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Investigating DISC1 to Explore its Therapeutic Potential Regarding Schizophrenia

by

Muhammad Qasim Khan

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In the name of Allah, the Most Gracious, the Most Merciful.

I dedicate this dissertation to the Almighty Allah, whose blessings, guidance, and strength have been my foundation throughout this journey. I am eternally grateful for His wisdom and mercy that have sustained me in every moment.To the Holy Prophet Muhammad (Peace Be Upon Him), a source of inspiration for striving towards knowledge and excellence. To my beloved parents, whose unwavering love, support, and prayers have been my source of motivation and strength. Their sacrifices and encouragement have shaped me and made this achievement possible. And to my supervisor, whose guidance, insight, and patience have been invaluable. Thank you for your mentorship and for believing in me every step of the way.

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CERTIFICATE OF APPROVAL

This is to certify that the research work presented in the dissertation, entitled "**Investigating DISC1 to Explore its Therapeutic Potential Regarding Schizophrenia**" was conducted under the supervision of **Dr. Syeda Marriam Bakhtiar**. No part of this dissertation has been submitted anywhere else for any other degree. This dissertation is submitted to the **Department of Bioinformatics & Biosciences, Capital University of Science and Technology** in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the field of **Biosciences**. The open defence of the dissertation was conducted on **May 12, 2025.**

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I solemnly declare that research work presented in the dissertation titled "**Investigating DISC1 to Explore its Therapeutic Potential Regarding Schizophrenia**" is solely my research work with no significant contribution from any other person. Small contribution/ help wherever taken has been duly acknowledged and that complete dissertation has been written by me.

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List of Publications

It is certified that following publication(s) have been made out of the research work that has been carried out for this dissertation:-

1. **Muhammad Qasim Khan**, Syed Babar Jamal, Muhammad Faheem & Syeda Marriam Bakhtiar (23 Feb 2025): 3-Dimensional structure prediction of C-terminal disrupted in schizophrenia 1: a suspected culprit of schizophrenia, Journal of Biomolecular Structure and Dynamics, DOI: 10.1080 / 0739-1102. 2025.2460079

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Abstract

DISC1 is a diverse, unique candidate gene implicated in debilitating, complex neuropsychiatric disorder such as schizophrenia. It is a 854 amino acid protein with a N-terminal (1-350 amino acids) head and C-terminal (351-854 amino acids) coiled coil region. We know that DISC1 is a scaffolding protein which coordinates with various protein interactors ensuring the essential function of neuronal proliferation, migration and differentiation. Schizophrenia being a multifactorial disorder which confers variety of symptoms (positive, negative and cognitive) and has both genetic and environmental causes. The current medication and therapeutics of schizophrenia lack efficacy and lead to multiple side effects. In this study we initially explored, analyzed DISC1 association with schizophrenia through meta-analysis which provided strong association. Due to the absence of available three-dimensional structure of DISC1 the gap between structure and function exists so to bridge that gap the three-dimensional structure prediction of DISC1 was conducted primarily focusing on C-terminal region because it is responsible for key molecular interactions. To further reinforce DISC1 function and its overlap with schizophrenia pathway enrichment was performed which enabled to identify three key interactors NDEL1 (NudE neurodevelopment protein 1-like 1), NDE1 (NudE neurodevelopment protein 1), and PAFAH1B1 (platelet activating factor acetylhydrolase 1b regulatory subunit 1) along with their associated pathways. This research contributes to a better understanding of schizophrenia's molecular underpinnings and provides promising directions for improving treatment options and supporting the patients impacted by this challenging disorder.

Keywords:

Schizophrenia, DISC1, Neurotransmitter, DSM-5, Pathway, Therapeutics

Contents

List of Figures

List of Tables

Abbreviations

5-HT2A	Serotonin 2A
ADD	Attention Deficit Disorder
AKT	Serine/Threonine-Specific Protein Kinase
API	Application Programming Interface
APOE	Apolipoprotein E
ASB3	Ankyrin Repeat and SOCS Box Containing 3
BBS1	Bardet-Biedl Syndrome 1
BBS4	Bardet-Biedl Syndrome 4
BDNF	Brain-derived neurotrophic factor
BP	Biological Processes
C17ORF59	Chromosome 17 open reading frame 59
CBT	Cognitive-Behavioral Therapy
CC	Cellular Components
CDC16	Cell Division Cycle 16
CEP170	Centrosomal Protein 170kda
CEP57	Centrosomal Protein 57kda
CNS	Central Nervous System
CNV	Copy Number Variation
COMT	Catechol-O-Methyltransferase
DAO	D-Amino-Acid Oxidase
DISC1	Disrupted In Schizophrenia 1
DIXDC1	Dix Domain Containing-1
DRD2	Dopamine Receptor D2

DTNBP1	Dystrobrevin Binding Protein 1
DYNC1/1	Dynein, Cytoplasmic 1, Intermediate Chain 1
DZ	Dizygotic Twins
EPSEs	Extrapyramidal Side Effects
ERK1/2	Extracellular Signal-Regulated Kinases 1 And 2
FEZ1	Fasciculation And Elongation Protein Zeta 1
FGAs	First-Generation Antipsychotics
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GO	Gene Ontology
GRAVY	Grand Average Of Hydropathicity
GRB2	Growth Factor Receptor-Bound Protein 2
GRIPAP1	Grip1 Associated Protein 1
GRM3	Glutamate Receptor, Metabotropic 3
GSK3	Glycogen Synthase Kinase 3
GTP	Guanosine Triphosphate
GWAS	Genome-Wide Association Studies
HMM	Hidden Markov Model
IFT20	Intraflagellar Transport 20
Kal7	Kalirin-7
LOMETS	Local Meta-Threading Server, Version 3
MF	Molecular Function
MF	Molecular Function
MTOC	Microtubule Organizing Center
MYD88	Myeloid Differentiation Primary Response Gene 88
MYF6	Myogenic Factor 6 Herculin
MZ	Monozygotic Twins
NDE1	nudE Neurodevelopment Protein 1
NDEL1	NudE Neurodevelopment Protein 1 Like 1
NMA	Normal Mode Analysis
NMDA	N-Methyl-D-Aspartate

NMDAR	N-Methyl-D-Aspartate (NMDA) Receptor
NRG1	Neuregulin 1
P4HA3	Prolyl 4-Hydroxylase, Alpha Polypeptide III
PAFAH1B1	Platelet Activating Factor Acetylhydrolase 1b
PCM1	Pericentriolar material 1
PDB	Protein Data Bank
PDE4B	Phosphodiesterase 4/phosphodiesterase 4B
PET	Positron Emission Tomography
pI	Isoelectric Point
PSD	Postsynaptic Density
PSPC1	Paraspeckle Component 1
REST	Representational State Transfer
RIBC1	Rib43a Domain With Coiled-Coils 1
RMS	Root Mean Square
RNF40	Ring Finger Protein 40, E3 Ubiquitin Protein Ligase
SAXS	Small-Angle X-Ray Scattering
SCZ	Schizophrenia
SGAs	Second-Generation Antipsychotics
SNPs	Single Nucleotide Polymorphisms
SSRIs	Selective Serotonin Reuptake Inhibitors
STX11	Syntaxin 11
TCL1B	T-Cell Leukemia/Lymphoma 1B
TLR3	Toll-Like Receptor 3
TNIK	TRAF2 And NCK Interacting Kinase

Symbols

$\geq$	Greater than or equal to
$<$	Less than
$>$	Greater than
$\leq$	Less than or equal to
$mmol/L$	Millimoles per Liter
mg/dL	Milligrams per Deciliter
g	Gram
α	Alpha
β	Beta
γ	Gamma
θ	Theta
λ	Lambda

Chapter 1

Introduction

1.1 Neurological Disorders a Global Problem

According to the World Health Organization (WHO), neurological disorders encompass a range of conditions affecting the central and peripheral nervous systems. This includes disorders involving the brain, spinal cord, cranial nerves, peripheral nerves, nerve roots, autonomic nervous system, neuromuscular junctions, and muscles [1]. Neurological disorders pose substantial barriers for healthcare systems globally. These disorders have the potential to greatly affect an individual's quality of life, resulting in impairments across physical, emotional, and cognitive domains [2]. The management of neurological disorders typically necessitates specialized care, involving access to medical professionals, diverse diagnostic technologies, and intricate treatment modalities. Regrettably, many real-world situations lack the necessary resources to deliver optimal care to individuals with neurological disorders. Moreover, the intricate nature of these conditions complicates both diagnosis and treatment, potentially resulting in misdiagnosis and delayed care. These factors can worsen symptoms, heighten the burden on patients and caregivers, and impede effective management strategies [3].

To effectively tackle these challenges, a holistic approach is essential. This approach should encompass enhancing access to care, investing in research to enhance diagnostic and treatment capabilities, and raising public awareness about neurological disorders.

By implementing these strategies, we can work towards improving outcomes for individuals affected by neurological conditions [4].

Symptoms of neurological disorders may encompass a range of manifestations, including immobility, muscle feebleness, diminished coordination, sensory loss, abnormal activity of the brain, cognitive misperception, pain, and variations in levels of mindfulness [5]. The etiology of neurological disorders is diverse and may encompass genetic conditions, congenital abnormalities, infections, lifestyle influences, and environmental health factors, including malnutrition, as well as injuries to the brain, spinal cord, or peripheral nerves. Neurological disabilities comprise a broad spectrum of conditions, including neuromuscular disorders, attention deficit disorder (ADD), autism spectrum disorders, learning disabilities and brain tumors. Additionally, certain neurological conditions are congenital, manifesting prior to birth [5].

Neurological disorders encompass a range of conditions, including dementia, mood disorders, and neuropsychiatric conditions like schizophrenia. These disorders present a complex challenge for clinical and preclinical researchers as they seek to unravel their pathophysiology and identify new therapeutic targets. The intricate nature of these conditions necessitates a comprehensive and multidisciplinary approach to advance our understanding and develop effective treatment strategies [6].

1.1.1 Schizophrenia

According to the American Psychiatric Association (APA); 'Schizophrenia is a chronic brain disorder that affects about one percent of the population. When schizophrenia is active, symptoms can include delusions, hallucinations, disorganized speech, cognitive difficulties, and lack of motivation are common symptoms of schizophrenia. However, with appropriate treatment, the severity of these symptoms can be significantly reduced, and the risk of recurrence can be minimized [7].

Secondly, according to National Health Services (NHS) UK; Schizophrenia is a chronic mental health disorder characterized by a diverse range of psychological symptoms. Schizophrenia presents with a variety of symptoms, which may include hallucinations

(perceiving sounds or visuals that do not exist in reality), delusions (strongly held false beliefs not grounded in evidence), and disorganized thinking and speech influenced by hallucinations or delusions [8]. Additional symptoms may involve a diminished interest in daily activities, neglect of personal care and hygiene, social withdrawal from friends and others, and a sense of emotional detachment or disconnection [9].

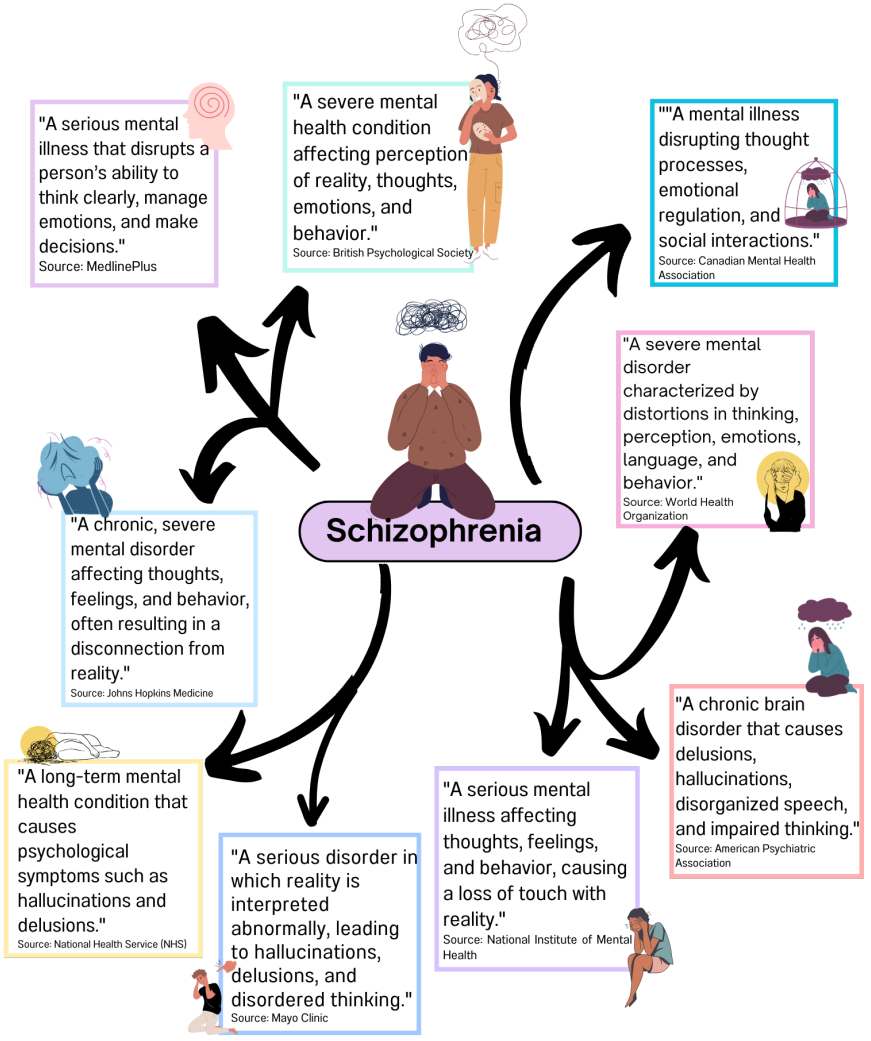


FIGURE 1.1: The figure indicates schizophrenia definition from different literature sources (MedlinePlus, British Psychological Society, Canadian Mental Health Association, World Health Organization, John Hopkins Medicine, National Health Services (NHS), Mayo Clinic, National Institute of Mental Health, American Psychiatric Association) providing diverse understanding of the disease.

Dementia praecox, which translates to early "mental enfeeblement," is an outdated term that was historically used to describe what is now known as schizophrenia. In

1911, Bleuler [8] introduced the term schizophrenia, proposing that its defining feature was the fragmentation of mental functions [10]. Today, the manifestations of schizophrenia are typically categorized into "positive" symptoms and signs, which encompass hallucinations, delusions, and disorganized thought processes, and "negative" symptoms, which include blunted affect, amotivation, poverty of speech, and social withdrawal. This classification framework helps clinicians and researchers better understand and address the diverse symptomatology associated with schizophrenia [11].

1.1.2 Prevalence of Schizophrenia

Schizophrenia affects approximately 1% of the global population and is recognized as one of the top 10 leading causes of disability worldwide [12].

This condition is associated with significant personal and social burdens, impacting the quality of life for those affected and their communities [13]. Individuals diagnosed with schizophrenia face an elevated risk of developing physical comorbidities, such as cardiovascular diseases, diabetes, obesity, and cancer, when compared to the general population. This increased vulnerability is associated with a notable reduction in life expectancy, estimated to be 15 to 20 years shorter than that of individuals without the disorder [14].

Additionally, individuals with schizophrenia frequently experience comorbid mental health conditions, with anxiety disorders being particularly common. Around 65% of individuals with schizophrenia also experience anxiety disorders, underscoring the complexity of their mental health issues and the need for comprehensive treatment approaches [12]. Moreover, patients with schizophrenia also have a significant prevalence of comorbid personality disorders [15].

Substance use disorders are prevalent among individuals with schizophrenia, affecting up to 70% of patients [16]. Patients with schizophrenia often experience low levels of long-term functional recovery, characterized by frequent relapses and the need for both voluntary and involuntary hospitalizations [17]. The disorder typically follows a

recurrent course, necessitating ongoing pharmacological treatment to manage symptoms effectively. This chronic nature of schizophrenia highlights the importance of comprehensive care strategies that include medication, therapy, and support systems to enhance recovery and improve the quality of life for those affected [18].

Schizophrenia is understood as a heterogeneous disorder characterized by a complex etiopathogenesis. The development of schizophrenia is shaped by a complex interaction of genetic, environmental, and psychosocial factors. This complexity underscores the variability in symptoms and treatment responses among individuals with schizophrenia, necessitating a personalized approach to diagnosis and management that considers these diverse contributing elements [19]. The precise prevalence of schizophrenia in Pakistan is currently unknown; however, estimates suggest it falls within the range of 1 to 2%.

Schizophrenia (SCZ) prevalence varies significantly between rural and urban populations across different provinces. In Punjab, it is estimated at 2.5% in urban areas and 2% in rural areas. Sindh reports a prevalence of 2% in urban regions and 1.5% in rural areas. In Khyber Pakhtunkhwa, the urban prevalence is around 2%, while rural areas show a slightly higher rate of 2.5%. Baluchistan has the lowest reported prevalence, with both urban and rural populations estimated at 1% [3].

The psychiatric patients seek assistance from traditional faith healers and religious practitioners who attribute mental illness to supernatural causes like spirit possession or divine testing. This trend is largely attributed to a shortage of mental health professionals and limited awareness about mental disorder [20]. The average age of onset for schizophrenia is usually around 21–25 in males and 25–30 in females [21].

In addition to ventricular enlargement, there are subtle yet significant reductions in brain volume and weight [22]. Imaging studies have highlighted the involvement of the hippocampus, association neocortex, and thalamus in various neurological disorders. Abnormalities have been observed across a diverse range of parameters, such as cortical thickness, cortical gyrification, hippocampal morphology, and cerebral asymmetry. Alterations in these brain regions are linked to cognitive and memory deficits,

emotional dysregulation, and impaired sensory processing, which are often characteristic of disorders such as Alzheimer's disease, schizophrenia, and major depressive disorder. Additionally, advanced neuroimaging techniques have revealed structural connectivity disruptions and changes in white matter integrity, which may contribute to the functional disorganization seen in these conditions. These findings underscore the importance of understanding both regional and network-level brain alterations to better interpret the pathophysiology of neurological disorders and to guide the development of targeted therapeutic interventions. [23].

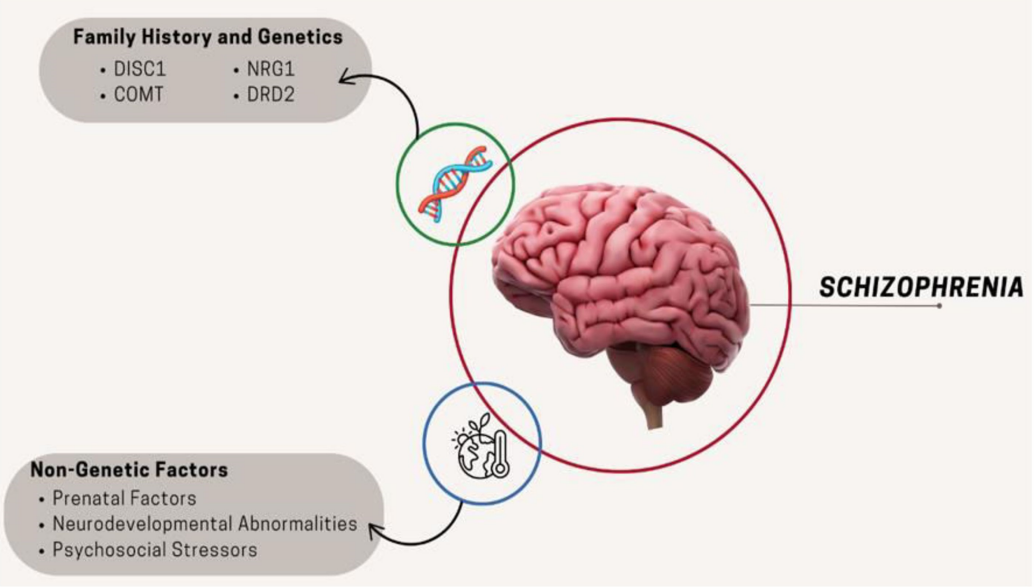


FIGURE 1.2: Schizophrenia Genetic and Non-Genetic risk factors [24], [25].

1.1.3 Etiology of Schizophrenia

1.1.3.1 Environmental Causes

Several environmental factors have been documented in association with schizophrenia, with major causes including obstetric complications, advanced parental age, urban living, and differences in socioeconomic status [26] (figure 1.2) increased susceptibility to schizophrenia has been linked to emergency cesarean sections, bleeding during pregnancy and preeclampsia [27] and low birth weight [28]. Forceps delivery and low birth weight are indicators of a potentially earlier onset of psychosis [29].

An increased paternal age, particularly 34 years and older, is connected to a higher risk of developing schizophrenia [24], have been associated with schizophrenia [30]. Childhood relocation from a rural area to an urban setting doubles the risk of developing schizophrenia [31] with risk increasing longer a child resides in an urban area [32]. Some studies suggest a connection between social inequality at birth and schizophrenia. It has been noted that socioeconomic status is linked to a increased risk of experiencing psychosis [33].

1.1.3.2 Genetic Causes

Schizophrenia is defined by a complex pattern of inheritance that includes the involvement of multiple genes and various biological processes as indicated in figure 1.2 [34]. The development of schizophrenia is strongly influenced by genetic factors. Although genetic factors clearly contribute to the disorder's etiology, the precise connection between multiple genes and the DNA and protein changes associated with schizophrenia remains unclear [35].

A. Pre-Molecular Genetics

In the early 20th century, family studies offered strong evidence that schizophrenia was significantly more common among relatives of those diagnosed with the disorder compared to the general population. These findings highlighted the potential genetic component of schizophrenia, implying that genetic factors could be essential in increasing the likelihood of developing the condition. This research laid the groundwork for further investigations into the genetic and familial aspects of schizophrenia, contributing to our understanding of its complex etiology [25].

Twin studies have verified that the concordance rate for schizophrenia is substantially higher in monozygotic (MZ) twins compared to dizygotic (DZ) twins. These outcomes suggest a strong genetic basis of the disorder, , since monozygotic (MZ) twins share 100% of their genetic material, whereas dizygotic (DZ) twins share approximately 50%, they provide valuable insights into the genetic influences on various traits and disorders.

The elevated concordance rate in MZ twins suggests that genetic factors are fundamental in influencing susceptibility to schizophrenia, although environmental and psychosocial influences also contribute to the disorder's development [25], [36]. Advancements in twin and adoption studies played a vital role in elucidating the familial clustering and concordance rates associated with schizophrenia [37].

Unaffected monozygotic (MZ) twins may harbor silent or non-expressed susceptibility genes for schizophrenia, which could predispose them to the disorder despite not exhibiting symptoms themselves. Conversely, research on discordant dizygotic (DZ) twins has revealed that the children of the DZ twin with schizophrenia are more likely to develop the disorder compared to the children of the unaffected DZ twin [38].

B. Molecular Genetics

The Human Genome Project (1990–2003) played a pivotal role in advancing molecular genetic research on schizophrenia. This global initiative sought to sequence the three billion base pairs of the human genome and identify all corresponding genes. In the early 1980s, during the emergence of molecular genetics, some researchers—though not universally—hypothesized that the availability of DNA data would clarify the biological causes of schizophrenia, as suggested by results from twin and adoption studies. The project's completion paved the way for genome-wide association studies (GWAS), which have since identified numerous genetic loci associated with schizophrenia. These discoveries have provided critical insights into the genetic architecture of the disorder, highlighting the complex interplay of multiple genes that may increase susceptibility [39]. Linkage analysis was the first DNA-based method used in schizophrenia research, aiming to identify genomic regions in samples from affected families, sibling pairs, or extended families, without focusing on specific allelic variants. This method estimated the linkage between schizophrenia and genomic loci by analyzing the co-segregation of genetic markers with specific phenotypic traits, such as a diagnosis within the schizophrenia spectrum [40]. The subsequent phase of molecular genetic research used the "candidate gene" approach, utilizing case-control study designs to investigate whether specific susceptibility genes were associated with the disorder. Unlike linkage analysis, the candidate gene approach can identify genes with alleles

that have minor effects, as long as the sample size is large enough. So far, more than 1,000 candidate genes have been examined (for further details, visit SZGene) (table 1.1) [40].

C. Genome Wide Association Studies Schizophrenia

Large-scale recent genomic studies have uncovered specific DNA variants and highlighted how different risk alleles contribute to the development of schizophrenia [41]. Genome-wide association studies (GWAS) have pinpointed over 200 risk loci with significant associations to schizophrenia (SCZ) [42] [43]. While recent large-scale studies have offered valuable insights into the genetic basis of schizophrenia (SCZ), challenges remain in fully understanding its genetic structure. One notable challenge is that most of the identified risk loci have been found in populations of European ancestry [44]. Given the wide-ranging differences in allele frequencies and patterns of linkage disequilibrium observed across various continental populations [45], performing genome-wide association studies (GWAS) in non-European populations could provide new perspectives and valuable insights into the genetic causes of schizophrenia (SCZ).

D. Single nucleotide polymorphisms (SNPs) Schizophrenia

Single nucleotide polymorphisms (SNPs), which are single base substitutions within the genome, are among the most commonly studied variants [46]. Individually, the identified SNPs have minor effects, and even when considered collectively, these loci, however, explain only a minor segment of the overall genetic susceptibility. The residual genetic risk is likely attributable to additional loci, uncommon genetic variations, along with intricate interactions between genes and between genes and environmental factors [47].

E. Copy number variation (CNV) Schizophrenia

Another type of genetic variation studied in schizophrenia research is copy number variation (CNV), which involves duplications or deletions of DNA sequences. CNVs can influence gene dosage and potentially disrupt normal gene function, this makes them vital for gaining insights into the genetic basis of complex conditions like schizophrenia [46].

It is evident that schizophrenia has strong genetic component. There are multiple candidate genes implicated in schizophrenia pathophysiology but the following candidate gene set is shortlisted from published literature from the last two decades.

TABLE 1.1: Candidate genes implicated in the pathophysiology of schizophrenia.

S.No.	**Gene**	**Location**	**Pathophysiology**	**Ref.**
1	APOE (Apolipo-protein E)	19q13.32 OMIM	Changes in APOE levels in individuals with schizophrenia can impact the development, and and repair of neurons.	[48]
2	BDNF (Brain-derived neurotrophic factor)	11p14.1 OMIM	Impaired Brain-Derived Neurotrophic Factor (BDNF) can affect plasticity, neurotransmission, and cognitive abilities, playing a role in the onset of schizophrenia.	[48]
3	COMT (Catechol-O-methyltra-nsferase)	22q11.21 OMIM	The COMT gene is situated in a specific area of the 22nd chromosome of the human genome, which genetic linkage studies have identified as harboring genes related to schizophrenia.	[49]
4	DAO (D-amino-acid oxidase)	12q24.11 OMIM	The enzyme D-amino acid oxidase (DAO or DAAO) is responsible	[50]

Table 1.1 continued from previous page

S.No.	Gene	Location	Pathophysiology	Ref.
			for metabolizing D-serine a modulator of the NMDA receptor (NMDAR). Elevated DAO activity may reduce D-serine levels, potentially leading to impaired NMDAR functioning in individuals with schizophrenia.	
5	DISC1 (Disrupted in schizo-phrenia 1)	1q42.2 OMIM	The DISC1 gene is affected by a balanced translocation, t(1;11) (q42.1;q14.3), in a prominent Scottish family, which has been associated with the development of schizophrenia.	[51]
6	DRD2 (Dopamine receptor D2)	11q23.2 OMIM	The dopamine hypothesis posits that the dopamine D2 receptor (DRD2) is a primary candidate gene linked to the risk of developing schizophrenia.	[52]
7	DTNBP1 (Dystrobrevin	6p22.3 OMIM	Dysbindin-1 has been associated with neuronal	[53]

Table 1.1 continued from previous page

S.No.	Gene	Location	Pathophysiology	Ref.
	binding protein 1)		development, and lower expression levels of dysbindin-1 mRNA and protein are frequently found in impaired brain regions of individuals with schizophrenia.	
8	NRG1 (Neuregulin 1)	8p12 OMIM	Genetic variations in NRG1 associated with schizophrenia have been connected to changes in the structure and function of the human brain.	[54], [55]
9	SLC6A3 Solute Carrier Family 6 Member 3 (Dopamine transporter)	5p15.33 OMIM	Variations in the SLC6A3 gene, which encodes the Dopamine Transporter (DAT), may affect the transporter's structure and function, potentially playing a role in the development of schizophrenia.	[56]
10	GRM3 (Glutamate receptor, metabo-	7q21.11-q21.12 OMIM	The gene that encodes metabotropic glutamate receptor 3 (GRM3) is regarded	[57]

Table 1.1 continued from previous page

S.No.	Gene	Location	Pathophysiology	Ref.
	tropic 3)		as a potential locus for genetic variants for genetic variants risk of schizophrenia.	

1.1.4 Symptoms of Schizophrenia

Schizophrenia encompasses a range of symptoms, including positive symptoms which include delusions and hallucinations, negative symptoms such as anhedonia, alogia, avolition, and social withdrawal, as well as cognitive symptoms, which encompass challenges in processing speed, visuospatial learning, attention, cognitive flexibility, problem-solving and working memory (table 1.2) [58].

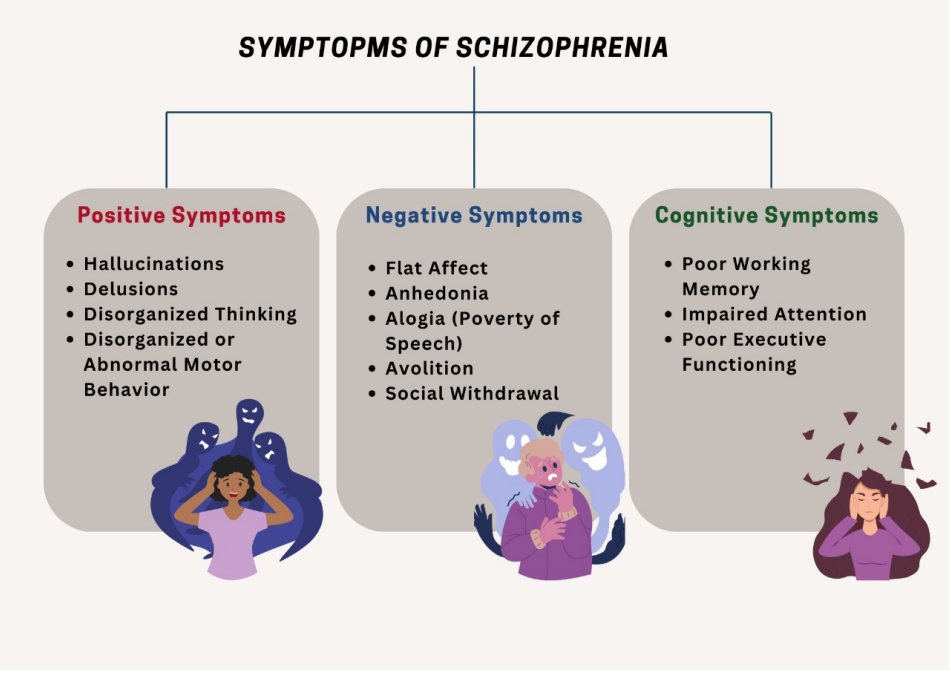


FIGURE 1.3: The figure indicates positive symptoms (delusions, hallucinations and disorganized behavior), negative symptoms (Flat affect, Anhedonia, Alogia, Avolition, Social Withdrawal), Cognitive Symptoms (Poor Working Memory, Impaired Attention, Poor Executive Functioning of schizophrenia such as delusions, hallucinations and disorganized behavior.

TABLE 1.2: Types of schizophrenia symptoms; positive symptoms, negative symptoms and cognitive symptoms.

S.No	Symptom	Description	Ref.
1	Positive	Excess or distortion of normal function manifests as symptoms such as delusions , hallucinations, and disorganized behavior. These symptoms reflect abnormal or exaggerated mental processes and are commonly referred to as positive symptoms.	[59]
2	Negative	Negative symptoms refer to a decrease or lack of typical behaviors associated with motivation and interest.This includes reduced drive (avolition), lack of pleasure (anhedonia),social withdrawal (asociality), and restricted emotional expressions, such as a flat affect or limited speech (alogia). These symptoms reflect a reduced ability to engage in purposeful actions and express emotions.	[60]
3	Cognitive Impairments	Cognitive impairments in schizophrenia are well-documented and include challenges with working memory, attention, processing speed and both visual and verbal learning. People with schizophrenia also tend to experience notable difficulties in reasoning,planning, abstract thinking, and problem-solving,which collectively impact their overall cognitive functioning.	[61]

Positive symptoms are characterized by the presence of exaggerated thoughts, perceptions, or behaviors, while negative symptoms represent the absence or reduction

of normal cognitive and emotional functions. The manifestation of these symptoms is linked to the complex interactions of neurotransmitters, particularly dopamine, within crucial brain regions like the frontal cortex, temporal lobe, and mesostriatal pathways (figure 1.3) [62].

Current medical management of schizophrenia primarily targets the regulation of neurotransmitter production and release. In addition to neurotransmitter imbalances, neuroanatomical changes are observed in the brains of individuals with schizophrenia, including decreased gray matter volume in areas like the prefrontal cortex, medial temporal lobe, and superior temporal lobe [59]. Brain MRI studies indicate structural irregularities in regions believed to impact general functioning in individuals with schizophrenia. These alterations, especially in crucial areas like the prefrontal cortex and temporal lobes, are linked to the cognitive and behavioral deficits that typify the disorder.

1.1.5 Diagnosis of Schizophrenia

A schizophrenia diagnosis requires the presence of at least two clinical symptoms, with one being a positive symptom. Positive symptoms include hallucinations, delusions, disorganized speech, and unusual motor behavior. Negative symptoms are marked by reduced emotional expression, social withdrawal, lack of pleasure, apathy, and a blunted affe [63].

