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COMPUTATIONAL ANALYSIS AND STRUCTURE-BASED DRUG DESIGN FOR MISFOLDING OF HUNTINGTON'S DISEASE FRAGMENT

Uma Kumari[1] Ekta Tyagi[1] Nehal Balhara[2] Ojas Singh[2]

[1]Senior Bioinformatics Scientist, Bioinformatics Project and Research Institute, Noida - 201301, India
[1]Project Trainee, Bioinformatics Project and Research Institute, Noida-201301,India
[2]Project Trainee, Bioinformatics Project and Research Institute,Noida-201301,India
[2]Project Trainee, Bioinformatics Project and Research Institute,Noida-201301,India
Corresponding Author Uma Kumari[1*]

Abstract

Huntington's disease (HD) is a destructive genetic condition inherited dominantly, primarily caused by the expansion of CAG repeats in exon 1 of the Huntington gene on chromosome 4. This expansion results in the production of mutant forms of the huntingtin protein (m-HTT) with abnormal polyglutamine sequences, initiating the disease's progression. The initial 17 residues of amino acids in huntingtin protein [HTT(1-17)] are critical in defending against various pathological manifestations both in laboratory experiments and in living organisms. A recent study investigates how a single-chain variable fragment (scFv) known as C4 effectively blocks the formation of amyloid structures by exon1 fragments of huntingtin under laboratory conditions. The research also explores the structural mechanisms underlying this inhibition and protection by analyzing the crystal structure of the C4 scFv and HTT(1-17) complex. The peptide interacts with specific residues (3-11), forming an amphipathic helix that binds to the antibody fragment. This binding occurs within a dimeric C4 scFv: HTT (1-17) complex, involving the hydrophobic surface and β-sheet interface. Further, elucidation through high-resolution NMR and physicochemical analysis in solution provides deeper insights into how C4 scFv effectively prevents HTT aggregation, thus demonstrating its potential as a therapeutic candidate. Furthermore, computational analysis will be conducted to assess the structural properties, total protein atoms, domains, and functions of protein samples of Huntington homologs related to a protein sequence of interest. This will be followed by an interactive examination of sequence-structure relationships, active sites, and bound chemicals. Active site identification is done using the PDB file format in PyMOL. Drug designing will be performed to study the interaction of Huntington's Disease receptors with associated ligands. Quality estimation of protein structure using server PROCHECK, ERRAT, and Ramachandran plot which identifies possible secondary structure protein can adapt. The alignment program uses clustal omega and InterPro Scan to generate a phylogenetic tree. CADD is used to dock the appropriate ligand to the binding site of the protein. Finally, STRING was used to determine potential protein-protein interaction.

Key Words: Huntington's disease, Drug designing, Quality estimation of protein, protein-protein interaction, structural analysis, phylogenetic relationships.

1. INTRODUCTION

Neurodegenerative diseases represent a formidable challenge in modern medicine, posing significant burdens on healthcare systems and society (Mukherjee S *et al*., 2020). These conditions, characterized by progressive degeneration of neuronal structures and function, often lead to debilitating symptoms and profound declines in quality of life. Among the myriad neurodegenerative disorders, Huntington's disease (HD) stands out as a particularly devastating condition, encompassing a complex interplay of genetic, molecular, and cellular abnormalities (Ganesh S *et al*., 2023). In addition to Huntington's disease, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) contribute to the global burden of neurological morbidity and mortality (Ciurea AV *et al*., 2023). While each of these diseases has distinct clinical manifestations and underlying pathological mechanisms, they share common features, including protein misfolding, aggregation, and neuronal dysfunction (Labbadia J *et al*., 2013).

Huntington's disease (HD) stands as one of the most challenging neurodegenerative disorders, portrayed by a devastating triad of motor dysfunction, cognitive decline, and psychiatric instability (Bano D *et al*., 2011). This hereditary condition exerts a profound impact on affected individuals and their families, often manifesting in mid-adulthood and progressing relentlessly over the course of 15 to 20 years until death. With an estimated prevalence of 5-10 cases per 100,000 individuals worldwide, HD represents a significant burden on healthcare systems and society at large (Conway R., 2016).At the heart of Huntington's disease lies a complex interplay of genetic mutations and molecular aberrations, prominently involving the misfolding and aggregation of

