

INTEGRATION OF MULTIOMICS DATA FOR NEUROLOGICAL DISORDERS

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

By

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**DEPARTMENT OF BIOINFORMATICS SCHOOL OF BIO AND CHEMICAL
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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 **S. JEY PRIYA(41738020)**, who carried out the final year project entitled **"INTEGRATION OF MULTIOMICS DATA FOR NEUROLOGICAL DISORDERS"** under my supervision from **January 2024** to **April 2024**.

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DECLARATION

I, **S. JEY PRIYA**, hereby declare that the Project Report entitled **INTEGRATION OF MULTIOMICS DATA FOR NEUROLOGICAL DISORDERS** done by me under the guidance of **Dr. DANIEL ALEX ANAND**, at **Sathyabama Institute of Science and Technology**, Jeppiaar Nagar, Rajiv Gandhi Road, Chennai-600119, Tamil Nadu, India, is submitted in partial fulfillment of the requirements for the award of **Bachelor of Science degree in Bioinformatics and Data Science**.

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CERTIFICATE

This is to certify that the dissertation entitled **"INTEGRATION OF MULTIOMICS DATA FOR NEUROLOGICAL DISORDERS"** was carried out by **Ms. S. Jey Priya (RegNo.41738020)**, Department of Bioinformatics and Data Science, Sathyabama Institute of Science and Technology, Chennai in partial fulfillment of the requirements of the award of the **Degree of Bachelor of Science in Bioinformatics and Data Science 2021-2024**, is a bonafide record of the project work done under my guidance and supervision. This thesis or part, therefore, has not been submitted elsewhere for any other degree or diploma.

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ABSTRACT

Neurological disorders, including Alzheimer's disease, depression, and epilepsy, present significant challenges to public health worldwide. Understanding the complex molecular mechanisms underlying these disorders is crucial for developing effective diagnostic and therapeutic strategies. Integrating multi omics data approaches, such as genomics, transcriptomics, proteomics, metabolomics, and epigenomics, offers a comprehensive framework for unravelling the molecular complexity of neurological disorders. In this review, we provide an overview of the application of multi omics data in Alzheimer's disease, depression, and epilepsy research, highlighting key findings and insights gained from genomic, transcriptomic, proteomic, metabolomic, and epigenomic analyses. We discuss the integration of multi omics data to elucidate disease pathogenesis, identify biomarkers, and inform personalized treatment approaches. Furthermore, we explore the role of resources such as DisGeNET, STRING database, TRUSST database, miRanda database, and HMDB in facilitating multi omics data analysis and interpretation. Finally, we discuss the challenges and future directions of multi omics research in neurological disorders and emphasize the importance of collaborative efforts and interdisciplinary approaches to address these complex diseases comprehensively.

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LIST OF ABBREVIATION

PCR	Polymerase chain reaction
MRI	Magnetic resonance imaging
AEDs	Antiepileptic drugs
AAC	Augmentative alternative communication
PEMs	Progressive myoclonus epilepsies
TMS	Trans cranial magnetic stimulation
VBM	Voxel-based MRI morphometry
MT	Motor threshold
SP	Silent period
PPI	Protein-protein interaction
GO	Gene ontology
MF	Molecular function
BP	Biological process
CC	Cellular component
STRING	Search tool for the retrieval of interacting genes

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CHAPTER – 1

INTRODUCTION

Neurological disorders encompass a broad spectrum of conditions affecting the brain, spinal cord, and nerves throughout the body. Among the most prevalent and impactful are Alzheimer's disease, depression, and epilepsy.

Alzheimer's disease, a progressive neurodegenerative disorder, is characterized by memory loss, cognitive decline, and changes in behavior. It is the most common cause of dementia, affecting millions worldwide. As the disease advances, individuals may experience difficulty with daily tasks, language problems, disorientation, mood swings, and ultimately a loss of independence. The exact cause of Alzheimer's remains elusive, but it involves the accumulation of abnormal proteins in the brain, leading to nerve cell damage and cell death. Genetic factors, environmental influences, and lifestyle choices are also believed to play a role (Alzheimer's Association).

Depression, a mood disorder characterized by persistent feelings of sadness, hopelessness, and loss of interest in activities, can significantly impair an individual's ability to function in daily life, affecting their relationships, work, and physical health. While the exact cause of depression is complex and multifactorial, it is believed to involve a combination of genetic, biological, environmental, and psychological factors. Imbalances in brain chemicals called neurotransmitters, particularly serotonin, norepinephrine, and dopamine, play a significant role in the development of depression. Treatment typically involves a combination of therapy, medication, lifestyle changes, and support from loved ones (National Institute of Mental Health).

Epilepsy, a chronic neurological disorder characterized by recurrent seizures, is caused by sudden, uncontrolled electrical disturbances in the brain. These seizures can vary widely in severity, frequency, and manifestation, depending on the area of the brain affected and the underlying cause. While epilepsy can

develop at any age, it often begins in childhood or later adulthood. Causes of epilepsy include genetic factors, brain injury, infection, stroke, tumors, and developmental disorders. Treatment typically involves antiepileptic medications to control seizures, although surgery, dietary therapy, and neurostimulation may be considered in some cases (Epilepsy Foundation).

1.1 OUTLINE

1.1.1 Alzheimer's:

Alzheimer's disease (AD) poses a significant and growing challenge to public health systems worldwide. With an aging population, the prevalence of AD is expected to rise dramatically in the coming decades, placing an increasing burden on healthcare resources and societal support networks. According to recent epidemiological studies (Smith et al., 2020), AD is now the leading cause of dementia globally, affecting millions of individuals and their families. Despite decades of research, the underlying mechanisms of AD remain incompletely understood, and effective disease-modifying treatments remain elusive. This introduction sets the stage for a comprehensive examination of current insights into AD pathophysiology, diagnosis, treatment, and the impact of the disease on patients and caregivers.

1.1.1.1 Alzheimer's Disease Epidemiology:

Alzheimer's disease (AD) presents a significant and growing public health challenge globally. Epidemiological studies have revealed several key trends and projections regarding the prevalence, incidence, and demographic factors associated with AD.

The prevalence of Alzheimer's disease is notably higher in older age groups, with the risk increasing exponentially after the age of 65 (Alzheimer's Association, 2020). However, early-onset AD, which occurs before the age of 65, represents a

smaller proportion of cases but tends to progress more rapidly and have a stronger genetic component.

Recent epidemiological data suggest a concerning trend of increasing prevalence and incidence rates of AD due to population aging and demographic shifts. With improvements in healthcare and longevity, the global population of older adults is growing, leading to a corresponding rise in the number of individuals affected by AD (Brookmeyer et al., 2018).

Moreover, demographic factors such as gender and socioeconomic status play significant roles in AD epidemiology. Women have a higher lifetime risk of developing AD compared to men, partly due to longevity and hormonal factors (Alzheimer's Association, 2020). Socioeconomic determinants, including education level, income, and access to healthcare, also influence the prevalence and incidence of AD, with individuals from disadvantaged backgrounds facing higher risks.

Understanding the epidemiology of Alzheimer's disease is crucial for informing public health policies, healthcare planning, and resource allocation to address the growing burden of this condition on individuals, families, and society as a whole.

1.1.1.2 Alzheimer's Disease Pathophysiology:

Alzheimer's disease (AD) is characterized by progressive neurodegeneration and the accumulation of abnormal protein aggregates in the brain, leading to cognitive decline and functional impairment. Understanding the pathophysiology of AD is essential for developing effective treatments and interventions.

The hallmark pathological features of AD include the presence of extracellular amyloid-beta ($A\beta$) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. $A\beta$ peptides are derived from the cleavage of amyloid precursor protein (APP) by beta-secretase and gamma-secretase enzymes. In AD, there is an imbalance between $A\beta$ production and clearance, resulting in the accumulation of $A\beta$ aggregates, which are neurotoxic and disrupt synaptic function.

The formation of NFTs, primarily composed of abnormal tau protein, is another key pathological event in AD. Tau is a microtubule-associated protein that stabilizes microtubules in neurons. In AD, tau becomes hyperphosphorylated, leading to its aggregation into insoluble fibrils and the disruption of microtubule function. This impairs axonal transport and contributes to neuronal dysfunction and cell death.

In addition to A β plaques and NFTs, neuroinflammation, oxidative stress, and synaptic dysfunction are also prominent features of AD pathophysiology. Microglial activation and the release of pro-inflammatory cytokines contribute to neuroinflammation, exacerbating neuronal damage. Oxidative stress, resulting from the imbalance between reactive oxygen species (ROS) production and antioxidant defenses, further damages neurons and exacerbates A β toxicity. Synaptic dysfunction, characterized by impaired neurotransmission and synaptic loss, underlies the progressive cognitive decline observed in AD patients (Hardy & Selkoe, 2002; Holtzman et al., 2011).

Genetic factors, including mutations in genes such as APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2), contribute to familial forms of AD and provide insights into disease mechanisms. However, the majority of AD cases are sporadic and likely involve complex interactions between genetic predispositions and environmental factors.

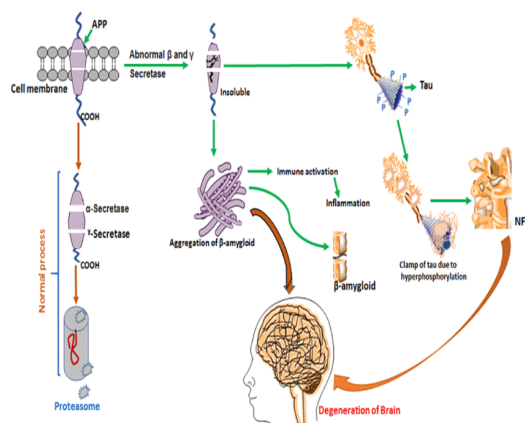


Fig 1.1 Pathophysiology of Alzheimer's Disease (Research Gate)

1.1.1.3 Treatment and Management Strategies:

Effective management of Alzheimer's disease (AD) involves a multi-faceted approach aimed at alleviating symptoms, slowing disease progression, and improving quality of life for patients and caregivers. Pharmacological interventions, non-pharmacological approaches, and supportive care measures are key components of AD management.