TABLE 1.3: The table indicates the criteria for schizophrenia diagnosis as per Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) [64]

DSM-5	**Criteria**
a.	Presence of at least two of the following symptoms for a minimum duration of one month, with at least one symptom being either (1), (2), or (3): 1. Delusions, 2. Hallucinations, 3. Disorganized speech

Table 1.3 continued from previous page

DSM-5	Criteria
	4. Catatonic behavior, 5. Negative symptoms
b.	There must be a significant and sustained decline in the individual's level of functioning compared to their previously attained baseline.
c.	Continuous signs of the disorder must persist for a minimum of six months, with at least one month involving symptoms that meet criterion a.
d.	Schizoaffective disorder, as well as depressive or bipolar disorders with psychotic features, must be ruled out as potential diagnoses.
e.	The disturbance is not caused by substance use or medical conditions.
f.	If a patient has a history of autism spectrum or communication disorders from childhood , schizophrenia diagnosis can be made in case of prominent delusions/halluciantions and other required symptoms of schizophrenia are present for at least 1 month.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), to diagnose schizophrenia, symptoms must result in a marked decline in social and occupational functioning for at least six months [65].

Additionally, the onset of symptoms typically occurs in late adolescence or early adulthood, often emerging gradually and worsening over time. Cognitive impairments, such as difficulties with attention, memory, and executive function, are also common.

1.1.6 Treatment of Schizophrenia

1.1.6.1 Mechanism of Antipsychotic Action

Dopamine D2 receptor antagonism in the brain represents a fundamental pharmacodynamic characteristic of all antipsychotic medications. This observation has led to the hypothesis that schizophrenia is linked to dysregulation within dopaminergic pathways, characterized by excessive dopaminergic activity in the mesolimbic pathway, contributing to the positive symptoms of psychosis, and diminished dopaminergic signaling in the mesocortical pathway, resulting in negative symptoms [66].

Support for the dopamine hypothesis arises not only from the success of D2 receptor antagonists but also from findings that D2 agonists can influence symptoms such as amphetamine, can may induce psychosis, while dopamine-depleting agents, such as reserpine, are effective in alleviating psychotic symptoms [66].

The antipsychotic effect has been consistently demonstrated when striatal D2 receptor occupancy exceeds 65%; however, further increases in D2 receptor blockade do not correlate with enhanced antipsychotic efficacy. Instead, higher levels of blockade are associated with the emergence of side effects, including extrapyramidal side effects (EPSEs) and hyperprolactinemia. A threshold for the development of EPSEs is observed at approximately 80% D2 receptor occupancy, while hyperprolactinemia arises when D2 blockade surpasses 72%. Blocking dopamine in the striatum is linked to a higher risk of extrapyramidal side effects (EPSEs) [67].

1.1.6.2 Types of Antipsychotics

When treating schizophrenia, both antipsychotic medications and non- pharmacological therapies are commonly employed. These treatments can lead to significant improvements in various outcomes. First-generation antipsychotics (FGAs), like haloperidol, are effective treatments but frequently lead to side effects such as extrapyramidal symptoms and, in some instances, tardive dyskinesia, which can affect patients' ability to adhere to treatment over the long term [68].

Second-generation antipsychotics (SGAs), beginning with clozapine, were introduced with expectations of equal or improved effectiveness, especially for managing negative symptoms, along with a reduced likelihood of extrapyramidal symptoms and tardive dyskinesia. However, SGAs can also lead to significant side effects, such as cardiovascular and endocrine complications, which makes their overall risk-benefit profile more complex than initially suggested (table 1.4) [68].

TABLE 1.4: First-generation antipsychotics and second-generation antipsychotics prescribed in schizophrenia [69].

S.No	**Antipsychotic Name**	**Antipsychotic**	**Prescribed to age group.**
		FGA, SGA	
1	Chlorpromazine	FGA	Adults and children under 12 years.
2	Haloperidol	FGA	Adults
3	Loxapine	FGA	Adults and children ≥12
4	Perphenazine	FGA	Adults and children ≥12
5	Prochlorperazine	FGA	Adults and children >2 and >20 pounds
6	Thiothixene	FGA	Adults and children ≥12 years
7	Thioridazine	FGA	Adults and children
8	Trifluoperazine	FGA	Adults and children
9	Aripiprazole	SGA	Adults and adolescents
10	Asenapine	SGA	Adults
11	Clozapine	SGA	Adults
12	Iloperidone	SGA	Adults
13	Olanzapine	SGA	Adults and adolescents
14	Paliperidone	SGA	Adults
15	Quetiapine	SGA	Adults and adolescents
16	Risperidone	SGA	Adults

1.1.6.3 Augmentation Therapy Schizophrenia

Clozapine is regarded as the most effective antipsychotic for individuals with treatment-resistant schizophrenia, about 40% to 70% of these individuals show only limited or partial improvement, even when adequate serum levels of clozapine are maintained [70–72]. For patients with ultra-resistant schizophrenia, several treatment approaches may be considered, including psychotherapy, [73] pharmacological augmentation, [74] repetitive transcranial magnetic stimulation, [75] or electroconvulsive therapy [76] The augmentation of clozapine with an additional pharmacological agent is commonly practiced in clinical settings, despite a lack of robust evidence indicating that the addition of a second medication will enhance its antipsychotic efficacy [77]. Commonly prescribed augmentation agents include lithium, sodium valproate, benzodiazepines, and several selective serotonin reuptake inhibitors (SSRIs), as well as the antipsychotics risperidone, haloperidol, and aripiprazole [78]. Given that clinicians frequently employ pharmacological augmentation strategies for patients with clozapine-resistant schizophrenia.

1.1.7 Management of Schizophrenia

There are various effective treatment options for individuals with schizophrenia. These include medications, psychoeducation, family-based interventions, cognitive-behavioral therapy, and psychosocial rehabilitation programs like life skills training. Access to facilitated assisted living, supported housing, and supported employment opportunities is also crucial for providing comprehensive care for individuals in this population (figure 1.4) [79].

1.1.7.1 Pathophysiology of Schizophrenia

There are three major hypotheses regarding the development of schizophrenia. The neurochemical abnormality hypothesis proposes that an imbalance in neurotransmitters, including dopamine, serotonin, glutamate, and GABA, plays a critical role in

the manifestation of psychiatric symptoms associated with the disorder (table 1.5).

TABLE 1.5: Hypothesis associated with schizophrenia pathophysiology.

S.No	Hypothesis	Pathophysiology	Ref.
1	Neurochemical abnormality hypothesis	The neurochemical abnormality hypothesis proposes that an imbalance of neurotransmitters — specifically dopamine, serotonin, glutamate, and GABA results in the psychiatric symptoms.	[79]
2	Dysconnection Hypothesis	Dysconnectivity in schizophrenia is marked by a distinct impairment in synaptic plasticity which arises from abnormal modulation of NMDA receptor function by neurotransmitters. such as dopamine, acetylcholine, and serotonin.	[80]
3	Synaptic Hypothesis	The loss of synapses disrupts the function of pyramidal neurons in the cortex, contributing to negative and cognitive symptoms. Additionally, this loss disinhibits projections to mesostriatal regions, resulting in dopamine overactivity and the emergence of psychosis.	[81]
4	Neuro-developmental Hypothesis	The neurodevelopmental model proposes those developmental insults occurring as early second trimester can disrupt normal brain mutation may activate pathological neural circuits during adolescence or young adulthood, leading to the onset of positive or negative symptoms.	[82]

The theory posits that four major dopaminergic pathways contribute to the development and manifestation of schizophrenia. According to this dopamine hypothesis, the positive symptoms of the disorder are attributed to an overactivation of D2 receptors along the mesolimbic pathway.

Meanwhile, reduced dopamine levels in the nigrostriatal pathway are believed to contribute to motor symptoms by affecting the extrapyramidal system. Additionally, decreased dopamine in the mesocortical pathway is thought to be responsible for the negative symptoms associated with schizophrenia [83].

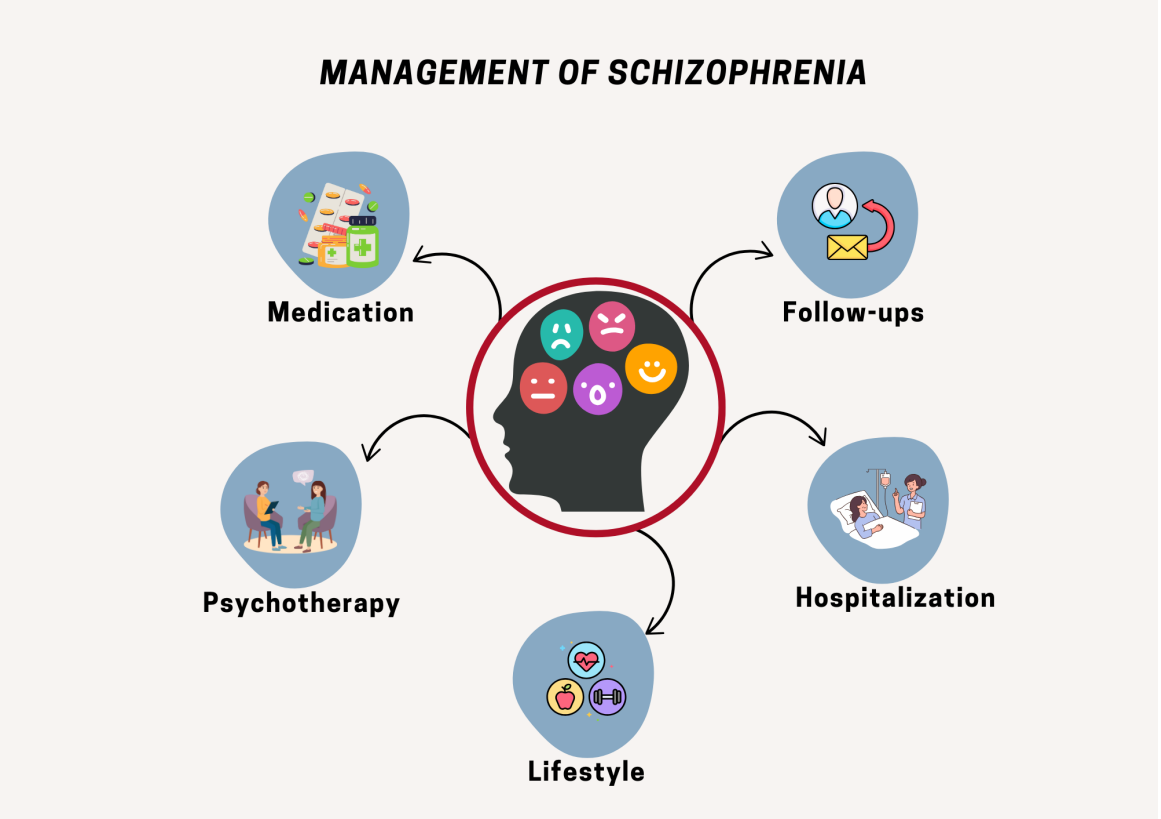


FIGURE 1.4: Management of schizophrenia psychotherapy and cognitive behavioral therapy (CBT) is an effective strategy to manage schizophrenia patients.

Additional symptoms, such as amenorrhea and reduced libido, may result from increased prolactin levels due to reduced availability of dopamine in the tuberoinfundibular pathway, often linked to its blockage. Research indicating that NMDA receptor antagonists can worsen both positive and negative symptoms in schizophrenia suggests a possible role for glutamatergic hypoactivity. Additionally, heightened

serotonergic activity has also been implicated in the development of schizophrenia [84].

Structural abnormalities in the brain, absence of gliosis (suggesting changes during prenatal development), and early motor and cognitive impairments have been linked to the onset of schizophrenia. Alternatively, the disconnect hypothesis highlights neuroanatomical alterations detected in PET and fMRI scans. Schizophrenia is associated with reduced gray matter volume in both the temporal and parietal lobes, as well as notable differences in the frontal lobes and hippocampus, which may underlie the cognitive and memory deficits characteristic of the disorder [85].

Schizophrenia is widely recognized as one of the most devastating mental illnesses, given its early onset and lasting effects, which frequently result in significant emotional and financial hardship for affected individuals and their families [86]. Despite extensive research, schizophrenia remains a diagnosis of exclusion, as none of its clinical features are uniquely definitive. Additionally, biochemical imaging, physiological tests, and psychological assessments typically lack the sensitivity and specificity needed to confirm the diagnosis conclusively [87]. The causes and development of schizophrenia are still not well understood. Recent research suggests that schizophrenia is a complex, multifactorial disorder involving multiple genes, each contributing a relatively small effect to overall susceptibility It has been proposed that a combination of intricate genetic and environmental factors may contribute to the development of the disease [69].

Research in genetics has pinpointed multiple susceptibility loci associated with an increased risk of schizophrenia, but their clinical significance in the pathogenesis of the disorder is still being established . It is stated that mental disorders are difficult to diagnose and treat and due to variety of symptoms and complex pathophysiology it is difficult to manage. As schizophrenia has a strong genetic basis so candidate genes can be targeted and effective treatment strategies can be designed. In this regard we have investigated Disrupted in schizophrenia 1 (DISC1) which is highly cited in literature and being a scaffolding protein and performs neurogenesis may serve as a good candidate to explore for its therapeutic potential. To comprehend a disorder,

it is essential to understand its related pathways and identify various components associated with the disorder. In this regard biological pathway analysis is an effective strategy to unravel the disorder and refine and improve its treatment methods.

When we look at schizophrenia holistically it is a complex disorder which is caused by both environmental and genetic causes. Genetics is a dominant factor in schizophrenia pathophysiology. The candidate gene approach provides a lead to explore and analyze this mental disorder and help in improving its current treatment by finding new therapeutic targets.

In this regard DISC1 gene is investigated as it functions as a major hub protein at the crossroads of neurodevelopment and neuronal signaling, So initially the determination of its three-dimensional structure would assist in understanding its molecular interactions and related pathways. Secondly pathway enrichment would reinforce DISC1 schizophrenia pathway nexus. These findings would pave way for exploring the therapeutic potential of DISC1.

1.2 Problem in Focus

Investigating DISC1 and its three-dimensional structure to unravel related pathways which provides insight into the underlying mechanisms of schizophrenia, helping to uncover new potential targets for treatment.

1.3 Gap Analysis

More than a century after its initial clinical description, schizophrenia continues to puzzle researchers. Its diverse symptoms and intricate causes, involving a combination of genetic and environmental influences, make it challenging to fully understand. Schizophrenia is typically categorized as a long-term condition with a cautiously optimistic prognosis. About one-third of individuals with schizophrenia are considered resistant to treatment [85]. Treatment resistance in schizophrenia may appear from

the initial episode or emerge as the illness progresses [86]. Schizophrenia cases that are unresponsive from the beginning often suggest more severe forms with neurodevelopmental roots. Conversely, when treatment resistance arises later after an initial positive response, it is generally preceded by multiple relapses. These relapses are frequently associated with medication non-adherence or treatment discontinuation [87] additionally, relapses and later-developing treatment resistance may be linked to the presence of other illnesses, including various physical health conditions.

Early differentiation between true treatment resistance and pseudo-resistance is crucial for applying targeted interventions. This approach can help address the underlying factors of pseudo-resistance, ultimately improving patient outcomes. Pseudo-resistant cases may involve misdiagnosed patients, those with compliance issues, individuals who have received insufficient doses or durations of treatment, patients with subtherapeutic plasma levels of antipsychotic medications, as well as those with medical or psychiatric comorbidities. Additionally, side effects from medications can sometimes mask or interfere with the therapeutic response to antipsychotics, can also create the appearance of treatment resistance [88].

Dopamine D2 receptors (D2Rs) are the primary targets of antipsychotic medications. These receptors are essential for mediating the therapeutic effects of antipsychotics, especially in managing symptoms related to conditions such as schizophrenia [89] some antipsychotic medications also block serotonin 2A (5-HT2A) receptors [90]. Unfortunately, many patients do not respond adequately to existing antipsychotic medications, and even when symptoms are well managed, functional outcomes often remain unsatisfactory.

This underscores the persistent challenges in treating schizophrenia and the necessity to develop more effective therapies that can improve symptoms and enhance patients' overall quality of life [91]. Current antipsychotic medications are linked to serious adverse effects, including extrapyramidal symptoms (such as tremors and muscle stiffness), tardive dyskinesia (involuntary movements), sexual dysfunction, weight gain, and a heightened risk of diabetes. These side effects can greatly affect the quality of life for patients being treated for schizophrenia and other psychotic disorders [92].

Proteins are large biopolymeric molecules composed of amino acid monomers, with 20 standard amino acids commonly found in biological systems. They play a variety of essential physiological roles, such as maintaining structural integrity, facilitating biochemical reactions as enzymes, acting as hormones, serving as key cellular components, and regulating programmed cell death. Protein structure is organized into four hierarchical levels: primary, secondary, tertiary, and quaternary [91].

Proteinopathy, also referred to as a protein conformational disorder or protein misfolding disease, comprises a group of disorders characterized by the structural instability of specific proteins, leading to dysfunction at the cellular, tissue, and organ levels. In these conditions, proteins fail to properly fold into their native structure, resulting in pathological effects. Misfolded proteins may either acquire toxic properties or lose their normal biological function, contributing to disease progression [90].

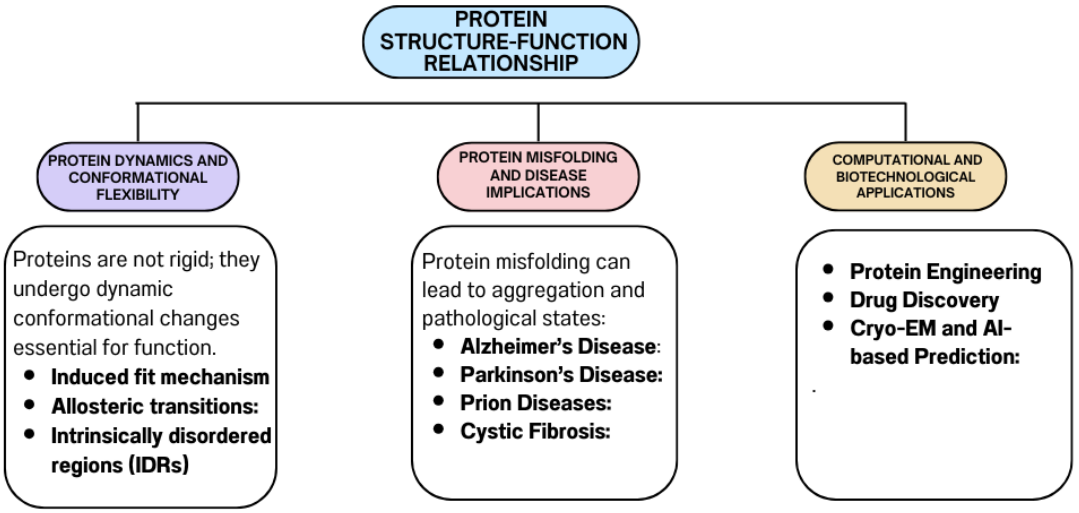


FIGURE 1.5: The figure refers to various paradigms of protein-structure relationships indicating protein dynamics, protein misfolding/disease implications and computational and biotechnological applications.

The precise pathophysiology of schizophrenia remains incompletely elucidated. However, two predominant hypotheses have been proposed: the dopamine hypothesis, which implicates dysregulation of dopaminergic signaling, and the glutamate hypothesis, which suggests abnormalities in glutamatergic neurotransmission as a contributing factor [89].

Schizophrenia is recognized as a neurodevelopmental disorder without a singular cause or clear boundaries, arising from complex gene–environment interactions that contribute to individual vulnerability. Beyond the dopamine and glutamate hypotheses, several additional theories have been proposed to elucidate the pathophysiology of schizophrenia. These findings highlight the multifaceted nature of schizophrenia, emphasizing the interplay between genetic predispositions and environmental factors in its development [88].

The linear sequence of amino acids in a protein, known as its primary structure. Hydrogen bonds between the amino hydrogen and carboxyl oxygen atoms in the protein backbone can lead to specific folding patterns, notably α-helices and β-sheets key components of a protein's secondary structure. Proteins often incorporate multiple α-helices and β-sheets, along with other less common structural motifs. The complete three-dimensional arrangement of these elements within a single polypeptide chain defines the protein's tertiary structure. This tertiary structure is stabilized by various interactions, including hydrogen bonds, salt bridges, and disulfide bonds [87].

When a protein consists of multiple polypeptide chains, referred to as subunits, their specific assembly constitutes the quaternary structure. These subunits interact through similar non-covalent interactions and disulfide bonds as observed in tertiary structures. The quaternary structure is essential for the protein's biological function, as it dictates the spatial arrangement and interaction of the subunits within the functional protein complex [86].

Understanding the native conformations of proteins is crucial, as their biological functions are primarily dictated by their tertiary structures. Experimental techniques such as nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography, and cryogenic electron microscopy (cryo-EM) are commonly employed to determine protein structures with high precision [6].

However, these experimental techniques are often costly and time-intensive, making it challenging to keep up with the rapidly growing database of protein sequences. In contrast, computational protein structure prediction methods, which infer protein

structures directly from amino acid sequences, offer a highly efficient and scalable alternative to experimental approaches [8, 10].

It is important to note that predicting a protein's structure solely from its sequence is feasible, as structural information is inherently encoded within the sequence itself. This concept is supported by Anfinsen's dogma, which states that an unfolded protein will spontaneously refold into its native conformation when placed in an appropriate aqueous environment under suitable conditions [9].

1.4 Protein Structure Prediction Methods

Current protein structure prediction methods can be categorized into two main approaches: template-based modeling (TBM) and free modeling (FM), also known as ab initio modeling. TBM relies on template proteins—proteins with experimentally determined structures—to predict the structure of a target protein. It can be further classified into homology modeling and threading. In contrast, FM does not depend on structural templates and instead predicts protein structures purely from sequence information. The fundamental principles and representative computational tools for these approaches are detailed below [13].

1.4.1 Homology modeling methods

The fundamental principle of homology modeling is that protein structures tend to be more evolutionarily conserved than their sequences. Consequently, homologous proteins—particularly those with close evolutionary relationships—typically share similar structural conformations. This allows for the construction of a target protein's structure by referencing the known structures of its homologs. A commonly employed method for identifying homologous proteins is sequence–sequence alignment, in which two proteins are considered homologous if their sequence similarity exceeds a certain threshold [12].

1.4.2 Deep-Learning Based Methods

Deep learning is driving a transformative revolution in scientific research, enabled by big data, advanced computational resources, and accessible machine learning toolkits. This impact extends to protein structural modeling, where deep learning enhances the prediction of protein structures from amino acid sequences and evolutionary information, facilitates the design of proteins with tailored functions, and aids in predicting protein properties and behaviors. These advancements are crucial for understanding and engineering biological systems at the molecular level [15].

Deep learning is driving a scientific revolution, propelled by big data, advanced computational resources, and user-friendly toolkits, significantly influencing various fields, including protein structural modeling. This domain encompasses predicting protein structures from amino acid sequences and evolutionary data, designing proteins with specific functions, and forecasting protein properties and behaviors. Such advancements are essential for comprehending and engineering biological systems at the molecular level [16].

The emergence of deep learning is renovating scientific research, fueled by the availability of large datasets, powerful computing systems, and accessible software frameworks. One of the basic areas experiencing significant impact is protein structure modeling. This field involves deducing protein shapes from their amino acid sequences and evolutionary patterns, engineering proteins with tailored functions, and anticipating their characteristics and behaviors. These developments are central for recognizing and operating biological systems at the molecular scale [**?**].

1.4.3 Threading methods

Unlike the homology modeling technique, which seeks to find a template with significantly high similarity to the target protein, the threading approaches aim to find a protein with the same structural fold. Thus, the core step of threading approaches is to calculate the compatibility of the target protein sequence with the structures of

templates, this approach depends on sequence–structure alignment rather than the sequence–sequence alignment used in homology modeling, allowing for the identification of structurally similar templates even when sequence similarity is low. [26, 27].

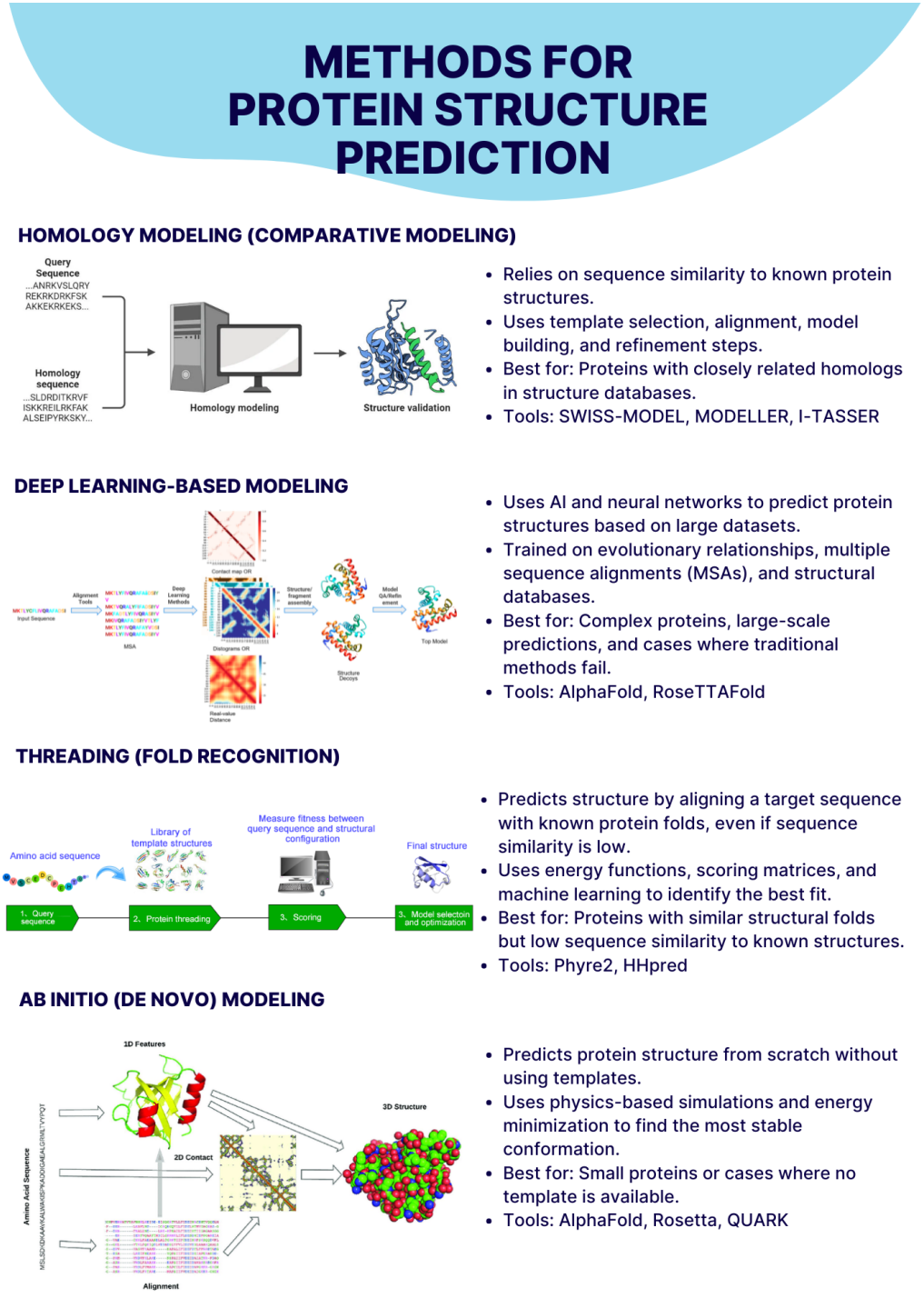


FIGURE 1.6: The figure indicates the various structure prediction approaches; Homology Modeling, Deep Learning Based Modeling, Threading Modeling and Ab Initio Modeling.

1.4.4 Ab initio prediction methods

Most ab initio prediction approaches are based on the fundamental principle that a protein naturally adopts the conformation with the lowest free energy. Consequently, structure prediction is achieved by either minimizing an energy function or directly simulating the protein folding processa [25, 34, 35].

So, schizophrenia as a complex disorder is difficult to diagnose and current treatments have side-effects so in this regard DISC1 as a genetic candidate is targeted and its structure is analyzed and related pathways are investigated to find new therapeutic targets.

1.5 Problem Statement

Analyzing DISC1 structure and associated pathways to elucidate the pathophysiology of schizophrenia and identify new therapeutic targets.

This research will answer the following questions:

1.6 Research Objectives

Objectives of the study are as follows:

1.6.1 Research Objective 1

To establish association between DISC1 and schizophrenia and their genetic variants.

1.6.2 Research Objective 2

Elucidation of three-dimensional structure of DISC1 to understand the structural attributes of DISC1 and how it interacts with its molecular partners.

1.6.3 Research Objective 3

DISC1 pathway enrichment using interactor databases and verifying interactor dataset to analyze associated pathways and explore therapeutic targets regarding schizophrenia.

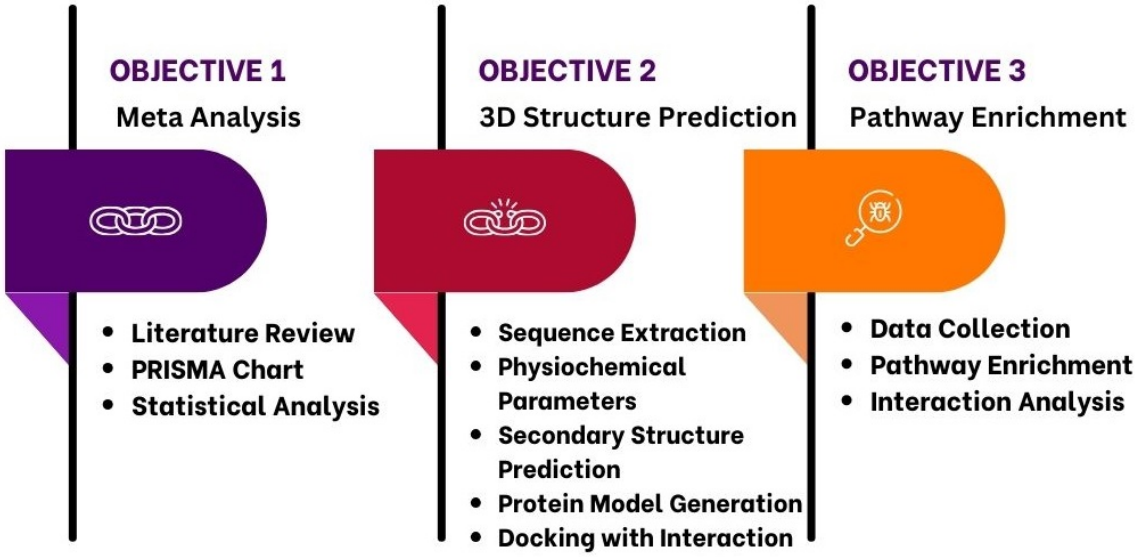


FIGURE 1.7: The figure indicates the research objectives of this study and the steps followed to execute them.

1.7 Significance of Study

Investigating the therapeutic potential of DISC1 which is a scaffolding protein and interacts with multiple molecular interactors to perform neurogenesis its mutation, polymorphism may cause neuropsychiatric symptoms and lead to schizophrenia. Schizophrenia is a disease with strong genetic component so to improve symptom-based schizophrenia treatment it is essential to explore DISC1 and its related pathway which may be insightful to uncover schizophrenia pathophysiology. Recent antipsychotics lack efficacy and have multiple side effects. Secondly the current pharmacological treatment also leads to treatment resistant condition in certain proportion of patients. Understanding these pathways will play a pivotal role in diagnostic and management strategies against schizophrenia.

1.8 Research Questions

Research Question 1

How does the three-dimensional structure prediction of DISC1 C-terminal enable us to explore key DISC1 interaction with its molecular partners?

Research Question 2

What is the significance of DISC1 pathway enrichment and how it can be used to find new therapeutic targets of schizophrenia?

Chapter 2

Literature Review

2.1 Disrupted in Schizophrenia 1 (DISC1)

The etiology of schizophrenia (SCZ) remains incompletely understood, with both environmental and genetic factors believed to contribute significantly to its development [93]. Since the identification of the disrupted in schizophrenia 1 (DISC1) gene; it is reported in a Scottish family with an unusually high incidence of schizophrenia (SCZ) and other psychiatric disorders [94], and is recognized as a potential risk gene for schizophrenia (SCZ) in various genetic and clinical association studies [95]. DISC1 orchestrates the transport of a broad spectrum of neuronal cargos, such as neurotransmitter receptors, mRNAs, vesicles, and mitochondria. It also plays a pivotal role in regulating neuronal morphology and synaptic function, positioning it as a key regulator of intracellular trafficking within neurons [96]. Degradation of the DISC1 has been demonstrated to result in neurodevelopmental abnormalities, indicating that the loss of DISC1 function disrupts mitochondrial dynamics within axons and dendrites [97].

2.1.1 DISC1 Gene Discovery

The disrupted in schizophrenia 1 (DISC1) gene locus was first identified as a risk factor in a large Scottish family. In this family, a balanced translocation between

chromosomes 1 and 11 was observed to co-segregate with schizophrenia, bipolar disorder, and recurrent major depression. This discovery marked an important milestone in understanding the genetic underpinnings of these psychiatric disorders [98].

Previous studies and statistical analysis indicate that inheriting the translocation increases the risk of developing psychiatric conditions by approximately 50-fold compared to the general population. This strong association underscores the significant impact of genetic factors in predisposing individuals to schizophrenia, bipolar disorder, and recurrent major depression [99].

Since 2000, numerous complementary research efforts have highlighted the significance of DISC1 in psychiatric disorders. Later genetic studies have reinforced that the DISC locus is associated with various psychiatric conditions and cognitive functions across diverse populations globally. This continuing research is expanding our knowledge of how DISC1 variations influence the intricate spectrum of psychiatric conditions and cognitive impairments [100].

