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A Bioinformatics Approach to Identify Hub Genes Across Schizophrenia, Anxiety, Bipolar Disorder, and Depressive Disorder for Network-Based Drug Discovery

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***Abstract*—This study employs a bioinformatics-based methodology to identify hub genes and potential drug targets for mental health disorders, specifically Anxiety Disorder, Bipolar Disorder, Schizophrenia, and Depressive Disorder. We systematically collected gene-related data from the National Center for Biotechnology Information (NCBI) for these conditions. Through protein-protein interaction analysis, we identified key hub genes: GSK3B, MAPT, NR3C1, ESR1, TNF, SOD1, APP, CREB1, NOS1, APOE, GNB3, DISC1, SIRT1, CACNA1C, and BDNF. Additionally, we identified potential therapeutic drugs targeting these hub genes, including Kaempferol BOSS, Simvastatin (CTD 00007319), Luteolin BOSS, Clozapine (CTD 00005693), Curcumin BOSS, Resveratrol, Melatonin (CTD 00006260), Felodipine, Apigenin BOSS, Docosahexaenoic Acid BOSS, Diazepam BOSS, and Alprazolam BOSS, using the DSigDB database. Our findings aim to provide a clearer understanding of gene interactions in interrelated mental health disorders and to identify common therapeutic drugs for these conditions.**

***Index Terms*—Mental health disorders, schizophrenia, anxiety, bipolar disorder, depression, hub genes, drug targets, bioinformatics, protein-protein interaction network, NCBI database, drug discovery**

I. Introduction

Mental disorders are a significant global health issue, affecting millions of individuals worldwide. These conditions cause substantial distress, impair daily functioning, and can lead to severe consequences such as disability or even loss of life. Mental disorders encompass a range of psychological syndromes that cause distress and disability, often reflecting an underlying psychobiological dysfunction. [1] [2]

Globally, around 13.4% of people are grappling with mental health issues. Specifically, about 6.5% of the population experiences anxiety disorders, while 2.6% faces Depressive Disorders (DD) [3]. Bipolar Disorders (BD), known for their chronic and recurrent nature, impact over 1% of the world's population [4]. Research predominantly focuses on conditions like Anxiety Disorder (AD) and Schizophrenia (SYZ), due to their widespread impact and complex nature [5]. Alarmingly, individuals with SYZ and major depression are at a higher risk of death from unnatural causes, including homicides and suicides [6]. Mental health disorders like AD, SYZ, BD and DD pose challenges in diagnosis and treatment due to their complex genetic mechanisms. Despite extensive research, these complexities hinder effective therapy development, necessitating innovative approaches to identify potential therapeutic targets.

Our research is motivated by the need to uncover the genetic underpinnings of mental health disorders such as AD, SYZ, BD and DD, and to facilitate the development of effective drug discovery strategies through a network-based approach. By identifying hub genes, we aim to pinpoint key molecular targets that could lead to more precise and effective treatments.

To achieve this, we construct a protein-protein interaction (PPI) network for the identified genes, utilizing network analysis techniques to pinpoint degree-based hub genes—those with the highest number of connections in the network. By analyzing the biological functions and pathways linked to these hub genes, we seek to provide new insights into the molecular basis of these disorders and identify promising targets for drug discovery.

The structure of this paper is as follows: Section II reviews related work. Section III describes the methodology. Section IV presents the results and discussion. Section V concludes the paper.

II. Literature Review

Mental health disorders significantly contribute to the global burden of disease, with various studies highlighting the elevated mortality rates associated with these conditions. This literature review focuses on the mortality risks linked to AD, SYZ, BD, and DD.

A. Anxiety Disorders

AD is not only prevalent but also poses serious health risks. According to the literature, 2.1% [6] of individuals with anxiety disorders died over a period of nearly ten years, which translates to 1,066 deaths out of the total sample. These individuals were found to have a higher risk of dying

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both naturally and unexpectedly compared to the general population. Interestingly, depression was present in 16.5% of those who died from unnatural causes, indicating a significant overlap between AD and DD in mortality risks [7].

B. Schizophrenia

SYZ is associated with alarmingly high mortality rates. Individuals diagnosed with SYZ have a death rate that is twice as high as the general population. The risk of suicide in this group is particularly high, with mortality rates 8.67 times greater than those without the disorder. Additionally, individuals with SYZ face elevated injury death rates (2.35 times higher), respiratory disease (2.00 times higher), and circulatory illness (1.64 times higher). Middle-aged individuals (40–59 years old) with SYZ have a 2.48 times higher risk of death. Moreover, there is a notable 1.45-fold increase in lung cancer death rates among SYZ patients [8].