the huntingtin (HTT) protein within neurons of the central nervous system (Gandhi J *et al*., 2019). The causative genetic defect in HD is an expansion of CAG trinucleotide repeats within the HTT gene, leading to an elongated polyglutamine (poly Q) stretch in the HTT protein (Stoyas CA *et al*., 2018). This expanded poly Q tract confers a propensity for HTT protein misfolding, aggregation into insoluble protein aggregates, and subsequent neuronal dysfunction and degeneration (Tabrizi SJ *et al*., 2020). Despite decades of intensive research, effective disease-modifying therapies for Huntington's disease remain elusive, underscoring the urgent need for innovative therapeutic strategies that address the underlying molecular pathology (Akyol S *et al*., 2023). While symptomatic treatments aimed at managing motor and psychiatric symptoms exist, they provide only limited relief and do not alter the course of disease progression (Novak MJ *et al*., 2011).

In recent years, there has been a paradigm shift in the approach to drug discovery and therapeutic intervention in neurodegenerative diseases, including Huntington's disease. Increasingly, researchers are turning to computational analysis and structure-based drug design as powerful tools to unravel the intricate molecular pathways underlying protein misfolding and aggregation and identify novel therapeutic targets (Dunkel P *et al*., 2012).

Computational analysis plays a pivotal role in elucidating the structural determinants of HTT misfolding and aggregation (Louros N *et al*., 2023). Molecular dynamics simulations, for example, allow researchers to explore the conformational landscape of mutant HTT protein and investigate how changes in protein structure contribute to pathogenicity. By simulating the behavior of atoms and molecules over time, these simulations provide valuable insights into the stability, flexibility, and interactions of mutant HTT protein, shedding light on its propensity for aggregation and toxicity (Moldovean SN *et al*., 2019). Protein-ligand docking studies represent another computational approach with significant implications for Huntington's disease research. By computationally modeling the binding interactions between small molecules and mutant HTT protein, researchers can identify potential drug candidates capable of modulating protein misfolding and mitigating neurodegeneration (Khan MQ *et al*., 2023). Structure-based virtual screening further enables the rapid identification of novel compounds with favorable binding affinities and pharmacological properties, expediting the drug discovery process (Lavecchia *et al*., 2013). In addition to experimental methods, computational structure-based analysis plays a crucial role in understanding HD pathogenesis. Molecular modeling methods, such as homology modeling and molecular dynamics imitations, allow researchers to predict the three-dimensional structure of mutant HTT protein and investigate its dynamic behavior at the atomic level. By simulating the folding and unfolding of mutant HTT protein, these computational approaches provide insights into the stability, flexibility, and aggregation propensity of the protein, aiding in the elucidation of its pathogenic mechanisms (Shafie *et al*., 2024).

Through a multidisciplinary approach that integrates computational modeling, bioinformatics, and structural biology techniques, this thesis seeks to shed light on the complex molecular landscape of Huntington's disease (Moldovean SN *et al*., 2019). By elucidating the structural determinants of protein misfolding and aggregation and identifying potential drug targets, this research aims to pave the way for the design and optimization of novel small-molecule therapeutics aimed at modulating protein misfolding and attenuating neurodegeneration in HD (Khan MQ *et al*., 2023).

This research endeavors to explore the intersection of computational analysis and structure-based drug design in the context of Huntington's disease, with a specific focus on understanding the misfolding dynamics of key fragments of the HTT protein. By leveraging advanced computational methodologies, including molecular dynamics simulations, protein-ligand docking studies, and structure-based virtual screening, this research aims to elucidate the structural basis of HTT misfolding and identify promising therapeutic targets for intervention. The introductory sections of this research will provide a comprehensive overview of Huntington's disease, encompassing its clinical manifestations, genetic etiology, and the molecular mechanisms underlying protein misfolding and aggregation. Subsequent chapters will delve into the principles of computational analysis and structure-based drug design, elucidating their significance in rational drug discovery and the development of precision therapeutics targeting HD. Ultimately, the insights gleaned from this research hold the potential to catalyze transformative advancements in the treatment of Huntington's disease. By harnessing the power of computational analysis and structure-based drug design, this thesis aims to offer new avenues for therapeutic intervention and provide hope to the millions of individuals worldwide affected by this devastating neurological disorder.