Efforts to model DISC1 disease biology in transgenic mice, and more recently in Drosophila and zebrafish, have been highly successful. These models have provided valuable insights into the biological mechanisms underlying psychiatric disorders associated with DISC1 dysfunction, enhancing our understanding of how genetic variations in DISC1 may contribute to these conditions [101].

The molecular effects of this translocation are notably complex. Recently, transcripts and abnormal proteins resulting from fusions between DISC1 and a gene on chromosome 11, known as Boymaw or FP1, have been identified. These fusions represent a novel aspect of how the translocation disrupts normal gene function and potentially contributes to the pathogenesis of psychiatric disorders within affected individuals [102].

The gene under study covers more than 200 kilobases and codes for a protein made up of 854 amino acids. This protein is associated with various cytoskeletal functions, including centrosome and microtubule dynamics, which are crucial for processes such as cell movement, neurite outgrowth, membrane receptor trafficking, and potentially

mitochondrial function. These roles underscore its importance in cellular processes critical for neuronal development and function, implicating its disruption in conditions like schizophrenia and other psychiatric disorders [103].

2.2 DISC1 Major Lead for Mental Disorders

Numerous cellular and molecular studies have reported DISC1's role in neurodevelopment and synaptic function [104]. These studies have established a foundation for developing biological hypotheses associated with major mental disorders. Subsequent research utilizing mouse models with DISC1 dysfunction has successfully demonstrated behavioral impairments in cognitive and emotional domains. These findings support the face validity of these models as reliable representations of various human psychiatric disorders [105]. DISC1 remains a pivotal molecular target for understanding the molecular pathology underlying specific aspects of major mental illnesses [106].

Recent findings from cellular biology studies have highlighted DISC1 as a valuable molecular lead, offering new insights not only into understanding pathophysiological processes but also for developing innovative therapeutic approaches. Notably, numerous proteins interacting with DISC1 have been identified as elements of the intracellular trafficking machinery in neurons, a topic that will be further explored in the following sections.

DISC1 seems to act as an adaptor, connecting various neuronal cargoes to their specific motor proteins through interactions with multiple binding partners [107], [108]. This viewpoint places DISC1 as a crucial coordinator of neuronal trafficking, responsible for the accurate spatial and temporal transport of cargoes—an essential process for normal neuronal development and functional stability.

Although the role of DISC1 in neurodevelopment has been thoroughly examined in prior research [107], a number of recent studies also highlight DISC1's role in regulating synaptic function during post-developmental stage [109], [110], [111].

Nevertheless, the precise mechanisms by which DISC1 governs both neurodevelopment and post-developmental synaptic functions are yet to be fully elucidated. In this context, we propose that the DISC1-associated neuronal trafficking machinery may serve as an integrated platform for coordinating both neurodevelopmental processes and neuronal functions. This integrative molecular framework could enhance our understanding of the disease trajectory, offering a unified perspective on its underlying mechanisms [112].

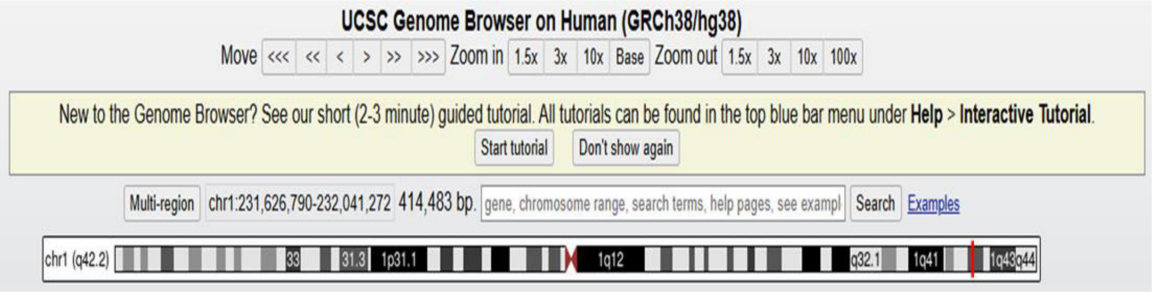


FIGURE 2.1: The figure indicates the genomic location of DISC1 gene on 1 q42.2 according to the UCSC browser

Growing genetic and clinical evidence has highlighted disrupted-in-schizophrenia 1 (DISC1) as one of the most influential risk genes linked to schizophrenia and other major psychiatric disorders. Advances in understanding DISC1's role in neuronal development and cellular signaling have been driven by identifying its binding partners, examining its expression patterns during development, and conducting functional studies on its activity [113].

2.3 DISC1 Protein

The DISC1 protein lacks any known enzymatic activity; instead, it influences multiple proteins by interacting with them to regulate their functional states and biological activities across time and location. Numerous potential interacting proteins have been identified through comprehensive yeast-two-hybrid screening [114], [115] where these molecular interactions have been investigated, a substantial portion has been confirmed through follow-up experimental studies. This validation reinforces the

understanding of how these genetic disruptions involving DISC1 and related genes, contribute to the pathophysiology of psychiatric disorders [116].

2.4 DISC1 Protein Structure

An analysis of the secondary structure of the full-length DISC1 protein, which comprises 854 amino acids in humans, predicts that it consists of two major domains: the N-terminal head domain and the C-terminal tail. In human DISC1, the N-terminal head domain spans approximately amino acids 1–350. Interestingly, this domain shows poor evolutionary conservation overall, with the exception of two highly conserved motifs: one is rich in arginine, while the other is abundant in serine and phenylalanine. These conserved motifs may indicate functional importance within the protein despite the overall lack of conservation across species [117].

The head domain is predicted to be predominantly disordered [118] in contrast, the C-terminal tail domain of human DISC1, covering roughly amino acids 350–854, is notably conserved across species. This region is predicted to have a structured composition, including multiple α-helices interspersed with at least four segments likely forming coiled-coil structures. These structural characteristics indicate that the C-terminal domain may play a key role in maintaining stable interactions and regulating DISC1 functionality within cellular environments [118].

The high-throughput Expression of Soluble Proteins by Random Incremental Truncation (ESPRIT) technique was employed to identify distinct folded regions of human DISC1 by evaluating the solubility of tens of thousands of recombinant DISC1 fragments. This method revealed four novel structured regions, labeled as D (amino acids 257–383), I (amino acids 539–655), S (amino acids 635–738), and C (amino acids 691–836) [119]. Interestingly, region D is located within a segment of DISC1 that was previously believed to be unstructured. Each of these identified regions contains either coiled–coil or α-helical structures, with three involved in DISC1 oligomerization. Notably, a chromosomal translocation occurring after amino acid 597 would impact

or entirely eliminate three of these domains. This translocation is strongly linked to major mental illnesses, underscoring the potential significance of these structured domains in DISC1's function and their possible role in psychiatric disorders [119] .

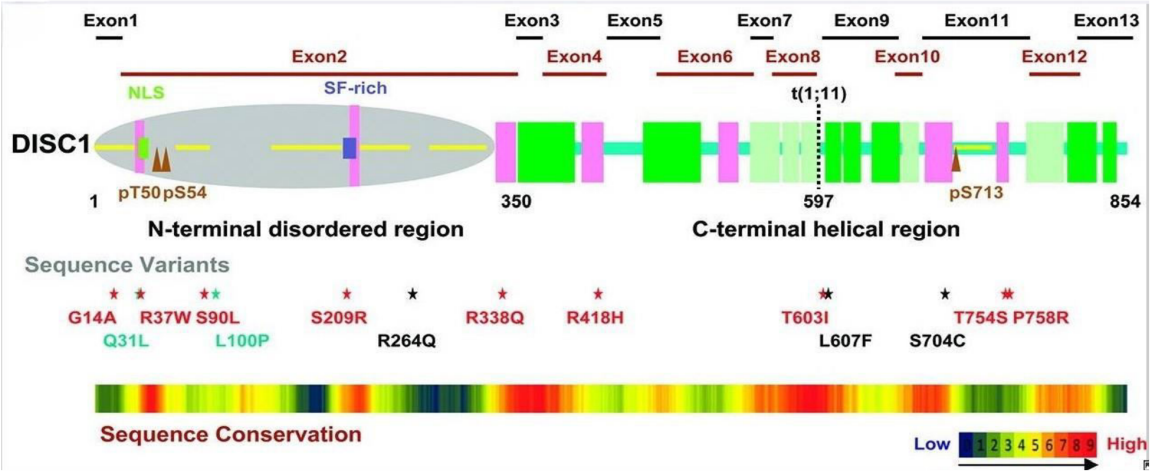


FIGURE 2.2: DISC1 gene, protein (N-terminals and C-terminal), DISC1 translocation breakpoint) [128].

TABLE 2.1: DISC1 protein attributes (Organism, Protein Length, Protein Mass, Subcellar Expression, Tissue Level Expression.

S.No	DISC1 Attributes	Description	Reference
1	Organism	Homo sapiens	[120]
2	Protein Length	854 amino acids	[121]
3	Protein Mass	93,611 (Da)	[121]
4	Subcellular Expression	cytoplasm, cytoskeleton, mitochondria.	[122], [123]
5	Tissue Level Expression	heart muscles, placenta, cerebral cortex, ovary.	[124]

2.5 DISC1 Expression

In various contexts and under different conditions, DISC1, which is known to exist in an oligomeric structure under normal circumstances, exhibits relatively rapid conformational changes. These changes in the protein's structure may be influenced by

interactions with binding partners, post-translational modifications, or environmental cues. Understanding these dynamic conformational changes is crucial for elucidating DISC1's functional roles in neuronal processes and its potential contributions to psychiatric disorders such as schizophrenia. The centrosome [123], cytoskeleton [125], mitochondria [122] ,cytoplasm [126],axon, and synapses [127] have all been found to contain DISC1 protein.

DISC1 expression is highest during central nervous system (CNS) development in both humans and rodents. It plays crucial roles during early brain development, influencing processes like neuronal proliferation, migration, and differentiation as development progresses, DISC1 expression gradually decreases [128], [129]. Recent work has indicated that DISC1 expression may also be observed in various classes of glial cells in both rodent and human tissues [130], [131].

Indeed, DISC1 has been shown to play role in the cellular functions of both oligodendrocytes and astrocytes [132]. DISC1 exhibits high expression levels in the placenta, brain and heart of humans [133], as well as in the testis, kidney, brain and heart of mice [134]. DISC1 expression in the brain is developmentally regulated, with its highest levels observed during the neonatal and infancy stages, followed by a gradual decline with age in the human brain [135].

It is important to recognize that DISC1 expression can be modulated by environmental factors. For instance, during viral infections, the activation of Toll-like receptor 3 (TLR3) induces the downregulation of DISC1 via the myeloid differentiation primary response gene 88 (MYD88) pathway. This downregulation results in reduced dendritic branching and impaired neuronal development [136].

These cytoarchitectural defects, such as abnormalities in dendritic organization, have been observed in individuals with schizophrenia [137], this suggests the critical role of DISC1 in regulating neuronal development during prenatal and neonatal stages. Given the association between impaired neuronal development and an increased risk of schizophrenia, the disorder is classified as a neurodevelopmental disorder [138].

2.6 DISC1 Interactors

DISC1 does not exhibit significant sequence homology to any established functional domains with specific enzymatic activities or recognized motifs. To predict its functional properties, researchers have investigated its binding partners using yeast two-hybrid screens and co-immunoprecipitation assays, as shown in previous studies [104], in these initial studies, a diverse array of DISC1 binding partners was identified, including proteins associated with the cytoskeleton and centrosome, such as nudE-like 1, lissencephaly-1, microtubule-associated protein 1A, β4-spectrin, and Bardet-Biedl Syndrome 4.

Additionally, DISC1 interacts with motor proteins, including kinesin-related protein 5 and dynein/dynactin, as well as adaptor proteins such as fasciculation and elongation protein zeta 1 (FEZ1) and Huntingtin-associated protein 1. Synaptic enzymes like Kalirin-7 have also been identified as DISC1 interactors. The protein exhibits a modular structure, with distinct regions serving as binding domains for specific interaction partners. Further investigations, including yeast two-hybrid screening and pathway analyses, have expanded the mapping of the DISC1 interactome [139].

These studies further implicate DISC1 in intracellular transport processes along the cytoskeletal network, reinforcing the notion that DISC1 contributes to neurodevelopment and synapse maturation by regulating neuronal trafficking mechanisms. Collectively, this evidence supports the idea that DISC1 plays a crucial role in controlling these processes through its involvement in intracellular transport [112].

DISC1 possesses a substantial number of confirmed interactors, along with numerous additional putative binding partners, indicating that it functions as a 'hub' protein within interaction networks [140]. DISC1 is hypothesized to function as a molecular scaffold, organizing multiple proteins into functional complexes. Detailed studies of specific interactions have identified several contact sites distributed along the length of DISC1. For example, the interaction between DISC1 and the PDE4 family of cAMP phosphodiesterases has been analyzed using peptide array mapping, providing insights into the structural basis of their association [141].

Although DISC1 may bind a single interactor at any given time at its multi-protein binding sites, it is also conceivable that multimerization allows for the simultaneous binding of multiple partners that share sequences on DISC1. Structural data currently indicate that the tail domain plays a role in self-association, while the head domain remains mostly unbound, potentially enabling interaction with up to eight proteins at the same binding sites within an octameric configuration.

This scenario is further complicated by evidence suggesting that certain binding partners may interact exclusively with specific forms of DISC1 multimers. This appears to be the case for NDEL1, which interacts with a binding site located within the DISC1 tail domain [142]additionally, NDEL1 has been reported to preferentially bind DISC1 octamers and oligomers rather than dimers or higher-order multimers formed from recombinant fragments [143], [144].

However, another study using full-length DISC1 reported that NDEL1 binding is not dependent on the specific type of DISC1 oligomer formed [145].

TABLE 2.2: The table indicates major DISC1 interactors and their functions.

S.No	DISC1 Interactor	Function	Ref.
1	Glycogen synthase kinase 3 (GSK3)	DISC1 directly interacts with GSK3, a pivotal component of the Wnt signaling pathway , acting as a significant enhancer of the canonical Wnt pathway.	[146]
2	Kalirin-7 (Kal7)	DISC1's interaction with Kal-7 regulates the activation of N-methyl type glutamate receptors.	[147]
3	Dopamine	Evidence suggests that DISC1 has a direct effect on	[148]

Table 2.2 continued from previous page

S.No	DISC1 Interactor	Function	Ref.
		dopamine release in the nucleus accumbens and on presynaptic and postsynaptic transmission.	
4	Dynein	DISC1 regulates the dynein protein complex at the centrosome, thereby modulating microtubule dynamics. This involvement suggests that DISC1 plays a role in microtubule transport, neuronal migration, neurite outgrowth, and axon development.	[149]
5	NudE Neurodevelopment Protein 1 Like 1 (NDEL1)	The NDEL1-DISC1 complex is hypothesized to play a role in neuronal migration and is linked to the pathophysiology of schizophrenia.	[150]
6	Fasciculation and elongation protein zeta-1 (FEZ1)	Fasciculation and Elongation Protein Zeta-1 (FEZ1) interacts with DISC1 to cooperatively regulate the dendritic growth of newly generated	[151]

Table 2.2 continued from previous page

S.No	DISC1 Interactor	Function	Ref.
		neurons in the adult mouse hippocampus.	
7	Phosphodiesterase 4/phosphodiesterase 4B (PDE4B)	PDE4B hydrolyzes Camp and DISC1 may influence cAMP signaling by modulating PDE4B activity.	[152]
8	Growth factor receptor-bound protein 2 (GRB2)	DISC1 is essential for neurotrophin-3 (NT-3)-induced axon elongation and ERK activation at the distal ends of axons, achieved by recruiting Grb2 to the axonal tips.	[153]
9	TNF receptor-associated factor 2 and NCK-interacting kinase (TRAF2)	Traf2 and Nck-interacting kinase (TNIK), an emerging disease risk factor, has been identified as a key synaptic partner of DISC1. Evidence suggests that the DISC1-TNIK interaction regulates synaptic composition and function by stabilizing the levels of critical postsynaptic density proteins.	[107]
10	Pericentriolar	PCM1 forms a complex	[154]

Table 2.2 continued from previous page

S.No	DISC1 Interactor	Function	Ref.
	material 1 (PCM1)	with DISC1 and BBS4 through distinct binding domains in each protein. Both DISC1 and BBS4 are necessary for the synergistic targeting of PCM1 and other cargo proteins, such as ninein, to the centrosome.	

In addition to its regulated multimerization, DISC1 has a propensity to aggregate, particularly under conditions of overexpression. In such cases, a substantial fraction of DISC1 becomes detergent-insoluble [154], [155]. This finding may have psychiatric relevance, as detergent-insoluble DISC1 has been identified in human brain tissue, with increased levels observed in postmortem samples from individuals diagnosed with schizophrenia or mood disorders [156].

Additionally, evidence suggests that dopamine plays a regulatory role in DISC1 aggregation and insolubility [157], at least in cell culture. Aggregated DISC1 fails to interact with NDEL1, suggesting that this potentially pathological process may impair DISC1 function by causing mislocalization and disrupting essential protein–protein interactions [158].

2.7 DISC1 Function

Emerging evidence supports the notion that DISC1 functions as a key regulator for numerous developmental processes in the nervous system. These processes include neuronal proliferation, migration, differentiation, and synaptic integration. By influencing these critical aspects of neural development, DISC1 plays a pivotal role in

ensuring proper brain formation and function, and disruptions in its activity are linked to the development of psychiatric disorders such as schizophrenia [159].

DISC1 has been implicated in multiple stages of neuronal development, including neuronal maturation, migration, morphogenesis, and synaptic integration [160]. According to the literature, depletion of endogenous DISC1 or the expression of mutant DISC1 (mutDISC1) disrupts neurite outgrowth and impairs normal cerebral cortex development [161].

2.7.1 DISC1, Microtubules Centrosome

The interactions of DISC1 with microtubule-associated proteins have been studied using biochemical methods. Immunofluorescent cell staining and biochemical analyses have demonstrated that DISC1 localizes to the centrosome, the primary microtubule-organizing center, and directly associates with microtubules [162].

2.7.2 Neuronal Proliferation, Migration, Differentiation

GSK3β preferentially interacts with DISC1 when it is non-phosphorylated at the S710 site, whereas BBS1 and BBS4 exhibit a stronger affinity for DISC1 when it is phosphorylated at S710. During embryonic development (E13–15), the phosphorylation of DISC1 at S710 increases, promoting its recruitment away from GSK3β-regulated WNT–β-catenin signaling through DISC1–BBS binding. This regulatory mechanism plays a crucial role in facilitating the transition from neuronal progenitor proliferation to neuronal migration [163].

2.7.3 DISC1, Spines and Synapses

Deficits in dendritic spines and glutamatergic neurotransmission are common across several mental illnesses with genetic associations to DISC1 [164]. Dendritic spines comprise the postsynaptic compartment of the majority of excitatory synapses in

the brain, and their morphology is intricately connected to neuronal activation and synaptic plasticity [165], [166]. Recent reports strongly support the localization and function of DISC1 at the postsynaptic density (PSD) and suggest its involvement in the development and maintenance of synapses.

2.7.4 Components at the Excitatory and Inhibitory Postsynapses

Emerging evidence suggests an additional mechanism by which neurons regulate neurotransmission through DISC1-dependent local trafficking at both excitatory and inhibitory postsynapses. In the resting state of excitatory postsynapses, DISC1 forms a complex with postsynaptic density proteins, contributing to synaptic stability and function [167]. DISC1 sequesters the guanine exchange factor Kalirin-7 at excitatory postsynapses, restricting its interaction with Rac1 guanosine triphosphatase (GTPase) [168].

2.7.5 Microtubule Based Transport

Among the described interactors of DISC1, proteins involved in microtubule-based transport are highly represented. These interactions underscore DISC1's role in facilitating the transport of cellular components along microtubules, which is crucial for processes such as intracellular trafficking, neuronal migration, and synaptic function [169].

2.7.6 Mitochondrial Transport

The Disrupted in Schizophrenia 1 (DISC1) protein itself adopts a partially mitochondrial localization. This localization suggests that DISC1 may have roles in mitochondrial function and dynamics, potentially influencing cellular energy metabolism, apoptosis, and other processes critical for neuronal health and function [170]. DISC1 is a

positive regulator of mitochondrial transport [171], [172] and schizophrenia-associated DISC1 mutations impair mitochondrial transport, function, and fusion [172], [173].

2.7.7 Neuronal Trafficking

Subsequent studies have broadened our understanding of the role of DISC1 in neuronal trafficking. DISC1-containing trafficking machinery is reported to transport a variety of cargoes, including organelles, mRNA, and neurotransmitter receptors. In each case, DISC1 functions as an adaptor protein that connects cargo to specific motor complexes by recruiting additional adaptor proteins. This adaptor role is essential for the efficient transport and precise localization of critical cellular components, thereby facilitating various neuronal functions and processes [174].

2.7.8 DISC1 Synaptic Plasticity

The synaptic location of DISC1 [175], together with recent evidence supporting its role in cortical synaptic plasticity, DISC1 appears to influence neural plasticity. Disruptions in this process may contribute to the development of psychiatric symptoms [176], [177]. DISC1 is known to interact with various signaling pathways involved in neuronal growth and synapse formation, suggesting its influence on synaptic stability and function. Aberrant DISC1 expression or function can interfere with these pathways, causing impaired communication between neurons. This disruption in synaptic plasticity is thought to contribute to the cognitive deficits, mood disturbances, and other psychiatric symptoms observed in disorders like schizophrenia [176], [177].

2.7.9 DISC1 as a Neuronal Cargo Adaptor

Subsequent studies have further elucidated the role of DISC1 in neuronal trafficking. Notably, the cargo transported by DISC1-associated trafficking machinery now includes organelles, mRNA, and neurotransmitter receptors. In each case, DISC1 functions as an adaptor protein, facilitating the connection between specific cargo and

designated motor complexes through the recruitment of additional adaptor proteins [178]. It is becoming increasingly evident that DISC1 regulates both short-distance trafficking (within the soma) and long-distance trafficking (between the soma and axons or dendrites), depending on the subcellular localization and specific functional requirements of each cargo. The following section will outline the key components and regulatory mechanisms involved in DISC1-mediated trafficking of various cargoes [178].

2.7.10 DISC1 Synaptic Pruning

Synaptic pruning is a fundamental neurodevelopmental process that refines neural circuits by eliminating redundant synapses while strengthening functionally relevant ones [179]. DISC1 has been shown to play a critical role in synaptic pruning, and its dysfunction may lead to abnormal spine morphology [180]. Overpruning of cortical synapses during critical neurodevelopmental periods has been suggested as a potential underlying factor in schizophrenia. Numerous studies examining postmortem brain samples from individuals with schizophrenia have reported a reduction in spine density on cortical and hippocampal pyramidal neurons [181]. This loss of dendritic spines may impair neural connectivity and disrupt signaling pathways essential for cognitive functions, contributing to the characteristic symptoms of schizophrenia. Furthermore, genetic variants associated with DISC1 and other related genes have been implicated in abnormal pruning processes, reinforcing the role of neurodevelopmental dysregulation in the pathogenesis of psychiatric disorders.

2.7.11 DISC1 Signal Transduction

Functional variations in DISC1 and/or PDE4 can influence their interaction and subsequently alter mitochondrial cAMP catabolism, leading to physiological and psychiatric consequences. A potential unifying link between schizophrenia and bipolar affective disorder—along with the interplay between DISC1 and PDE4—may exist at both the cognitive level, affecting learning and memory, and the molecular level, through

dysregulation of cAMP signaling. This connection suggests that disruptions in these pathways could contribute to the cognitive deficits and other symptoms observed in these psychiatric disorders. [154] .

2.7.12 Dopamine D2 Receptor

Additionally, DISC1 has been shown to interact with the dopamine D2 receptor (D2R), a key target of most currently available antipsychotic medications. This interaction suggests a potential causal role in the manifestation of psychiatric disorders and provides a promising pathway for the development of novel therapeutic strategies to treat these conditions [182].

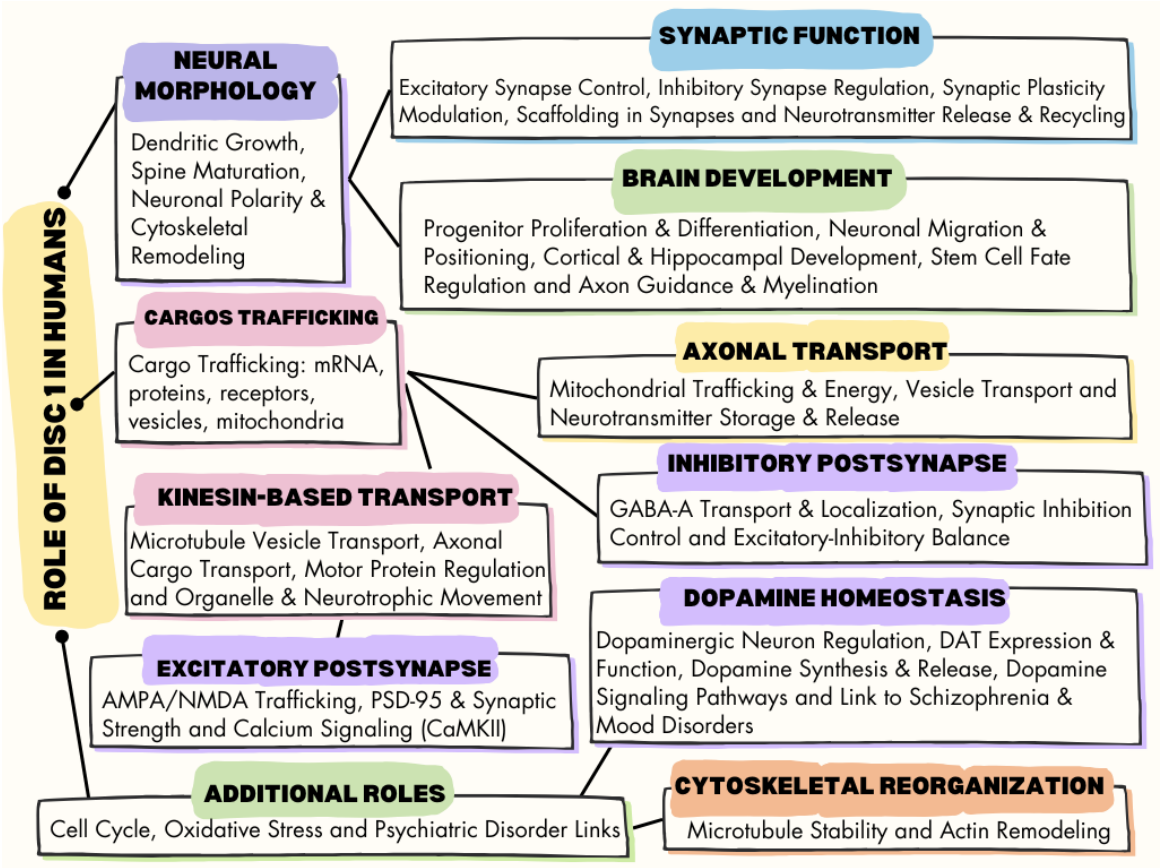


FIGURE 2.3: The figure indicates the various roles of DISC1 protein in humans.

DISC1 is positioned at the intersection of several neurodevelopmental pathways, potentially influencing the pathology of major mental illnesses. It acts as a scaffold,

binding numerous other proteins, some of which have been identified as independent risk factors for major mental illnesses [183].

2.8 DISC1 Polymorphisms

The DISC1 gene is associated with brain structure and cognitive function. More recent studies have confirmed that the DISC1 gene is one of the most closely linked genes to schizophrenia [184], [185] additionally, three primary risk alleles in the DISC1 gene have been identified: rs1538979 (T), rs821577 (G), and rs821633 (C), which are closely associated with an increased risk of developing schizophrenia [186], [187].

One of the most extensively studied DISC1 single-nucleotide polymorphisms (SNPs) is rs821616, which is a non-synonymous mutation that results in the translation of either serine (Ser) (A allele) or cysteine (Cys) (T allele) at codon 704 in exon 11 [188]. Notably, this polymorphism constitutes a variation not only at the genetic sequence level but also at the protein sequence level of DISC1.

At the molecular level, overexpression of the serine variant at codon 704 via viral transduction has been shown to significantly enhance the phosphorylation of Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2), increasing their biological activity [189], [190]. ERK1/2, in turn, regulates the phosphorylation state of tyrosine hydroxylase, the rate-limiting enzyme in dopamine biosynthesis, thereby enhancing its activity and leading to an increase in dopamine synthesis by up to two-fold [191], [192].

Social anhedonia, a symptom characterized by diminished pleasure in social interactions, has been reported to often precede the onset of core psychotic symptoms in schizophrenia [193] [194] is more evident in carriers of the risk allele for rs821633 compared to carriers of the risk alleles for rs1538979 and rs821577.

Several previous studies have investigated DISC1 gene polymorphisms among individuals with schizophrenia in China[195], [196] however, none of these studies have explored the relationship between DISC1 gene polymorphisms and the age of onset of schizophrenia.

Previous studies have indicated an association between Disrupted in Schizophrenia 1 (DISC1) polymorphisms, specifically rs821616 and rs821597, and schizophrenia (SCZ) risk in overall populations. In particular, these DISC1 polymorphisms have been associated with increased susceptibility to schizophrenia in the Chinese population when analyzed in subgroup analyses based on ethnicity. This highlights the potential relevance of these genetic variants in specific ethnic groups and their contribution to schizophrenia susceptibility [197]. In the Iranian population, robust associations have been observed between schizophrenia and specific genetic markers. These include the T allele (Phe607) SNP rs6675281, as well as markers rs2255340 and rs2738864, all of which show significant allelic associations with schizophrenia. These findings suggest a potential genetic predisposition involving these markers in individuals of Iranian descent who develop schizophrenia [198].

The literature indicates DISC1 markers for schizophrenia in Caucasian and East-Asian populations in Malaysia, focuses on the role of rs2509382 located at 11q14.3, a region involved in the mutual translocation associated with DISC1 (t(1;11) (p42.1;q14.3)). The findings support the idea that the DISC1 gene serves as a susceptibility marker for schizophrenia. Specifically, rs2509382 in the mutual translocation region of DISC1 is identified as a susceptibility marker for schizophrenia among males in Malaysia [199]. A key objective of genetics and genomics research in psychiatric disorders is to identify dysregulated biological pathways and uncover potential targets for pharmacological interventions. The genetic starting point does not necessarily have to explain a significant portion of schizophrenia liability itself; rather, it is sufficient if genetic disruption can lead to the development of schizophrenia [99].

2.9 DISC1 Pathways

2.9.1 DISC1 Neuronal Morphology Migration

The microtubule organizing center (MTOC), or centrosome, plays a crucial role in orchestrating the highly complex and intricate regulation of the neuronal microtubule

network, which is essential for proper development, morphology, and migration of neurons [200]. Numerous lines of evidence indicate that DISC1 is a component of a protein complex located at the centrosome and references therein) and plays a critical role in cytoskeletal processes related to neuronal migration, such as nucleokinesis and neurite outgrowth. LIS1, NDE1, and NDEL1 represent a trio of centrosomal proteins that interact with DISC1 [201], [202].

2.9.2 DISC1 Cell Cycle, Transport, Nucleokinesis

DISC1 plays pivotal roles in regulating cell cycle progression, facilitating dynein-mediated transport along microtubules, and coordinating nucleokinesis [203], [204]. The axonal localization of NDEL1 and LIS1 is known to depend on the expression of DISC1 [205].

2.9.3 DISC1 in Cerebral Cortex Development

Disrupted in Schizophrenia 1 (DISC1) plays a critical role in regulating cell proliferation in the developing cerebral cortex through the canonical Wnt signaling pathway [206]. DISC1 suppresses glycogen synthase kinase 3 beta (GSK3β) activity through direct protein interaction, leading to the stabilization of β-catenin, which is essential for appropriate progenitor proliferation via the Wnt signaling pathway. Subsequent studies have identified DIX domain-containing 1 (DIXDC1), a homolog of the Wnt signaling regulators Disheveled and Axin, as an interacting partner of DISC1. Together, DISC1 and DIXDC1 co-regulate GSK3β/β-catenin signaling to ensure proper cell proliferation [207], [208].

2.9.4 DISC1 and Glutamate Signaling for Synaptic Function

Early reports indicated that DISC1 plays a role in neurite outgrowth [209]. Subsequent findings highlight roles for DISC1 in regulating dendritic spines at the glutamate

synapse [210]. Rac1 is activated by Kalirin-7, leading to increased spine size following NMDA glutamate receptor activation. However, DISC1 interacts with Kalirin-7, preventing it from accessing and activating Rac1 until NMDA receptor activation triggers the release of Kal-7 and subsequent spine enlargement. Pharmacological tools that modulate the Kalirin-7/DISC1 interaction could potentially regulate spine maintenance [211].

2.9.5 DISC1 and NMDA-R

Some of the DISC1-related signaling pathways, including the GABA-R and NMDA-R pathways, enable DISC1 to regulate the timing of various neural developmental stages and guide new neurons to their correct positions in the dentate gyrus [212]. N-methyl-D-aspartate receptor (NMDAR) function is regulated at multiple levels, including subunit expression, composition, and dynamic modulation of its surface and synaptic localization. This regulation occurs through various mechanisms, such as controlling NMDAR forward trafficking to the plasma membrane, facilitating its insertion into synapses, and mediating its internalization via endocytosis [213].

The essential GluN1 subunit is a component of all NMDARs, typically assembling with additional subunits such as GluN2A and GluN2B. GluN1 is produced in excess and retained within the endoplasmic reticulum (ER), where NMDARs undergo assembly before being transported to the Golgi apparatus and subsequently to the cell surface. Each step of NMDAR forward trafficking is precisely regulated to maintain the appropriate receptor density at the cell surface and synapse. Disruptions in the genetic regulation of this trafficking process can impair NMDAR function, potentially leading to alterations in synaptic strength and plasticity [213]. DISC1 is essential for various processes in both the developing and adult brain [214], and has been linked to NMDAR function by regulating downstream processes that are fundamental to synaptic plasticity [215]. DISC1 also regulates microtubule-based cargo transport in neurons, facilitating the trafficking of mitochondria, synaptic vesicles, and messenger RNAs [216], and interacts with the motor protein adaptors TRAK1 and TRAK2 [217].