C. Bipolar Disorder

BD also significantly increases mortality risk. The standardized mortality ratio (SMR) for individuals with bipolar disorder is 2.8, indicating a higher risk of death compared to the general population. The risk is particularly pronounced in younger age groups (15–29 years old), who face the largest risk. Overall, individuals with BD have a marginally elevated annual risk of mortality, emphasizing the chronic and severe nature of the disorder [9].

D. Depressive Disorder

DD is another major mental health disorder linked to increased mortality. An analysis of 25 trials involving 106,628 patients, of which 6,416 had depression, revealed that depressed individuals have a 1.81-fold increased risk of death compared to those without depression. This significant finding underscores the profound impact of DD on overall mortality and the critical need for effective management and intervention strategies [10].

E. Hub Gene Finding and Drug Discovery

Hosen et al. [11] identified the top 15 hub genes and suggested drug compounds targeting these genes, providing insights into more effective therapeutic strategies for BD and stroke.

Furthermore, Shadhin et al. [12] expanded the scope by including Coronary Heart Disease (CHD) and SYZ in their research. They examined genetic mutations across all four diseases, identified key hub genes, and explored protin-drug interations. Islam et al. [13] analyzed the gene regulatory network and PPI network related to AD, revealing a strong link between diabetes, kidney disease, and stroke as contributors to severe anxiety disorders. Nevertheless, their study did not include any recommendations for potential drug compounds.

F. Research Gap and Our Contribution

Despite extensive research on hub gene identification and drug discovery related to AD, nBD, and SYZ, a significant gap remains concerning the mental disorder DD. To address this issue, our study utilizes a bioinformatics approach to uncover hub genes associated with AD, SYZ, BD, and DD while proposing promising drug candidates. By integrating these findings, we aim to enhance understanding and treatment options for these interconnected mental health disorders.

III. Methodology

In this section, we outline our research methodology, which begins with the collection of relevant genes associated with AD, SYZ, BD, and DD from the National Center for Biotechnology Information (NCBI) [14]. We subsequently identify hub genes by analyzing PPI networks and examining their topological properties. Additionally, we investigate potential drugs for these four diseases. Figure 1 visually illustrates the step-by-step activities of the proposed research methodology.

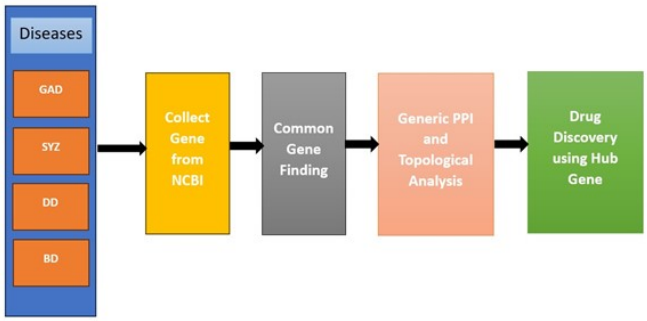

Fig. 1: Proposed model for identifying hub genes and corresponding drugs for anxiety, schizophrenia, bipolar disorder, and depression.

A. Data Collection

We collected gene data samples from the National Center for Biotechnology Information (NCBI), accessible at https://www.ncbi.nlm.nih.gov/gene/. Initially, we retrieved a total of 981, 4244, 921, and 526 genes for AD, SYZ, BD, and DD, respectively, across all species. We then focused specifically on genes associated with *Homo sapiens*, yielding 274, 1901, 770, and 444 genes for AD, SYZ, BD, and DD, respectively, as shown in Table I.

TABLE I: Gene counts for various diseases across all species and *Homo sapiens*

Diseases	All species' Genes	*Homo sapiens* Genes
AD	981	274
SYZ	4244	1901
BD	921	770
DD	526	444

B. Identifying Common Genes

Identifying common genes is essential for discovering hub genes across the four diseases [15]. To achieve this, we utilize the pandas library in Python [16] to determine the intersection of genes among the four diseases. Subsequently, we employ Venny, a tool accessible at https://bioinfogp.cnb.csic.es/tools/venny/, to visually represent the results, which aids in understanding the relationships between the genes.

C. Protein-Protein Interaction

Understanding how proteins work together in complex networks is essential for deciphering their functions and the underlying mechanisms of diseases [17]. To elucidate protein interactions and functions, we conducted a rigorous analysis of protein-protein interactions (PPI), providing insights into the biological pathways and processes in which these proteins are involved. This analysis is crucial for identifying hub genes and potential therapeutic targets [18].