Pharmacological treatments for AD primarily target symptomatic relief and include cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. Cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, work by increasing levels of acetylcholine in the brain, thereby enhancing cognitive function and alleviating symptoms of memory loss and confusion. NMDA receptor antagonists, such as memantine, modulate glutamate neurotransmission and may help improve cognitive function and behavioral symptoms in moderate to severe AD (Alzheimer's Association, 2020).

Non-pharmacological approaches play a crucial role in AD management and focus on maximizing cognitive function, promoting physical and social engagement, and providing support for patients and caregivers. Cognitive stimulation therapies, such as reminiscence therapy and reality orientation therapy, aim to engage patients in mentally stimulating activities and enhance cognitive abilities. Physical exercise, nutrition management, and social activities can also help improve overall well-being and slow cognitive decline in AD patients.

Supportive care measures are essential for addressing the diverse needs of AD patients and their caregivers. This may include assistance with activities of daily living (ADLs), respite care services, caregiver education and support programs, and access to community resources and support groups. Advance care planning, including discussions about end-of-life care preferences and palliative care options, is also important for ensuring the dignity and comfort of AD patients as the disease progresses (Alzheimer's Association, 2020).

While current treatments for AD focus on symptom management, ongoing research efforts are aimed at developing disease-modifying therapies that target the underlying pathological mechanisms of AD. These may include approaches targeting A β and tau pathology, neuroinflammation, synaptic dysfunction, and other molecular pathways implicated in disease progression (Cummings & Morstorf, 2014).

1.1.2 Depression:

Depression, a prevalent and debilitating mental health disorder, poses significant challenges to individuals, families, and healthcare systems worldwide. According to recent research, depression affects an estimated 322 million people globally, making it one of the leading causes of disability and disease burden (Cuijpers et al., 2020). Additionally, studies have shown that depression is associated with increased mortality rates and a higher risk of comorbid medical conditions, further highlighting its significant impact on public health (Chang et al., 2017). Despite advancements in research and treatment, depression remains underdiagnosed and undertreated, with profound implications for quality of life and societal well-being. This paper aims to explore the multifaceted nature of depression, including its etiology, symptomatology, and various treatment modalities, in order to foster a deeper understanding of this complex condition and inform strategies for improved management and care.

1.1.2.1 Depression Causes:

The causes of depression are multifactorial, involving complex interactions between biological, psychological, and environmental factors. Understanding these underlying causes is crucial for developing effective prevention and treatment strategies.

Biological factors play a significant role in the development of depression. Genetic predispositions, neurotransmitter imbalances (particularly involving serotonin, dopamine, and norepinephrine), and alterations in brain structure and function

have been implicated in depression risk (Sullivan et al., 2018). Research suggests that individuals with a family history of depression are at a higher risk of developing the disorder, highlighting the hereditary component of depression (Peterson et al., 2014).

Psychological factors also contribute to the onset and maintenance of depression. Stressful life events, such as trauma, loss, or chronic stress, can trigger depressive episodes in susceptible individuals (Kendler et al., 1999). Personality traits such as neuroticism and low self-esteem have been associated with increased vulnerability to depression (Klein et al., 2011). Additionally, maladaptive cognitive patterns, such as negative thinking styles and rumination, can perpetuate depressive symptoms and contribute to the recurrence of depressive episodes (Beck et al., 1979).

Environmental factors, including socio-economic status, social support networks, and cultural influences, play a significant role in shaping depression risk. Adverse childhood experiences, poverty, social isolation, and discrimination can increase vulnerability to depression (Lorant et al., 2003). Moreover, cultural norms and attitudes towards mental health may influence help-seeking behaviors and access to appropriate care among individuals experiencing depression (Demyttenaere et al., 2004).

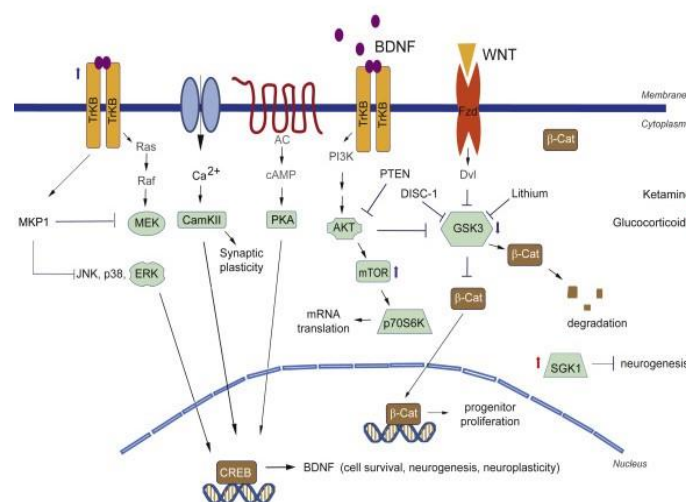


Fig 1.2 Molecular Mechanism of Depression (Science Direct)

1.1.2.2 Treatment Approaches:

Treatment for depression typically involves a combination of pharmacotherapy, psychotherapy, lifestyle modifications, and support interventions tailored to the individual's needs and preferences. The goal of treatment is to alleviate symptoms, prevent relapse, and improve overall functioning and quality of life.

Pharmacotherapy: Antidepressant medications are commonly used as first-line treatment for moderate to severe depression. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) are among the classes of antidepressants prescribed. These medications work by modulating neurotransmitter levels in the brain, particularly serotonin and norepinephrine, to alleviate depressive symptoms.

Psychotherapy: Various forms of psychotherapy, including cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and psychodynamic therapy, are effective in treating depression. CBT helps individuals identify and modify negative thought patterns and behaviors associated with depression, while IPT focuses on improving interpersonal relationships and resolving conflicts. Psychodynamic therapy explores unconscious conflicts and past experiences contributing to depressive symptoms.

Electroconvulsive Therapy (ECT): ECT may be recommended for severe, treatment-resistant depression or when a rapid response is needed. ECT involves the administration of electrical currents to the brain under general anesthesia, resulting in a controlled seizure. It is thought to modulate neurotransmitter activity and promote neuroplasticity, leading to symptom improvement in some individuals.

Transcranial Magnetic Stimulation (TMS): TMS is a non-invasive brain stimulation technique that involves delivering magnetic pulses to targeted areas of the brain associated with depression. It is typically used for individuals who have not responded to antidepressant medication. TMS is thought to modulate neural activity and promote neurogenesis, leading to symptom relief.

Lifestyle Modifications: Engaging in regular physical exercise, maintaining a balanced diet, practicing relaxation techniques (e.g., mindfulness meditation, deep breathing exercises), and ensuring adequate sleep hygiene can complement other treatment modalities and promote overall well-being. These lifestyle modifications can help reduce stress, improve mood, and enhance resilience against depressive symptoms.

Supportive Interventions: Peer support groups, family therapy, and community resources can provide valuable emotional support and practical assistance to individuals with depression and their caregivers. Education about depression, coping strategies, and self-management skills can empower individuals to actively participate in their recovery process.

1.1.3 Epilepsy:

Epilepsy, a neurological disorder characterized by recurrent seizures, is a significant global health concern affecting millions of individuals worldwide. Studies have estimated the prevalence of epilepsy to range from 5 to 10 per 1,000 people, with higher rates reported in low- and middle-income countries (Ngugi et al., 2010; Fiest et al., 2017). The burden of epilepsy extends beyond the seizures themselves, encompassing various psychosocial, economic, and healthcare challenges for patients and their families (Fisher et al., 2014). Despite advancements in treatment and management, epilepsy remains associated with significant morbidity and mortality, underscoring the need for improved understanding and access to care (Sander, 2003).

1.1.3.1 Epilepsy Epidemiology:

The epidemiology of epilepsy encompasses the study of its prevalence, incidence, distribution, and determinants in populations. Understanding the epidemiology of epilepsy is crucial for public health planning, resource allocation, and the development of preventive strategies.

- Prevalence:

Epidemiological studies have estimated the prevalence of epilepsy to range from 5 to 10 per 1,000 people, with variations observed across different age groups and geographic regions (Ngugi et al., 2010; Fiest et al., 2017). Higher prevalence rates have been reported in low- and middle-income countries, highlighting disparities in epilepsy burden (Ngugi et al., 2010).

- Incidence:

Research on the incidence of epilepsy provides insights into the rate at which new cases occur within populations. Studies have documented varying incidence rates of new-onset seizures and epilepsy diagnoses, with factors such as age, sex, and underlying etiology influencing incidence patterns (Forsgren et al., 2005; Hesdorffer et al., 2011).

- Distribution:

Epidemiological investigations have identified geographical and demographic variations in the distribution of epilepsy. Disparities in epilepsy prevalence and incidence have been observed across different regions, countries, ethnic groups, and socioeconomic strata, highlighting the role of social determinants of health in shaping epilepsy burden (Ngugi et al., 2010; Baxendale et al., 2013).

- Determinants:

Determinants of epilepsy encompass a wide range of factors contributing to its occurrence and distribution in populations. These determinants may include genetic predisposition, brain injuries, infections, environmental exposures, and socio-economic status (Berg et al., 2011; Fisher et al., 2014). Epidemiological research aims to identify and characterize these determinants to inform preventive strategies and interventions.

1.1.3.2 Molecular Mechanism of Epilepsy:

- **Ion Channel Dysfunction:**

Epilepsy is often associated with abnormalities in ion channel function, disrupting the balance of excitatory and inhibitory neurotransmission in the brain. Mutations in voltage-gated ion channels, such as sodium, potassium, and calcium channels, can lead to hyperexcitability and increased neuronal firing, contributing to seizure generation (Catterall et al., 2010; Noebels, 2015).

- **GABAergic Inhibition:**

Dysfunction of gamma-aminobutyric acid (GABA)-mediated inhibitory signaling plays a critical role in epilepsy pathogenesis. Alterations in GABA receptor subunit composition, synaptic GABA release, and GABAergic interneuron function have been implicated in various epilepsy syndromes (Fritschy & Panzanelli, 2014; Houser et al., 2012).