2.9.6 DISC1 and GABA

Among external regulatory factors, the neurotransmitter gamma-aminobutyric acid (GABA) plays a crucial role in modulating the proliferation of neural progenitor cells and facilitating the development of new neurons in the adult brain [218]. As the primary inhibitory neurotransmitter in the central nervous system, gamma-aminobutyric acid (GABA) induces hyperpolarization in mature neurons. This effect is achieved by maintaining low intracellular chloride concentrations, which is facilitated by the high expression of the neuronal potassium-chloride cotransporter (KCC2), a key chloride exporter [219].

2.9.7 DISC1 and AKT Signaling in Adult Hippocampal Neurogenesis

AKT, a serine/threonine-specific protein kinase, plays a pivotal role in neuronal function by phosphorylating a wide array of substrates upon activation. This phosphorylation cascade regulates numerous critical cellular and neurodevelopmental processes, including glucose metabolism, apoptosis, cell proliferation, gene transcription, cell migration, morphogenesis, dendritic development, synapse formation, and synaptic plasticity [220], [221]. AKT signaling is integral to the PI3K-AKT-mTOR pathway, a critical pathway for cellular survival and growth, which has been linked to neuroprotection and cognitive function. Dysregulation of AKT activity has been implicated in various neurological disorders, including schizophrenia and Alzheimer's disease, as it may affect synaptic stability and neuronal resilience. This underscores AKT's essential role in maintaining neural network integrity and adaptability in the brain.

2.10 DISC1 Pathway Analysis and Therapeutics

DISC1 serves as a hub protein with numerous binding partners. Therefore, it is essential to enhance scientific understanding of the specificity between DISC1 and

each of its protein partners, including details about the specific binding domains of DISC1 for each protein. Additionally, it is important to highlight how the DISC1 protein network intersects with and interacts within the biological pathways identified by extensive genetic studies [222].

Intervening with targeted biological pathways and precise protein interactions presents an opportunity for drug discovery. However, the validation of this specificity will be the paramount challenge that must be overcome to prevent unforeseen and potentially disastrous side effects. These different models will serve as invaluable templates for validating the exact specificity and potential side effects that may arise from interventions through DISC1 and its myriad protein interactors.

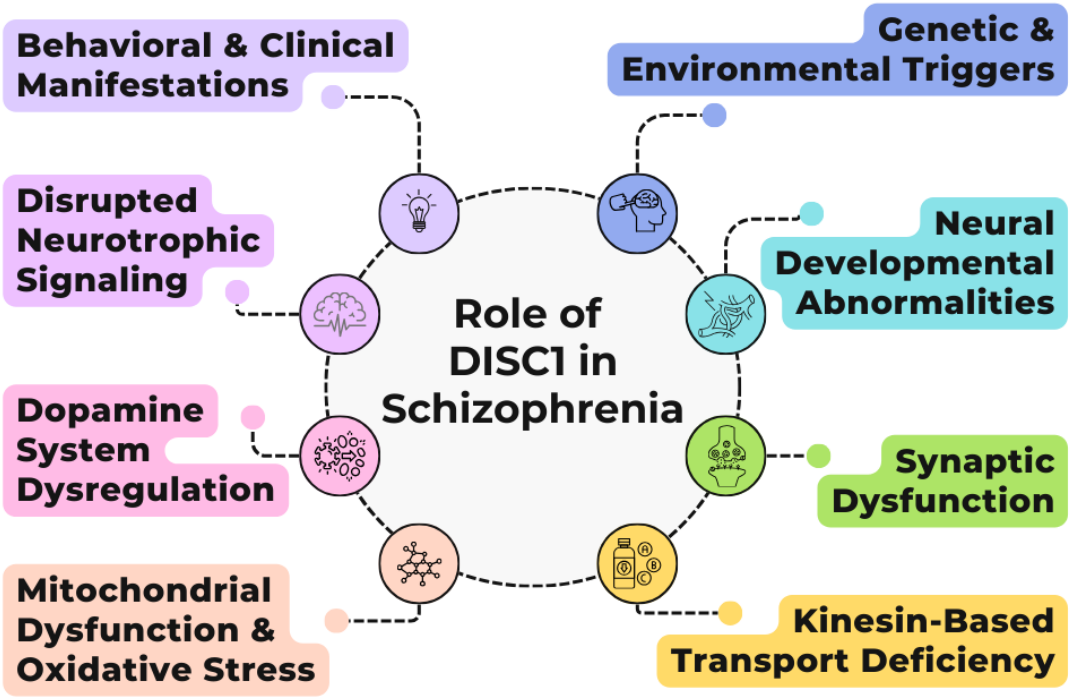


FIGURE 2.4: The figure DISC1 protein and how various processes, mechanisms and pathways may lead to schizophrenia.

Chapter 3

Research Methodology

3.1 DISC1 Schizophrenia Meta Analysis

3.1.1 What is Meta-analysis?

Meta-analysis is a quantitative method used to systematically combine and analyze research findings. Since its introduction in the 1970s, along with modern techniques for research synthesis, it has significantly impacted various scientific disciplines. This approach has played a crucial role in establishing evidence-based practices and reconciling conflicting research results [223].

3.1.2 Significance of Meta-analysis

A meta-analysis is a rigorous analysis form serves as a powerful research tool due to its unique characteristics. However, conducting and interpreting a meta-analysis can be complex.

This approach addresses the limitations of small sample sizes and rare outcomes by combining data from multiple studies to produce a more precise overall estimate. Additionally, it enhances statistical power and facilitates the assessment of inconsistencies across different study results [224].

3.1.3 Steps of DISC1 Schizophrenia Meta-analysis

3.1.3.1 Literature Search

In this study we searched the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) from January 2015 until January 2025, using the keywords "schizophrenia", "DISC1", and "association". It provided a total of n=389 studies. Table 3.1 indicates the year-wise studies of DISC1 schizophrenia.

TABLE 3.1: The table indicates DISC1 schizophrenia association meta-analysis studies between 2015 to 2025.

Year	DISC1 Studies
2025	3
2024	16
2023	16
2022	28
2021	25
2020	33
2019	41
2018	51
2017	43
2016	63
2015	70
Total Studies	389

3.1.3.2 Inclusion and Exclusion Criteria

The meta-analysis included studies that met the following criteria:

1. Examined the relationship between DISC1 single nucleotide polymorphisms (SNPs) and schizophrenia in human subjects.

2. Included a healthy control group for comparison.
3. Provided sufficient data to calculate odds ratios (ORs), 95% confidence intervals (CIs), and p-values.
4. Diagnosed schizophrenia based on either the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5.

3.1.3.3 Data Extraction

In the DISC1 meta-analysis the studies were filtered, and a total of n=6 studies were extracted. The dataset includes the following parameters:

1. First Author & Year: Identifies the study.
2. Published Year: Year of publication.
3. Country: Location of study.
4. Case & Control: Number of cases and controls in the study.
5. Odd Ratio (OR) & P-Value: Effect size and statistical significance.
6. DISC1 SNPs: Specific genetic markers analyzed.
7. Association with Schizophrenia: Whether the study found an association.

3.1.3.4 Statistical Analysis

The DISC1 schizophrenia association was analyzed by analyzing log-ORs and 95% Cis [225]. Heterogeneity between individual studies was assessed by python server Matplotlib (https://matplotlib.org/)the X^2-based Q test and I2 statistic to ensure that each study was suitable for inclusion in the meta-analysis [226]. Pooled effect sizes across studies were calculated using the random effects model if the p value for heterogeneity was <0.05. Publication bias was computed by a funnel plot [227].

Meta-analysis Odd Ratio (OR)

The Odds Ratio (OR) is a statistical measure used to determine the association between exposure (e.g., genetic mutation) and an outcome (e.g., schizophrenia). It is calculated from a 2x2 contingency table of cases and controls. To calculate OR Microsoft Excel can be used using formulas; (A*D) / (B*C) in spreadsheet cells.

Interpretation of OR

1. OR = 1 → Indicates no relationship between exposure and the disease.
2. OR > 1 → Suggests that exposure raises the likelihood of developing the disease.
3. OR < 1 → Implies that exposure has a protective effect against the disease [225].

Forest Plot Meta-analysis

A forest plot is a crucial tool in meta-analysis because graphically it represents the effect size (Odds Ratio) along with confidence intervals for individual studies [228]. It aids in evaluating heterogeneity among the included studies. Python's matplotlib and statsmodels is used to create the forest plot It presents the overall pooled estimate derived from the meta-analysis, typically using a random-effects model.

Heterogeneity Analysis

Heterogeneity in meta-analysis refers to differences in study outcomes across various studies. StatsDirect refers to statistical measures of heterogeneity as "non-combinability" statistics to aid users in interpreting the results effectively [229].

The python packages (statsmodels.stats.meta DerSimonian-Laird random-effects model) and (scipy.stats.chi2 Cochran's Q test) are utilized.

Interpretation values for I^2:

1. 0–25% → Low heterogeneity (fixed-effects model appropriate).

2. 25–50% → Moderate heterogeneity.
3. 50–75% → Substantial heterogeneity.
4. >75% → High heterogeneity (random-effects model recommended) [230].

Interpretation for Cochran's Q Statistic

1. A significant Q test (p ¡ 0.10) suggests heterogeneity.
2. However, it lacks power with few studies and is overly sensitive with many studies [230]

Funnel Plot Meta-Analysis

A forest plot provides a visual summary of the odds ratios (ORs) from a dataset along with their confidence intervals (CIs) [231]. A funnel plot is an essential tool in meta-analysis for detecting publication bias and small-study effects. In this analysis, we utilized Matplotlib (https://matplotlib.org/) to generate the funnel plot.

Significance of Funnel Plot:

A funnel plot was used to assess whether the included studies were influenced by publication bias and potential bias in outcome reporting. This plot is a scatter diagram where intervention effect estimates from individual studies are displayed on the horizontal axis, while the standard error of the estimated effect is plotted on the vertical axis [231] .

3.2 DISC1 Structure Prediction

DISC1 was first linked to major psychiatric disorders in the year 2000 [232] Its significance has been repeatedly validated and replicated across numerous independent genetic studies [233] To date, no experimental three-dimensional structures, either full-length or partial/fragmented, have been determined for DISC1. Furthermore, the

biophysical characterization of the full-length protein remains largely unexplored [117]. In the absence of structural information for DISC1, experimental studies have predominantly focused on utilizing shorter constructs and domain delineations derived from sequence analysis [234]. The figure 3.1 indicates DISC1 C-terminus Protein Structure Prediction Flow Chart.

3.2.1 Investigation of DISC1 Physiochemical Attributes

Why study physiochemical parameters of disease proteins?

Moreover, recent research has demonstrated that the functional properties of unfolded or hydrolyzed proteins differ from those of intact proteins [235]. This highlights the structure–function relationship of proteins. From a structural standpoint, further research on protein conformation, aggregation, molecular weight, isoelectric point, surface hydrophilicity/hydrophobicity, and binding properties is essential to bridge the knowledge gap between protein discovery and practical applications [236].

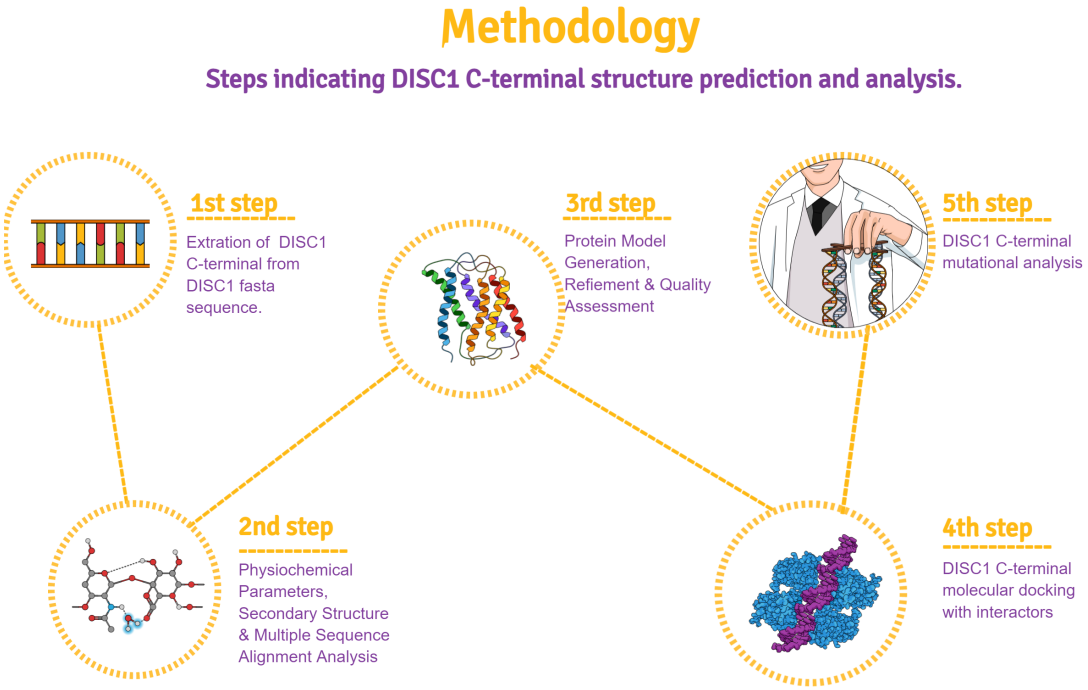


FIGURE 3.1: DISC1 C-terminus Protein Structure Prediction Flow Chart.

To explore the physiochemical properties of disease target proteins the ProtParam server is widely used. This server is designed to compute an extensive range of physical and chemical properties for proteins, offering researchers valuable insights into protein characteristics. Its interface is indicated in figure 3.2 which is user friendly and enables users to calculate physiochemical parameters of proteins on the basis of proteins stored in UniprotKB database. Among the parameters it calculates are the molecular weight, which gives an understanding of the protein's mass, and the theoretical isoelectric point (pI), which helps predict the pH at which the protein carries no net charge. Additionally, it analyzes the amino acid composition, providing a breakdown of the protein's building blocks, and the atomic composition, which gives a detailed account of the elements present [237].

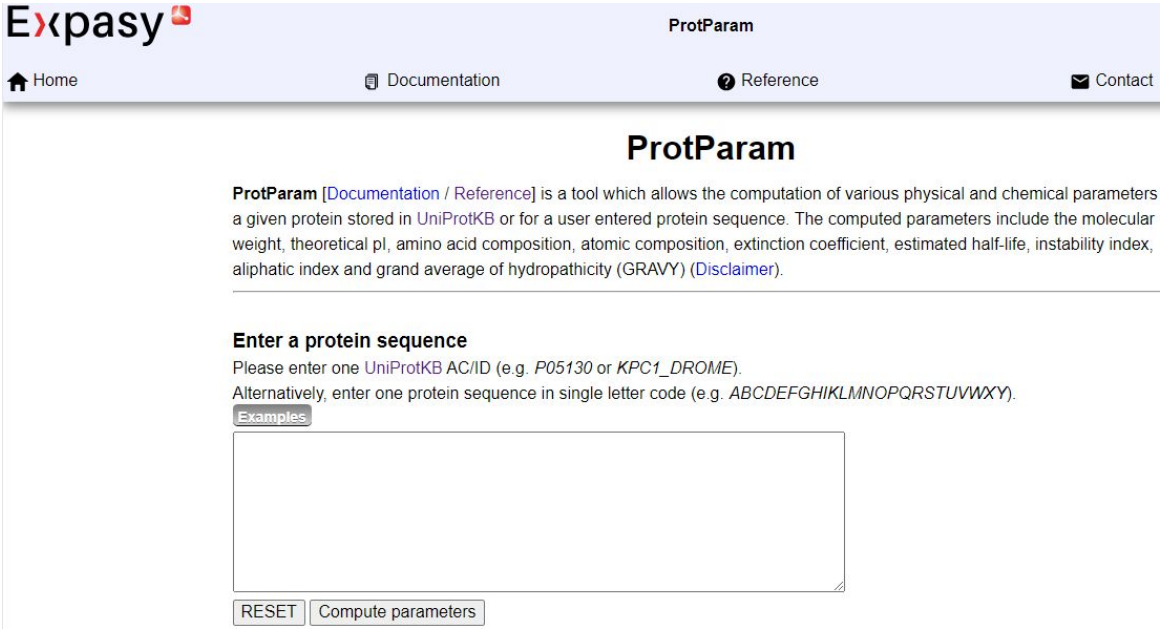


FIGURE 3.2: This tool calculates parameters such as molecular weight, amino acid composition, theoretical pI, instability index, aliphatic index, and grand average of hydropathicity (GRAVY).

ProtParam also estimates the extinction coefficient, which is useful for studying protein-protein interactions and determining protein concentration in solution. Other critical parameters include the protein's estimated half-life, offering predictions about the protein's stability within different biological systems, and the instability index, which predicts whether a protein is stable or unstable in a test tube. Furthermore, it calculates the aliphatic index, which reflects the volume occupied by aliphatic side

chains, and the grand average of hydropathicity (GRAVY), a value indicating the protein's overall hydrophobic or hydrophilic nature [237].

By entering a protein sequence manually or importing it from UniProtKB, users can swiftly access a detailed dataset at https:// web. expasy. org/protparam/. ProtParam serves as an essential tool for researchers aiming to analyze protein structures, functions, and stability, making it indispensable for studying protein behavior in various biological and experimental conditions. This tool calculates parameters such as molecular weight, amino acid composition, theoretical pI, instability index, aliphatic index, and grand average of hydropathicity (GRAVY).

3.2.2 DISC1 Secondary Structure Prediction

The secondary structure of a protein arises from hydrogen bonds formed between atoms of the polypeptide backbone. Specifically, hydrogen bonds form between the partially negative oxygen of the carbonyl group (C=O) and the partially positive nitrogen of the amide group (N-H) in different peptide bonds [238].

Key Features of Secondary Structure:

1. Hydrogen bonding stabilizes specific structural patterns.
2. These hydrogen bonds do not involve amino acid side chains; instead, they occur solely between backbone atoms.
3. Most proteins contain segments that coil or fold in characteristic patterns, significantly influencing the overall protein shape.

Common Secondary Structure Motifs:

Alpha-Helix (α-helix):

1. A right-handed coil stabilized by hydrogen bonds between every fourth amino acid.

2. Common in structural proteins like keratin.

Beta-Pleated Sheet (β-sheet):

1. Formed by hydrogen bonding between parallel or antiparallel strands of the polypeptide.

2. Contributes to the strength of structural proteins like silk fibroin.

These fundamental secondary structures play a critical role in determining the tertiary and quaternary structures of proteins, ultimately affecting their function [238].

PSIPRED is a two-stage artificial neural network designed to predict the secondary structure of a protein based on its sequence profile. It offers higher prediction accuracy compared to traditional statistical methods like Chou-Fasman and GOR (Garnier-Osguthorpe-Robson) [239].

There are different tools available for secondary structure prediction as indicated in table 3.2. These tools provide effective means to analyze the secondary structure of respective proteins.

TABLE 3.2: The table indicates different secondary structure prediction servers of JPred4, RaptorX, PredictProtein and CFSSP

S. No.	Servers	Utility	Ref.
1	JPred4	The JPred protein secondary structure prediction server utilizes the JNet algorithm, one of the most accurate methods for predicting secondary structures.	[240]
2	RaptorX	This server employs DeepCNF (Deep Convolutional), Neural Fields	[241]

Table 3.2 continued from previous page

S. No.	Servers	Utility	Ref.
		a powerful deep learning-based model, to simultaneously predict: Secondary structure (SS), Solvent accessibility (ACC), Disorder regions (DISO).	
3	PredictProtein	PredictProtein was a pioneer in integrating evolutionary information with machine learning for protein analysis.	[242]
4	CFSSP Server	The Chou-Fasman Secondary Structure Prediction (CFSSP) algorithm is an early computational method used to predict protein secondary structure. It is based on the statistical analysis of known . protein structures obtained through X-ray crystallography	[243]
5	PROTEUS2	Modern secondary structure prediction. methods leverage advanced computational techniques to improve accuracy. These approaches integrate various strategies, including multi-sequence alignment, structure-based mapping, and deep learning models	[244]

The PSIPRED Workbench offers a comprehensive collection of advanced protein structure prediction methods, which can be accessed both interactively through a web browser or programmatically via its REST API, its interface is indicated in figure 3.3.

This flexibility makes it suitable for individual analyses as well as integration into automated workflows. In addition to providing these tools online, all of the algorithms are available for download, making it possible to conduct high-throughput analyses on local systems.

The platform uses amino acid sequences as input to predict a wide range of structural features. One of its key functions is the prediction of secondary structures, including alpha-helices, beta-strands, and coils, which are essential for understanding a protein's 3D conformation. Moreover, PSIPRED predicts regions of disorder, which are protein segments that do not adopt a stable structure and may play important roles in signaling or regulatory functions.

For membrane-associated proteins, it predicts transmembrane helix packing, providing insights into how these proteins span cellular membrane [245].

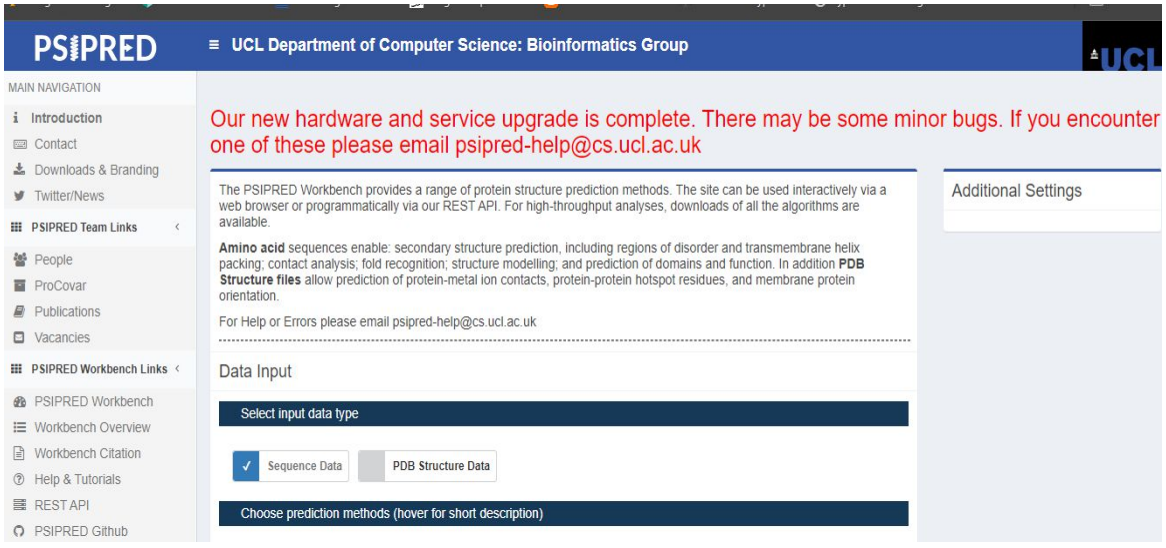


FIGURE 3.3: The figure indicates the interface of Psipred Secondary Structure Protein Prediction server.

Additionally, the use of PDB structure files facilitates the prediction of protein-metal ion interactions, identification of hotspot residues in protein-protein interfaces, and determination of the orientation of membrane proteins. By utilizing input FASTA sequences, PSIPRED generates predictions of secondary structures, detailing components such as coils, alpha-helices, and beta-strands, which are then represented through graphical outputs

3.2.3 DISC1 C-terminal Model Development by Different Protein Servers

3.2.3.1 IntFOLD

The IntFOLD server offers a comprehensive and integrated platform for multiple aspects of protein structure prediction and analysis. It provides a unified interface as indicated in figure 3.4. It provides a unified interface for predicting tertiary structure and 3D modeling of proteins, allowing users to generate detailed structural models from primary amino acid sequences. These models are based on homology modeling, threading, or ab initio techniques, depending on the availability of similar protein templates.

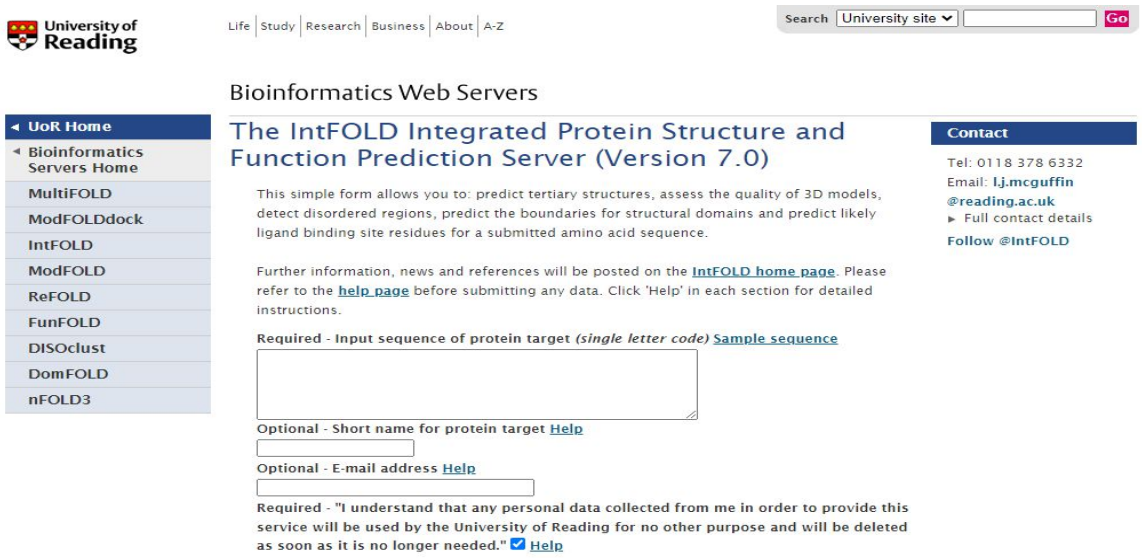


FIGURE 3.4: The figure indicates IntFOLD protein server interface where the DISC1 C-terminal fasta sequence is input to generate protein model.

In addition to producing 3D models, the server also provides quality estimates for each model, assessing their accuracy and reliability through scoring systems that evaluate various structural parameters. This is critical for identifying potential errors in the predicted models [246]. A unique feature of IntFOLD is its ability to refine or correct structural errors in the predicted models. Users have the option to refine regions of the structure that may exhibit inaccuracies, thereby improving the overall

quality and precision of the final model. This capability is particularly valuable for enhancing model reliability in regions where template-based methods may fall short, or for proteins with no close homologs. In addition to structure prediction, IntFOLD also offers intrinsic disorder prediction, which identifies regions in the protein sequence that lack a stable structure. These disordered regions often play important roles in protein function, particularly in signaling, regulation, and interactions with other biomolecules [246].

3.2.3.2 LOMETS (Local Meta-Threading Server, version 3)

LOMETS (Local Meta-Threading Server, version 3) represents an advanced meta -server as indicated in figure 3.5 represents an advanced meta-server designed for template-based protein structure prediction as well as structure-based functional annotation. This next-generation tool combines the power of multiple threading algorithms to enhance the accuracy and reliability of protein structure prediction.

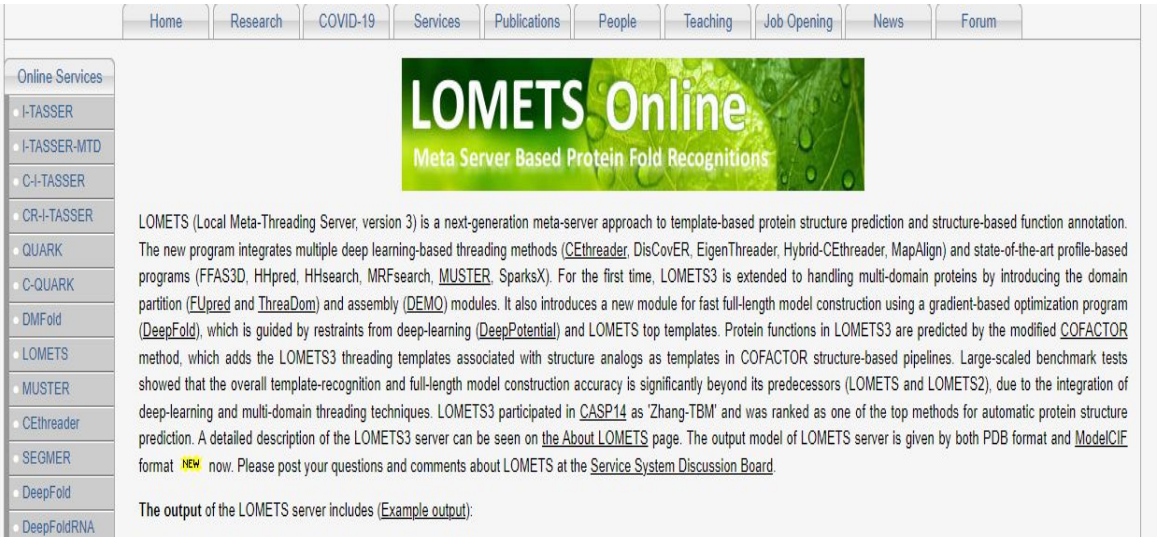


FIGURE 3.5: The figure indicates LOMET protein server interface where the DISC1 C-terminal fasta sequence is input to generate protein model.

Unlike traditional threading methods, LOMETS integrates cutting- edge deep learning-based approaches, leveraging the ability of machine learning models to capture complex patterns and relationships within protein sequences and structures. By incorporating these advanced methods, LOMETS improves the identification of suitable

templates, even in cases where distant homologs are involved, thereby producing more precise structural models [247].

3.2.3.3 Phyre2 Server

Phyre2 is a web-based suite of tools specifically developed for the prediction and analysis of protein structure, function, and the impact of mutations as indicated in figure 3.6. The platform leverages sophisticated techniques for remote homology detection, which allows it to predict 3D structures even for proteins with limited or no homologous templates. By comparing the input protein sequence against a large database of known structures, Phyre2 can generate reliable models based on structural similarities.

FIGURE 3.6: The figure indicates Phyre2 protein server interface where the DISC1 C-terminal fasta sequence is input to generate protein model.

In this study, the intensive mode of Phyre2 was employed to build highly detailed protein models. This mode enhances the modeling process by utilizing a combination of extensive search algorithms and refinement techniques, ensuring that even challenging proteins with distant homologs receive accurate and comprehensive 3D structural predictions. The intensive mode is particularly useful for generating high-resolution models, offering deeper insights into protein folding, function, and potential mutation effects [248].

3.2.4 Protein Model Analysis and Refinement

The protein structures were evaluated and analyzed using a combination of bioinformatics tools. MolProbity (http://molprobity.biochem.duke.edu/) was employed to generate Ramachandran plots, providing insights into the stereochemical quality of the protein models by examining the dihedral angles of the amino acid residues.

Additionally, the SAVES v6.0 server (https://saves.mbi.ucla.edu/) was utilized, incorporating the ERRAT server for identifying potential errors in the non-bonded interactions of the protein model, and the QMEAN server (https://swissmodel. expasy. org/qmean/) to assess the overall quality of the model based on a variety of statistical and structural features. These combined analyses ensured a thorough validation of the predicted protein structures.

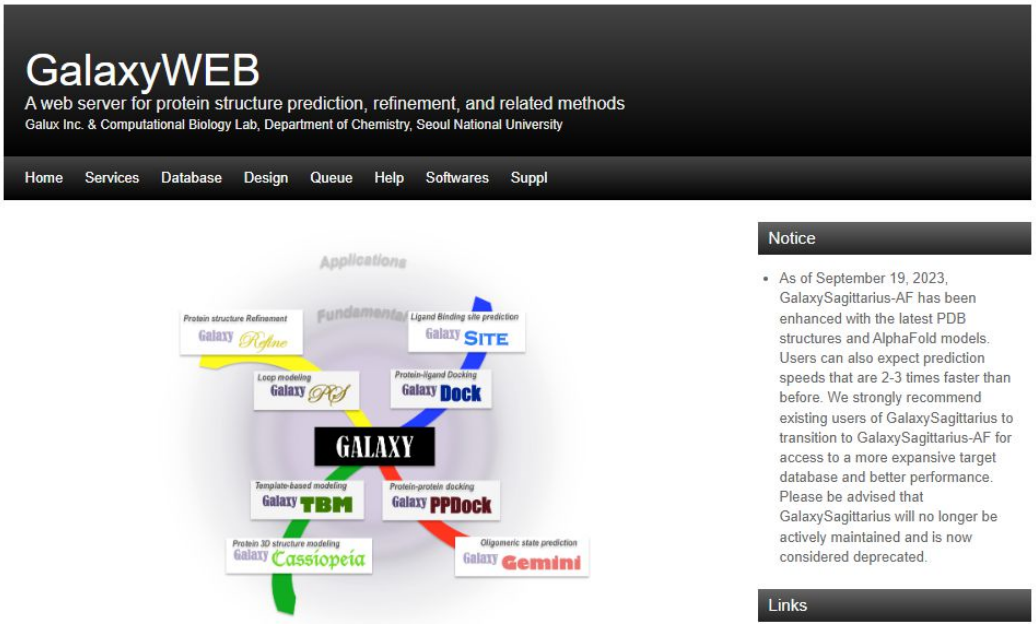


FIGURE 3.7: The figure indicates GalaxyWEB protein refinement server where the generated model of DISC1 C-terminus is uploaded to be refined and enhance its quality.

The GalaxyWEB server predicts protein structures from sequences through a combination of template-based modeling and ab initio refinement for loop or terminus regions its interface is indicated in figure 3.7. This approach generates highly reliable core structures by aligning the target sequence to multiple template structures, ensuring that conserved regions are accurately modeled. For regions where the templates

are unreliable, such as loops or termini, the server employs an optimization-based refinement method using ab initio techniques to improve structural accuracy [249].

