606.ENSPO000046899 1	9606.ENSPO000043922 8	0.999	0.999
MTRNR2L12	MTRNR2L8	9606.ENSPO000046899 1	9606.ENSPO000043966 6	0.999	0.999
MTRNR2L12	MTRNR2L10	9606.ENSPO000046899 1	9606.ENSPO000044215 9	0.248	0.618
MTRNR2L12	MTRNR2L11	9606.ENSPO000046899 1	9606.ENSPO000047486 1	0.407	0.407
MTRNR2L12	MTRNR2L6	9606.ENSPO000046899 1	9606.ENSPO000047368 6	0.398	0.499
MTRNR2L6	MTRNR2L1	9606.ENSPO000047368 6	9606.ENSPO000043922 8	0.819	0.895
MTRNR2L6	MTRNR2L8	9606.ENSPO000047368 6	9606.ENSPO000043966 6	0.819	0.93
MTRNR2L6	MTRNR2L7	9606.ENSPO000047368 6	9606.ENSPO000043998 5	0.12	0.75
MTRNR2L6	MTRNR2L10	9606.ENSPO000047368 6	9606.ENSPO000044215 9	0.819	0.886
MTRNR2L6	MTRNR2L12	9606.ENSPO000047368	9606.ENSPO000046899	0.398	0.499

		6	1		
MTRNR2L6	MTRNR2L11	9606.ENSF0000047368 6	9606.ENSF0000047486 1	0.457	0.665
MTRNR2L7	MTRNR2L8	9606.ENSF0000043998 5	9606.ENSF0000043966 6	0.109	0.718
MTRNR2L7	MTRNR2L11	9606.ENSF0000043998 5	9606.ENSF0000047486 1	0.107	0.622
MTRNR2L7	MTRNR2L6	9606.ENSF0000043998 5	9606.ENSF0000047368 6	0.12	0.75
MTRNR2L8	MTRNR2L1	9606.ENSF0000043966 6	9606.ENSF0000043922 8	0.999	0.999
MTRNR2L8	MTRNR2L7	9606.ENSF0000043966 6	9606.ENSF0000043998 5	0.109	0.718
MTRNR2L8	MTRNR2L10	9606.ENSF0000043966 6	9606.ENSF0000044215 9	0.426	0.725
MTRNR2L8	MTRNR2L11	9606.ENSF0000043966 6	9606.ENSF0000047486 1	0.623	0.762
MTRNR2L8	MTRNR2L6	9606.ENSF0000043966 6	9606.ENSF0000047368 6	0.819	0.93
MTRNR2L8	MTRNR2L12	9606.ENSF0000043966 6	9606.ENSF0000046899 1	0.999	0.999
NR4A2	ATF3	9606.ENSF0000034447 9	9606.ENSF0000034435 2	0.316	0.75

CHAPTER 6

SUMMARY AND CONCLUSION

This study conducted a meticulous analysis to identify biomarkers associated with bipolar disorder and schizophrenia, employing rigorous methodology and bioinformatics tools. Through differential gene expression analysis and functional enrichment, common molecular pathways were elucidated, shedding light on the shared mechanisms underlying these psychiatric disorders.

The identification of key genes such as MTRNR2L6, MTRNR2L8, and others through protein-protein interaction analysis underscores their potential as biomarkers for diagnostic and therapeutic purposes. These findings offer promising avenues for future research, including validation studies in independent cohorts to confirm the reproducibility and robustness of the identified biomarkers.

Moreover, the integration of multi-omics data and advanced analytical techniques holds great promise for unraveling the complex molecular landscape of bipolar disorder and schizophrenia. Machine learning algorithms could be leveraged to develop predictive models for disease diagnosis and prognosis, enhancing precision medicine approaches in psychiatry.

In addition, functional studies to elucidate the biological roles of the identified biomarkers are crucial for understanding their implications in disease pathogenesis. Furthermore, exploring the therapeutic potential of targeting these biomarkers could lead to the development of novel treatments tailored to the molecular profiles of individual patients.

Looking ahead, the implementation of precision psychiatry, guided by the identification of biomarkers and their associated pathways, offers a transformative approach to personalized diagnosis and treatment. By harnessing the power of molecular profiling, clinicians can optimize therapeutic interventions, ultimately improving patient outcomes and quality of life.

In conclusion, this study advances our understanding of the molecular mechanisms underlying bipolar disorder and schizophrenia, providing a foundation for further research aimed at translating these findings into clinical practice. By identifying biomarkers and elucidating disease pathways, this research contributes to the ongoing efforts to address the unmet needs of individuals affected by these debilitating psychiatric disorders.

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