2. MATERIALS AND METHOD

The study begins by accessing the Protein Data Bank (PDB) using the unique identifier (PDB ID: 4RAV) to retrieve the target biological sample, ensuring the integrity and authenticity of the structural data. A comprehensive validation process is conducted by cross-referencing the obtained sample with the Molecular Modelling Database (MMDB), prioritizing structures with high experimental reliability and quality. Detailed overviews and pictorial analyses of the sample's macromolecular structure are procured using the PDBsum web server, encompassing critical structural features, chain composition, and intricate interactions within the biomolecular assembly.A meticulous three-dimensional analysis of the sample is conducted using RasMol, a versatile molecular visualization tool known for its ability to depict complex molecular structures. The atomic composition of the sample is explored, with a focus on identifying and scrutinizing hydrogen bond interactions, spatial arrangement, and van der Waals interactions to elucidate the structural intricacies and functional significance of the macromolecular assembly.A comprehensive sequence analysis is initiated to discern the underlying genetic information encoded within the sample. BLAST is employed against relevant biological sequence databases, followed by multiple sequence alignment using COBALT, leveraging a constraint-based approach to unveil conserved domains, evolutionary relationships, and potential functional motifs within the sample, facilitating a deeper understanding of its biological significance.The advanced visualization capabilities of PyMOL are leveraged to further dissect and manipulate the attributes of the sample, enabling the identification of key structural features and active drug-target sites critical for therapeutic intervention and drug design endeavours.Sophisticated protein-ligand docking studies are conducted utilizing the CB-Dock2 server to explore potential therapeutic avenues, with a specific focus on addressing Huntington's disease. Computational algorithms are employed to predict the binding affinity and mode of ligands to the target

protein, providing valuable insights into the feasibility and efficacy of prospective drug candidates.The structural integrity and reliability of the sample are validated through a rigorous assessment process using computational tools available on the SAVES server. State-of-the-art methods such as ERRAT and PROCHECK are employed to evaluate key structural parameters, including stereochemical correctness and Ramachandran plot analysis, ensuring the robustness of the structural model.The CATH (Class, Architecture, Topology, Homology) database is incorporated into the methodology to provide a comprehensive structural classification of the protein sample obtained from PDB ID: 4RAV. Utilizing CATH, researchers gain deeper insights into the evolutionary relationships, structural motifs, and functional implications of the protein sample within the broader context of protein structure classification, augmenting the understanding of its biological significance and potential role in disease mechanisms, including Huntington's disease pathology. Nebcutter is integrated into the methodology to analyze the DNA sequence associated with the protein sample, providing additional insights into the genetic organization and regulatory elements associated with the protein sample's DNA sequence, complementing the structural and functional analyses conducted using other bioinformatics tools. Advanced bioinformatics techniques are employed to elucidate the functional significance of the sample within the context of biological pathways. Multiple sequence alignment and motif analysis are conducted, and the STRING database is utilized to unravel intricate protein-protein interactions and connect the biological sample to relevant KEGG pathway networks, providing crucial insights into the underlying molecular mechanisms of Huntington's disease pathology and potential therapeutic targets.By meticulously following this detailed methodology, researchers can unravel the complex interplay between structure and function in biological macromolecules, offering profound insights into disease mechanisms and facilitating the development of novel therapeutic strategies to combat debilitating conditions such as Huntington's disease.

3. RESULTS

3.1 Validation of structure (4rav) using server tools:

ERRAT (Quality estimation of protein):

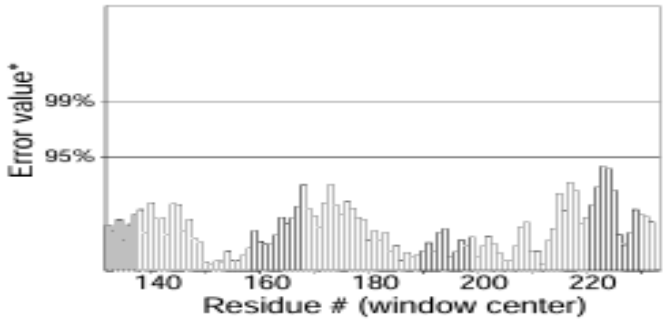


Figure 3.1: ERRAT result showing amino acid distribution in error or non-error region. With Overall quality factor analysis 96.270.