In addition to structure prediction, GalaxyWEB allows users to submit models for refinement only. In this mode, users can provide an initial protein structure and specify the loop or terminus regions that need refinement, enhancing the accuracy of those regions without altering the overall model. This makes it a versatile tool not only for de novo structure prediction but also for improving existing protein models. The GalaxyWEB server is freely accessible to the scientific community at http://galaxy.seoklab.org/.

3.2.5 Docking C-terminal DISC1 structure with NDEL1 and ATF4

The ClusPro server (https://cluspro.org) is a popular and powerful tool designed for protein–protein docking. Its user-friendly interface to perform docking, requiring only two Protein Data Bank (PDB) files (receptor) and (ligand) to initiate the process. While the default setup is straightforward, ClusPro also includes a variety of advanced features that allow users to customize their docking experiments.

These options include the ability to exclude unstructured regions of proteins, apply attractive or repulsive forces, integrate pairwise distance restraints, construct homo-multimeric complexes, incorporate data from small-angle X-ray scattering (SAXS) experiments, and identify potential heparin-binding sites. These advanced settings provide researchers with greater flexibility and control, enabling more accurate and biologically relevant docking predictions [250].

Then Cluspro server was used to perform docking with our predicted DISC1 C-terminal protein model and understand its docking behavior and implications. In the case of our study, we used DISC1 C-terminal as receptor molecule and interactors NDEL1 and ATF4 as ligands. As already discussed, protein docking is an important research method in biological research which allows us to study protein-protein inter-

actions and related phenomenon. There are multiple protein docking servers available and some of the important servers are indicated in table 3.3.

TABLE 3.3: The table includes protein docking servers of Autodock, HADDOCK, PatchDock, ZDOCK and CB Dock.

S. No	Docking Platform	Utility	Ref
1.	Autodock	Predicts ligand-protein interactions for drug discovery.	[251]
2.	HADDOCK	Uses interaction restraints to guide docking.	[252]
3.	PatchDock	Optimizes molecular shape complementarity for accurate docking.	[253]
4.	ZDOCK	Predicts protein-protein complex structures.	[254]
5.	CB-Dock	Automates protein-ligand docking with binding site identification.	[255]

3.2.6 Validating DISC1 (ATF4, NDEL1) Docking by Molecular Dynamic (MD)

iMODS is a powerful tool that enables the exploration of normal modes and the generation of feasible transition pathways between two homologous structures, even for large macromolecules. Its unique internal coordinate formulation enhances the efficiency of Normal Mode Analysis (NMA) and broadens its usability while ensuring stereochemistry is implicitly preserved. The platform offers vibrational analysis, motion animations, and morphing trajectories at various resolution levels, allowing users to interactively examine molecular movements. iMODS is an interactive molecular dynamics server designed to analyze and visualize protein flexibility and conformational changes based on Normal Mode Analysis (NMA). It provides both basic and

advanced functionalities, making it useful for non-expert users as well as experienced researchers in structural biology and computational biophysics [256].

TABLE 3.4: The table includes molecular dynamic platforms of MDWeb, GROMACS, CGMD, AMBER and LAMMPS.

S. NO.	**Molecular Dynamic Platform**	**Utility**	**Ref.**
1.	MDWeb	Provides protocols for structure preparation, MD simulations, and trajectory analysis.	[257]
2.	GROMACS	Simulates biomolecules in various solvent environments.	[258]
3.	CGMD	Reduces computational cost while preserving key molecular interactions.	[259]
4.	AMBER	Used for MD simulations of biomolecules like proteins and nucleic acids.	[260]
5.	LAMMPS	Simulates molecular systems and materials.	[261]

3.2.7 Mutational Analysis of DISC1 C-terminus

UCSF Chimera is a comprehensive software tool designed for the interactive visualization and in-depth analysis of molecular structures and their associated data. This versatile program supports a wide range of formats, enabling users to visualize not only molecular structures but also complex datasets such as density maps, molecular dynamics trajectories, and sequence alignments. Its intuitive interface makes it easy to explore structural details, perform comparative analyses, and generate high-quality

images and animations. UCSF Chimera is available free of charge for noncommercial purposes, making it an accessible resource for researchers and educators in the field of structural biology. In addition to its visualization capabilities, the software offers various analytical tools that facilitate tasks such as structure editing, docking, and the identification of functional sites. Whether used for research, education, or presentations, UCSF Chimera provides a powerful and flexible platform for studying molecular interactions and dynamics at multiple levels of detail [240].

In this study, the predicted DISC1 C-terminus and DISC1 C-terminus docked complexes with molecular interactors NDEL1 and ATF4 were visualized using UCSF Chimera. This software enabled detailed structural analysis of the complexes, providing insights into the potential binding interfaces and interactions. Secondly, the study investigated two genetic polymorphisms in the DISC1 C-terminal region, specifically Leu607Phe and Ser704Cys, utilizing UCSF Chimera to visualize these mutations. This visualization allowed researchers to assess the possible structural and functional impacts of these polymorphisms on DISC1's interactions with binding partners, offering a deeper understanding of their potential role in psychiatric disorders [240].

3.3 Phylogenetic Analysis

Phylogenetic analysis starts with the alignment of nucleotide or amino acid sequences [241] obtained from an annotated genome sequencing database [242] provided in FASTA format, which includes putative or expressed protein sequences, RNA sequences, or DNA sequences. It is important to emphasize that collecting high-quality sequences is crucial for accurate phylogenetic analysis, as only homologous sequences can be used to reliably assess evolutionary relationships. There are several tools available for sequence alignment, each offering different features and capabilities. Popular platforms include Clustal W, Clustal X, MUSCLE, T-Coffee, and MAFFT, with Clustal Omega being the most commonly used due to its efficiency and ability to handle large datasets. Proper sequence alignment is a critical step, as it lays the foundation for subsequent phylogenetic inference and ensures meaningful comparison

across homologous regions [243], [244], (http://www.ebi.ac.uk/Tools/msa/clustalo/), which can be accessed online or downloaded free of charge.

The DISC1 phylogenetic analysis was performed using the CLUSTAL OMEGA (https: // www. ebi.ac.uk/ jdispatcher/msa/clustalo) tool. The fasta sequences of DISC1 (Human Q9NRI5), DISC1(Gorilla G3RDY7), DISC1(Dog A0A8I3MD42), DISC1(Bat G1P4P4), DISC1(Mouse Q811T9), and DISC1(Rabbit G1SYZ7)was retrieved from UniprotKB database interface indicated in figure 3.8 and then input to the CLUSTAL OMEGA tool to construct the phylogenetic tree the parameters were kept as default.

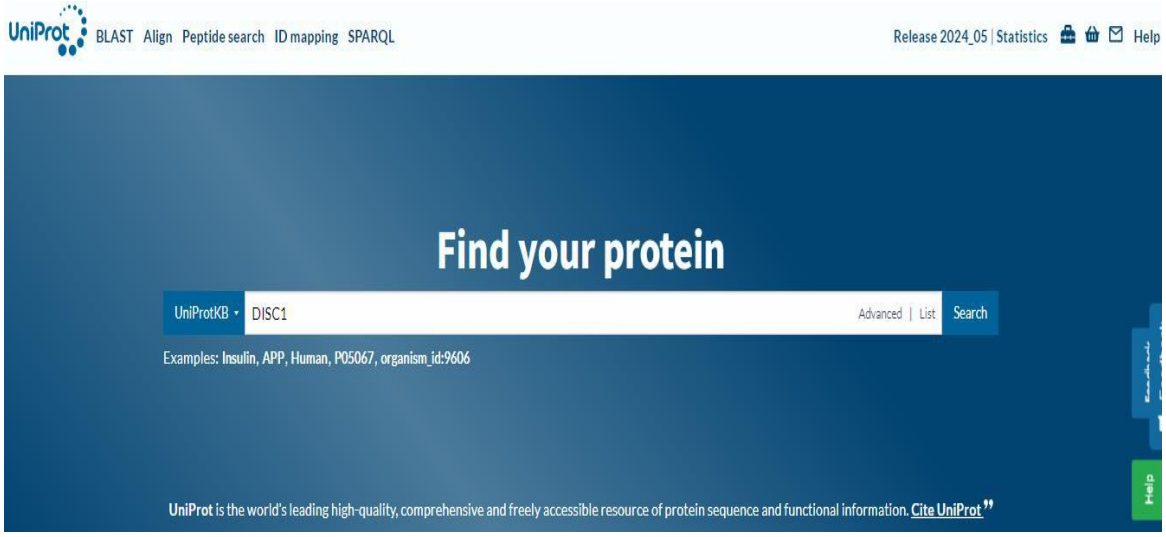


FIGURE 3.8: The UniprotKB interface is indicated where the DISC1 keyword was searched to extract the fasta sequences of various DISC1 species.

Clustal Omega (https://www.ebi.ac.uk/jdispatcher/msa/clustalo) (figure 3.9) is a next- generation multiple sequence alignment program designed to efficiently align three or more sequences. It employs advanced methods such as seeded guide trees and Hidden Markov Model (HMM) profile-profile techniques to produce high-quality alignments. Unlike basic alignment tools, Clustal Omega is optimized for handling large and complex datasets, making it ideal for aligning up to 4,000 sequences or files with a maximum size of 4 MB.

For cases involving only two sequences, it is recommended to use a pairwise sequence alignment tool instead, as Clustal Omega is tailored specifically for larger-scale alignments. This powerful tool is widely used in bioinformatics research due to its ability

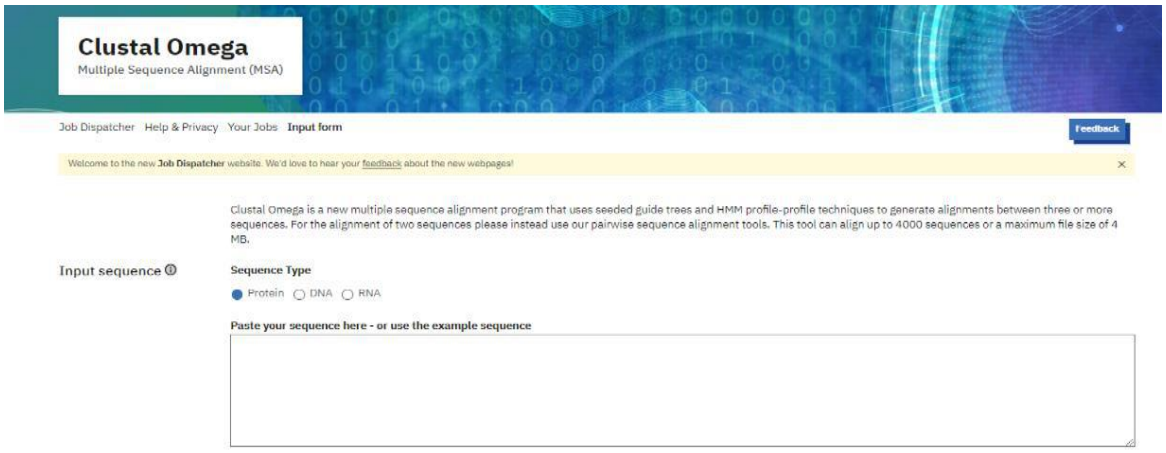


FIGURE 3.9: The Clustal Omega interface is indicated where the fasta sequences of DISC1 human and other DISC1 species is input in the Clustal Omega tab.

to generate accurate alignments quickly, even for extensive datasets, and is available both as an online service and as a downloadable program for offline use.

3.4 DISC1 Pathway Enrichment

It is evident that DISC1 is a protein responsible for neurogenesis variation in its expression or mutation may produce a dysfunctional protein leading to neuropsychiatric conditions such as schizophrenia. In the DISC1 pathway enrichment methodology we performed the following steps as indicated in figure 3.10.

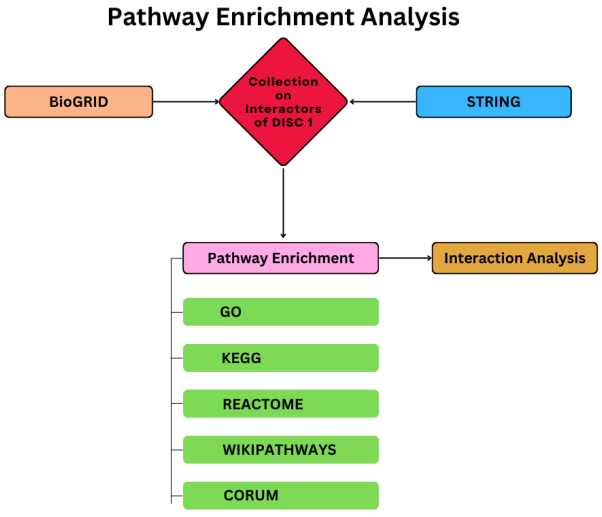


FIGURE 3.10: DISC1 Pathway Enrichment

3.4.1 Data Collection

The BioGRID database (https://thebiogrid.org/) was utilized to retrieve DISC1 interactors verified through high throughput studies. So, the keyword 'DISC1' was input in the tab of BioGRID database to extract the different DISC1 interactors. The STRING database (https://string-db.org/) was used to extract DISC1 interactors which was supported by high experimental evidence.

3.4.2 Developing a List of Genes

In this step after data collection a list of genes is generated from both the databases BIOGRID and STRING. This gene list consists of DISC1 interactors which are supported by both experimental evidence and high throughput analysis. We know that both these databases are rich resource to extract molecular interactors associated with the respective gene.

3.4.3 g:Profiler Pathway Enrichment Analysis

The g:Profiler (https://biit.cs.ut.ee/gprofiler/convert) is a web-based server which has user friendly interface. It provides pathways enrichment and diverse functional attributes regarding your input gene dataset.

The g:Progiler server is in connection with Ensembl database and it is updated regularly. Secondly more than four hundred species are now supported by this server making it more reliable and accurate.

g:GOSt is a powerful tool for functional enrichment analysis, helping to uncover biological significance in gene lists. Are you using it for a specific dataset related to your molecular dynamics or protein simulationpowerful tool for functional enrichment analysis, helping to uncover biological significance in gene lists [262].

The g:Profiler generates 'PATHWAY ENRICHMENT' results on the basis of following parameters.

1. Gene Ontology (GO) Molecular Function (MF)
2. Gene Ontology (GO) Biological Processes (BP)
3. Gene Ontology (GO) Cellular Components (CC)
4. Gene Ontology (GO) Molecular Function (MF)
5. Pathways:
   (a) **KEGG** (https: //www. genome. jp/kegg/),
   (b) **REACTOME** (https:// reactome. org/),
   (c) **WIKIPATHWAYS** (https: // www. wikipathways. org/)
6. The comprehensive resource of mammalian protein complexes (CORUM)

3.5 Analyze Interactions:

The pathway enrichment results will ultimately lead to predict suitable therapeutic targets for schizophrenia which is a complex disorder and lacks effective treatment.

3.6 Overall Methodology of Research

The research methodology focuses on understanding the genetic basis of schizophrenia through the investigation of the "Disrupted in Schizophrenia 1" (DISC1) gene. The study begins by identifying schizophrenia as a complex neuropsychiatric disorder with significant genetic contributions. DISC1 is selected as a candidate gene due to its critical role in neural development and synaptic functioning. Structural analysis, specifically of the C-terminal region of the DISC1 protein, is conducted to understand its molecular properties and interactions. Phylogenetic analysis is then performed to examine the evolutionary conservation of DISC1 across species, providing insights into its biological importance. Finally, pathway enrichment analysis is used to identify molecular networks involving DISC1, with the aim of predicting potential therapeutic

targets for schizophrenia. This systematic approach integrates genetics, bioinformatics, and therapeutic prediction to unravel the role of DISC1 in schizophrenia pathophysiology.

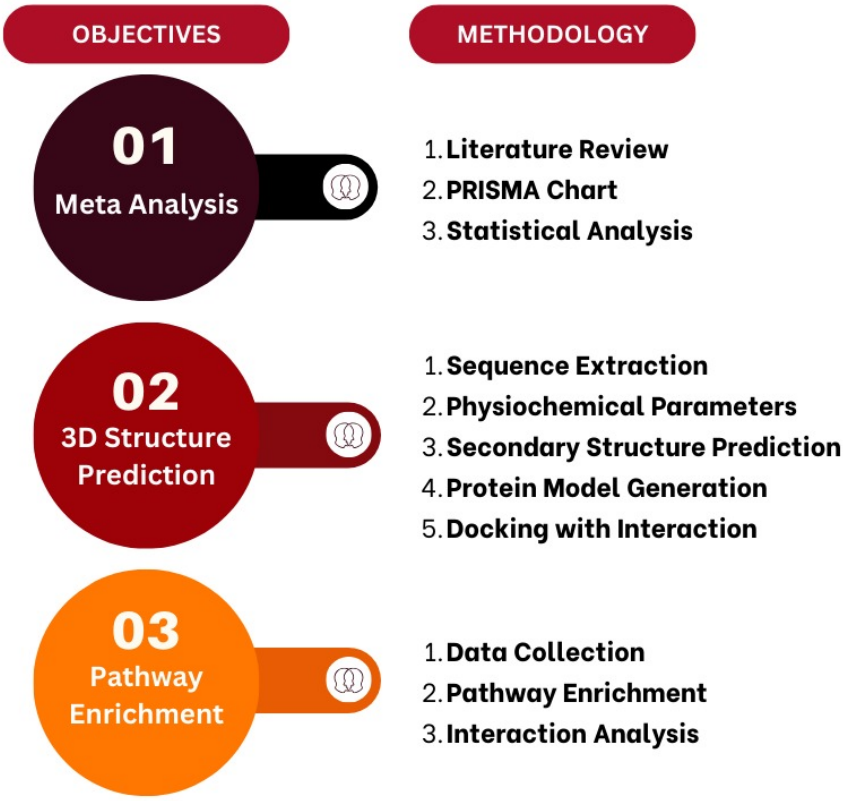


FIGURE 3.11: Overall methodology of research project

Chapter 4

Results

4.1 DISC1 Meta-Analysis Results

Meta-analysis as already discussed is a quantitative means to investigate multiple studies on a specific subject area which guides and assist researchers to draw findings, inferences through statistical analysis. In the initial step of DISC1 schizophrenia meta-analysis PRISMA chart [263] was formulated as indicated in Figure 4.1 a total of n=389 studies were identified and after applying the inclusion exclusion criteria, n=6 studies were first screened and later included in the meta-analysis.

TABLE 4.1: The table indicates DISC1 schizophrenia source table where the included studies are included; n=6 between the years 2015 to 2025.

S.No.	First Author	Country	Case	Control	Odd Ratio	P-Vaue
1	Shokouhifar et al 2018	Iran	402	376	1.0597	0.009241
2	Hea et al 2016	Chinese	248	236	1.0361	0.152
3	Gou et al 2018	Chinese	28	21	1.3136	0.788
4	Hu	Chinese	315	482	0.5943	0.032

Table 4.1 continued from previous page

S.No.	First Author	Country	Case	Control	Odd Ratio	P-Vaue
	et al 2015					
5	Norlelawati	Malaysia	225	350	0.5978	0.03
	et al 2015					
6	Xin Luo	Chinese	1447	1154	1.5082	0.0476
	et al 2016					

The following parameters were selected from the studies; First Author & Year', 'Published Year', 'Country', 'Case & Control', 'Odd Ratio (OR) & P-Value', 'DISC1 SNPs' and 'Association with schizophrenia' this data was used to formulate DISC1 schizophrenia source table as indicated in table: 4.1 and 4.2

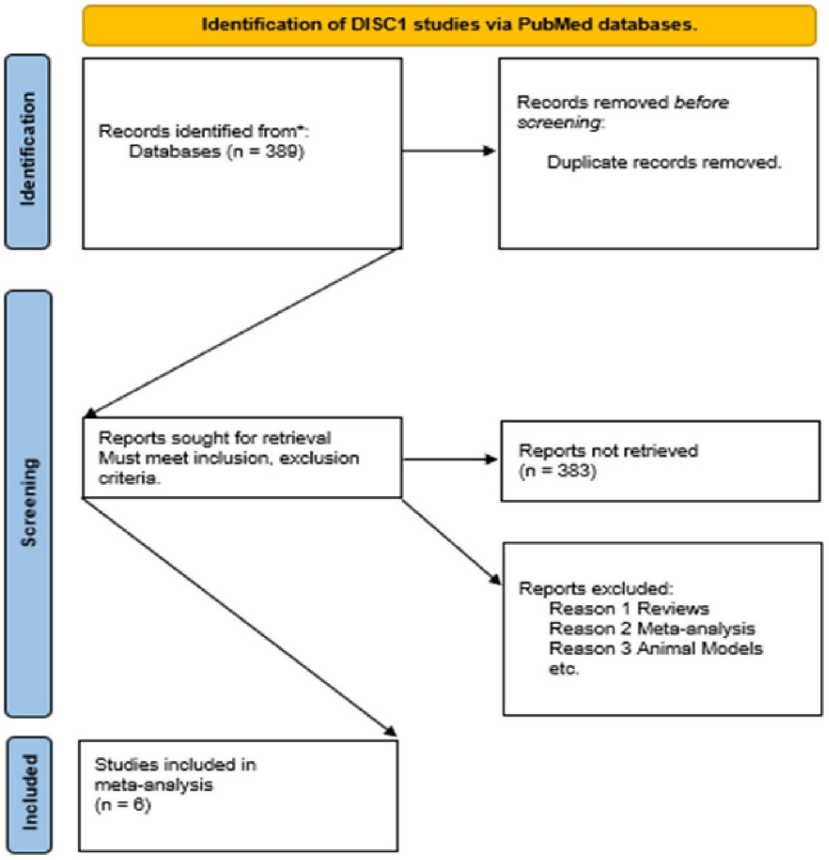


FIGURE 4.1: DISC1 schizophrenia (Prisma Chart) The figure indicates Prisma chart for the total studies n=389, screened studies n=6 were included as per inclusion exclusion criteria.

TABLE 4.2: The table indicates DISC1 SNP association schizophrenia

First Author	**DISC1 SNPs**	**Assocation**
Shokouhifar et al 2018	rs6675281	Yes
Hea et al 2016	rs821616 rs821597	Yes
Gou et al 2018	rs821616 rs2738880	Yes
Hu et al 2015	rs821633	Yes
Norlelawati et al 2015	rs4658971, rs1538979, rs2509382	Yes
Xin Luo et al 2016	rs821616	Yes

4.1.1 Meta-Analysis Results

4.1.1.1 Case-Control Sizes:

According to the study data from DISC1 schizophrenia case range from 28 to 1447 and controls from 21 to 1154.

4.1.1.2 Odds Ratio (ORs)

The calculated Odds Ratio from the studies indicates the following ranges.

1. Mean OR: 1.018 (suggests a slight association).
2. ORs range from 0.594 to 1.508, indicating varying effects across studies.
3. Threshold of ORs

According to (Bland JM and Altman DG, 2000) [225, 264] the threshold values for ORs are indicated below;

1. OR = 1 → No association between exposure and the disease.
2. OR > 1 → Exposure increases the risk of the disease.
3. OR < 1 → Exposure is protective against the disease

4.1.1.3 P-Values

As per the data from the DISC1 schizophrenia source table, the following information is extracted. Finding from p-values of DISC1 schizophrenia studies:

1. Some studies show significant associations ($p < 0.05$), while others do not.
2. The smallest p-value (0.009) suggests a strong association in at least one study.

4.1.1.4 Forest Plot Results

According to the forest plot results as indicated in Figure 4.2: the x-axis (Odds Ratio Scale) and y-axis (Study Labels). The dashed vertical line with OR = 1 (indicates no effect), meaning there is no link between exposure and outcome. If a study's confidence interval (CI) intersects this line, the result is not statistically significant. The red dots represent the Odds Ratio (OR) for each study. The blue horizontal lines indicate the 95% Confidence Intervals (CI). The studies where CIs surpass OR = 1 indicate non-significant results.

4.1.1.5 Heterogeneity Analysis Results

The heterogeneity analysis of DISC1 schizophrenia is performed to analyze the variability in the studies and whether these studies are consistent or there are differences by chance.

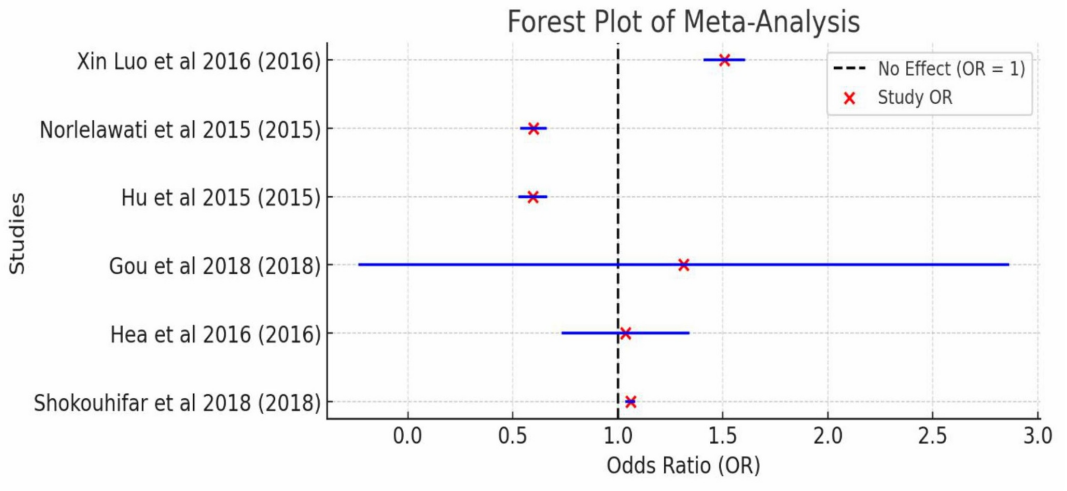


FIGURE 4.2: Forest plot of DISC1 schizophrenia meta-analysis indicates plot indicate intermediate sort of results where some studies show association (ORs>1) and others lack substantial association (ORs<1).

1. Cochran's Q: 16.14 (indicates variability between the studies).
2. P-value for Heterogeneity: 0.0064 (statistically meaningful, indicating true differences between studies).
3. I^2 Statistic: 69.02% (greater heterogeneity, implying substantial variability in study results).

4.1.1.6 Interpretation for Heterogeneity Analysis

1. A significant Q test ($p < 0.10$) suggests heterogeneity.
2. Since $I^2 > 50\%$ and the heterogeneity is significant, a random-effects meta-analysis is more appropriate [230].

4.1.1.7 Funnel Plot Results

A funnel plot is a crucial tool in meta-analysis to assess publication bias and small-study effects. Publication bias occurs when studies with non-significant or negative

results are less likely to be published. The funnel plot refer to Figure: 4.3 indicates partial publication bias as certain studies have lower ORs against standard error (SE) on y-axis.

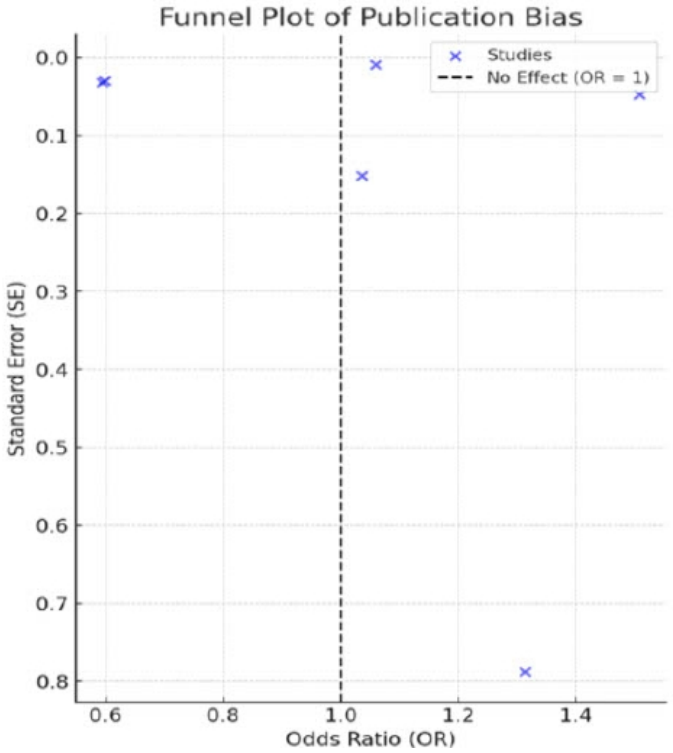


FIGURE 4.3: A funnel plot is used to assess publication bias in meta-analyses. It plots the effect sizes (odds ratios) against their standard errors (or sample sizes). A symmetrical funnel shape suggests low publication bias, while asymmetry indicates possible bias.

4.2 DISC1 Structure Prediction Results

4.2.1 Determination of DISC1 C-terminal Physiochemical Parameters

The aliphatic index of a protein refers to the proportion of its volume occupied by aliphatic side chains, including alanine, valine, isoleucine, and leucine. This index is considered a contributing factor to enhancing the thermostability of globular proteins [265]. The aliphatic index is computed using the following formula Aliphatic index =

X(Ala) + a * X(Val) + b * (X(Ile) + X(Leu)) [265].

The results of this study indicate that DISC1 C-terminus has a high aliphatic index of 93.15 which indicates it is a thermally stable protein when there is variation in temperature range.

The GRAVY (Grand Average of Hydropathicity) value for a peptide or protein is calculated as the arithmetic mean of the hydropathy values of its constituent amino acids. It is determined by summing the individual hydropathy values of all amino acids in the sequence and dividing by the total number of residues [266]. In this study the result indicates a negative Grand Average of Hydropathicity (GRAVY) value of -0.589 indicates that the protein has an overall hydrophilic nature. This suggests that the protein is more likely to interact with aqueous environments due to the predominance of polar or hydrophilic amino acid residues.

The half-life of a protein refers to the predicted time required for half of the protein's amount to degrade or disappear after its synthesis within a cell. ProtParam calculates this value based on the "N-end rule," which links the protein's half-life to the identity of its N-terminal residue. Predictions are provided for three model organisms: human, yeast, and E. coli [267].

The N-end rule is based on observations that the identity of a protein's N-terminal residue plays a crucial role in determining its stability in vivo. This rule suggests that certain N-terminal amino acids can influence the rate of protein degradation, thereby affecting the overall half-life of the protein within the cell [268], [269].

In our study the half-life of DISC1 C-terminus is highest 20 hours (mammalian reticulocytes in vitro) and lowest >10 hours (Escherichia coli, in vivo) overall the half-life of a protein can be few minutes to several days. The half-life of DISC1 has been estimated to be approximately 6 hours. However, this duration can be extended when the UPS is inhibited, indicating that DISC1 undergoes ubiquitin modification before being degraded [270]. The coordination of protein synthesis and degradation, along with the regulation of protein lifespan, is crucial for most biological processes, highlighting the importance of protein half-life [271].

The molecular weight (Mw) and theoretical isoelectric point (pI) of a protein are calculated using the Compute pI/Mw tool (https://web.expasy.org/compute_pi/). This tool enables the computation of these parameters for a given list of UniProtKB entries or user-submitted sequences. The theoretical pI represents the pH at which the protein carries no net charge, while the molecular weight reflects the sum of the atomic masses of the amino acid residues in the sequence. As per our results DISC1 C-terminus has a length of 504 amino acids with high molecular weight of 57283.28 Da.

TABLE 4.3: Physiochemical parameters of DISC1 C-terminus demonstrating the length of amino acid, theoretical isoelectric point, aliphatic index, hydrophobicity, molecular weight, and estimated half-life.

UniProt Access. No:	**Protein Length (Amino Acids)**	**Mol. Weight (Daltons)**	**Theoretic Isoelec. Point (PI)**	**Est. Half-life (Hours)**	**Grand Average of hydro pathicity**	**Aliphatic Index**
Q9NRI5	504	57283.28	5.44	20 hours (mammal reticulocytes, in vitro). 30 min (yeast, in vivo). >10 h (E. coli, in vivo).	-0.589	93.15

Proteins are positively charged when the pH of the environment is below their isoelectric point (pI) and negatively charged when the pH is above their pI. The pI of proteins can vary significantly, ranging from highly acidic values around 4.0 to strongly alkaline values near 12.0, depending on the amino acid composition of the protein [272].

According to the results of our study, the low isoelectric point of 5.4 indicates an acidic nature of the DISC1 C-terminus protein. This acidic pI suggests that the DISC1 C-terminus carries a net negative charge at physiological pH, which could influence its interactions with other proteins and cellular components, potentially impacting its stability and function within the cellular environment.

4.2.2 DISC1 C-terminus Secondary Structure Prediction

The secondary structure of the DISC1 C-terminus (amino acids 351-854) was predicted using the Psipred server, which classifies the structure into three main types:

1. **Alpha helices (H):** Regions where the protein forms a coiled, helical structure stabilized by hydrogen bonds.
2. **Beta sheets (E):** Extended, sheet-like structures formed by hydrogen bonding between backbone atoms in different strands.
3. **Coils (C):** Irregular regions without a defined secondary structure, often acting as flexible linkers between helices and sheets.

TABLE 4.4: The DISC1 C-terminus (amino acids 351-854) secondary structure predicted using Psipred server indicating alpha helix, beta sheets, and coils.

S.No	Secondary Structure Type	No of residues in the C-terminal DISC1 protein
1	Alpha Helix	384
2	Coil	120
3	Beta Sheet	0

In this study the DISC1 C-terminal sequence (residues 351-854) was input into Psipred, which generated a visual representation Figure 4.4: showing the specific regions forming helices, sheets, and coils as indicated in Table 4.4. The results indicate C-terminal DISC1 protein dominated by alpha helix (384 amino acid) and coil (120 amino acid).