Cytoscape, accessible at https://cytoscape.org/, is a trusted tool for analyzing these interactions and constructing comprehensive networks [19]. In our study, we employed Cytoscape to create PPI networks for the identification of common and hub genes. By focusing on these hub genes, we can gain deeper insights into the molecular mechanisms underlying AD, SYZ, BD, and DD, as well as identify potential targets for drug discovery.

D. Finding Hub Genes

To identify hub genes within the PPI network, we utilized NetworkAnalyst to construct the network using data from the STRING interactome database, with a confidence score cutoff of 900. The network was visualized using Cytoscape. To further refine our analysis, we employed the Cytohubba plugin [20] for Cytoscape, which specializes in identifying key hub genes based on various topological metrics. Cytohubba enabled us to pinpoint genes with a high degree of centrality and other significant topological properties, thereby highlighting the most influential genes within the network.

E. Identifying Drugs

In the process of identifying potential therapeutic drugs, we utilize the DSigDB database, which contains 22,527 gene sets [21]. Access to this database is facilitated through the Enrichr platform (https://amp.pharm.mssm.edu/Enrichr/).

The steps involved in this process are as follows:

1) Common Gene Set Input: Input the list of identified hub genes from our topological analysis into Enrichr.
2) Enrichr Analysis: Use Enrichr to identify significant associations between the hub genes and potential drug compounds listed in the DSigDB database.
3) Result Retrieval: Extract the results of the enrichment analysis, focusing on the drugs that show significant interactions with the hub genes.
4) Interpretation: Interpret the results, highlighting the most promising drug candidates for further investigation.

By leveraging the extensive data in the DSigDB database and the powerful analytical tools provided by Enrichr, we can uncover potential therapeutic agents associated with AD, SYZ, BD, and DD.

IV. Results and Discussions

A. Common Gene Findings

In the process of common gene identification, we utilized a standard Python programming approach to find common genes among four mental health disorders: AD, SYZ, BD, and DD. Specifically, we focused on AD-DD, SYZ-DD, and BD-DD pairs, resulting in 87, 230, and 156 common genes, respectively. From the intersection of AD-SYZ-DD-BD, we identified 56 common genes. These genes include:

P2RX7, ZNF804A, HTR1B, TPH1, HTR2A, FTO, NGF, IL1B, LEP, BDNF, GSK3B, GABRA2, GDNF, FMR1, HTR2C, IL6, S100B, COMT, OXTR, CACNA1C, GNB3, HTR1A, ESR1, GABRA3, DRD2, NTRK2, TNF, CYP2C19, CHRNA7, SLC6A3, NOS1, FKBP5, SLC6A2, SLC6A4, CYP2D6, DRD3, MAOA, SOD1, IGF1, CRH, CRP, ADCYAP1, NR3C1, MAPT, DISC1, CREB1, GRM7, CTNND2, TPH2, APOE, CXCL8, IL18, SIRT1, GAD1, APP, and CNR1.

We visualized the intersection of all four diseases' genes using the online Venny tool available at https://bioinfogp.cnb.csic.es/tools/venny/. The resulting Venn diagram is shown in (Fig. 2).

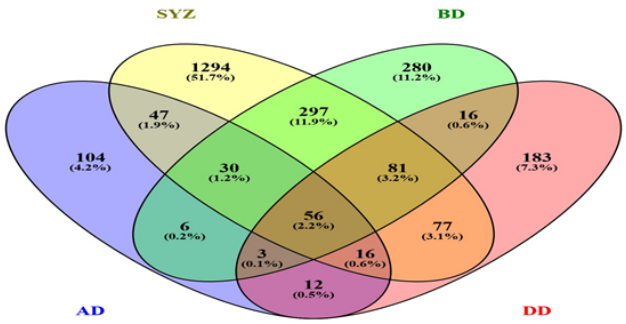

Fig. 2: Intersection diagram of genes for AD, SYZ, BD, and DD using Venny tool

B. PPI Analysis Result

The PPI network was constructed for the common genes of AD, SYZ, BD, and DD. The analysis revealed that the PPI network consists of 716 nodes, 947 edges, and 37 seed nodes. After creating a Simple Interaction Format (SIF) file using NetworkAnalyst, we built the actual PPI network using Cytoscape.

In the network, the yellow nodes indicate the most significant hub genes, which have degree values ranging from 20 to 168. From this analysis, we identified 14 nodes that are the most significant hub genes among AD, SYZ, BD, and DD. The results of this analysis are illustrated in Figure (Fig. 3).