PROCHECK Server (model validation):

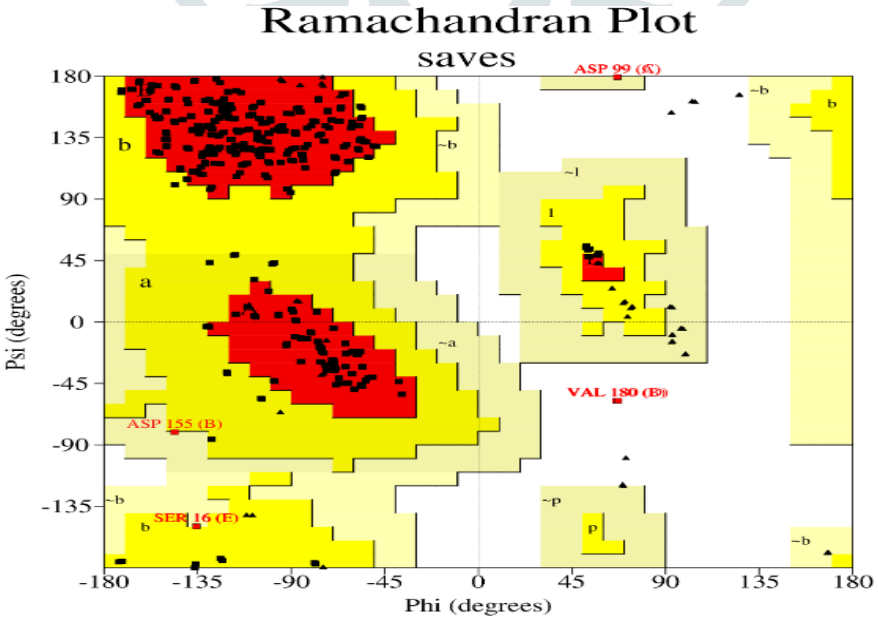


Figure 3.2: Validation of protein structure using Ramachandran plot of PROCHECK analysis (4RAV).

3.2 Three-Dimensional Analysis:

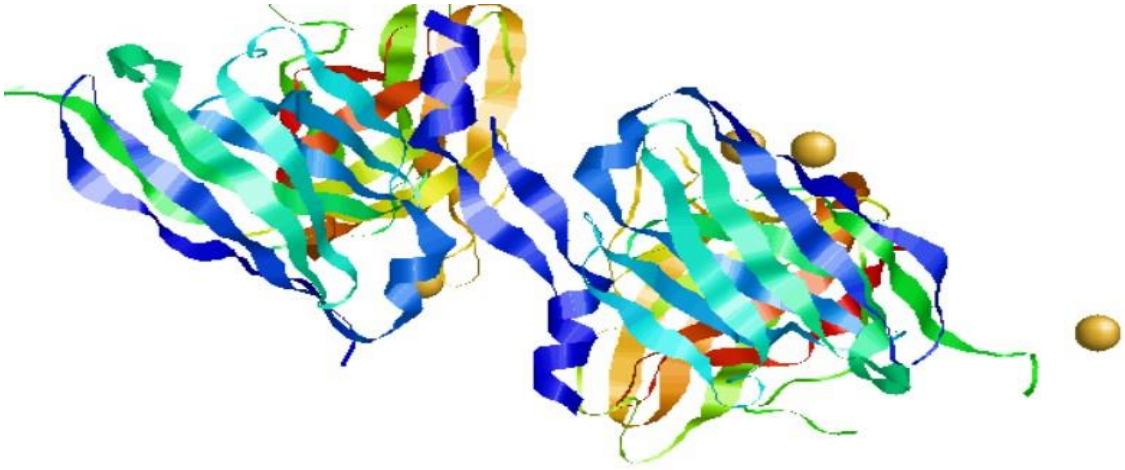


Figure 3.3: Representing protein sample(4rav) in ribbon format 3D structure in RasMol.