- **Glutamatergic Excitation:**

Excessive glutamatergic excitatory neurotransmission contributes to seizure activity in epilepsy. Dysregulation of glutamate receptors, synaptic glutamate release, and glutamate transporter function can lead to neuronal hyperexcitability and seizure propagation (Lau & Zukin, 2007; Lerma et al., 2016).

- **Synaptic Plasticity:**

Aberrant synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), has been implicated in epilepsy pathophysiology. Altered synaptic strength, connectivity, and network reorganization may contribute to the development of epileptic circuits and recurrent seizure activity (Scharfman & McCloskey, 2009; Sutula & Dudek, 2007).

- **Neuroinflammation:**

Inflammatory processes within the brain, including microglial activation, cytokine release, and blood-brain barrier dysfunction, have been implicated in epileptogenesis and seizure generation. Neuroinflammation may amplify neuronal

hyperexcitability and promote epileptic network formation (Vezzani et al., 2016; Eyo et al., 2017).

- Genetic Susceptibility:

Genetic factors play a significant role in epilepsy etiology, with mutations in various genes associated with increased seizure susceptibility and epilepsy risk. Advances in genomic technologies have facilitated the identification of genetic variants underlying monogenic and polygenic forms of epilepsy (Scheffer et al., 2017; Thomas et al., 2017).

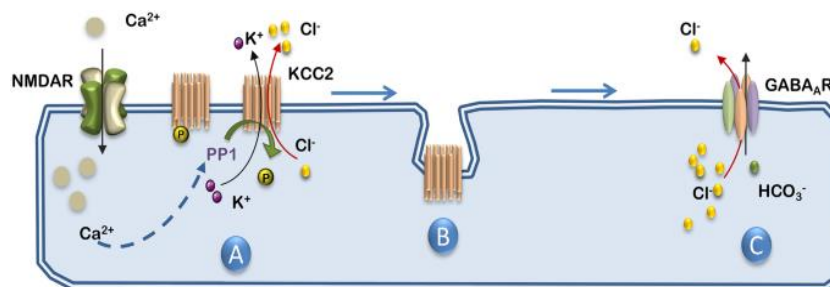


Fig 1.3 Molecular Mechanism of Epilepsy (Springer)

1.1.3.3 Treatment Approaches:

- Antiseizure Medications (ASMs):

Antiseizure medications are the cornerstone of epilepsy treatment, with a wide range of medications available to control seizures. First-line medications such as carbamazepine, valproate, and lamotrigine are often prescribed based on seizure type, patient age, and comorbidities (French et al., 2018; Kwan et al., 2011).

- Surgical Interventions:

For individuals with drug-resistant epilepsy, surgical interventions may be considered to remove or disconnect the epileptogenic focus. Resective surgeries, such as temporal lobectomy or lesionectomy, aim to remove the seizure focus while preserving neurological function (Engel Jr et al., 2012; Wiebe et al., 2001).

- **Dietary Therapies:**

Dietary therapies, such as the ketogenic diet and modified Atkins diet, have been shown to be effective in reducing seizure frequency, particularly in children with refractory epilepsy. These high-fat, low-carbohydrate diets induce ketosis, which may modulate neuronal excitability and seizure threshold (Martin et al., 2016; Kossoff & Wang, 2013).

- **Neurostimulation Therapies:**

Neurostimulation devices, including vagus nerve stimulation (VNS), responsive neurostimulation (RNS), and deep brain stimulation (DBS), provide adjunctive treatment options for individuals with drug-resistant epilepsy. These devices modulate neural activity and may help reduce seizure frequency and severity (Ryvlin et al., 2014; Morrell, 2011).

- **Complementary and Alternative Therapies:**

Complementary and alternative therapies, such as acupuncture, herbal remedies, and yoga, are sometimes used as adjunctive treatments for epilepsy. While evidence supporting their efficacy is limited, some individuals may experience benefits in seizure control and overall well-being (Szaflarski et al., 2018; Kwan et al., 2010).

- **Lifestyle Modifications:**

Lifestyle modifications, including regular sleep patterns, stress management techniques, and avoidance of seizure triggers, play a crucial role in epilepsy management. Maintaining a healthy lifestyle can help reduce seizure frequency and improve overall quality of life (Martini et al., 2017; Malow et al., 2015).

1.1.4 Omics:

Omics technologies, encompassing genomics, proteomics, metabolomics, transcriptomics, and other 'omics' disciplines, have revolutionized biomedical research by enabling comprehensive analysis of biological systems at various molecular levels. These technologies offer unprecedented insights into the intricate molecular mechanisms underlying physiological processes, disease pathogenesis, and drug responses (Venter et al., 2001; Aebersold & Mann, 2003).

The emergence of omics approaches can be traced back to landmark achievements such as the completion of the Human Genome Project, which laid the foundation for large-scale genomic sequencing and analysis (Lander et al., 2001). Subsequent advancements in high-throughput sequencing, mass spectrometry, and bioinformatics have fueled the rapid expansion of omics methodologies, enabling researchers to characterize complex biological systems in unprecedented detail (Aebersold & Mann, 2016; Schuster, 2008).

The integration of omics data with clinical and phenotypic information has transformed our understanding of disease etiology and progression, paving the way for personalized medicine approaches tailored to individual patients' molecular profiles (Collins & Varmus, 2015; Hood & Friend, 2011). Moreover, omics technologies hold immense potential for applications beyond human health, including agriculture, environmental science, and biotechnology (Hirschhorn & Daly, 2005; Hallmann et al., 2019).

Despite the transformative impact of omics technologies, their widespread adoption and implementation pose significant challenges. Issues such as data standardization, interoperability, and ethical considerations surrounding data privacy and consent require careful attention (Kohane et al., 2015; Rinaldi et al., 2018). Moreover, the complexity of omics data necessitates advanced computational and analytical tools for data interpretation and knowledge extraction (LeCun et al., 2015; Papatheodorou et al., 2018).

1.1.4.1 Omics Technologies Overview:

Omics technologies encompass a diverse array of methodologies aimed at comprehensively characterizing biological systems at various molecular levels. These approaches have transformed biomedical research by enabling high-throughput analysis of genomes, proteomes, metabolomes, transcriptomes, and other molecular components.

- **Genomics:**

Genomics, the study of an organism's entire DNA sequence, has been revolutionized by next-generation sequencing (NGS) technologies, allowing for

rapid, cost-effective sequencing of whole genomes (Schuster, 2008). Genome-wide association studies (GWAS) have identified genetic variants associated with complex diseases and traits, providing insights into disease etiology and personalized medicine approaches (Hirschhorn & Daly, 2005).

- Proteomics:

Proteomics focuses on the large-scale study of proteins, their structures, functions, and interactions within biological systems. Mass spectrometry-based proteomics techniques enable the identification and quantification of thousands of proteins in complex samples, facilitating the characterization of cellular pathways and protein networks (Aebersold & Mann, 2003).

- Metabolomics:

Metabolomics aims to profile and quantify small molecules (metabolites) present in biological samples, offering insights into cellular metabolism, biochemical pathways, and disease mechanisms. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry are commonly used analytical platforms for metabolomic analysis (Fiehn, 2002).

- Transcriptomics:

Transcriptomics involves the study of RNA transcripts produced by genes within a cell or tissue, providing information on gene expression patterns, alternative splicing events, and regulatory mechanisms. Microarray and RNA sequencing (RNA-seq) technologies enable genome-wide analysis of gene expression profiles and transcriptome dynamics (Wang et al., 2009).

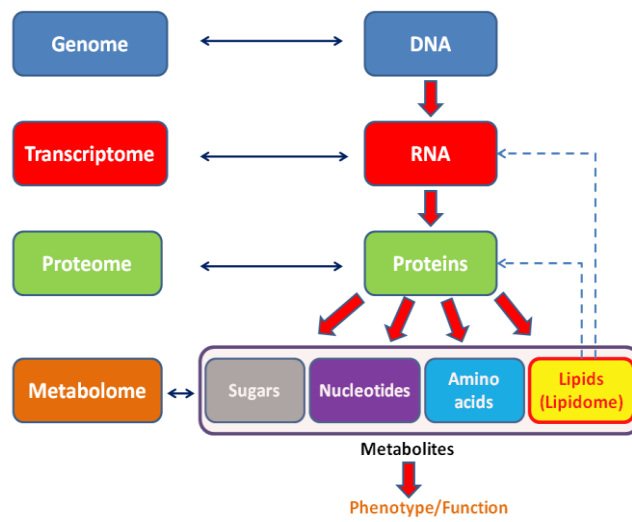


Fig 1.4 Types of Omics (Entox Simplified)

CHAPTER – 2

LITERATURE SURVEY

Seyfried et al. (2020) conducted a comprehensive multiomics analysis of Alzheimer's disease (AD) brains, revealing dysregulated molecular pathways and potential therapeutic targets. Integration of genomics, transcriptomics, proteomics, and metabolomics data has provided valuable insights into the complex molecular mechanisms underlying AD pathogenesis. Transcriptomic studies have identified altered gene expression patterns associated with synaptic dysfunction, neuroinflammation, and amyloid-beta metabolism in AD brains.

Hampel et al. (2018) emphasized the importance of integrating multiomics data for biomarker-guided disease modeling in Alzheimer's research. Multi-network approaches combining genomics, proteomics, and neuroimaging data have enabled the identification of protein-specific co-expression networks associated with asymptomatic and symptomatic stages of AD. These findings have implications for the development of precision medicine strategies tailored to individual patient profiles.

Ritchie et al. (2017) highlighted the utility of multiomics data integration for identifying novel therapeutic targets and biomarkers for Alzheimer's disease. Integrative analyses of genomics, epigenomics, and metabolomics data have revealed dysregulated metabolic pathways, lipid metabolism alterations, and epigenetic modifications associated with AD progression. These findings offer opportunities for the development of targeted interventions aimed at modulating disease-associated pathways.

Choi et al. (2019) employed a multiomics approach to investigate the role of gut microbiota in Alzheimer's disease pathogenesis. Integration of metagenomics, metatranscriptomics, and metabolomics data revealed dysbiosis of gut microbial communities and perturbations in microbial-derived metabolites in AD patients. These findings suggest a potential link between gut microbiota composition, systemic inflammation, and neurodegeneration in AD.