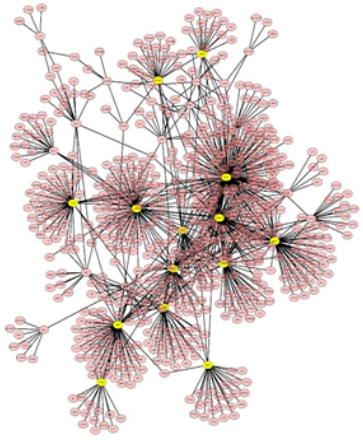

Fig. 3: PPI network of common genes for AD, SYZ, BD, and DD. Yellow nodes represent the most significant hub genes.

C. Top 15 Hub Genes

The topological properties of the Protein-Protein Interaction (PPI) network were analyzed to identify the top 15 hub genes. Key metrics such as degree, betweenness centrality, clustering coefficient, and topological coefficient were evaluated to determine the most significant genes in the network. The results are summarized in Table II and visualized in Fig. 4.

The top 15 hub genes, which exhibit the highest degree values, include ESR1, GSK3B, NR3C1, SIRT1, and APP. These genes are identified as central to the network due to their extensive interactions with other proteins. Conversely, genes such as TNF, SOD1, and NOS1 show a clustering coefficient of 0.0, indicating a lower level of significance in terms of network integration compared to other genes.

The analysis reveals important relationships among these top genes, providing insights into their roles within the network and their potential relevance to drug discovery for the targeted diseases.

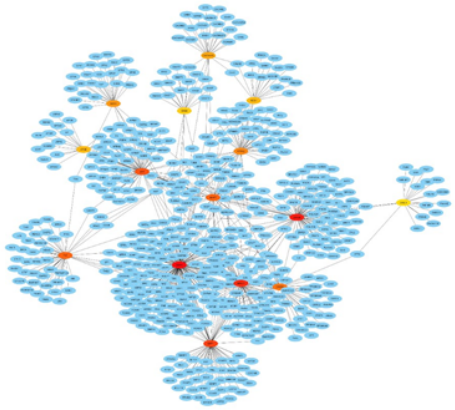

Fig. 4: Interaction of the top 15 genes based on degree from the PPI network. Genes are represented with their respective interactions.

TABLE II: Top 15 most responsible genes based on degree from the PPI network using Cytoscape.

Protein Name	Degree	Betweenness Centrality	Closeness Centrality	Clustering Coefficient	Topological Coefficient
ESR1	168	0.4700	0.4169	0.0015	0.0162
GSK3B	88	0.2851	0.4032	0.0055	0.0154
NR3C1	80	0.1467	0.3742	0.0076	0.0221
SIRT1	67	0.1370	0.3595	0.0095	0.0206
APP	64	0.1896	0.3704	0.0069	0.0205
MAPT	47	0.1077	0.3480	0.0176	0.0294
TNF	47	0.1245	0.3194	0.0000	0.0452
CREB1	44	0.0879	0.3657	0.0180	0.0309
NTRK2	43	0.1056	0.3170	0.0078	0.0539
SOD1	28	0.0763	0.3104	0.0000	0.0516
CACNA1C	25	0.0622	0.2464	0.0033	0.0527
NOS1	21	0.0532	0.3073	0.0000	0.0900
APOE	21	0.0429	0.2825	0.0381	0.0573
GNB3	20	0.0513	0.2485	0.0053	0.0593
DISC1	18	0.0490	0.2920	0.0065	0.0574

D. Predictive Drug Compounds

To identify potential therapeutic drug compounds, we utilized the Enrichr online tool available at https://maayanlab.cloud/Enrichr/ with the DSigDB database. The selection process for drug compounds involved evaluating p-values and adjusted p-values. Table III summarizes the proposed drugs that are most effective against the common Differentially Expressed Genes (DEGs) associated with AD, SYZ, BD, and DD. These drugs were selected based on their efficacy and relevance to the DEGs.

TABLE III: Proposed drug compounds for integrated common DEGs associated with AD, SYZ, BD, and DD.