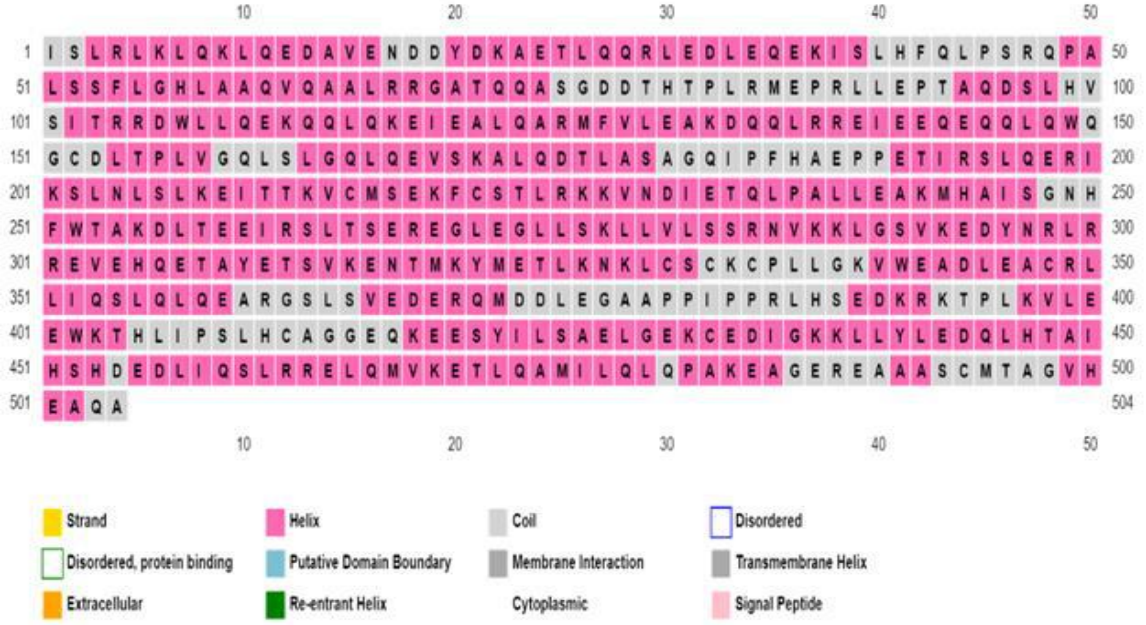


FIGURE 4.4: Secondary structure prediction of DISC1 by Psipred Server indicates coil and helix, the C-terminal DISC1 protein (Amino Acids: 351-854) structure is alpha helix dominated (pink) and coil (grey).

4.2.3 DISC1 C-terminus Protein Model Generation

Protein models of the DISC1 C-terminus were generated using the protein prediction servers IntFOLD, LOMETS, and Phyre2. The models produced by these servers are detailed in Table 4.5, and their structural quality was assessed using different evaluation tools. The Ramachandran plot was used to analyze the models stereochemical properties, indicating the favored and allowed regions of backbone dihedral angles. A high percentage of residues in these regions, with a value close to 100%, signifies a high-quality protein model. Additionally, the ERRAT server was employed to evaluate the overall quality of the models by plotting error values against residue positions. The resulting quality factor provides an assessment of model accuracy, with scores approaching 100 considered highly reliable. The QMEAN Z-score was also used to evaluate the global quality and geometric consistency of the models. This score compares the predicted model to experimentally solved structures, with values close to zero indicating good agreement between the modeled and actual structures. These combined analyses provide a comprehensive evaluation of the DISC1 C-terminus mod-

els, helping to ensure their reliability for further study.

TABLE 4.5: The protein models of the DISC1 C-terminus generated by IntFOLD, Phyre2, and LOMETS servers were evaluated using several quality assessment tools, including the Ramachandran plot, QMEAN score, and ERRAT score.

S. No.	**Model**	**Method**	**Ramachandran Plot**		**Qmean**	**Errat**
			Favoured Observ.	**Allowed Observ.**	**Z-Score**	
1	IntFOLD Model 1	Automated Prediction	86.10%	93.20%	-3.19	96.517
2	IntFOLD Model 2	Automated Prediction	80.90%	88%	-5.78	92.677
3	IntFOLD Model 4	Automated Prediction	90.60%	96.20%	-0.63	97.25
4	IntFOLD Model 4	Automated Prediction	90.20%	95.20%	-1.23	93.120
5	IntFOLD Model 5	Automated Prediction	85.30%	90.20%	-3.64	94.853
6	Lomets Model 1	Local Meta Threading	90.40%	97.60%	-3.45	82.186
7	Lomets Model 2	Local Meta Threading	91.20%	97%	-3.32	86.004
8	Lomets Model 3	Local Meta Threading	91.60%	98.40%	-2.65	88.307
9	Lomets Model 4	Local Meta Threading	90.80%	98%	-3.37	83.871
10	Lomets Model 5	Local Meta Threading	92.20%	98.80%	-2.76	89.315
11	Phyre2	Homology Detection Method	71.50%	86.50%	-17.09	49.38

1. **Ramachandran Plot:** This plot assesses the stereochemical quality of the protein models by indicating the percentage of residues in favored and allowed regions. A higher percentage in the favored region indicates better model quality.

   Ramachandran Plot (Thresholds in Structural Validation)

   (a) Ramachandran favored (>98% of residues) – Good structure.

   (b) Ramachandran outliers (<0.1%) – Poor structure quality; needs refinement.

   (c) Thresholds for well-refined structures [273]

2. **QMEAN score:** The QMEAN Z-score evaluates the global quality of the models, focusing on the geometric and structural consistency. A value closer to zero suggests a higher degree of similarity to experimentally solved structures, indicating a reliable model [274].

   QMEAN Z-score (Threshold Values)

   (a) |Z-score| $\leq$ 1.0 $\rightarrow$ Good quality (within range of experimental structures)

   (b) |Z-score| 1.0 – 2.0 $\rightarrow$ Acceptable but slightly deviates from experimental structures

   (c) |Z-score| $>$ 2.0 $\rightarrow$ Potentially unreliable model [274].

3. **ERRAT score:** This score measures the overall quality of the protein model by plotting the error values of each residue. A score approaching 100 indicates high model accuracy and reliability [275].

   ERRAT Score Interpretation

   (a) $\geq$ 95% $\rightarrow$ High-quality model (Comparable to high-resolution crystal structures)

   (b) 80% – 95% $\rightarrow$ Acceptable model (Common for good homology models)

   (c) $<$ 80% $\rightarrow$ Poor model (Significant structural errors, requires refinement).

4. The detailed results from the Ramachandran plot, QMEAN, and ERRAT analysis for each model are summarized in Table 4.5.

5. These results allow comparison of the models to determine the most suitable candidate for further refinement and investigation.

The analysis of the C-terminus DISC1 protein models enabled us to shortlist LOMETS model 5 model no: 10 in the list as having the highest structural quality. Ramachandran plot analysis demonstrated that 92.2% of residues were in favored regions, with 98.8% in allowed regions, reflecting excellent stereochemical accuracy. The ERRAT score of 89.3145 further indicated a high level of overall model quality. Although the QMEAN Z-score was -2.76, slightly deviating from the ideal, it remained within an acceptable range, suggesting a reasonable match with experimental protein structures.

TABLE 4.6: The C-terminal DISC1 protein, specifically Lomet Model 5, was selected for refinement using GalaxyWEB due to its superior Ramachandran Plot score compared to other models.

Model	**Refinement Method**	**Ramachandran Plot**		**Qmean Z-Score**	**Errat**
		Favoured Observ.	**Allowed Observ.**		
Lomet Model 5	ab initio modeling	95.80%	99.80%	-1.08	89.899

Due to these strong results, LOMETS model 5 was selected for refinement using the GalaxyWEB server. After refinement, the model underwent an additional round of quality validation, including Ramachandran plot analysis, QMEAN scoring, and ERRAT evaluation, with the results detailed in Table 4.6. Following refinement, the overall quality of the LOMET Model 5 was significantly enhanced, with Ramachandran Plot values showing 95.8% favored observations and 99.8% allowed observations, a Qmean Z-score of -1.08, and an Errat value of 89.999. These metrics indicate a structurally reliable model with minimized steric clashes, making it a robust choice for subsequent structural and functional analyses. A comparative analysis of the newly developed C-terminal DISC1 model with available models from AlphaFold and crystal complex structures in PDB (Protein Data Bank) developed through NMR (Nuclear Magnetic Resonance) indicated in table 4.7 highlights the structural advantage

and utility of our respective model. This analysis focuses on several key quality and structural parameters, which are summarized in Table 4.8. The developed C-terminal DISC1 model demonstrates significant improvements in terms of structural reliability and accuracy.

TABLE 4.7: Crystal structures of DISC1 C-terminal constructs are available in the Protein Data Bank (PDB).

S. No.	**Accession No.**	**Description**	**Species**	**Residues in complex.**	**Ref.**
1	5YI4	Solution Structure of the DISC1/Ndel1 complex.	Mus musculus	DISC1–>88 NDEL1–>47	[272]
2	6IRR	Solution structure of of DISC1/ATF4 complex	Mus musculus	DISC1–>88 ATF4–>36	[276]

TABLE 4.8: A comparative analysis was conducted between the newly developed DISC1 model and previously established DISC1 structures derived from AlphaFold and NMR complex studies.

S.NO	**Model**	**Ramachandran Plot**		**Qmean**
		Favoured Observation	**Allowed Observation**	
1	Lomet Model 5	95.80%	99.80%	-1.08
2	Alpha Fold DISC1	77.50%	89.30%	-8.06
3	DISC1/ATF4 (6IRR)	88.50%	94.70%	-3.62
4	DISC1/NDEL1 (5YI4)	85.30%	97.90%	-3.79

This analysis focused on structural and functional parameters, providing insights into model accuracy and reliability. The refined DISC1 model not only surpasses the AlphaFold prediction in terms of structure quality and refinement scores but also offers a complementary view to the NMR complex, bridging the gap between experimental and computational predictions.

4.3 Visualization of the Determined C-terminal DISC1 Structure

The DISC1 C-terminal structure, spanning 504 amino acids (from residues 351 to 854), was initially determined using the Lomet Server and subsequently refined using the GalaxyWEB server for enhanced accuracy and structural quality. After refinement, the structure was visualized and analyzed using Chimera, a molecular modeling tool as indicated in figure 4.5. This approach ensured that the refined structure accurately represents the C-terminal domain of DISC1, providing insights into its conformation and potential functional regions.

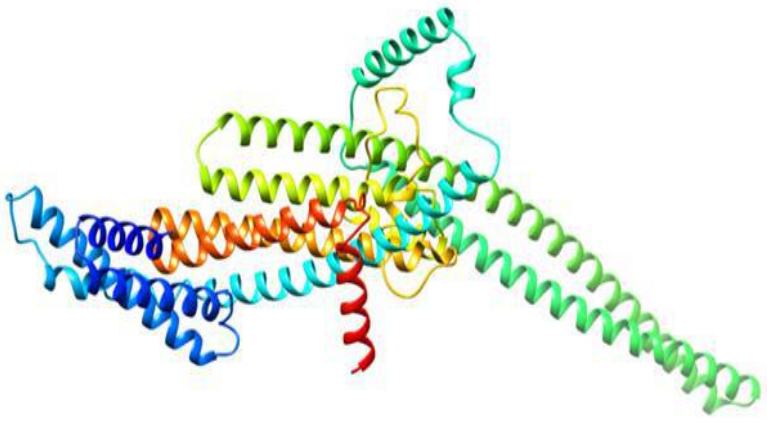


FIGURE 4.5: The DISC1 C-terminal structure determined by Lomet Server and then later refined by Galaxy Web server. The structure generated by the tool Chimera.

The segment spanning amino acids 765-854 as indicated in figure 4.6, which contains a coiled-coil domain, functions as a key dimerization domain, enabling DISC1 molecules to pair up. Meanwhile, the region between amino acids 668-747 serves as an oligomerization domain, facilitating the formation of larger protein complexes. Dimerization has been found to be crucial for the orderly assembly of these oligomers, highlighting its essential role in maintaining DISC1's structural and functional organization.

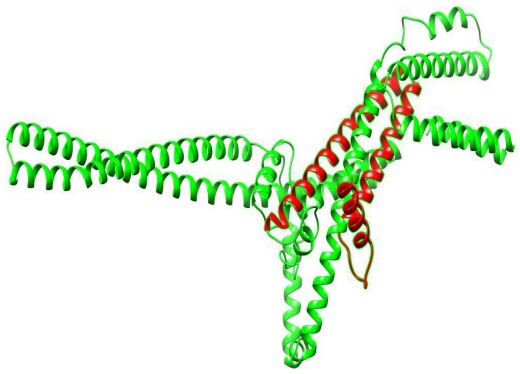


FIGURE 4.6: The C-terminal region of DISC1, spanning amino acids 351–854, shown in green, includes the coiled-coil dimerization domain, highlighted in red, which extends from amino acids 765–854.

4.4 DISC1 C-terminal Protein Docking with its Interactors (ATF4, NDEL1)

The protein docking was conducted regarding the C-terminal region of DISC1 and its known interactors, ATF4 and NDEL1. The docking was performed using default parameters in the Caspro server, where the predicted C-terminal model of DISC1 was used as the receptor. For the interactors, the Protein Data Bank (PDB) file for NDEL1 (PDB ID: 5YI4) was uploaded as the ligand, and the same procedure was followed for ATF4, using the PDB file 6IRR.

The results of the docking simulations are summarized in Table 4.9, which details the configurations (members) and weighted scores for the docking clusters of DISC1-NDEL1 and DISC1-ATF4. The table also highlights the representative structures at

the center of each cluster with the lowest energy, indicating the most stable interactions.

Additionally, Figure 4.7 and 4.8 present visual representations of the docking results, showing the interactions between DISC1 and NDEL1, as well as DISC1 and ATF4, respectively. ClusPro is a widely used protein-protein docking server that leverages fast Fourier transform (FFT) algorithms to efficiently explore binding conformations. It performs rigid-body docking with energy-based scoring and clustering to predict the most likely complex structures [277]. These findings provide valuable insights into how the Leu607Phe and Ser704Cys polymorphisms may alter DISC1's interactions with its key partners, potentially impacting its functional role in cellular processes.

TABLE 4.9: The table outlines the clusters for DISC1-NDEL1 and DISC1-ATF4, showing their respective configurations and representative structures at the center with the lowest energy. It also provides the corresponding weighted scores for each cluster.

Cluster	**Members**	**Representative**	**Weighted Score**
DISC1-NDEL1	78	Center	-722.2
		Lowest Energy	-926.2
DISC1-ATF4	184	Center	-680
		Lowest Energy	-827.3

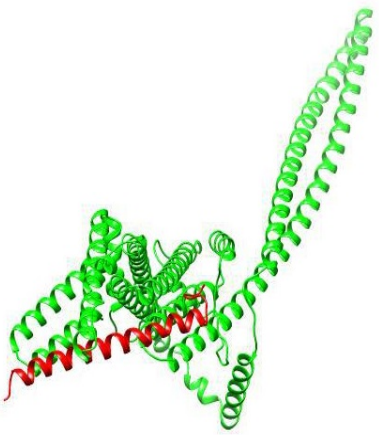


FIGURE 4.7: The figure indicates docking between DISC1 (green) and NDEL1 (red).

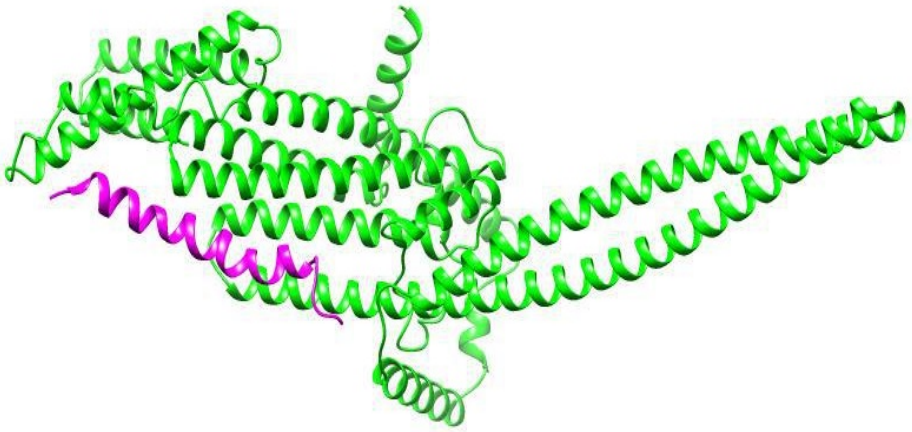


FIGURE 4.8: The figure indicates docking between DISC1 (green) and ATF4 (magenta).

4.5 Simulating the Structural Flexibility of DISC1 C-terminal with its Docked Interactors (ATF4, NDEL1)

In this study, the iMODs server was employed to evaluate the structural flexibility of the docked complexes of NDEL1-DISC1 and ATF4-DISC1 through Normal Mode Analysis (NMA). The analysis was performed by integrating the NMA with the coordinates of the docked complexes to assess their dynamic behavior.

The B-factor graph showcases the average root mean square (RMS) values, while the B-factor plot highlights the stable structural characteristics of the docked molecules, as shown in Figure 4.9, and Figure 4.10.

Additionally, the covariance matrix is represented in a color-coded graph, which effectively illustrates the different types of molecular motions, including correlated, uncorrelated, and anti-correlated movements. This visualization provides valuable insights into the dynamic interactions and stability of the docked complexes.

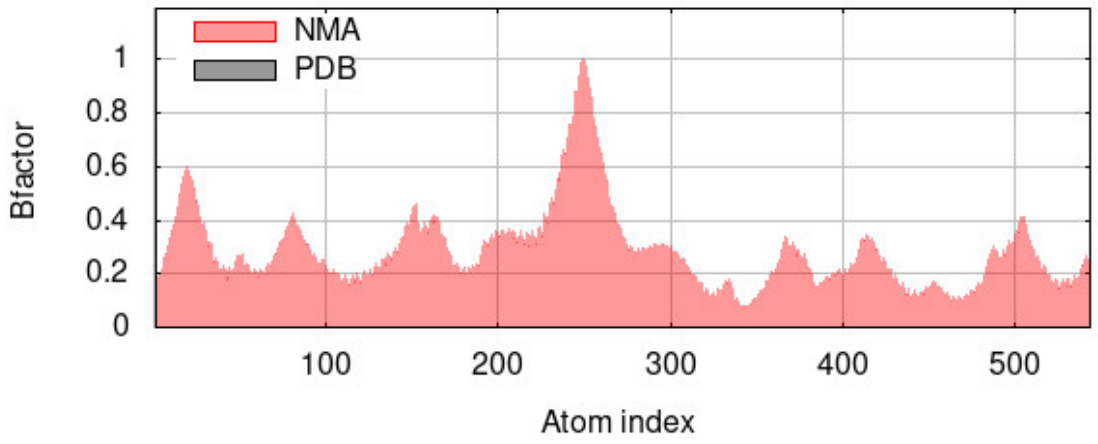


FIGURE 4.9: Results of iMOD for DISC1-ATF (B Factor).

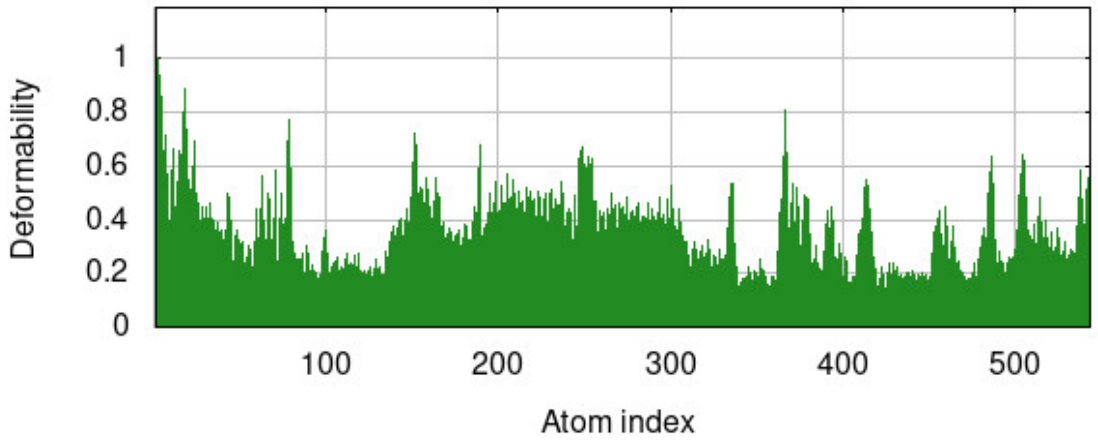


FIGURE 4.10: Results of iMOD for DISC1-ATF4 (Deformability Plot)

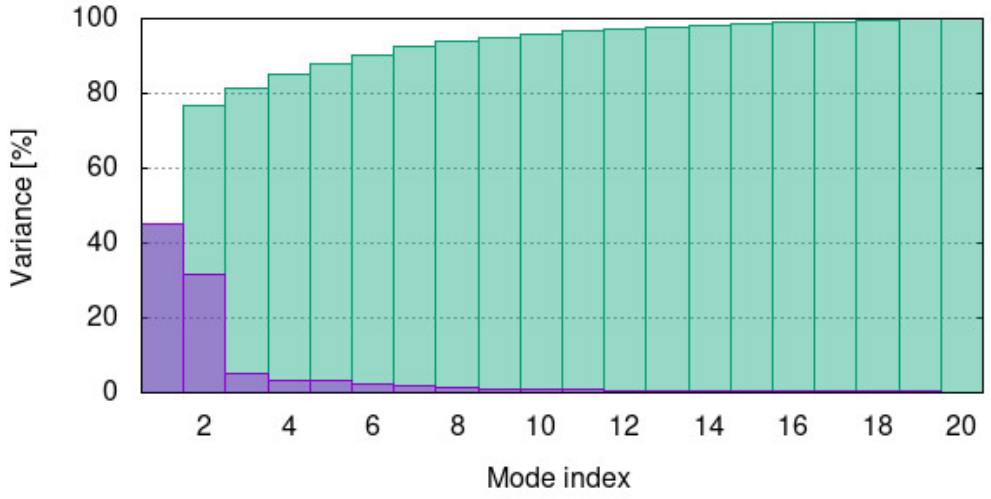


FIGURE 4.11: Results of iMOD for DISC1-ATF4 (Variance Plot)

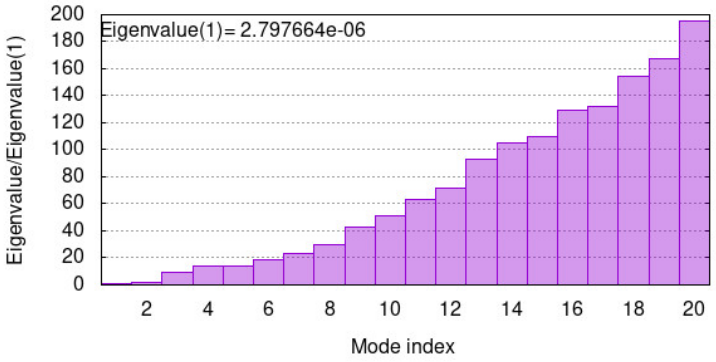


FIGURE 4.12: Results of iMOD for DISC1-ATF4 (Eigenvalue).

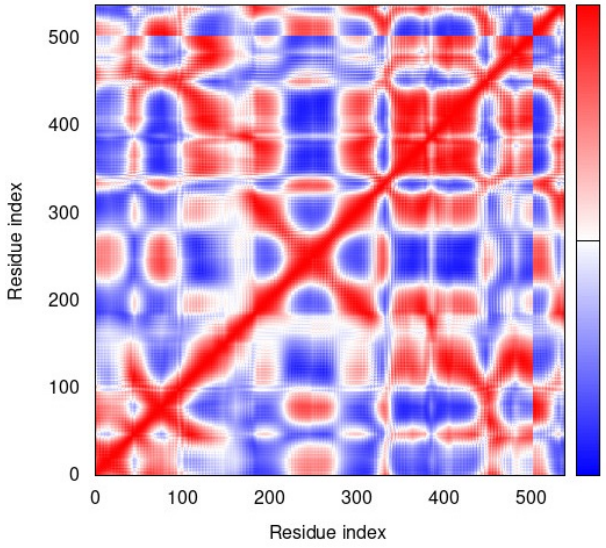


FIGURE 4.13: Results of iMOD for DISC1-ATF4 (Covariance Matrix Analysis).

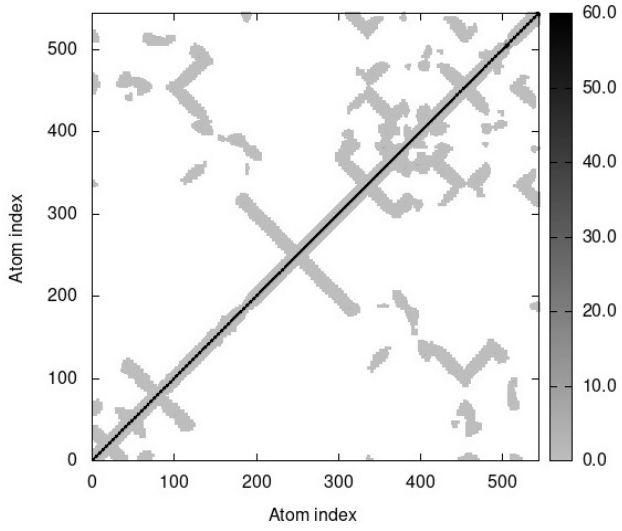


FIGURE 4.14: Results of iMOD for DISC1-ATF4 (Elastic Network Model).

For the DISC1-ATF4 complex, the iMODs results, shown in Figure 4.12, revealed an eigenvalue of 2.797664e–06. It is important to note that the eigenvalue is inversely related to the variance associated with each normal mode, as illustrated in Figure 4.11. This inverse relationship indicates that lower eigenvalues correspond to greater flexibility in the protein complex, providing insight into the stability and flexibility of the DISC1–ATF4 interaction.

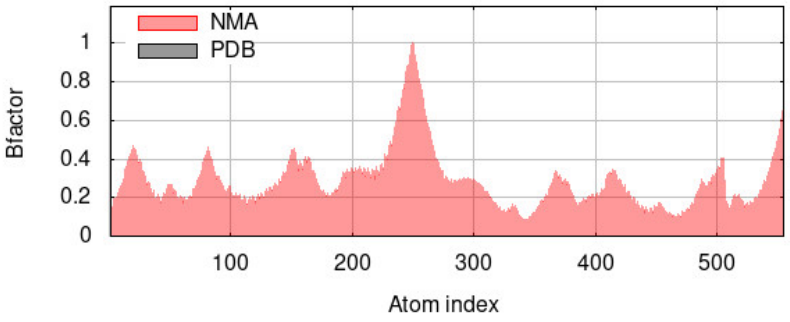


FIGURE 4.15: Results of iMOD for DISC1-NDEL1 (B Factor).

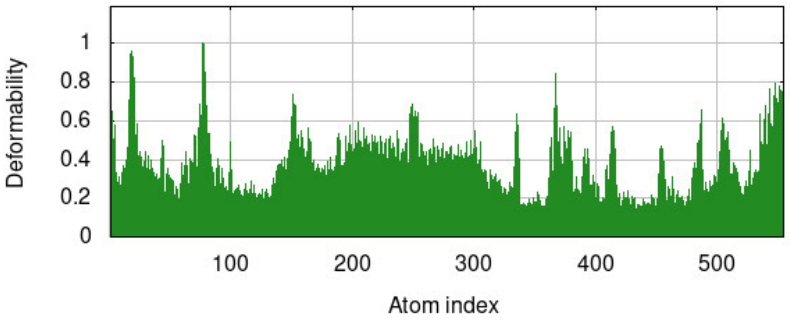


FIGURE 4.16: Results of iMOD for DISC1-NDEL1 (Deformability Plot).

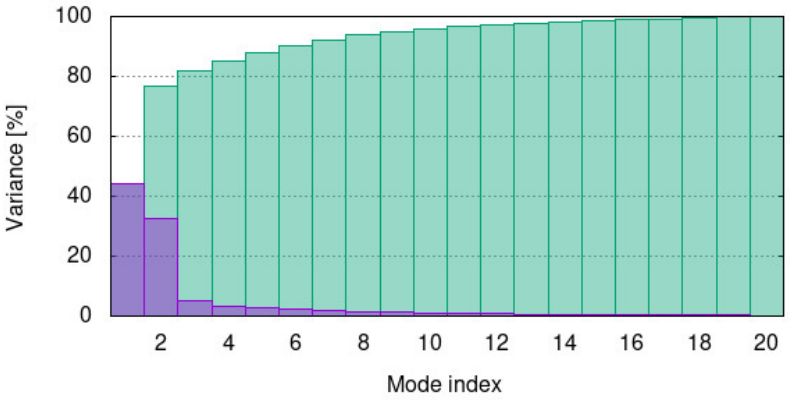


FIGURE 4.17: Results of iMOD for DISC1-NDEL1 (Variance Plot).

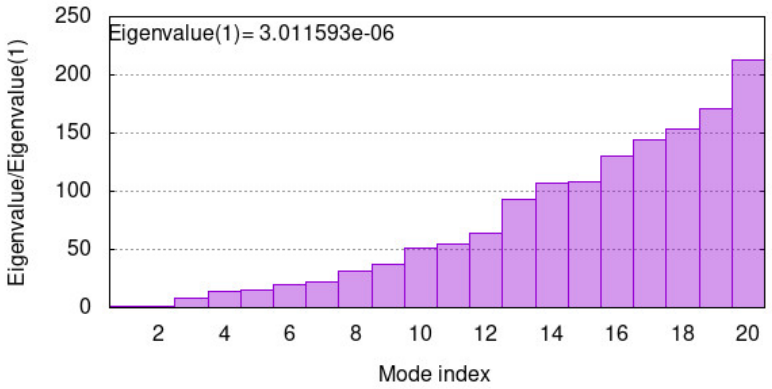


FIGURE 4.18: Results of iMOD for DISC1-NDEL1 (Eigenvalue).

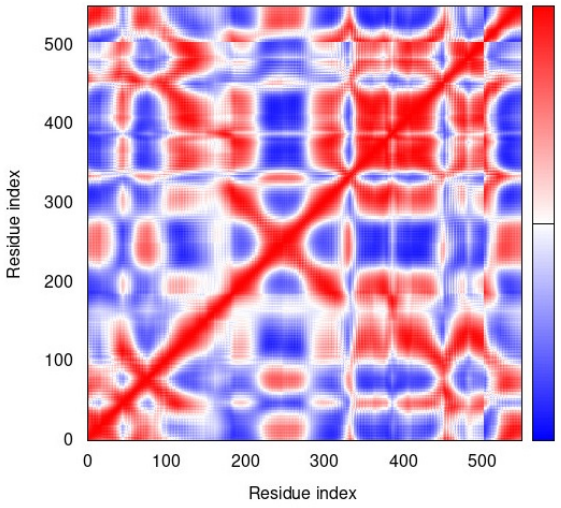


FIGURE 4.19: Results of iMOD for DISC1-NDEL1 (Covariance Matrix Analysis).

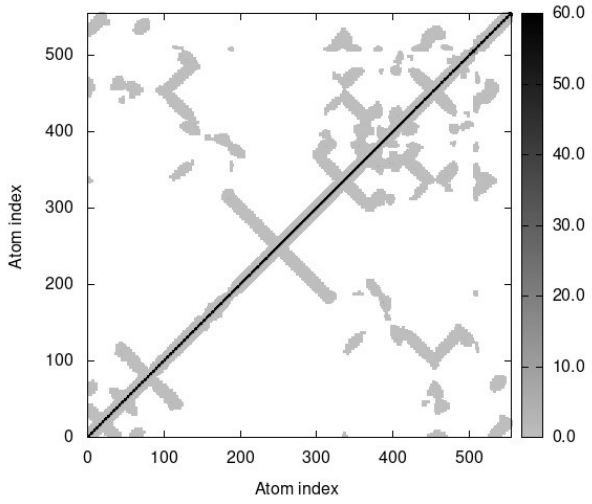


FIGURE 4.20: Results of iMOD for DISC1-NDEL1 (Elastic Network Model).

The iMODs analysis for the DISC1–NDEL1 complex, presented in Figure 4.18, produced an eigenvalue of 3.011593e–06. Additionally, it is important to highlight that the eigenvalue and variance show an inverse relationship for each normal mode, as demonstrated in Figure 4.17. This relationship suggests that a lower eigenvalue corresponds to increased flexibility within the DISC1–NDEL1 complex, providing further insights into its dynamic properties and stability.

4.6 DISC1 C-terminus Mutational Analysis

The DISC1 polymorphisms play a crucial role in the context of this study, particularly two specific variants: Leu607Phe and Ser704Cys. The Leu607Phe polymorphism has been shown to disrupt the regulation and nuclear targeting of ATF4-mediated transcription, potentially leading to altered gene expression patterns. On the other hand, the Ser704Cys polymorphism affects the binding affinity of NDEL1, a protein that is essential for neurite outgrowth, thereby influencing neuronal development and connectivity. The figure 4.21. 4.22; illustrate the structural differences between the wild-type DISC1 C-terminal and the mutated versions of the DISC1 C-terminal. These visual representations help to emphasize the functional implications of the identified polymorphisms, highlighting how these mutations may impact DISC1's interactions with its partners and contribute to neurodevelopmental processes. Understanding the consequences of these polymorphisms is critical for elucidating their potential roles in psychiatric disorders and the broader implications for brain function and development.

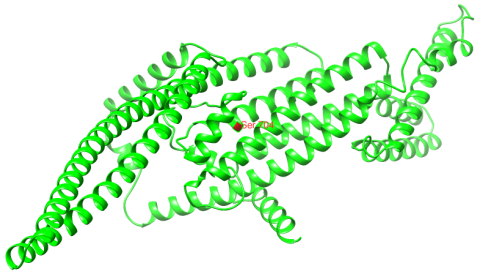


FIGURE 4.21: Wild type Serine 704 (red).