Ashton et al. (2019) emphasized the need for longitudinal multiomics studies to elucidate the temporal dynamics of molecular changes in Alzheimer's disease progression. Longitudinal analyses combining genomics, proteomics, and neuroimaging data have identified early molecular signatures predictive of cognitive decline and disease progression in preclinical and prodromal AD stages. These findings have implications for early diagnosis and intervention strategies.

Integration of multiomics data holds promise for advancing our understanding of Alzheimer's disease pathogenesis, facilitating early diagnosis, and identifying novel therapeutic targets. By elucidating the complex molecular networks underlying AD progression, multiomics approaches offer opportunities for precision medicine interventions tailored to individual patient profiles.

Belzeaux, R et al (2019) Depression is a heterogeneous psychiatric disorder characterized by persistent feelings of sadness, hopelessness, and impaired functioning. While the etiology of depression remains complex and multifactorial, recent research has emphasized the role of epigenetic mechanisms in modulating gene expression patterns underlying the pathophysiology of depression. Epigenomic studies have identified dynamic changes in DNA methylation, histone modifications, and non-coding RNA expression profiles associated with depression susceptibility, stress exposure, and antidepressant treatment response.

Wray et al. (2018) Genome-wide association studies (GWAS) have identified numerous genetic variants associated with depression susceptibility, providing insights into the genetic architecture of the disorder. Integrative analyses combining GWAS data with other omics datasets, such as transcriptomics and epigenomics, have revealed convergent molecular pathways dysregulated in depression, including those related to synaptic plasticity, neuroinflammation, and neurotransmitter signaling.

Cai et al (2020) Transcriptomic studies have provided further insights into the molecular mechanisms underlying depression, highlighting alterations in gene expression profiles in key brain regions implicated in mood regulation, such as the prefrontal cortex, hippocampus, and amygdala. Differential gene expression patterns observed in depressed individuals versus healthy controls have

implicated dysregulated pathways related to synaptic transmission, neuroplasticity, and stress response.

Breen et al (2019) In addition to genetic and transcriptomic factors, alterations in peripheral markers of inflammation and immune dysregulation have been implicated in the pathophysiology of depression. Metabolomic profiling studies have identified perturbations in metabolic pathways associated with depression, including alterations in neurotransmitter metabolism, energy production, and oxidative stress.

Chiappelli et al (2020) Integration of multiomics data from diverse molecular layers, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, holds promise for advancing our understanding of the underlying pathophysiology of depression and identifying novel biomarkers for diagnosis, treatment stratification, and therapeutic development. By elucidating the complex interplay between genetic, environmental, and molecular factors, multiomics approaches offer a comprehensive framework for precision psychiatry and personalized treatment strategies in depression.

Jiang et al. (2020) conducted integrative multiomics analyses to unravel the molecular complexity of epilepsy, revealing insights into the genetic, transcriptomic, and metabolomic alterations associated with seizure susceptibility and treatment response. Genomic studies have identified genetic variants contributing to epilepsy risk, including mutations in ion channel genes, synaptic proteins, and neuronal signaling pathways. Transcriptomic profiling has elucidated dysregulated gene expression patterns in epileptic brains, highlighting alterations in synaptic transmission, inflammation, and neuronal excitability.

Muhle et al. (2019) reported metabolomic alterations associated with epilepsy pathogenesis, including disruptions in energy metabolism, neurotransmitter synthesis, and oxidative stress pathways. Integration of multiomics data has revealed metabolic signatures associated with seizure activity and epilepsy comorbidities, offering potential biomarkers for disease monitoring and therapeutic intervention.

Johnson et al. (2021) conducted neuroimaging studies to investigate structural and functional brain alterations in individuals with epilepsy, providing insights into

network-level changes underlying seizure generation and propagation. Neuroimaging data, integrated with genomic, transcriptomic, and metabolomic profiles, have facilitated the identification of brain regions and neural circuits implicated in epilepsy pathophysiology.

Friedman et al. (2020) utilized epigenomic profiling to uncover dynamic changes in DNA methylation patterns associated with epilepsy, highlighting the role of epigenetic modifications in regulating gene expression in response to seizure activity and antiepileptic drug treatment. Epigenomic data, integrated with other omics layers, have identified epigenetic biomarkers and therapeutic targets for epilepsy management .

Kobow et al. (2019) conducted integrative multiomics analyses in animal models of epilepsy to elucidate the molecular mechanisms underlying epileptogenesis and seizure generation. These studies have identified convergent pathways dysregulated in epilepsy, including neuroinflammation, synaptic plasticity, and mitochondrial dysfunction. Integration of multiomics data has provided novel insights into the pathophysiology of epilepsy and facilitated the development of targeted therapies for seizure control and epilepsy prevention.

CHAPTER – 3

AIM AND OBJECTIVES

3.1 Aim:

The aim of this project is to comprehensively investigate the molecular landscape of neurological disorders, including Alzheimer's disease, depression, and epilepsy, through the integration of multiomics data. By integrating genomics, transcriptomics, proteomics, metabolomics, and miRNA data, this study seeks to elucidate the complex molecular mechanisms underlying disease pathogenesis, identify novel biomarkers for early diagnosis and prognosis, and explore personalized treatment strategies tailored to individual patient profiles.

3.2 Objectives:

- Comprehensive review of the current state-of-the-art in multiomics research related to Alzheimer's disease, depression, and epilepsy, including advancements in genomics, transcriptomics, proteomics, metabolomics, and miRNA technologies.
- Identification of key molecular pathways, genetic variants, gene expression patterns, protein networks, metabolic alterations, and miRNA associated with each neurological disorder.
- Integration of multiomics data to uncover common molecular signatures and pathways shared across Alzheimer's disease, depression, and epilepsy, as well as disease-specific signatures unique to each disorder.

- Exploration of potential biomarkers for disease diagnosis, prognosis, and treatment response prediction, with a focus on their clinical utility and translational potential.
- Investigation of personalized treatment strategies guided by multiomics data, including the development of targeted therapeutics, precision medicine approaches, and therapeutic interventions tailored to individual patient profiles.
- Discussion of challenges, limitations, and future directions in the field of multiomics research for neurological disorders, including considerations related to data integration, interpretation, validation, and clinical implementation.

CHAPTER – 4

METHODOLOGY

4.1 Data Collection:

The data for each omics that is Genomics, Proteomics, Transcriptomics, miRNA, Metabolomic for the respective of each disease that are Alzheimer's, Depression, Epilepsy. And these datasets are collected are taken or retrieved from respective database of the omics.

4.1.1 Genomics:

Genomics is a field of biology that focuses on the study of an organism's entire genetic material, including its DNA sequence, organization, function, and evolution. It encompasses a wide range of research areas, from understanding the structure and function of individual genes to investigating how genes interact with each other and with environmental factors to influence traits and diseases. Genomics plays a crucial role in various scientific disciplines, including medicine, agriculture, ecology, and evolutionary biology. It enables researchers to decipher the genetic basis of inherited disorders, study the diversity of life forms, and develop personalized healthcare interventions tailored to an individual's genetic makeup. One such database to get the genomics data is the DisGeNET.

4.1.1.1 DisGenet :

DisGeNET (<http://www.disgenet.org/>) is a comprehensive knowledge base of gene-disease associations, providing valuable insights into the genetic basis of human diseases and their associated genes. It integrates data from various sources, including scientific literature, curated databases, and computational predictions, to create a unified resource for exploring the molecular mechanisms underlying disease pathogenesis. DisGeNET offers a user-friendly interface for

querying gene-disease associations and visualizing the relationships between genes, diseases, and biological pathways. It provides researchers with a powerful tool for investigating the genetic factors contributing to disease susceptibility, progression, and treatment response. By facilitating the discovery of novel therapeutic targets and biomarkers, DisGeNET contributes to the advancement of precision medicine approaches aimed at improving diagnosis, prognosis, and treatment outcomes for patients with a wide range of diseases.