Drug	P-Value	Adjusted P-Value	Associated Genes
Kaempferol BOSS	6.020e-12	6.950e-9	GSK3B, MAPT, NR3C1, ESR1, TNF, SOD1
Simvastatin CTD 00007319	1.525e-11	1.174e-8	GSK3B, CREB1, MAPT, NR3C1, ESR1, TNF, SOD1, APP
Luteolin BOSS	5.044e-11	2.775e-8	GSK3B, MAPT, ESR1, TNF, SOD1, APP
Clozapine CTD 00005693	2.524e-10	7.284e-8	GSK3B, MAPT, GNB3, TNF, DISC1, NR3C1
Curcumin BOSS	3.142e-10	8.061e-8	APP, MAPT, TNF, NR3C1, ESR1, SOD1, SIRT1
Resveratrol	8.450e-10	1.501e-7	GSK3B, CREB1, MAPT, NR3C1, ESR1, TNF, SOD1, APP, NOS1, APOE
Melatonin CTD 00006260	9.814e-10	1.511e-7	APP, MAPT, NR3C1, ESR1, SIRT1
Felodipine	2.157e-9	2.620e-7	CACNA1C, MAPT, NR3C1, ESR1
Apigenin BOSS	6.986e-9	4.481e-7	GSK3B, MAPT, NR3C1, ESR1, TNF
Docosahexaenoic Acid BOSS	3.181e-8	1.469e-6	APP, MAPT, APOE, TNF, SOD1
Diazepam BOSS	2.206e-7	5.787e-6	APP, NR3C1, ESR1, TNF, SOD1
Alprazolam BOSS	2.568e-7	6.376e-6	APP, NR3C1, ESR1, TNF, SOD1

E. Comparative Analysis

We conducted a comparative analysis of our findings alongside existing research (Table IV). Hosen et al. identified 10 hub genes and recommended specific drugs for conditions such as BD and Stroke. Shadhin et al. focused on 8 hub genes associated with AD, Diabetes, Kidney Disease, and Stroke, analyzing protein-drug interactions but not proposing any drugs. They aimed to develop a targeted therapy for bipolar disorder in the future. Islam et al. researched AD, Diabetes, Kidney Disease, and Stroke diseases, identifying 11 hub genes without recommending drug candidates.

In our research, we identified 15 hub genes associated with AD, BD, Stroke, and other disorders, along with a comprehensive list of potential drugs. This highlights the potential of our findings to contribute to therapeutic advancements.

TABLE IV: Comparative analysis of Research Findings on Diseases, Hub Genes, and Proposed Drugs

Author	Diseases	Hub Gene	Proposed Drugs
Hosen et al. [11]	BD and Stroke	CBL, LY96, TLR5, TRAF6, TLR4, YWHAZ, HLA-A, PTK2B, SH3KBP1, UBE2D2	Berberine BOSS, Soflavone BOSS, Uteolin BOSS, Etradecanoic Acid TTD, Losartan BOSS
Shadhin et al. [12]	BD, Stroke, CHD and SYZ	ESR1, TNF, SREBF2, APOE, NOS3, TCF7L2, IL1B, CRP	N/A
Islam et al. [13]	AD, Diabetes, Kidney Disease, and Stroke	TNF, IL6, TGFB1, ADIPOQ, CRP, BDNF, PON1, SOD1, ICAM1, IL8, AGT	N/A
Our Research	AD, BD, SYZ and DD	GSK3B, MAPT, NR3C1, ESR1, TNF, SOD1, APP, CREB1, NOS1, APOE, GNB3, DISC1, SIRT1, CACNA1C, BDNF	Kaempferol BOSS, Simvastatin CTD 00007319, Luteolin BOSS, Clozapine CTD 00005693, Curcumin BOSS, Resveratrol, Melatonin CTD 00006260, Felodipine, Apigenin BOSS, Docosahexaenoic Acid BOSS, Diazepam BOSS, Alprazolam BOSS

V. Conclusion

This study has successfully identified common genes associated with AD, SYZ, BD, and DD through a comprehensive analysis of gene data sourced from the National Center for Biotechnology Information (NCBI). By leveraging Python for gene intersection analysis and Cytoscape for PPI network construction, we identified 56 common genes among the four disorders, including key hub genes such as ESR1, GSK3B, NR3C1, CREB1, MAPT, TNF, SOD1, APP, SIRT1, DISC1, APOE, NOS1, CACNA1C, and GNB3. Our analysis identified potential drug compounds using the DSigDB database, including kaempferol, simvastatin, luteolin, clozapine, curcumin, resveratrol, melatonin, felodipine, apigenin, docosahexaenoic acid, diazepam, and alprazolam providing valuable insights into therapeutic targets for these mental health conditions.

Future research will build upon this foundational work by integrating machine learning approaches [22] [23] and graph learning methods [24] to enhance prediction accuracy and identify novel therapeutic targets. By applying machine learning techniques to gene expression data and analyzing gene regulatory networks, we aim to refine our understanding of disease mechanisms and improve the drug discovery process.

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