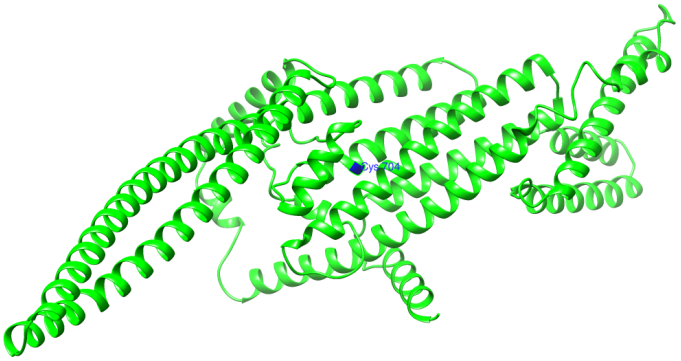


FIGURE 4.22: Mutated 704 Cysteine (blue).

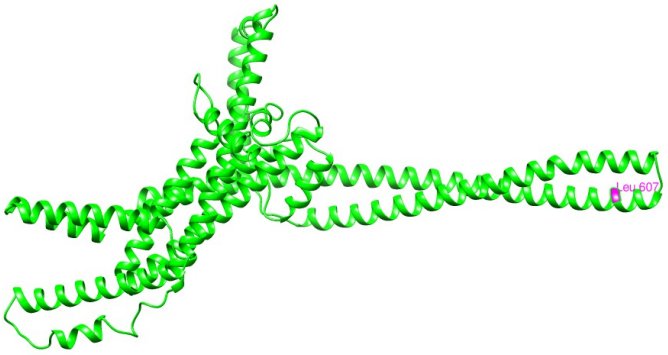


FIGURE 4.23: Wild type Leucine 607(magenta).

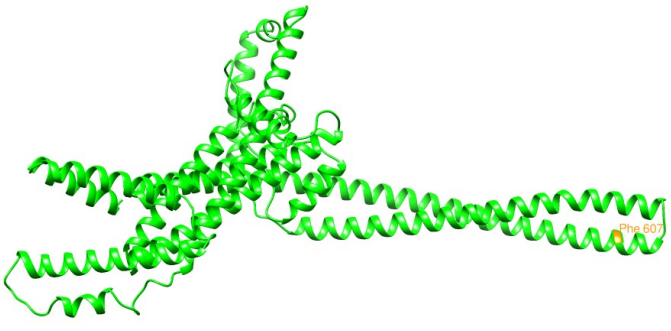


FIGURE 4.24: Mutated 607 Phenylalanine (golden).

The mutation of Serine 704 to Cysteine has been shown to impact neurite outgrowth significantly. This change in amino acid composition can alter the binding affinity and interaction dynamics of DISC1 with its partner proteins, such as NDEL1, which is crucial for neuronal development. Consequently, this mutation may hinder the proper signaling pathways involved in neurite extension, potentially leading to impaired neuronal connectivity and function. Understanding this mutation's effects is vital for exploring its implications in neurodevelopmental processes and related disorders. The substitution of Leucine 607 with Phenylalanine disrupts nuclear targeting and compromises the regulatory function of ATF4-mediated transcription. This amino acid change can interfere with the ability of DISC1 to effectively localize to the nucleus, where it plays a crucial role in modulating gene expression. As a result, this mutation may lead to altered transcriptional activity of ATF4, potentially affecting cellular responses to stress and contributing to the development of neuropsychiatric disorders. Understanding the impact of this substitution is essential for elucidating its broader implications in neuronal signaling and regulation as indicated in figure 4.23 and 4.24.

4.7 DISC1 Phylogenetic Analysis

The results of phylogenetic analysis Figure 4.25 indicate that DISC1 (Human), DISC1 (Chimpanzee) are evolutionarily related and DISC1 (Gorilla) is also close to them. The humans, chimpanzee and gorilla are of order primates under the class mammalia so they share common protein evolutionarily. The DISC1(Dog) species diverged from human, chimpanzee and gorilla but they have a common ancestor.

Secondly, DISC1 (Bat) and DISC1 (Mouse) are evolutionarily close to each other, sharing a common ancestor. Although DISC1 (Rabbit) is divergent from DISC1 (Human), evolutionary data suggest that it is closely related to DISC1 (Mouse) and DISC1 (Bat). This pattern highlights shared genetic sequences and structural features among these species.

The overall sketch of the phylogenetic analysis provides an evolutionary overview of the DISC1 protein across different species, revealing both conserved regions that

may be critical to function and lineage-specific variations that could influence species-specific roles of DISC1 in neurodevelopmental processes.

TABLE 4.10: The table indicates the parameters DISC1 UniprotKB identifiers, Species Name and Protein Lengths. They are used to generate phylogenetic tree of DISC1 and its related species.

S.No	**DISC1 UniprotKB Identifier**	**Species**	**Protein Length Amino Acids**
1	Q9NRI5	HUMAN	854
2	A0A8I3MD42_CANLF	DOG	816
3	A0A2R9ANZ6_PANPA	CHIMPANZEE	835
4	G3RDY7_GORGO	GORILLA	858
5	G1P4P4_MYOLU	BAT	835
6	Q811T9	MOUSE	852
7	G1SYZ7	RABBIT	859

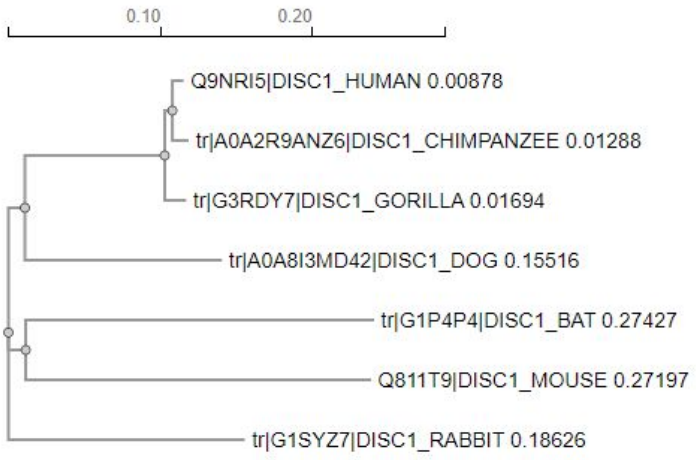


FIGURE 4.25: The figure indicates phylogenetic analysis results of DISC1 (human) with other species DISC1 (Gorilla), DISC1 (Chimpanzee), DISC1 (Dog) and DISC1 (Rabbit), DISC1 (Mouse) and DISC1 (Bat).

In this study phylogenetic analysis was performed through the different fasta sequences of DISC1 (Human Q9NRI5) and other species DISC1 (Dog A0A8I3MD42), DISC1 (Chimpanzee A0A2R9ANZ6), DISC1 (Gorilla G3RDY7), DISC1 (BAT G1P4P4), DISC1 (Mouse Q811T9) and DISC1 (Rabbit G1SYZ7) as indicated in table 4.10.

4.8 DISC1 Pathway Enrichment

4.8.1 Step-I: Data Collection

The BioGRID database (https://thebiogrid.org/) was employed to identify interaction partners of the DISC1 protein that had been validated through high-throughput experimental studies. To accomplish this, the keyword "DISC1" was entered into the search function of the BioGRID platform, allowing the retrieval of various DISC1 interactors from a comprehensive list of experimentally supported interactions. In addition to BioGRID, the STRING database (https://string-db.org/) was utilized to further explore DISC1 interactors.

The STRING database specializes in compiling protein-protein interactions based on a wide range of data, including those with strong experimental evidence. By using both databases, extraction and cross-referencing of robust list of DISC1 interactors is performed, supported by multiple forms of experimental validation, enhancing the confidence in the identified interactions.

4.8.2 Step-II Developing a Gene List:

In the first step, (STRING, BioGRID) databases are utilized from which DISC1 interactors are extracted. Now in this step the extracted genes are filtered and a gene list is established which will aid to input data for performing DISC1 pathway enrichment analysis. It is already indicated that the extracted DISC1 interactors are supported by strong experimental evidence. In the String database (Table: 4.11) a total of eight DISC1 interactors are retrieved supported by experimental evidence and in the Bio-

GRID database (Table 4.12) a total of twenty-one DISC1 interactors are shortlisted which are in alignment with high throughput studies.

TABLE 4.11: String Database (DISC1 Interactors).

S. NO.	**Interactor**	**ENSEMBL Gene ID**	**Exper. Evidence**	**Score**
1	NDEL1 (nudE neurodevelopment 1-like 1)	ENSG00000166579	Yes	0.999
2	NDE1 (nudE neurodevelopment protein 1)	ENSG00000072864	Yes	0.999
3	PDE4B (Phosphodiesterase 4B)	ENSG00000184588	Yes	0.998
4	PCNT (Pericentrin)	ENSG00000160299	Yes	0.983
5	GSK3B (Glycogen Synthase Kinase 3 Beta)	ENSG00000082701	Yes	0.977
6	DIXDC1 (DIX Domain Containing 1)	ENSG00000150764	Yes	0.961
7	DRD2 (Dopamine Receptor D2)	ENSG00000149295	Yes	0.958
8	PAFAH1B1 Platelet Activating Factor Acetylhydrolase 1b Regulatory Subunit 1	ENSG00000007168	Yes	0.954

Another key observation from the analysis of these two datasets is the identification of three interactors that are common to both, underscoring their significance as critical DISC1 molecular interactors.

TABLE 4.12: BioGRID Database (DISC1 Interactors)

S.No.	Interactor	Description	Evidence
1	NDEL1	nudE neurodevelopment protein 1-like 1)	4
2	C17ORF59	Chromosome 17 open reading frame 59	4
3	CEP170	centrosomal protein 170kDa	2
4	GRIPAP1	GRIP1 associated protein 1	3
5	NDE1	nudE neurodevelopment protein 1	3
6	PAFAH1B1	platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 (45kDa)	2
7	TNIK	TRAF2 and NCK interacting kinase	2
8	IFT20	intraflagellar transport 20	2
9	STX11	syntaxin 11	3
10	AIMP2	aminoacyl tRNA synthetase complex-interacting multifunctional protein 2	2
11	ASB3	ankyrin repeat and SOCS box containing 3	2
12	CDC16	cell division cycle 16	2
13	CEP57	Centrosomal protein 57kDa	2
14	DYNC1/1	dynein, cytoplasmic 1 intermediate chain 1	2
15	MYF6	myogenic factor 6 herculin	2
16	P4HA3	prolyl 4-hydroxylase,	2

Table 4.12 continued from previous page

S.No.	Interactor	Description	Evidence
		alpha polypeptide III	
17	PSPC1	paraspeckle component 1	2
18	RIBC1	RIB43A domain with coiled-coils C38	
19	RNF40	Ring finger protein 40 , E3 ubiquitin protein	2
20	SKP2	S-phase kinase-associated protein 2, E3 ubiquitin protein ligase	2
21	TCL1B	T-cell leukemia/lymphoma 1B	2

The fact that these shared interactors appear in both datasets further emphasizes their importance, as they are supported by robust experimental data from independent sources. This convergence of evidence from BioGRID and STRING highlights the strong likelihood of their involvement in DISC1-related molecular pathways, as validated by established wet lab experiments (refer to Table 4.13).

TABLE 4.13: Common DISC1 interactors are present in both String and BioGRID data sets.

S.No	DISC1 Interactor	Databases String/BioGRID
1	nudE neurodevelopment protein 1-like 1 (NDEL1)	Yes
2	nudE neurodevelopment protein 1 (NDE1)	Yes
3	platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 (PAFAH1B1)	Yes

4.8.3 Step-III DISC1 Pathway Enrichment Analysis:

In this step the DISC1 interactors data set is input to the g:Profiler Server (https: //biit.cs .ut.ee/ gprofiler/ gost) g:Profiler is a crucial tool for biologists aiming to uncover and interpret the molecular mechanisms and biological processes driving their research.

Its advanced features, user-friendly interface, and emphasis on meeting the needs of researchers make it a standout web service for performing gene set enrichment analysis. By providing insights into gene functions, pathways, and interactions, g:Profiler facilitates a deeper understanding of the biological context of experimental data, making it an invaluable resource for modern biological research [278].

In this study g:Profiler was employed to perform the functional enrichment analysis, also referred to as over-representation analysis (ORA) or gene set enrichment analysis (GSEA), on a provided list of genes. This process involves mapping the input genes to various well-established biological databases and identifying statistically significant functional categories or pathways that are over-represented in the gene set.

By doing so, it reveals key biological processes, molecular functions, and cellular components related to the gene set. Data for the analysis is regularly retrieved from multiple comprehensive sources. This includes the Ensembl database for general genomic information, as well as specialized versions like the Ensembl Genomes for fungi, plants, and metazoans.

For parasite-specific gene sets, data from WormBase ParaSite is used. The tool integrates several functional annotations, such as the widely used Gene Ontology (GO), which categorizes genes based on biological processes, cellular components, and molecular functions.

In this study DISC1 interactor dataset was input to the g:Profiler server tab it generated a graphical representation indicating the following parameters on the x-axis; whereas the y-axis indicate negative log of adjusted p-value as indicated in Figure 4.26.

1. Gene Ontology (GO) Molecular Function (MF)
2. Gene Ontology (GO) Biological Processes (BP)
3. Gene Ontology (GO) Cellular Components (CC)
4. Pathways:
   (a) KEGG (https://www.genome.jp/kegg/)
   (b) REACTOME (https:// reactome .org/),
   (c) WIKIPATHWAYS (https://www.wikipathways.org/),
   (d) CORUM The comprehensive resource of mammalian protein complexes.

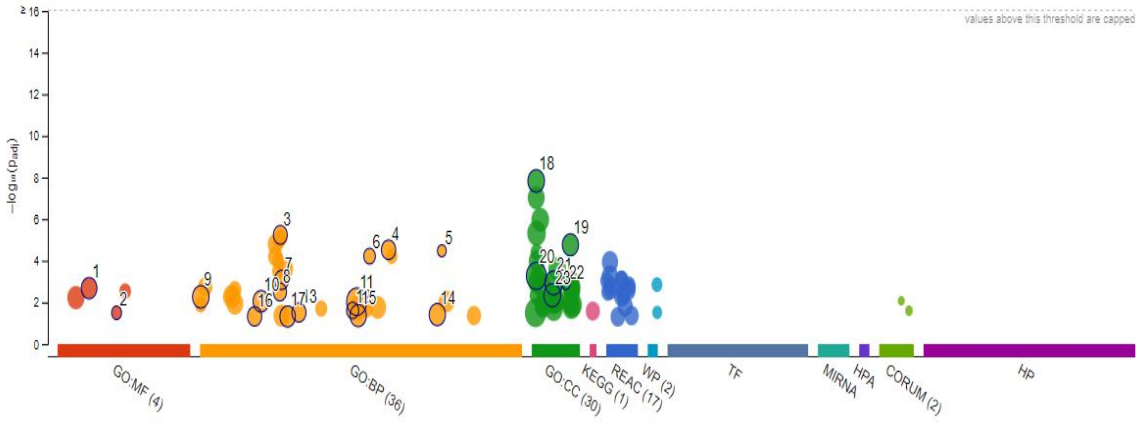


FIGURE 4.26: The figure indicates the graphical representation of DISC1 interactor dataset. It includes x-axis with different parameters and y-axis with negative log of adjusted p-value.

A. Gene Ontology (GO) Molecular Function (MF)

In this study GO Molecular Function (MF) parameter refer to different genes where the significant results highlight the functions of cytoskeletal binding, cell division and structural organization.

B. Gene Ontology (GO) Biological Processes (BP)

According to this study GO Biological Processes (BP) parameter overlap with multiple processes, components of neurogenesis contributing in its synthesis, migration and proliferation of the nervous system and related processes.

C. Gene Ontology (GO) Cellular Components (CC)

The Gene Ontology (GO) Cellular Components (CC) results also provide a wider picture indicating multiple cellular components forming cellular vesicles, cell junctions, spindle fibers and synapse. This indicates that the gene set is overlapping with diverse cellular components in different processes. (detailed result in figure 4.27)

D. Enriched Pathways

The results indicate the enriched pathway as per KEGG database (https:// www. genome. jp/ kegg/) TERM ID: KEGG:04110 (Cell cycle) involving the DISC1 interactors SKP2, CDC16, GSK3B) involved in this enriched pathway. (detailed result file in supplementary material) As per the results of REACTOME database multiple pathway genes indicate enrichment (detailed result file in supplementary material) from Centrosome maturation, Organelle biogenesis and maintenance, Cell Cycle. In the case of WIKIPATHWAY the significant hits are as follow; (17p13 3 YWHAE copy number variation), (PAFAH1B1 copy number variation).

E. The comprehensive resource of mammalian protein complexes (CORUM)

According to the CORUM results two hits are in this study they are indicated as; PDE4B-DISC1 complex, HTT-DISC1-PDE4B complex. The DISC1 pathway enrichment analysis results, as illustrated in Figure 4.26, serve as a foundational resource by comprehensively detailing the enriched gene sets associated with DISC1, along with a variety of parameters pertinent to each set. This file includes information on gene interactions, biological processes, and molecular functions, offering a robust framework for researchers aiming to uncover potential therapeutic interventions.

The enriched gene sets have been carefully examined to reveal meaningful associations that underscore the importance of DISC1 in various cellular mechanisms, particularly those linked to neurodevelopmental and neuropsychiatric processes. Following an extensive enrichment analysis, three DISC1 molecular partners have emerged as particularly significant in the context of schizophrenia pathophysiology: NDEL1, NDE1, and PAFAH1B1.

Each of these proteins plays a critical role in neuronal migration, synaptic function, and cytoskeletal dynamics—key processes often disrupted in schizophrenia. NDEL1 and NDE1, for example, are involved in microtubule regulation, which is essential for proper neuronal development, while PAFAH1B1 has been implicated in brain structure integrity and neuronal migration.

Given these roles, targeting these proteins could help modulate pathways associated with schizophrenia-related abnormalities. This discovery provides a promising direction for future research, where these DISC1 partners could be further studied and potentially leveraged as therapeutic targets to alleviate or modify schizophrenia-associated pathology. Consequently, this enrichment analysis file is invaluable for researchers seeking to deepen their understanding of DISC1's molecular interactions and its broader implications in therapeutic development for neuropsychiatric disorders.

The figure 4.27 provides a detailed summary of gene ontology (GO) and pathway enrichment analysis conducted on the DISC1 protein and its molecular interactors, with data visualized across several categories. Each section sheds light on the potential functions, cellular localization, and biological roles of these proteins, as well as the pathways they are involved in. This comprehensive analysis enables a deeper understanding of the significance of DISC1 in various cellular contexts, particularly its role in neurodevelopment and cell cycle regulation, which have implications in neurological disorders such as schizophrenia. Here is a breakdown of each section in detail.

4.8.4 GO (Molecular Function)

4.8.4.1 The Gene Ontology

The Molecular Function (GO) category of DISC1 focuses on its biochemical roles in the cell. DISC1 is involved in protein binding, GTPase binding, microtubule regulation, synaptic signaling, apoptosis regulation, and transcription factor activity. These functions are crucial for neuronal signaling, development, and synaptic plasticity.

DISC1's role in maintaining neuronal structure and regulating cell survival links it to neurodevelopmental and psychiatric disorders. Disruptions in any of these functions could contribute to conditions like schizophrenia and bipolar disorder, highlighting the need for further research into its molecular pathways.

4.8.4.2 Tubulin Binding (GO:0015631)

This term signifies that some DISC1 interactors have a strong affinity for tubulin, a critical structural protein that forms microtubules within the cytoskeleton. Tubulin binding is essential for maintaining cellular shape, enabling intracellular transport, and organizing components during cell division.

4.8.4.3 Gamma-Tubulin Binding (GO:0035371) and Cytoskeletal Protein Binding (GO: 0008092)

These terms indicate that certain interactors are involved in binding with components of the cytoskeleton, specifically gamma-tubulin, which plays a crucial role in microtubule nucleation at the centrosome. The cytoskeletal protein binding function suggests that these proteins participate in stabilizing and restructuring the cytoskeleton.

4.8.4.4 Dynactin Binding (GO:0031242)

Dynactin is a multiprotein complex essential for cellular transport, aiding the motor protein dynein in moving vesicles and organelles along microtubules. The binding affinity for dynactin suggests that DISC1 and its interactors may be involved in intracellular transport processes, which are critical for neuron function and development.

The statistical significance of each molecular function is indicated by the –log(Padj) values displayed as bars next to each term, with higher values representing stronger statistical support.

A heatmap further contextualizes these functions across multiple conditions or datasets, visually displaying the degree of association each molecular function has with specific proteins or experimental conditions. This information provides insights into the molecular roles of DISC1 interactors, emphasizing their involvement in cytoskeletal dynamics and intracellular transport mechanisms.

4.8.5 GO (Biological Process)

The Gene Ontology: Biological Process (GO) category illustrates the broader biological roles that DISC1 and its interactors fulfill in the cellular and organismal context, particularly processes relevant to neurodevelopment.

Terms like Cerebral Cortex Development, Neuroblast Proliferation, Neural Precursor Cell Proliferation, Neuron Migration, and Wnt Signaling Pathway suggest that DISC1 interactors are heavily involved in neural development. These processes are crucial for brain structure formation and neural connectivity, indicating that DISC1 has roles in establishing brain architecture.

Positive Regulation of Biological Processes, Establishment of Cell Polarity, and Intracellular Transport highlight DISC1's function in guiding cell organization and intracellular transport, which are fundamental in the development of complex neural networks and cellular communication pathways.

These biological processes are shown with their statistical enrichment values, represented by –log(Padj), indicating the level of significance associated with each process. Additionally, the heatmap shows associations of specific processes across different datasets or experimental conditions, providing an overview of how these biological roles vary by context.

This analysis supports the notion that DISC1 and its interactors play crucial roles in brain development, neurogenesis, and cellular transport, underscoring their potential relevance in understanding neuropsychiatric disorders.

4.8.6 GO (Cellular Component)

The Gene Ontology: Cellular Component (GO) category specifies the subcellular localization of DISC1 and its interactors, revealing where within the cell these proteins primarily operate: Key terms such as Centrosome (GO:0005813), Microtubule Organizing Center, Cytoskeleton, Synapse, and Neuron Projection indicate that DISC1 and its interactors are localized in structural components critical for cellular organization and neural connectivity. The presence of DISC1 in the Spindle (GO:0005819) during cell division further supports its role in mitotic regulation, suggesting that it may be involved in orchestrating cellular organization and chromosome segregation during cell division.

Localization to the Axon and Plasma Membrane Bound Cell Projection highlights DISC1's involvement in the structural integrity and functional organization of neurons, which are essential for neural signaling and plasticity. The cellular component analysis, with statistical significance displayed as –log(Padj), underscores DISC1's critical localization in cellular structures that govern cell shape, division, and neural connectivity. The heatmap displays which proteins are associated with these cellular locations, providing insights into the specific roles DISC1 and its interactors may play in cellular architecture and neural signaling pathways.

4.8.7 KEGG Pathways

The KEGG (Kyoto Encyclopedia of Genes and Genomes) Pathway analysis highlights the specific metabolic and signaling pathways that DISC1 and its interactors participate in.

Cell Cycle (KEGG): This pathway indicates that DISC1 and its interactors have roles in regulating the cell cycle, a fundamental process for cell growth, division, and maintenance. This suggests that DISC1 may be involved in processes that support cellular proliferation, which is particularly important in neural progenitor cells during brain development.

The significance of the cell cycle pathway is illustrated by –log(Padj), with a heatmap showing the association of proteins or samples within this pathway. These insights point towards DISC1's potential involvement in proliferative processes, with implications for neurogenesis and neural maintenance.

4.8.8 REACTOME (Reactome Pathways)

Reactome Pathways analysis reveals DISC1's involvement in a range of processes relevant to the cell cycle and mitosis: Pathways such as Cell Cycle Mitotic, M Phase, Spindle Checkpoint, and Separation of Sister Chromatids suggest that DISC1 interactors play crucial roles in mitotic cell division, particularly in processes that ensure the accurate segregation of chromosomes.

Additional terms, such as AURKA Activation by TPX2 and G2/M Transition, highlight DISC1's association with regulatory pathways that control the progression of cells through critical phases of the cell cycle. This analysis, with –log(Padj) values to indicate pathway significance, demonstrates DISC1's potential role in maintaining cellular fidelity during division, an essential function for brain development and repair. The pathway heatmap shows protein associations within these cell cycle processes, reinforcing DISC1's role in supporting cell division.

4.8.9 WP (WikiPathways)

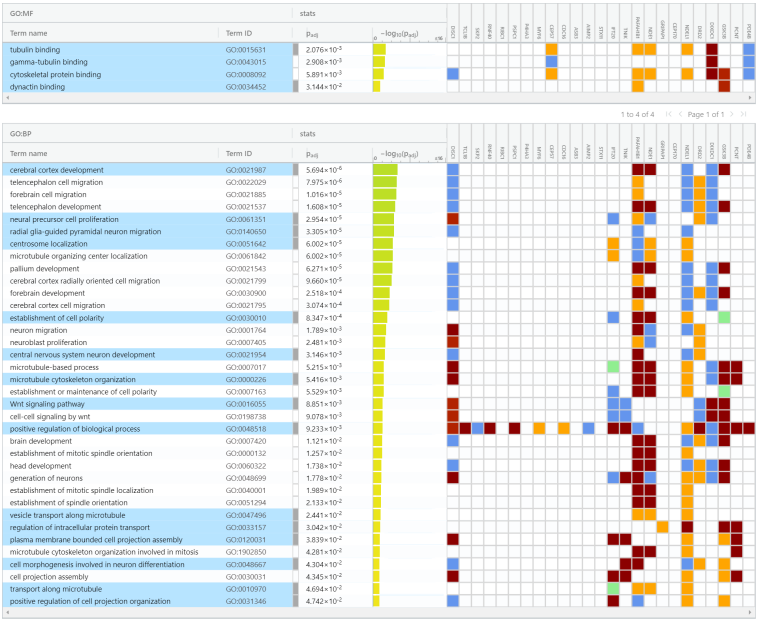
The WikiPathways (WP) analysis captures additional pathways, focusing on gene copy number variations (CNVs) associated with DISC1. Notable terms such as 1p31.3 YWHAE Copy Number Variation and PAFAH1B1 Copy Number Variation imply that variations in DISC1 and its interactors may be implicated in neurodevelopmental or neuropsychiatric disorders. These CNVs may impact neural circuitry or synaptic plasticity, potentially contributing to conditions such as schizophrenia.

The statistical significance of these CNVs is illustrated through –log(Padj) values, and the heatmap highlights the involvement of specific samples or conditions. This

analysis suggests that genetic variations in DISC1 may be an underlying factor in its association with psychiatric disorders.

4.8.10 CORUM (Core Database of Complexes)

CORUM provides insight into specific protein complexes involving DISC1, highlighting its physical interactions with other proteins. Complexes such as PDE4B– DISC1 and HTT–DISC1–PDE4B underscore the role of DISC1 in cellular signaling, particularly pathways that influence neuronal signaling and synaptic transmission. The significance of each protein complex is shown through –log(Padj) values, with the heatmap representing sample-specific associations. These complexes support DISC1's functional importance in neural pathways, with potential implications for targeting DISC1 in therapeutic strategies for neuropsychiatric disorders. This figure **??** illustrates a multi-dimensional enrichment analysis that provides insights into the roles of DISC1 and its interactors in cellular processes, localization, and pathways. DISC1's involvement in neurodevelopment, cytoskeletal organization, and cell cycle regulation highlights its potential as a therapeutic target in conditions like schizophrenia. By integrating findings from multiple databases, this analysis underscores the significance of DISC1 in neural function and presents avenues for future research to explore DISC1 as a focal point in the pathology and treatment of psychiatric disorders.



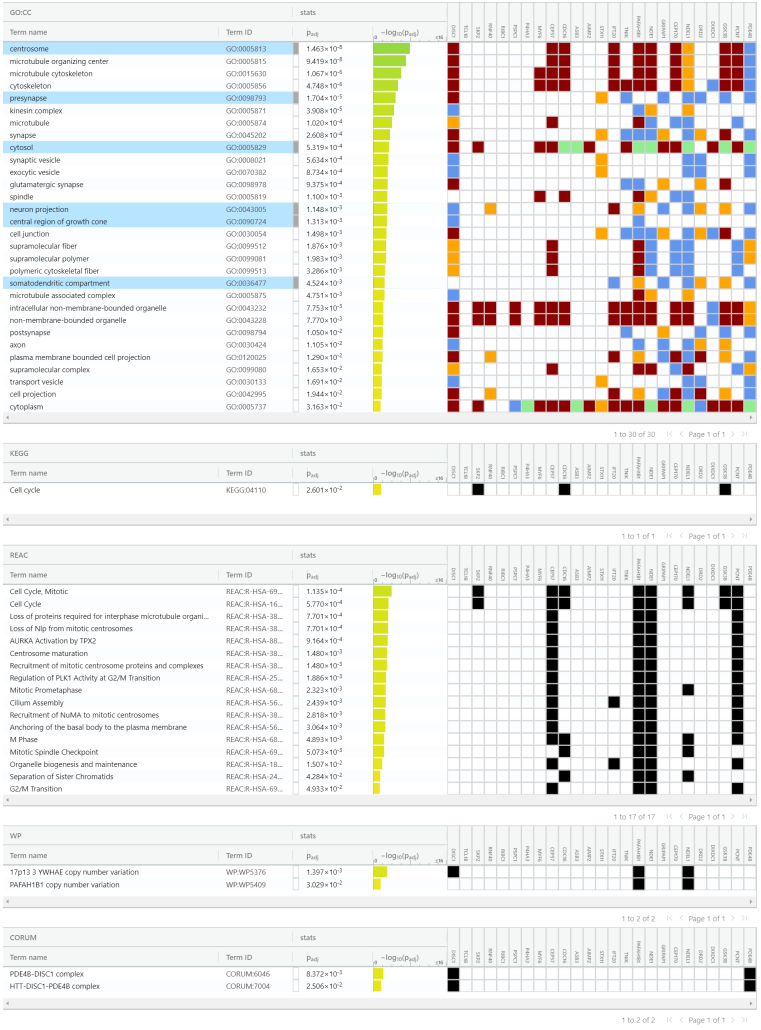


FIGURE 4.27: Overall DISC1 pathway enrichment results.

Chapter 5

Discussion

This study aims to address the therapeutic potential of schizophrenia where in the initial step meta-analysis was performed to create a bridge between DISC1 and schizophrenia. The meta-analysis was conducted from the studies of the last decade which strongly indicated association between DISC1 and schizophrenia. These findings would pave way in understanding the diverse functional nature of DISC1 as a scaffolding protein which binds with more than two hundred binding partners and performing the key function of neuronal proliferation, migration and differentiation.

Secondly the determination of three-dimensional structure prediction of DISC1 C-terminal would enhance our understanding of DISC1 as a suitable therapeutic target because previously there was limited information available regarding the key molecular interactions in the absence of crystal structure. This current study will enable us to align broad functional aspects with therapeutic utility of schizophrenia [279].

Lastly DISC1 pathway enrichment was performed to find out three three key molecular interactors of NDEL1, NDE1, PAFAH1B1 also known as Lissencephaly 1 (LIS1). These molecular interactors can be targeted to exploit the therapeutic potential of schizophrenia. Our previous understanding regarding Disrupted in schizophrenia 1 (DISC1) originally identified from a gene directly disrupted by a balanced translocation in a large Scottish family with a high loading of major mental illness [280].

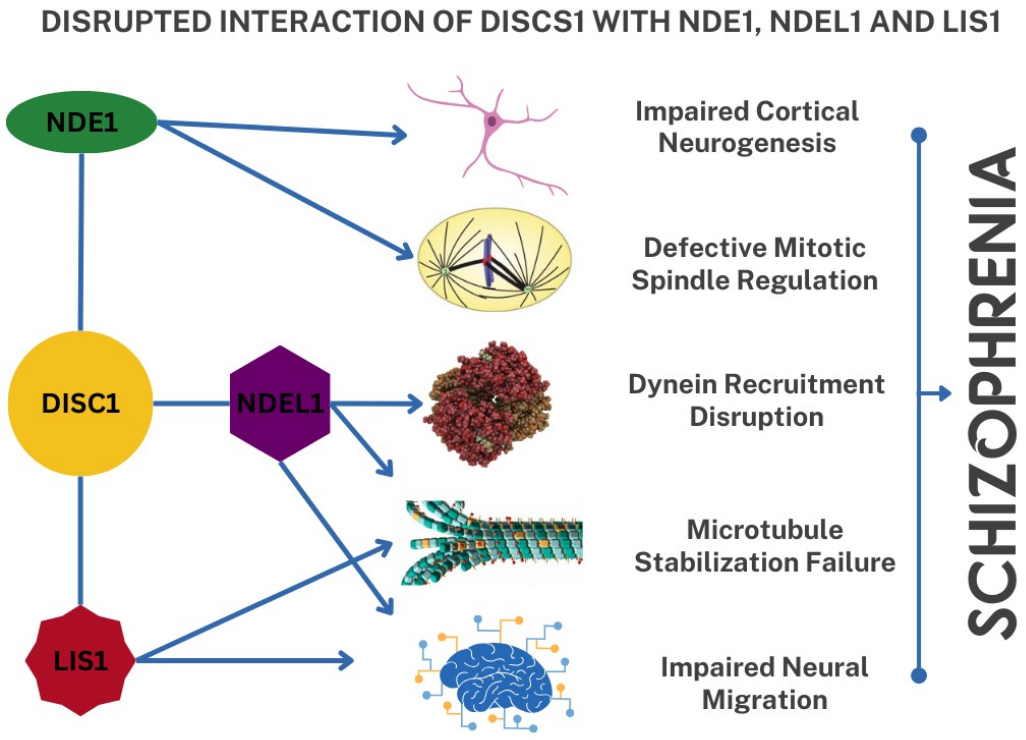


FIGURE 5.1: The figure indicates the DISC1 interactors (NDEL1, PAFH1B1(LIS1)) screened, shortlisted in the pathway enrichment analysis and their role in schizophrenia pathophysiology highlighting the importance of these proteins as therapeutic agents

The term "DISCopathies" was previously introduced to describe a group of brain disorders linked to abnormalities in the DISC1 protein, treating them as a unified disease category. DISC1 plays a central role in multiple neurodevelopmental pathways, at least some of which contribute to the underlying mechanisms of major psychiatric disorders. Functioning as a scaffold protein, DISC1 interacts with various other proteins several of which are independently associated with increased risk for serious mental health conditions [281].