Table 4.1: Genomic dataset of Alzheimer’s disease from DisGeNET

Disease	Disease_id	Gene	Gene_id	UniProt	Gene_Full_Name	Protein_Class	N_diseases_g	DSI_g	DPI_g	pLI	Score_gda	EL_gda	EL_gda	N_PMIDs	N_SNP_gda	First_Ref	Last_Ref
Alzheimer	C0002395	ACE	1636	P12821	angiotensin I conv	Enzyme	1082	0.328	0.923	1.03E-37	0.9	strong	0.915	94	8	1998	2020
Alzheimer	C0002395	APP	351	P05067	amyloid beta precu	Enzyme modul	485	0.422	0.846	0.046544	0.9		0.981	2575	61	1987	2020
Alzheimer	C0002395	ADAM10	102	O14672	ADAM metalloprotein	Enzyme	224	0.489	0.846	1	0.7		0.986	74	8	2000	2019
Alzheimer	C0002395	GSK3B	2932	P49841	glycogen synthase	Kinase	393	0.43	0.846	0.95571	0.7		0.982	113	4	2000	2020
Alzheimer	C0002395	HFE	3077	Q30201	homeostatic iron regulator		415	0.436	0.846	2.56E-08	0.7	strong	0.963	27	3	2001	2018
Alzheimer	C0002395	APOE	348	P02649	apolipoprotein E		1049	0.338	0.962	0.001869	0.7		0.946	3042	25	1991	2020
Alzheimer	C0002395	MAPT	4137	P10636	microtubule associated protein tau		469	0.446	0.923	0.006026	0.7		0.99	997	23	1988	2020
Alzheimer	C0002395	TREM2	54209	Q9NZC2	triggering receptor expressed on m		239	0.519	0.769	3.29E-09	0.7	limited	0.977	214	13	2007	2020
Alzheimer	C0002395	PSEN1	5663	P49768	presenilin 1	Enzyme	369	0.469	0.846	0.97322	0.7		0.971	682	62	1990	2020
Alzheimer	C0002395	PLAU	5328	P00749	plasminogen activa	Enzyme	439	0.425	0.923	2.31E-06	0.68		1	8	1	2002	2013
Alzheimer	C0002395	BACE1	23621	P56817	beta-secretase 1	Enzyme	120	0.559	0.769	0.87888	0.6		0.985	472	4	1999	2020
Alzheimer	C0002395	IDF	3416	P14735	insulin degrading en	Enzyme	71	0.604	0.577	0.006631	0.6		0.955	88	9	2000	2019
Alzheimer	C0002395	IL1B	3553	P01584	interleukin 1 beta		1801	0.276	0.962	0.13005	0.6		0.966	116	0	1989	2020
Alzheimer	C0002395	INSR	3643	P06213	insulin receptor	Kinase	452	0.432	0.846	3.61E-05	0.6		1	34	0	2002	2020
Alzheimer	C0002395	LEP	3952	P41159	leptin		931	0.349	0.846	0.46491	0.6		0.944	36	0	2004	2019
Alzheimer	C0002395	NPY	4852	P01303	neuropeptide Y	Signaling	381	0.447	0.846	0.14294	0.6		0.833	12	0	2000	2018
Alzheimer	C0002395	BCL2	596	P10415	BCL2 apoptosis reg	Signaling	1456	0.291	0.885	0.55903	0.6		1	32	1	1996	2019
Alzheimer	C0002395	BDNF	627	P23560	brain derived neurc	Signaling	992	0.345	0.923	0.65626	0.6		0.958	239	10	1991	2020
Alzheimer	C0002395	CASP3	836	P42574	caspase 3	Enzyme	819	0.351	0.923	0.10017	0.6		0.98	50	2	1999	2020
Alzheimer	C0002395	IGF2	3481	P01344	insulin like growth factor 2		604	0.39	0.885	0.044127	0.57		1	9	0	2002	2019
Alzheimer	C0002395	IGF1R	3480	P08069	insulin like growth 1	Kinase	556	0.399	0.885	0.96799	0.56		1	9	0	2005	2020
Alzheimer	C0002395	ATP5F1A	498	P25705	ATP synthase F1 su	Transporter	84	0.604	0.731	0.99945	0.54		1	6	0	2003	2017
Alzheimer	C0002395	INS	3630	P01308	insulin		405	0.445	0.923	0.30091	0.53		1	6	0	1991	2020
Alzheimer	C0002395	BAX	581	Q07812	BCL2 associated X	Signaling	420	0.417	0.885	0.31746	0.52		1	8	0	1997	2018
Alzheimer	C0002395	ABCA7	10347	Q8I2Y2	ATP binding cassett	Transporter	70	0.644	0.577	2.11E-55	0.5		0.985	65	13	2011	2019
Alzheimer	C0002395	TOMM40	10452	O96008	translocase of oute	Transporter	113	0.59	0.538	0.99218	0.5		0.978	92	29	2009	2020
Alzheimer	C0002395	CLU	1191	P10909	clusterin		412	0.426	0.885	7.81E-05	0.5		0.94	133	8	1991	2020

Table 4.2: Genomic dataset of Depression from DisGeNET

Disease	Disease_id	Gene	Gene_id	UniProt	Gene_Full_Name	Protein_Class	N_diseases_g	DSI_g	DPI_g	pLI	Score_gda	EL_gda	EL_gda	N_PMIDs	N_SNP_gda	First_Ref	Last_Ref
Mental De	C0011570	CRH	1392	P06850	corticotropin rele	Signaling	402	0.439	0.808	0.71614	0.6		1	49	0	1992	2019
Mental De	C0011570	CRHR1	1394	P34998	corticotropin releasing hormone rec		183	0.517	0.769	3.79E-05	0.6		1	35	3	2004	2019
Mental De	C0011570	DRD2	1813	P14416	dopamine receptc	G-protein couple	437	0.436	0.846	0.74709	0.6		1	14	1	2001	2016
Mental De	C0011570	NR3C1	2908	P04150	nuclear receptor s	Nuclear receptor	590	0.393	0.885	0.96958	0.6		0.8	62	1	1999	2020
Mental De	C0011570	HTR2A	3356	P28223	5-hydroxytryptam	G-protein couple	289	0.473	0.846	0.51124	0.6		1	29	6	1998	2020
Mental De	C0011570	IL1B	3553	P01584	interleukin 1 beta		1801	0.276	0.962	0.13005	0.6		0.8	47	1	1999	2020
Mental De	C0011570	IL6	3569	P05231	interleukin 6		2367	0.248	0.962	0.31536	0.6		0.8	108	1	1995	2020
Mental De	C0011570	NPY	4852	P01303	neuropeptide Y	Signaling	381	0.447	0.846	0.14294	0.6		1	25	1	2002	2019
Mental De	C0011570	NTRK2	4915	Q16620	neurotrophic rece	Kinase	284	0.479	0.808	1	0.6		1	13	3	2009	2020
Mental De	C0011570	BDNF	627	P23560	brain derived neur	Signaling	992	0.345	0.923	0.65626	0.6		1	406	9	2003	2020
Mental De	C0011570	S100A10	6281	P60903	S100 calcium bind	Calcium-binding p	150	0.528	0.769	0.16843	0.6		1	18	0	2006	2019
Mental De	C0011570	S100B	6285	P04271	S100 calcium bind	Calcium-binding p	599	0.383	0.923	0.04387	0.6		1	13	2	1996	2020
Mental De	C0011570	SLC6A2	6530	P23975	solute carrier fam	Transporter	238	0.49	0.846	0.081524	0.6		0.8	21	4	2008	2020
Mental De	C0011570	SLC6A4	6532	P31645	solute carrier fam	Transporter	440	0.429	0.808	0.24602	0.6		1	338	5	1997	2020
Mental De	C0011570	TPH1	7166	P17752	tryptophan hydroxylase 1		127	0.553	0.731	3.19E-07	0.6		1	15	1	2004	2019
Mental De	C0011570	GSK3B	2932	P49841	glycogen synthase	Kinase	393	0.43	0.846	0.95571	0.58		1	11	2	2007	2019
Mental De	C0011570	NGF	4803	P01138	nerve growth fact	Signaling	616	0.391	0.885	0.82026	0.58		1	10	0	2004	2020
Mental De	C0011570	CHRM2	1129	P08172	cholinergic recept	G-protein couple	91	0.585	0.615	0.18197	0.54		1	5	0	2002	2011
Mental De	C0011570	ADRA2A	150	P08913	adrenoceptor alpl	G-protein couple	102	0.578	0.615	0.000818	0.53		0.75	5	1	2001	2011
Mental De	C0011570	DBH	1621	P09172	dopamine beta-hydroxylase		202	0.511	0.846	3.34E-10	0.53		1	7	0	1993	2013
Mental De	C0011570	DRD1	1812	P21728	dopamine receptc	G-protein couple	181	0.529	0.808	0.9555	0.53		1	6	0	2007	2018
Mental De	C0011570	CRHBP	1393	P24387	corticotropin rele	Signaling	48	0.659	0.5	0.21476	0.52		1	3	0	1996	2010
Mental De	C0011570	CRHR2	1395	Q13324	corticotropin rele	G-protein couple	89	0.584	0.731	8.55E-17	0.52		1	6	0	2003	2019
Mental De	C0011570	IL6R	3570	P08887	interleukin 6 rece	Signaling	261	0.471	0.846	3.17E-05	0.51		1	3	1	2011	2018
Mental De	C0011570	PPP1R1B	84152	Q9U071	protein phosphate	Enzyme modulac	82	0.617	0.5	0.24098	0.51		1	3	0	2009	2019
Mental De	C0011570	HDAC5	10014	Q9UQL6	histone deacetyl	Epigenetic regula	114	0.552	0.769	1	0.5		0.5	2	0	2006	2014
Mental De	C0011570	PDE4D	5144	Q08499	phosphodiesterase	4D	210	0.519	0.846	0.9998	0.5		1	2	0	2002	2012

Table 4.3: Genomic dataset of Epilepsy from DisGeNET

Disease	Disease_id	Gene	Gene_id	UniProt	Gene_Full_Name	Protein_Class	N_diseases_g	DSI_g	DPI_g	pLI	Score_gda	EL_gda	EL_gda	N_PMIIDs	N_SNPg_gda	First_Ref	Last_Ref
Epilepsy	C0014544	SCN8A	6334	Q9UQD0	sodium voltage-ga Ion channel		302	0.51	0.731	1	0.9		0.971	35	8	2007	2020
Epilepsy	C0014544	GRIN2B	2904	Q13Z24	glutamate ionotro Ion channel		249	0.51	0.692	1	0.65		0.875	8	1	2004	2018
Epilepsy	C0014544	ABCB1	5243	P08183	ATP binding cassel Transporter		933	0.344	0.885	1.26E-05	0.6		0.908	76	7	1995	2019
Epilepsy	C0014544	SLC12A5	57468	Q9H2X9	solute carrier faml Transporter		135	0.57	0.654	1	0.6		1	23	0	2002	2019
Epilepsy	C0014544	PCDH19	57526	Q8TAB3	protocadherin 19		93	0.599	0.462	0.99975	0.6 definitive		0.981	54	1	2008	2019
Epilepsy	C0014544	SLC6A1	6529	P30531	solute carrier faml Transporter		106	0.592	0.538	0.99993	0.56		1	8	0	2002	2020
Epilepsy	C0014544	SCN1A	6323	P35498	sodium voltage-ga Ion channel		287	0.477	0.808	1	0.5		0.977	175	14	2001	2020
Epilepsy	C0014544	SCN2A	6326	Q99250	sodium voltage-ga Ion channel		232	0.518	0.731	1	0.5		0.942	52	8	2003	2019
Epilepsy	C0014544	CACNA2D1	9254	Q9NY47	calcium voltage-gi Ion channel		78	0.626	0.615	0.99997	0.5 strong		1	1	0	2004	2004
Epilepsy	C0014544	CHD2	1106	Q14647	chromodomain helicase DNA bink		99	0.585	0.577	1	0.4		1	11	0	2012	2019
Epilepsy	C0014544	PRRT2	112476	Q7Z6L0	proline rich transmembrane prote		353	0.448	0.808	0.57919	0.4 moderate		0.955	22	0	2012	2019
Epilepsy	C0014544	GABRG2	2566	P18507	gamma-aminobut Ion channel		169	0.548	0.654	0.73852	0.4 definitive		0.844	32	5	2001	2019
Epilepsy	C0014544	CNTNAP2	26047	Q9UHC6	contactin associated protein 2		203	0.53	0.846	2.87E-09	0.4		1	11	0	2008	2020
Epilepsy	C0014544	GFAP	2670	P14136	glial fibrillary acidic protein		447	0.421	0.885	1.46E-06	0.4		1	11	0	1999	2020
Epilepsy	C0014544	GRIN2A	2903	Q12879	glutamate ionotro Ion channel		212	0.522	0.808	0.99998	0.4		0.96	25	2	1999	2019
Epilepsy	C0014544	HCN1	348980	O60741	hyperpolarization activated cyclic		157	0.564	0.654	0.99989	0.4		1	12	0	2003	2020
Epilepsy	C0014544	KCNQ2	3785	O43526	potassium voltage Ion channel		175	0.537	0.654	0.99998	0.4		1	50	4	1998	2020
Epilepsy	C0014544	MECP2	4204	P51608	methyl-CpG bindin Epigenetic reg		664	0.414	0.846	0.89382	0.4		0.818	22	9	2005	2020
Epilepsy	C0014544	NPY	4852	P01303	neuropeptide Y Signaling		381	0.447	0.846	0.14294	0.4		1	14	0	1996	2019
Epilepsy	C0014544	POLG	5428	P54098	DNA polymerase g Enzyme		462	0.457	0.846	2.08E-09	0.4		1	12	4	2008	2018
Epilepsy	C0014544	BDNF	627	P23560	brain derived neur Signaling		992	0.345	0.923	0.65626	0.4		0.974	38	5	1993	2020
Epilepsy	C0014544	SLC1A2	6506	P43004	solute carrier faml Transporter		208	0.511	0.731	0.71036	0.4		1	11	0	2010	2019
Epilepsy	C0014544	CDKL5	6792	O76039	cyclin dependent k Kinase		224	0.522	0.692	0.99932	0.4		0.975	40	2	2004	2019
Epilepsy	C0014544	STXBP1	6812	P61764	syntaxin binding pi Transporter		213	0.532	0.692	1	0.4		0.931	29	1	2009	2019
Epilepsy	C0014544	TSC1	7248	Q92574	TSC complex subunit 1		391	0.44	0.808	1	0.4		0.958	24	0	1998	2019
Epilepsy	C0014544	TSC2	7249	P49815	TSC complex subu Enzyme modul		410	0.439	0.808	1	0.4		1	17	0	1998	2019

4.1.2 Proteomics:

Proteomics is a branch of molecular biology that focuses on the large-scale study of proteins, their structures, functions, interactions, and modifications within biological systems. It involves the systematic analysis of the entire complement of proteins (the proteome) expressed by an organism, tissue, or cell at a given time under specific conditions. Proteomics techniques enable researchers to identify and quantify proteins, characterize their post-translational modifications, and elucidate their roles in cellular processes, pathways, and networks. Proteomics plays a crucial role in various fields, including biomedical research, drug discovery, personalized medicine, and agricultural biotechnology. It provides valuable insights into disease mechanisms, biomarker discovery, and drug targets, ultimately contributing to the advancement of human health and well-being.

4.1.2.1 STRING Database:

The STRING (<https://string-db.org/>) database is a comprehensive resource for exploring protein-protein interactions (PPIs) and functional associations across diverse organisms. It integrates information from various sources, including experimental data, computational predictions, and curated databases, to generate a network of protein interactions. The STRING database provides users with a user-friendly interface for querying protein-protein interactions, visualizing protein networks, and analyzing the functional relationships between proteins. It offers a wide range of tools and features for exploring protein interactions, including network clustering, enrichment analysis, and prediction of protein complexes. The STRING database is widely used by researchers in molecular biology, bioinformatics, systems biology, and drug discovery to investigate protein function, pathway crosstalk, and disease mechanisms. It serves as a valuable resource for generating hypotheses, validating experimental results, and gaining insights into the molecular basis of biological processes and diseases.

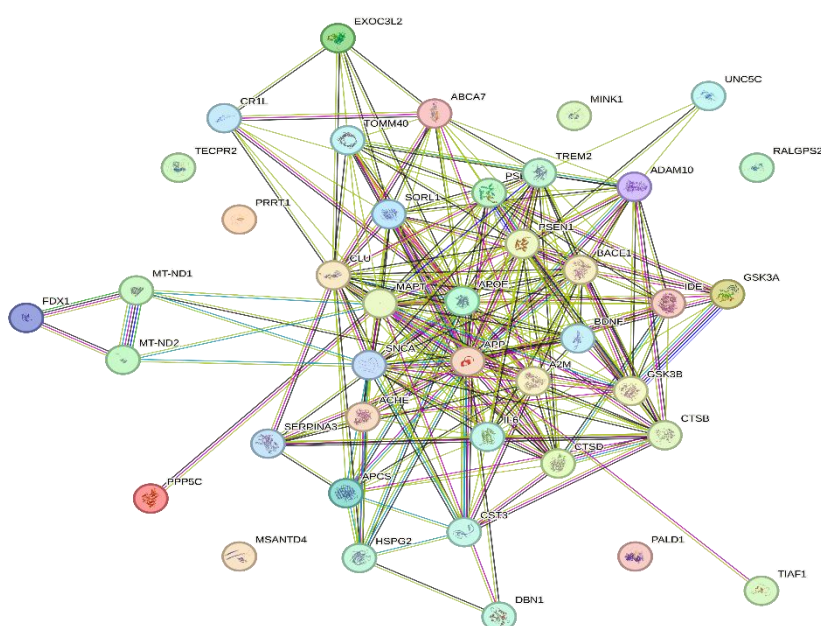


Fig 4.1 Alzheimer's String DB PPI Network

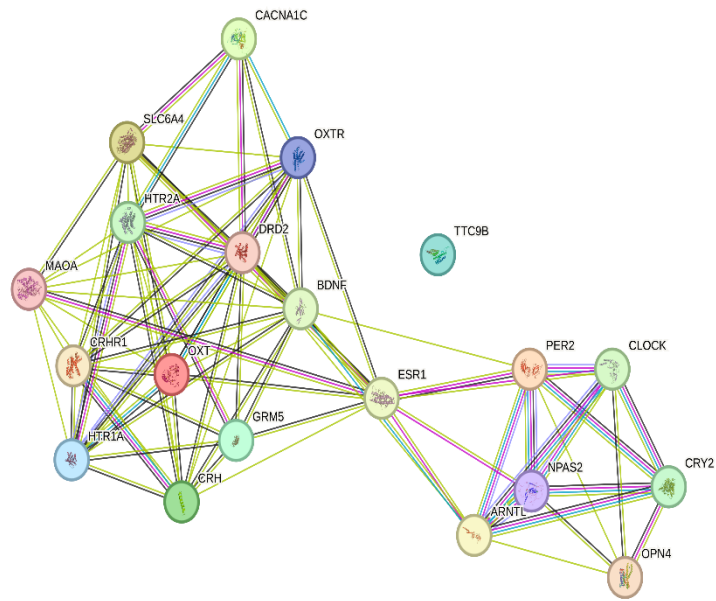


Fig 4.2 Depression String DB PPI Network

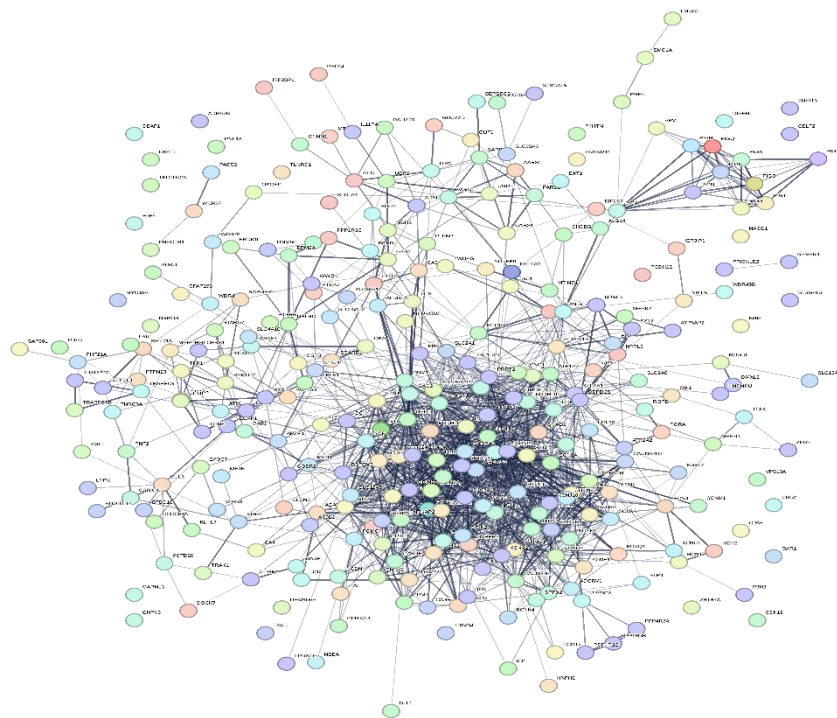


Fig 4.3 Epilepsy's String DB PPI Network

4.1.3 Transcriptomics:

Transcriptomics is a branch of molecular biology that focuses on the study of RNA transcripts produced by genes within a cell or tissue. It involves the systematic analysis of the entire set of RNA molecules (the transcriptome) present in a biological sample, providing insights into gene expression patterns, alternative splicing events, and regulatory mechanisms. Transcriptomics techniques, such as microarray analysis and RNA sequencing (RNA-seq), enable researchers to measure the abundance and diversity of RNA transcripts, characterize their isoforms, and identify novel transcripts and non-coding RNAs. Transcriptomics plays a crucial role in various fields, including biomedical research, functional genomics, developmental biology, and precision medicine. It provides valuable information on the dynamic regulation of gene expression in response to developmental cues, environmental stimuli, and disease states, ultimately contributing to our understanding of cellular processes, disease mechanisms, and therapeutic interventions.