The notion of protein structure-function riddle has been the prism of this study where DISC1 physiochemical parameters provide a new dimension of DISC1 protein and its role in schizophrenia pathophysiology. Let me shed light on the various determined physiochemical parameter such as aliphatic index 93.15 (thermally stable intracellular protein); negative GRAVY value -0.589 (hydrophilic nature), DISC1 protein calculated half-life variable (20 hours; 30 Minutes; 10 hours) in various cell lines indicate the

utility of this protein to perform the key functions; neuronal migration, proliferation and signaling emulating functional importance of DISC1 protein.

The predicted secondary structure of DISC1 C-terminus is alpha-helix dominated (76% residues). DISC1 is a large protein of 854 amino acids with a proportional high molecular weight stationed intracellularly to act as a hub protein and interact with other molecular partners. There is a gap between the available protein structures of DISC1 whether in protein data bank (https://www.rcsb.org/) or alpha fold (https://alphafold.ebi.ac.uk/) so in this study DISC1 C-terminal through threading approach generating a useful model after confirming through various structure validation tools. So, this study is effective in using DISC1 C-terminus as a tool to unravel functional significance in schizophrenia pathophysiology.

The analysis of DISC1 pathway enrichment has revealed three key molecular interactors: NDEL1, NDE1, and PAFAH1B1. As a crucial scaffolding protein, DISC1 plays a fundamental role in modulating various signaling pathways essential for cortical and hippocampal development. Its broad network of protein interactions allows it to influence multiple neurodevelopmental processes, underscoring its significance in brain function [282].

One of the most significant binding proteins is Nuclear Distribution Element-Like 1 (NDEL1), also known as Nudel. Along with its closely related paralog, NDE1 (also referred to as NudE), it serves as a crucial neurodevelopmental protein with essential roles in brain development and function [283].

NDEL1 plays a multifaceted role in neurodevelopment, with a particular emphasis on cortical formation. It contributes to this process by regulating the motor protein dynein and interacting with Lissencephaly 1 (LIS1), which is encoded by the PAFAH1B1 gene. This interaction is crucial for proper neuronal migration and brain development [284].

The proper functioning of DISC1 and its binding partners, NDEL1 and NDE1, is essential for neurodevelopmental processes that are often disrupted in schizophrenia (SZ). These proteins play key roles in neuronal migration, synaptic formation, and

intracellular signaling, all of which are crucial for normal brain development and function [285].

This study explores the intricate and debilitating nature of schizophrenia, with a focus on identifying new therapeutic targets to more effectively address its complex pathology. Like many psychiatric disorders, schizophrenia is diagnosed and treated based on its symptoms, which can vary significantly among individuals. These variations often lead to diverse treatment strategies tailored to specific manifestations, such as hallucinations, delusions, cognitive deficits, or social withdrawal. Despite progress in psychiatric research, managing schizophrenia remains a significant challenge due to its unclear underlying mechanisms, which stem from a combination of genetic and environmental influences. The disorder's multifaceted nature complicates both its comprehension and treatment, as no single factor or pathway fully accounts for its development.

Research on the genetic basis of schizophrenia has consistently highlighted a strong hereditary component, with genetic predisposition playing a crucial role in an individual's susceptibility to the disorder. Studies involving families, twins, and adoptions provide substantial evidence for schizophrenia's heritability, indicating that multiple genes contribute to the overall risk, each exerting a relatively small effect.

This study employs a candidate gene approach, which focuses on specific genes that are either known or suspected to be linked to schizophrenia. By conducting a detailed analysis of these genes, the research aims to uncover the molecular mechanisms underlying the disorder. Investigating the pathways associated with these genes enables researchers to identify dysfunctional biological processes, offering valuable insights into potential therapeutic targets for more effective treatment strategies. This study follows a systematic, step-by-step approach to ensure a comprehensive investigation. It first considers the role of environmental factors in schizophrenia, recognizing their complex interactions with genetic predisposition. Various environmental influences have been linked to an increased risk of schizophrenia, including prenatal and perinatal complications such as maternal infections, malnutrition, and oxygen deprivation, all of which may disrupt fetal brain development.

Additional risk factors include advanced parental age, urban living conditions, and socioeconomic disadvantages. These elements, whether individually or in combination, can impact brain development and function, thereby increasing susceptibility to schizophrenia. Gaining deeper insights into these environmental risks may help in developing preventive strategies and interventions, potentially reducing the likelihood of schizophrenia in genetically predisposed individuals.

After analyzing environmental factors, this study shifts its attention to genetic influences, employing a candidate gene approach to explore the complex genetic framework of schizophrenia. Among the key genes implicated in schizophrenia research is Disrupted in Schizophrenia 1 (DISC1) this gene has gained prominence due to its crucial involvement in neurodevelopment and synaptic regulation.

As a scaffolding protein, DISC1 interacts with multiple molecular partners that play essential roles in brain development, cellular signaling, and neurotransmission. Structural disruptions or mutations in DISC1 have been associated with dysfunctions in these critical processes, many of which are commonly observed in individuals affected by schizophrenia. Therefore, an in-depth analysis of DISC1 and its related pathways can offer valuable insights into the disorder's underlying mechanisms, potentially paving the way for novel therapeutic strategies.

In the next phase, the study progresses into the molecular pathways associated with DISC1, utilizing pathway enrichment analysis to explore how these pathways may be disrupted in schizophrenia. This analytical approach identifies clusters of genes and proteins that interact within specific biochemical networks, providing insights into how genetic variations influence biological functions.

By examining pathways linked to DISC1, the study aims to uncover key biochemical processes that may be impaired in schizophrenia. These may include synaptic plasticity, neurogenesis, and intracellular signaling cascades, all of which are essential for cognitive function and emotional regulation. A thorough investigation of these enriched pathways allows researchers to better understand their molecular roles and identify potential targets for therapeutic intervention.

The study identifies several enriched pathways associated with essential cellular functions, including neurotransmitter release, synaptic signaling, and neuroplasticity. Disruptions in these pathways are commonly linked to the cognitive and behavioral symptoms observed in schizophrenia. By focusing on these molecular pathways, the research aims to pinpoint specific intervention points where targeted therapies, such as pharmaceuticals or other treatment strategies, could be developed to restore normal function. Beyond identifying potential therapeutic targets, the pathway analysis offers a deeper insight into the biochemical and physiological abnormalities underlying schizophrenia, contributing to a more comprehensive understanding of the disorder.

In conclusion, this study takes a comprehensive approach to understanding schizophrenia by examining both environmental and genetic influences. Utilizing the candidate gene approach, it highlights the significance of genetic pathways, particularly those involving DISC1, in the pathology of the disorder. Through pathway enrichment analysis, the research uncovers key molecular interactions and signaling cascades that may serve as potential therapeutic targets.

By identifying and mapping these disrupted pathways, the study provides new directions for therapeutic research, aiming to develop treatments that directly address the underlying biological mechanisms of schizophrenia. This approach not only contributes to symptom management but also advances efforts to target the root causes of this complex mental health disorder, ultimately improving treatment strategies and patient outcomes.

DISC1 plays a critical role in regulating neuronal migration, ensuring the proper formation of cortical layers during brain development. It also facilitates synapse formation, which is essential for establishing and maintaining neural connectivity. Additionally, DISC1 supports intracellular signaling pathways that influence neuronal communication, further highlighting its importance in neurodevelopment and brain function.DISC1 dysfunction has been strongly linked to schizophrenia, with evidence suggesting that mutations or altered expression levels can disrupt normal brain development. Disruptions in DISC1-regulated pathways may contribute to neurodevelopmental abnormalities, affecting neuronal migration, differentiation, and synaptic

formation. Additionally, synaptic dysfunction resulting from impaired DISC1 interactions may lead to altered neurotransmission, increasing susceptibility to psychiatric disorders like schizophrenia. and intracellular signaling deficits could underlie psychiatric symptoms.

Understanding DISC1's functional disruptions could provide crucial insights into the neuropathology of schizophrenia, shedding light on how its altered interactions and signaling pathways contribute to the disorder. Given its broad role in neurodevelopment and synaptic regulation, DISC1 remains a high-value therapeutic target for developing novel treatment strategies aimed at mitigating schizophrenia's complex pathophysiology. The research highlights DISC1's role as a key scaffolding protein, integrating multiple pathways essential for neurogenesis, synaptic plasticity, and intracellular signaling. This underscores its central function in brain development and its potential as a therapeutic target in schizophrenia research.

DISC1 interacts with multiple molecular partners, organizing key neurodevelopmental pathways that are essential for brain formation and function. Through these interactions, DISC1 plays a pivotal role in supporting the structural and functional integrity of neuronal networks, ensuring proper neuronal signaling, connectivity, and maintenance. Disruptions in these pathways may contribute to neurological and psychiatric disorders, highlighting DISC1 as a critical target for further research and therapeutic development. DISC1 plays a key role in neuronal differentiation, migration, and maturation, essential processes in brain development. Additionally, it contributes to synaptic strength and plasticity, which are crucial for learning and memory. These functions highlight DISC1's importance in maintaining neural circuit integrity, and disruptions in its activity may be linked to cognitive deficits and neuropsychiatric disorders. Understanding these roles can aid in developing therapeutic interventions targeting DISC1-related pathways.

DISC1 plays a crucial role in pathways that regulate neuronal communication and homeostasis. Its interactions help maintain proper synaptic signaling and intracellular transport, ensuring stable neuronal function. Disruptions in DISC1 function can lead to abnormal neurotransmission, which may contribute to increased susceptibility to

psychiatric disorders, including schizophrenia. Understanding these disruptions could provide valuable insights into the molecular mechanisms underlying mental health conditions, paving the way for targeted therapeutic strategies.

Given its broad functional influence, DISC1 is a promising target for schizophrenia research. Its involvement in neuronal development, synaptic plasticity, and intracellular signaling highlights its critical role in maintaining brain function and integrity. Understanding DISC1's molecular interactions could lead to novel therapeutic interventions aimed at stabilizing neuronal function and mitigating the complex pathology of schizophrenia. By targeting DISC1-related pathways, researchers may develop alternative treatments that address the limitations of existing pharmacological therapies.

By investigating DISC1's molecular network, your study could advance therapeutic strategies aimed at restoring neuronal stability and cognitive function in schizophrenia patients. The study aims to decipher the genetic basis of schizophrenia by investigating DISC1's molecular interactions and the pathways it influences. This approach holds promise for identifying novel therapeutic targets, especially for patients who do not respond to current treatments.

Analyzing DISC1's contribution to schizophrenia at the cellular and genetic levels is crucial for understanding its role in neurodevelopment and brain function. This investigation focuses on how DISC1 regulates synaptic function, neuronal maintenance, and intracellular signaling, all of which are essential for proper neuronal connectivity and brain integrity. Disruptions in DISC1's function may lead to abnormal neurodevelopmental processes, contributing to psychiatric disorders like schizophrenia. By examining these mechanisms, researchers can identify potential intervention strategies that target DISC1-related pathways.

Identifying the genes and molecular pathways influenced by DISC1 is essential for understanding its role in neurodevelopment and psychiatric disorders. By mapping key regulatory networks, researchers can uncover mechanisms that may contribute to schizophrenia pathophysiology. This approach could highlight critical molecular

interactions and signaling cascades involved in neuronal development, synaptic function, and intracellular transport, providing insights into potential therapeutic targets for treating schizophrenia and related conditions.

Exploring DISC1 and its interactors as drug targets could open new avenues for therapeutic interventions in psychiatric disorders, particularly schizophrenia. Given DISC1's central role in neurodevelopment, synaptic plasticity, and intracellular signaling, targeting its protein interaction network may offer innovative strategies to modulate dysfunctional pathways. This research provides a foundation for alternative treatments that address the limitations of existing pharmacological therapies, potentially leading to more effective and personalized approaches for managing psychiatric conditions.

By shedding light on DISC1's functional network, this research contributes to a deeper understanding of schizophrenia and may pave the way for innovative therapeutic strategies.

DISC1 plays a crucial role in neuronal processes, with its dynamic conformational changes and widespread cellular presence linking it to essential functions in neurodevelopment and synaptic signaling.

DISC1 localizes to multiple key neuronal structures, reflecting its diverse functional roles. In the centrosome and cytoskeleton, it supports neuronal migration and intracellular transport within mitochondria, DISC1 is implicated in neuronal energy metabolism and cellular homeostasis, essential for maintaining neuronal health. In the cytoplasm and axons, it plays a role in neuronal differentiation and axon elongation, which are crucial for proper neural circuit formation. At synapses, DISC1 influences synaptic plasticity and signal transduction, processes fundamental for cognitive function and neural communication.

During early central nervous system (CNS) development, DISC1 is highly expressed, playing a crucial role in neuronal proliferation, migration, and differentiation, which are fundamental for proper brain formation. In the later stages and adulthood, DISC1 expression levels decline, suggesting that its primary function is in early neurodevel-

opment. However, residual DISC1 activity may still contribute to neuronal maintenance and synaptic function, indicating its ongoing relevance in brain stability and connectivity. The temporal regulation of DISC1 suggests that disruptions during early neurodevelopment could have long-term consequences, potentially contributing to schizophrenia and related psychiatric disorders. Additionally, its localization to key neuronal structures, including the centrosome, cytoskeleton, mitochondria, and synapses, highlights its essential role in maintaining brain integrity and function. These factors make DISC1 a compelling target for therapeutic research, as understanding its molecular interactions could pave the way for novel treatment strategies for neurodevelopmental disorders. The spatial and temporal regulation of DISC1 expression highlights its diverse biological roles beyond neurodevelopment.

In humans, DISC1 exhibits its highest expression in the brain, heart, and placenta, emphasizing its critical role in neurodevelopment and systemic physiological functions. In mice, DISC1 is strongly expressed in the brain, heart, kidney, and testis, suggesting a conserved but slightly varied expression pattern across species. These tissue-specific expression profiles indicate that DISC1 may have broader biological functions beyond neurodevelopment, potentially influencing other organ systems. During neonatal and infancy stages, DISC1 expression peaks, aligning with critical periods of brain formation and synaptic connectivity. As the brain matures, DISC1 expression declines with age, suggesting a shift from its developmental roles to neuronal stabilization. This regulation highlights the protein's crucial involvement in early neurodevelopment and its potential role in maintaining neural circuits in adulthood.

DISC1's early high expression underscores its essential role in neuronal growth, migration, and synaptic formation. The progressive decline in its expression may indicate a transition from active neurodevelopment to the maintenance of neural circuits. Understanding these expression patterns provides valuable insights into how dysregulation of DISC1 could contribute to neurodevelopmental disorders such as schizophrenia.

However, this developmental regulation implies that any early disruptions in DISC1 function may have lasting consequences on brain structure and function, potentially contributing to neurodevelopmental disorders such as schizophrenia. Alterations in

the timing or levels of DISC1 expression could affect critical neurodevelopmental processes, leading to abnormal connectivity and brain architecture. A crucial objective of this research has been to determine the three-dimensional structure of DISC1, a large protein composed of 854 amino acids. However, full-length crystal structures of DISC1 remain unavailable, with only limited structural data currently deposited in databases such as the Protein Data Bank (PDB).

This lack of comprehensive structural information poses a challenge in understanding DISC1's molecular mechanisms, particularly its role in neurodevelopment and synaptic function. The DISC1 protein remains partially uncharacterized in terms of 3D structure, as only small segments of its complexes are available in the Protein Data Bank (PDB, https://www.rcsb.org/). This limited structural data hinders a complete understanding of DISC1's molecular interactions and its role in neurodevelopmental processes. Structurally, DISC1 is divided into two primary domains. The N-terminal domain (amino acids 1–350) is largely disordered and flexible, enabling it to interact dynamically with multiple binding partners. In contrast, the C-terminal domain (amino acids 350–854) is more structured and plays a crucial role in intracellular interactions, particularly in processes such as neuronal transport and synaptic signaling. This structural distinction highlights the functional versatility of DISC1, with the N-terminal domain facilitating adaptable protein interactions, while the C-terminal domain contributes to the stability and regulation of key cellular pathways.This structural duality suggests that DISC1's flexibility and stability are essential for its diverse functions in the brain, influencing pathways related to synaptic plasticity, cellular transport, and neural development.

Further structural studies are essential to uncover additional details about DISC1's molecular configuration and functional dynamics. A more in-depth understanding of its 3D structure could provide crucial insights into the molecular mechanisms by which DISC1 contributes to neurodevelopmental processes and its association with psychiatric disorders. By clarifying these structural features, researchers can identify potential therapeutic targets, offering new opportunities to modulate DISC1-related pathways in conditions like schizophrenia. Such findings could pave the way for ther-

apeutic strategies aimed at stabilizing DISC1 function or compensating for its dysfunction, ultimately contributing to advancements in mental health treatments. The N-terminal region of DISC1 is characterized by a disordered structure with minimal evolutionary conservation across species. This suggests that the N-terminal domain may not be essential for maintaining DISC1's core structural integrity or universal biological functions. Instead, its variability implies a potential role in species-specific or context-dependent processes.

In contrast, the C-terminal region of DISC1 (spanning approximately residues 350–854 in humans) exhibits high evolutionary conservation. This strong conservation suggests that the C-terminal domain is integral to DISC1's fundamental biological roles, particularly in neurodevelopment, synaptic regulation, and protein-protein interactions. These findings reinforce the idea that the C-terminal segment serves as the primary functional region of DISC1, contributing significantly to its role in mental health and neurological disorders.

The C-terminal tail of DISC1 is predicted to exhibit a highly structured conformation, primarily consisting of alpha-helices arranged in an orderly and stable pattern. Notably, this domain features at least four regions with a strong propensity for coiled-coil formation, a structural motif that is well-known for facilitating stable protein-protein interactions.

These coiled-coil regions likely serve as key docking sites for DISC1's molecular partners, reinforcing its role as a scaffolding protein in essential cellular and neurobiological processes. Given its conserved and functionally significant architecture, the C-terminal domain of DISC1 is central to its biological activity, particularly in pathways related to neurodevelopment, synaptic organization, and psychiatric disorders such as schizophrenia. The C-terminal region of DISC1 plays a pivotal role in cellular and neurological functions, serving as a crucial structural and functional domain that facilitates DISC1's involvement in neurodevelopment, synaptic stability, and neural signaling. The high degree of conservation and structural stability of this domain suggest its essential contribution to key molecular pathways associated with mental health.

Given its importance in modulating functions implicated in schizophrenia and other neuropsychiatric disorders, the C-terminal region is a focal point for research aiming to uncover DISC1's influence on brain function and disease mechanisms. Understanding its structural characteristics and interaction networks can provide deeper insights into potential therapeutic targets, paving the way for more precise interventions in mental health disorders. To gain deeper insights into the structural characteristics of DISC1, studies have examined its secondary structure, revealing that it is predominantly composed of alpha-helices. Structural data from the Protein Data Bank (PDB) provide crucial information on DISC1's interactions with key molecular partners. Notably, two PDB entries—PDB ID 5YI4 (DISC1/Ndel1 complex) and PDB ID 6IRR (DISC1/ATF4 complex)—offer high-resolution crystal structures that elucidate the conformational arrangement of DISC1 in complex with its interactors.

These structural models highlight critical interaction interfaces, shedding light on potential binding sites essential for DISC1's function. By analyzing these structural details, researchers can better understand how DISC1 mediates neurodevelopmental and synaptic processes, which may have significant implications for therapeutic strategies targeting DISC1-related pathways in schizophrenia and other neuropsychiatric disorders.

Based on the structural data, the C-terminal region of DISC1 was analyzed using a threading-based modeling approach to construct an accurate structural model. This technique facilitated an in-depth investigation of the C-terminal domain's interactions with molecular partners, genetic polymorphisms, and neuropsychiatric pathways. Through this modeling process, the structural quality of the DISC1 C-terminal domain was refined, improving its predictive accuracy for interaction sites and enhancing its utility as a framework for functional studies. The resulting model provides a valuable structural basis for examining DISC1's molecular interactions and its role in key regulatory pathways linked to schizophrenia.

By mapping these interactions, researchers can gain insights into how genetic variations within DISC1, particularly in its C-terminal region, influence neurodevelopment and synaptic function. This refined model serves as a critical tool for studying

DISC1's therapeutic potential, offering a foundation for the development of targeted interventions that modulate DISC1's role in neuropsychiatric disorders.

This study conducted a comprehensive analysis of the DISC1 (Disrupted in Schizophrenia 1) protein, focusing on its evolutionary significance and the therapeutic potential of its interaction network. DISC1 is widely recognized for its critical role in neurodevelopmental processes and its association with mental health disorders, particularly schizophrenia.

5.1 Evolutionary Analysis of DISC1

The evolutionary significance of DISC1 was explored by constructing a phylogenetic tree comparing the human DISC1 protein sequence with that of six other species: mouse, chimpanzee, bat, rabbit, gorilla, and dog. These species were selected to represent a range of evolutionary proximities to humans, allowing for a detailed assessment of DISC1's evolutionary trajectory across mammalian lineages. Our phylogenetic analysis traced common ancestry, evolutionary divergence, and sequence similarities between species. Notably, the study found a particularly close evolutionary relationship between human DISC1 and its orthologs in gorilla and chimpanzee, aligning with the shared classification of these species within the order Primates in the class Mammalia. This high degree of conservation suggests that DISC1 plays fundamental roles in neurodevelopment and brain function, which have been preserved across millions of years. The strong phylogenetic conservation of DISC1 in primates supports the hypothesis that this gene is critical to advanced cognitive functions, synaptic integrity, and neural signaling.

5.2 Protein Interaction Network of DISC1

A crucial aspect of this study involved mapping DISC1's protein interactors and analyzing the biological pathways they influence. Understanding DISC1's interaction

network is essential, as these protein-protein interactions play a fundamental role in neurodevelopment and other cellular processes. To achieve this, DISC1 interaction data were retrieved from two well-established databases:

- STRING (https://string-db.org/): Offers extensive interaction data supported by high-throughput experiments and computational predictions.
- BioGRID (https://thebiogrid.org/): Focuses on experimentally validated protein-protein interactions across different species.

To ensure the accuracy and relevance of the data, strict selection criteria was applied, including only experimentally validated interactors identified through high-throughput studies. This stringent approach resulted in the identification of eight DISC1 interactors from STRING and 21 additional interactors from BioGRID, yielding a high-confidence dataset of DISC1-associated proteins.

Among these interactors, three proteins—NDEL1 (NudE neurodevelopment protein 1-like 1), NDE1 (NudE nuclear distribution protein 1), and PAFAH1B1 (platelet-activating factor acetylhydrolase 1b regulatory subunit 1)—were consistently identified in both STRING and BioGRID databases. The recurrence of these proteins across multiple data sources highlights their crucial role in the DISC1 interaction network. Given their well-established functions in neuronal migration and cytoskeletal organization, these interactors are likely key regulators of DISC1's role in maintaining brain structure and function, reinforcing their potential as therapeutic targets in neuropsychiatric disorders such as schizophrenia.

5.3 Pathway Enrichment Analysis

After identifying DISC1 interactors, a pathway enrichment analysis was conducted to examine the biological processes and cellular functions linked to DISC1 and its associated proteins. The results highlight DISC1's involvement in several critical cellular mechanisms, including:

1. Cell Division: DISC1 interactors regulate the cell cycle and mitotic division, processes essential for cellular proliferation and tissue development.

2. Neuronal Proliferation and Migration: Key interactors, such as NDEL1 and NDE1, play vital roles in neuronal migration, a crucial process in brain development that ensures proper neuronal positioning, connectivity, and function.

3. Cytoskeletal Organization: DISC1's interactions with cytoskeletal proteins are fundamental for cellular structure maintenance and intracellular transport, both essential for neuronal stability and function.

4. Synaptic Function and Stability: Several DISC1 interactors participate in synaptic stability and plasticity, which are key processes for learning and memory. This aligns with DISC1's established role in supporting neural network integrity.

These findings emphasize DISC1's multifaceted role in neurodevelopment and brain function, reinforcing its significance as a potential therapeutic target in neuropsychiatric disorders such as schizophrenia.

These enriched pathways emphasize the significance of DISC1's interaction network in various neurobiological processes critical to brain development and cognitive function. Since disruptions in these pathways are associated with neuropsychiatric disorders like schizophrenia, gaining deeper insight into the specific roles of DISC1 and its interactors lays the groundwork for identifying new therapeutic strategies. Understanding these molecular mechanisms may aid in the development of targeted interventions aimed at restoring neuronal stability and cognitive processes in affected individuals.

5.3.1 Therapeutic Implications and Future Directions

The findings from this study present promising avenues for therapeutic research in schizophrenia. Current treatment options often have limited efficacy and may cause adverse side effects, highlighting the need for novel therapeutic targets. The pathway enrichment analysis underscores the role of DISC1 and its interactors in key neurob-

iological processes, suggesting that modulating these pathways could help address the disorder's underlying mechanisms. Targeting DISC1's interaction network, particularly proteins such as NDEL1, NDE1, and PAFAH1B1, could provide alternative treatment strategies. By focusing on these interactors and their associated pathways, researchers may develop interventions that enhance synaptic function, promote neuronal stability, and strengthen cellular resilience. These approaches have the potential to offer significant therapeutic benefits for individuals affected by schizophrenia and related neuropsychiatric disorders.

In conclusion, this study offers a comprehensive analysis of DISC1's evolutionary conservation, its interactome, and its role in key neurobiological pathways. These insights strengthen the case for DISC1 and its associated molecular network as promising therapeutic targets, opening new avenues for research that may lead to more effective treatment strategies for schizophrenia and other neuropsychiatric disorders. By enhancing our understanding of DISC1's involvement in complex cellular mechanisms, this research provides a foundation for innovative therapeutic approaches. It addresses critical gaps in schizophrenia treatment and contributes to the broader advancement of mental health therapeutics, with the potential to improve patient outcomes and quality of life.

Chapter 6

Conclusion and Future Work

6.1 Conclusion

Schizophrenia is a complex neuropsychiatric disorder that, although less prevalent than some other mental health conditions, presents a significant challenge to global healthcare. Those affected often experience severe disruptions in cognitive, emotional, and social functioning, which can hinder their ability to engage fully in daily life and contribute to society. Beyond the individual, the disorder also places a substantial burden on families and communities, leading to notable social and economic consequences. Therefore, there is an urgent need for more effective treatments that address the fundamental causes and key biological pathways associated with schizophrenia.

Research has increasingly recognized genetic factors as critical in the development of schizophrenia. This study aims to enhance this understanding by examining a well-established molecular candidate: the Disrupted in Schizophrenia 1 (DISC1) gene. DISC1 functions as a scaffolding protein that interacts with multiple molecular pathways, playing a crucial role in neurodevelopment and synaptic regulation.

By investigating the genetic, structural, and functional properties of DISC1, this study seeks to provide deeper insights into its involvement in schizophrenia's pathophysiology and explore potential therapeutic targets for more effective treatment strategies.

This study places particular emphasis on the DISC1 C-terminal region due to its critical role in binding various molecular interactors that regulate downstream signaling pathways. By integrating structural and pathway analyses, this research seeks to identify potential therapeutic targets, especially DISC1 interactors of NDEL1, NDE1 and PAFAH1B1 identified through pathway enrichment from different data sources performing the important function of neuronal migration, synaptic function and cytoskeletal dynamics which may be leveraged in future treatment strategies.

A comprehensive review of existing literature highlights the significance of genetic factors in the development of schizophrenia, with DISC1 emerging as one of the key genes implicated. DISC1 has been found to influence essential neural processes such as migration, synaptic formation, and cognitive-related signaling pathways—all of which are frequently disrupted in individuals with schizophrenia. Prior research has linked structural variations, mutations, and other alterations in DISC1 to an elevated risk of developing the disorder. The decision to focus on DISC1 is well-supported, as its network of interactions spans multiple neurodevelopmental and synaptic pathways, both of which are fundamental to maintaining normal cognitive function.

To gain a comprehensive insight into DISC1's involvement in schizophrenia, this study adopted a multi-dimensional approach. The primary focus was to analyze the three-dimensional structure of the DISC1 protein, with particular emphasis on its C-terminal region due to its key role in facilitating molecular interactions. Structural investigations were carried out using advanced computational techniques, including molecular dynamics simulations and homology modeling, to determine the spatial organization of DISC1 and predict how its conformation influences interactions with other proteins. Understanding these structural characteristics is crucial, as such molecular interactions play a fundamental role in neurobiological processes that may become dysregulated in schizophrenia.

Building on the structural analysis, this study explored the evolutionary significance of DISC1 by comparing its sequence across multiple species. This comparative approach aimed to determine the extent of DISC1's conservation and its functional importance in various organisms. Genes that remain highly conserved across evolution typically

play vital roles in fundamental biological processes. Identifying these conserved regions can offer valuable insights into DISC1's role in neural function and its potential evolutionary link to human neuropsychiatric disorders. Through phylogenetic analysis and sequence alignment, key regions of DISC1 were found to be preserved across species, suggesting that these segments are critical for its role in brain function.

A key aspect of this study involved examining the interactions between DISC1 and its molecular partners through pathway enrichment analysis. This approach helped uncover interconnected pathways that may contribute to the development of schizophrenia. Using pathway enrichment tools such as KEGG, Reactome, and STRING, the study identified several biological pathways influenced by DISC1, including synaptic signaling, neurogenesis, and cell cycle regulation. By mapping these interactions, a set of genes associated with these pathways was highlighted as potential candidates for further investigation into the molecular mechanisms underlying schizophrenia. These identified genes may serve as biomarkers or therapeutic targets, as they are involved in crucial cellular processes that are often disrupted in schizophrenia.

The results of the pathway enrichment analysis highlight DISC1 as a key molecular hub within a network of pathways essential for brain development and function. Many of these pathways are directly involved in synaptic signaling and neural plasticity, both of which are commonly disrupted in schizophrenia. By pinpointing genes that closely interact with DISC1, this study provides a foundation for further research into their roles in neuropsychiatric conditions. Modulating these DISC1-associated pathways or targeting specific genes identified in this analysis could pave the way for potential therapeutic strategies to mitigate the symptoms or progression of schizophrenia.

These findings have significant implications for therapeutic advancements in schizophrenia. A deeper understanding of DISC1's function and its interactions with other proteins could aid in identifying potential drug targets or biomarkers for early diagnosis. If specific genes within the DISC1 pathway are confirmed to contribute to schizophrenia, they could serve as foundations for targeted drug development. This approach may ultimately support the implementation of personalized medicine strategies, allo-

wing treatments to be tailored based on an individual's genetic profile, thereby improving therapeutic outcomes.

In summary, this study has advanced our understanding of schizophrenia's molecular and genetic foundations by investigating DISC1 as a key candidate gene. Through structural analysis, evolutionary comparisons, and pathway interaction studies, this research has highlighted potential therapeutic targets. Future studies, including in vivo experiments and clinical trials, are essential to confirm these findings and assess the clinical viability of targeting DISC1-related pathways. The insights gained from this study pave the way for the development of more precise and effective treatments for schizophrenia, offering new possibilities for improved disease management and validation of the DISC1 C-terminus.

6.2 Future Work and Recommendation

6.2.1 Advancing DISC1 Research for Schizophrenia Treatment

Exploring the DISC1 (Disrupted-in-Schizophrenia 1) gene presents a promising avenue for revolutionizing schizophrenia treatment by addressing critical gaps in current mental health care. Today's diagnostic and therapeutic approaches largely depend on observable symptoms rather than underlying neurochemical and genetic mechanisms. By investigating DISC1, researchers can pave the way for more personalized and targeted interventions that focus on the biological foundation of schizophrenia.

6.2.2 Uncovering Genetic Foundations for Innovative Treatments

This approach not only improves treatment precision but also deepens our understanding of schizophrenia's intricate pathophysiology. Gaining clearer insights into

genetic risk factors allows the field to move beyond symptom-based management and work toward addressing the fundamental biological mechanisms underlying the disorder. The N-terminal DISC1 structure also need to be predicted and then both these predicted structures can be sent to wet lab analysis for x-ray crystallography and NMR analysis.

6.2.3 Addressing Quality of Life Challenges Through Modern Technology

Schizophrenia profoundly impacts cognitive function. Leveraging modern technological advancements in neurochemistry, robotics, and artificial intelligence can pave the way for innovative support systems. These technologies have the potential to enhance therapeutic interventions, improve daily functioning, and strengthen mental resilience, ultimately transforming the way schizophrenia is managed and experienced.

6.2.4 Expanding Treatment Possibilities Through Technological Synergy

Integrating advanced technologies with existing schizophrenia research could significantly expand treatment possibilities. This fusion enables a more comprehensive understanding of the disorder, addressing its complexities from multiple perspectives. By leveraging this technological synergy, clinicians may develop more personalized and precise therapeutic strategies.

6.2.5 Aiming for Social and Ethical Progress Through Better Treatment

Enhancing schizophrenia treatments goes beyond scientific advancement—it is a crucial social and ethical responsibility. Tackling the challenges of this disorder demonstrates a commitment to supporting the mental health community and promoting

overall societal well-being. Investing in innovative and compassionate care reflects our shared obligation to address the pressing needs of individuals affected by schizophrenia and other mental health conditions.

6.2.6 Fostering Inclusion and Hope for Schizophrenia Patients

Embracing an inclusive approach can provide schizophrenia patients with hope and motivation, enabling them to build lives centered on well-being. Creating a supportive and accepting environment not only enhances their quality of life but also strengthens society as a whole. When individuals with schizophrenia receive the care and encouragement they need, they can actively participate in their communities, fostering a more compassionate and interconnected society.

By combining research advancements, compassionate care, and technological innovation, a more inclusive and supportive world is created. This commitment ensures that individuals from all backgrounds have the opportunity to lead meaningful lives, fostering a society that values diversity, connection, and shared progress.

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