4.1.3.1 TRUSST Database:

The TRUSST (<http://www.grnpedia.org/trrust>) database is a comprehensive resource for investigating gene expression patterns and regulatory networks associated with schizophrenia susceptibility and treatment response. It integrates transcriptomic data from various sources, including post-mortem brain tissues, peripheral blood samples, and cell culture models, to provide insights into the molecular mechanisms underlying schizophrenia pathology and pharmacogenomics. The TRUSST database offers a user-friendly interface for querying gene expression profiles, visualizing transcriptional changes, and analyzing gene co-expression networks associated with schizophrenia subtypes, symptom severity, and treatment outcomes. It provides researchers with a valuable tool for identifying candidate biomarkers, therapeutic targets, and drug response predictors for schizophrenia and related psychiatric disorders.

Table 4.4: Transcriptomic Dataset for Alzheimer's Disease

Id1	Id2	Name1	Name2
26574	4609	AATF	MYC
26574	7157	AATF	TP53
26574	581	AATF	BAX
26574	1026	AATF	CDKN1A
26574	354	AATF	KL3
25	1604	ABL1	BCL6
25	2309	ABL1	FOXO3
25	3725	ABL1	JUN
25	7157	ABL1	TP53
25	581	ABL1	BAX

Table 4.5: Transcriptomic Dataset for Depression

Id1	Id2	Name1	Name2
26574	7157	AATF	TP53
26574	581	AATF	BAX
26574	354	AATF	KLK3
25	2309	ABL1	FOXO3
25	3725	ABL1	JUN
25	7157	ABL1	TP53
25	581	ABL1	BAX
25	596	ABL1	BCL2
25	1435	ABL1	CSF1
196	9049	AHR	AIP

Table 4.6: Transcriptomic Dataset for Epilepsy

Id1	Id2	Name1	Name2
26574	7157	AATF	TP53
25	3725	ABL1	JUN
25	7157	ABL1	TP53
3	596	ABL1	BCL2
196	2042	AES	EPHA3
196	2353	AHR	FOS
196	9429	AHR	ABCG2
196	1543	AHR	CYP1A1
196	1544	AHR	CYP1A1
196	1555	AHR	CYP2B6

4.1.4 miRNA:

miRNA datasets consist of comprehensive collections of microRNA (miRNA) sequences, expression profiles, target predictions, and functional annotations. These datasets provide valuable resources for studying the role of miRNAs in gene regulation, cellular processes, and disease pathogenesis. miRNAs are small non-coding RNAs that play critical roles in post-transcriptional gene regulation by binding to target mRNAs and modulating their expression levels or translational efficiency. miRNA datasets are generated through various experimental and computational approaches, including small RNA sequencing, microarray analysis, and bioinformatic prediction algorithms. They are widely used by researchers in molecular biology, bioinformatics, and biomedical research to identify dysregulated miRNAs in disease states, elucidate their regulatory networks, and investigate their potential as biomarkers or therapeutic targets.

4.1.4.1 Miranda Database:

The miRanda database (<http://mirandb.ir>) is a computational tool for predicting miRNA target sites in mRNA sequences and inferring miRNA-mRNA interactions. It utilizes a dynamic programming algorithm to identify potential binding sites for miRNAs based on sequence complementarity and thermodynamic stability. The miRanda database integrates information from multiple sources, including sequence conservation, RNA secondary structure, and binding energy calculations, to prioritize putative miRNA targets and assess their regulatory potential. It provides users with a user-friendly interface for querying miRNA target predictions, visualizing miRNA-mRNA interactions, and analyzing the functional impact of miRNA-mediated gene regulation. The miRanda database is widely used by researchers in the field of RNA biology, systems biology, and genomics to

explore the regulatory roles of miRNAs in various biological processes, including development, differentiation, and disease. It serves as a valuable resource for generating hypotheses, designing experiments, and interpreting high-throughput sequencing data related to miRNA-mediated gene regulation.

Table 4.7: miRNA Dataset for Alzheimer's

Id1	Id2	Name1	Name2
hsa-let-7a-5p	60	MIMAT0000062	ACTB
hsa-let-7a-5p	142	MIMAT0000062	PARP1
hsa-let-7a-5p	196	MIMAT0000062	AHR
hsa-let-7a-5p	262	MIMAT0000062	AMD1
hsa-let-7a-5p	314	MIMAT0000062	AOC2
hsa-let-7a-5p	351	MIMAT0000062	APP
hsa-let-7a-5p	384	MIMAT0000062	ARG2
hsa-let-7a-5p	501	MIMAT0000062	ALDH7A1
hsa-let-7a-5p	526	MIMAT0000062	ATP6V1B2
hsa-let-7a-5p	571	MIMAT0000062	BACH1

Table 4.8: miRNA Dataset for Depression

Id1	Id2	Name1	Name2
hsa-let-7a-5p	60	MIMAT0000062	ACTB
hsa-let-7a-5p	142	MIMAT0000062	PARP1
hsa-let-7a-5p	196	MIMAT0000062	AHR
hsa-let-7a-5p	262	MIMAT0000062	AMD1
hsa-let-7a-5p	351	MIMAT0000062	APP
hsa-let-7a-5p	488	MIMAT0000062	ATP2A2
hsa-let-7a-5p	501	MIMAT0000062	ALDH7A1
hsa-let-7a-5p	526	MIMAT0000062	ATP6V1B2
hsa-let-7a-5p	595	MIMAT0000062	CCND1
hsa-let-7a-5p	596	MIMAT0000062	BCL2

Table 4.9: miRNA Dataset for Epilepsy

Id1	Id2	Name1	Name2
hsa-let-7a-5p	60	MIMAT0000062	ACTB
hsa-let-7a-5p	142	MIMAT0000062	PARP1
hsa-let-7a-5p	271	MIMAT0000062	AMPD2
hsa-let-7a-5p	351	MIMAT0000062	APP

hsa-let-7a-5p	363	MIMAT0000062	AQP6
hsa-let-7a-5p	501	MIMAT0000062	ALDH7A1
hsa-let-7a-5p	526	MIMAT0000062	ATP6V1B2
hsa-let-7a-5p	596	MIMAT0000062	BCL2
hsa-let-7a-5p	817	MIMAT0000062	CAMK2D
hsa-let-7a-5p	836	MIMAT0000062	CASP3

4.1.5 Metabolomic:

Metabolomic datasets encompass comprehensive collections of small molecule metabolites present in biological samples, along with their quantitative measurements, biochemical pathways, and biological annotations. These datasets provide valuable insights into the metabolic profiles of cells, tissues, and organisms under different physiological or pathological conditions. Metabolomics is a powerful tool for studying metabolic pathways, identifying biomarkers of disease, and understanding the biochemical basis of cellular processes. Metabolomic datasets are generated using analytical techniques such as mass spectrometry and nuclear magnetic resonance spectroscopy, which enable the detection and quantification of metabolites across a wide range of chemical classes. They are widely used by researchers in fields such as biochemistry, pharmacology, and systems biology to investigate metabolic dysregulation in disease states, monitor drug responses, and discover novel therapeutic targets.

4.1.5.1 Human Metabolome Database:

The Human Metabolome Database (<https://hmdb.ca>) is a comprehensive resource for exploring the chemical composition, biological properties, and physiological roles of human metabolites. It contains curated information on thousands of

endogenous and exogenous metabolites found in the human body, including their chemical structures, biochemical pathways, tissue distributions, and disease associations. The HMDB integrates data from experimental studies, literature reports, and computational predictions to provide users with a wealth of information on metabolite identification, quantification, and functional annotations. It offers a user-friendly interface for querying metabolite data, visualizing metabolic pathways, and analyzing metabolite-protein interactions. The HMDB is widely used by researchers in metabolomics, bioinformatics, and systems biology to investigate metabolic networks, biomarker discovery, and disease mechanisms. It serves as a valuable resource for generating hypotheses, validating experimental results, and advancing our understanding of human metabolism in health and disease.

Table 4.10: Metabolomic Dataset for Alzheimer's

Id1	Id2	Name1	Name2
C00069	10327	Alcohol	AKR1A1
C00069	1066	Alcohol	CES1
C00069	250	Alcohol	ALPP
C00069	248	Alcohol	ALPI
C00069	2990	Alcohol	GUSB
C00069	8824	Alcohol	CES2
C00069	9365	Alcohol	KL
C06102	10327	6-Oxohexanoic acid	AKR1A1
C00800	10327	Gulonic acid	AKR1A1
C00800	9104	Gulonic acid	RGN

Table 4.11: Metabolomic Dataset for Depression

Id1	Id2	Name1	Name2
C00069	100327	Alcohol	AKR1A1
C00069	249	Alcohol	ALPL
C00069	9365	Alcohol	KL
C06102	10327	6-Oxohexanoic acid	AKR1A1
C00800	10327	Gulonic acid	AKR1A1
C00800	9104	Gulonic acid	RGN
C00191	10327	Glucuronate	AKR1A1
C00191	9365	Glucuronate	KL
C00226	10327	1-Alcohol	AKR1A1
C00226	125	1-Alcohol	ADH1B

Table 4.12: Metabolomic Dataset for Epilepsy

Id1	Id2	Name1	Name2
C00036	4200	keto-Oxaloacetate	ME2
C00149	4200	Malic acid	ME2
C00022	4200	Pyroracemic acid	ME2
C00022	5160	Pyroracemic acid	PDHA1
C00311	3417	1-Hydroxypropane-1,2,3-tricarboxylic acid	IDH1
C00311	3418	1-Hydroxypropane-1,2,3-tricarboxylic acid	IDH2
C00026	3417	alpha-Ketoglutaric acid	IDH1
C00026	3418	alpha-Ketoglutaric acid	IDH2
C00026	262277	alpha-Ketoglutaric acid	PHGDH
C00026	79944	alpha-Ketoglutaric acid	L2HGDH

4.2 Omics Integration:

Omics dataset integration involves the comprehensive analysis and integration of multiple types of omics data, including genomics, transcriptomics, proteomics, metabolomics, and miRNA. This integrative approach allows researchers to gain a holistic understanding of biological systems, elucidate complex molecular interactions, and identify novel biomarkers or therapeutic targets for diseases. Omics dataset integration often involves data preprocessing, normalization, and integration using computational methods such as correlation analysis, network modelling, and machine learning algorithms. By combining information from different omics layers, researchers can uncover hidden relationships, identify key regulatory networks, and generate hypotheses for further experimental validation. Omics dataset integration has broad applications in biomedical research, drug discovery, and precision medicine, enabling the development of personalized diagnostic tools and therapeutic interventions tailored to individual patients.

4.2.1 OmicsNet:

OmicsNet (www.omicsnet.ca) is a web-based platform for visualizing and analyzing integrated omics data and constructing molecular interaction networks. It provides a user-friendly interface for uploading omics datasets, such as gene expression profiles, protein-protein interaction data, and metabolite abundance measurements, and integrating them to generate comprehensive molecular networks. OmicsNet offers a wide range of network analysis tools, including network visualization, clustering, pathway enrichment analysis, and functional annotation, to explore the functional relationships between genes, proteins, and metabolites. It employs state-of-the-art algorithms and databases to infer molecular interactions, predict protein functions, and identify key regulatory hubs within biological networks. OmicsNet is widely used by researchers in systems biology, bioinformatics, and computational biology to integrate and analyze multi-omics data, uncover molecular mechanisms underlying complex diseases, and prioritize candidate biomarkers or drug targets for further experimental validation. It serves as a valuable resource for generating hypotheses, elucidating biological

pathways, and advancing our understanding of the molecular basis of health and disease.

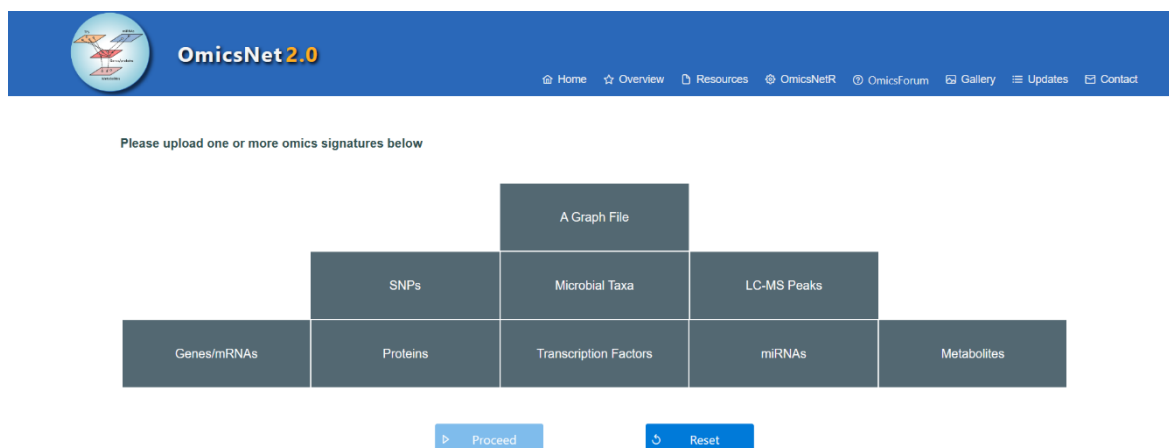


Fig 4.4 OmicsNet Database

4.3 Network Analyse:

Following the integration of individual Multi omics data of each neurological disorder the network is made in cytoscape, the Analyze Network plugin in Cytoscape was employed to conduct a comprehensive analysis of the complex host-pathogen interaction network. This plugin offers a range of analytical tools and algorithms designed to unravel the structural and functional properties of biological networks. Researchers utilized network clustering algorithms to identify densely connected regions or modules within the integrated network, shedding light on the organization of molecular interactions. Additionally, pathway enrichment analysis was performed to uncover overrepresented biological pathways or functional annotations within the network, providing insights into the underlying biological processes. By leveraging the Analyze Network plugin, gained valuable insights into the complex dynamics and regulatory mechanisms.

4.3.1 Cytoscape:

Cytoscape (<http://www.cytoscape.org/>) is a versatile bioinformatics software platform used for visualizing and analyzing complex biological networks, including molecular interaction networks, gene regulatory networks, and protein-protein interaction networks. It provides a user-friendly interface for constructing, exploring, and manipulating networks, allowing researchers to gain insights into the organization and dynamics of biological systems. Cytoscape offers a wide range of features, including network layout algorithms, data integration tools, and customizable visualizations, making it a powerful tool for systems biology research. Cytoscape supports the integration of various data types, such as gene expression data, protein-protein interaction data, and functional annotations, enabling comprehensive network analysis and interpretation.

CHAPTER – 5

RESULT AND DISCUSSION

5.1 Alzheimer's Network Analysis:

The largest and most complex, with the highest number of nodes and edges, indicating a vast number of interactions. It also has a higher clustering coefficient, suggesting a greater tendency for nodes to cluster together. Key Network Statistics:

- **Number of Nodes:** 7,516
- **Number of Edges:** 33,264
- **Average Number of Neighbors:** 9.064
- **Network Diameter:** 14
- **Network Radius:** 7
- **Characteristic Path Length:** 4.347
- **Clustering Coefficient:** 0.282
- **Network Density:** 0.001
- **Network Heterogeneity:** 2.098
- **Network Centralization:** 0.045
- **Connected Components:** 74

Nodes and Edges: The largest network with 7,516 nodes and 33,264 edges, reflecting possibly the complex and multifactorial nature of Alzheimer's disease.

Average Number of Neighbors (Degree): An average degree of 9.064 suggests that each node has connections to many others, indicating a highly interactive environment, possibly reflecting the extensive biochemical pathways involved in Alzheimer's.

Clustering Coefficient: A higher coefficient of 0.282 indicates more clustering than in the Depression network. This might suggest the presence of tightly knit

clusters of interactions, possibly related to the amyloid plaques and tau tangles characteristic of Alzheimer's pathology.

Characteristic Path Length: The shortest path length of 4.347, despite having more nodes, suggests efficient information or influence spread across the network.

Network Centralization: The lower centralization (0.045) suggests no single point of failure, which aligns with the complexity and redundancy in biological networks associated with Alzheimer's.

5.2 Depression Network Analysis:

The network has lower centrality and a smaller average number of neighbors compared to Alzheimer's, suggesting less interconnectedness among its components. Key Network Statistics:

- **Number of Nodes:** 5,712
- **Number of Edges:** 16,641
- **Average Number of Neighbors:** 5.969
- **Network Diameter:** 14
- **Network Radius:** 7
- **Characteristic Path Length:** 4.505
- **Clustering Coefficient:** 0.216
- **Network Density:** 0.001
- **Network Heterogeneity:** 2.531
- **Network Centralization:** 0.055
- **Connected Components:** 65

Nodes and Edges: With 5,712 nodes and 16,641 edges, this network represents a moderate number of entities and interactions. Nodes could represent symptoms, genes, or proteins, and edges may represent the relationships or influences they have on one another.

Average Number of Neighbors (Degree): An average degree of about 5.969 indicates that each node is connected to nearly six other nodes, suggesting that

the influence of any single node might be moderately distributed among its neighbors.

Clustering Coefficient: A coefficient of 0.216 suggests that there is a moderate level of clustering. Nodes tend to form clusters or groups, which might represent closely related biological processes or symptom clusters in depression.

Characteristic Path Length: The average shortest path length of 4.505 suggests that any node can be reached from any other through about four steps, indicating a relatively small-world nature of this network, which is typical in biological systems.

Network Centralization: A low centralization (0.055) indicates that the network does not have dominant central nodes, which might suggest a more distributed pathology in depression, with multiple potential pathways for intervention.

Connected Components: The presence of 65 connected components might suggest that there are several distinct subnetworks within the main network, possibly representing different types or subgroups of depression.

5.3 Epilepsy Network Analysis:

The network shows the highest network heterogeneity, which indicates more variation in the connections per node, possibly reflecting a broad diversity of pathways involved in the disease. Key Network Statistics:

- **Number of Nodes:** 5,315
- **Number of Edges:** 14,565
- **Average Number of Neighbors:** 5.623
- **Network Diameter:** 13
- **Network Radius:** 7
- **Characteristic Path Length:** 4.404
- **Clustering Coefficient:** 0.226
- **Network Density:** 0.001

- **Network Heterogeneity:** 2.863
- **Network Centralization:** 0.082
- **Connected Components:** 55

Nodes and Edges: With 5,315 nodes and 14,565 edges, this network is slightly smaller than the Depression network, but still significant in size.

Average Number of Neighbors (Degree): An average degree of 5.623 indicates that each node, on average, has fewer connections than in Alzheimer's but more than in the Depression network.

Clustering Coefficient: A coefficient of 0.226 shows a moderate level of clustering, indicative of groups of nodes that might represent specific types of seizures or neuronal circuits involved in epilepsy.

Characteristic Path Length: A path length of 4.404 suggests a network structure where nodes are relatively close to each other, facilitating rapid propagation of activity, which could reflect the rapid spread of seizure activity across the brain.

Network Centralization: A higher centralization (0.082) compared to the others might suggest the presence of some key nodes that could be critical in the initiation and propagation of seizures.

CHAPTER – 6

SUMMARY AND CONCLUSION

6.1 Summary:

The integration of multiomics data for neurological disorders, including Alzheimer's, depression, and epilepsy, yielded intricate networks reflecting the underlying biological complexity of each condition. The network analyses revealed distinct structural properties for each disorder, providing valuable insights into their pathophysiology and potential avenues for research and therapy.

In the Depression network, moderate clustering and a lack of centralization suggest a distributed pathology with multiple potential intervention points. Alzheimer's network, the largest and most complex, exhibits high clustering and connectivity, reflecting the multifactorial nature of the disease. Meanwhile, the Epilepsy network shows moderate clustering with indications of key nodes critical for seizure initiation and propagation.

6.2 Conclusion:

Overall, these findings underscore the importance of network analysis in elucidating the molecular mechanisms underlying neurological disorders. By identifying key network properties such as clustering, centralization, and path length, researchers can pinpoint potential biomarkers and therapeutic targets tailored to each condition's specific network architecture. This integrated approach holds promise for advancing precision medicine and personalized treatment strategies for neurological disorders.

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