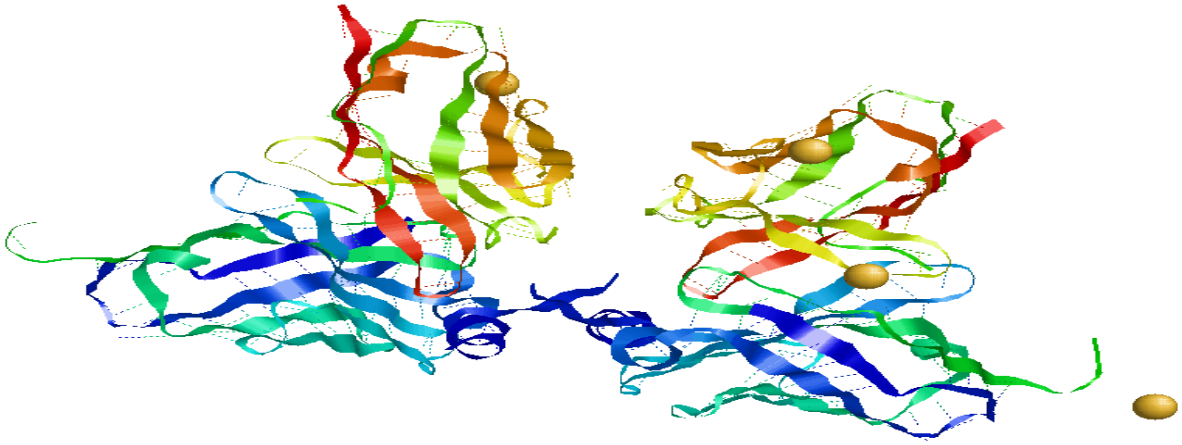


Figure 3.4: Representing hydrogen bond with a dotted line in the sample (4rav).

3.3 Sequence Analysis and Alignment:

Sequence Analysis:

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
Chain A, single-chain Fv, VH [Homo sapiens]	Homo sapiens	252	252	100%	4e-84	100.00%	126	4RAV_A
anti-huntingtin intrabody single chain Fv antibody [synthetic construct]	synthetic construct	248	248	100%	1e-80	97.66%	242	ACA53373.1
Chain B, P1A4 Fab Heavy Chain [Homo sapiens]	Homo sapiens	222	222	95%	6e-71	89.43%	221	7KKH_B

Figure 3.5: Representing BLAST output of Chain A, B showing sequence similarity of chain A with the synthetic construct of anti-Huntington single chain.

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
Chain B, Single-chain Fv, VL [Homo sapiens]	Homo sapiens	238	238	100%	9e-79	100.00%	117	4RAV_B
anti-huntingtin intrabody single chain Fv antibody [synthetic construct]	synthetic construct	223	273	94%	3e-71	100.00%	242	ACA53373.1
immunoglobulin lambda light chain VLJ region [Homo sapiens]	Homo sapiens	199	199	94%	2e-63	87.27%	128	AAO47766.1
IGL c1919_light_IGLV2-14_IGLJ2 [Homo sapiens]	Homo sapiens	198	198	93%	3e-63	89.19%	111	QEP11980.1
IGL c4023_light_IGLV2-14_IGLJ2 [Homo sapiens]	Homo sapiens	197	197	93%	6e-63	88.29%	111	QEP14084.1

Figure 3.6: Representing sequence similarity BLAST output of Chain B, D showing 100% identity sequence identity with synthetic construct anti-Huntington intrabody single chain fv antibody.

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
Chain E, Huntingtin [Homo sapiens]	Homo sapiens	57.9	57.9	100%	2e-09	100.00%	17	4RAV_E
Chain A, Huntingtin [Homo sapiens]	Homo sapiens	57.9	57.9	100%	2e-09	100.00%	18	2LD0_A
huntingtin [Pan troglodytes]	Pan troglodytes	57.9	57.9	100%	1e-08	100.00%	36	ACJ05082.1

Figure 3.7: Representing BLAST output of Chain E, and F.

Figure 3.8: Representing amino acid sequence, domain, homologous superfamily and unintegrated light chain giving an overview of the protein family and domain.

Alignment:

COBALT, which is a constraint-based tool to determine multiple sequence alignment is used to evaluate mismatches (in red) and matches (in Gray) and membrane preference.

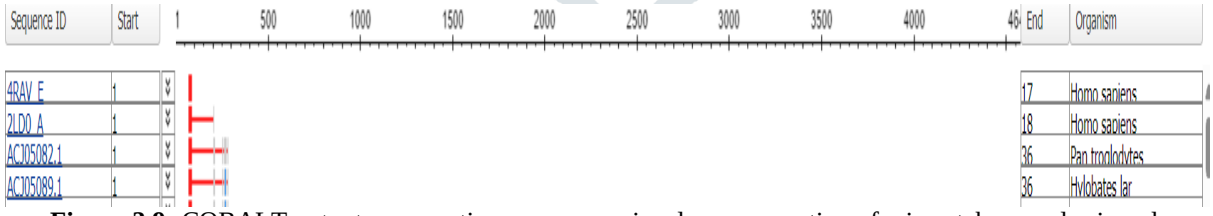


Figure 3.9: COBALT output representing panorama view large proportion of mismatch are color in red.

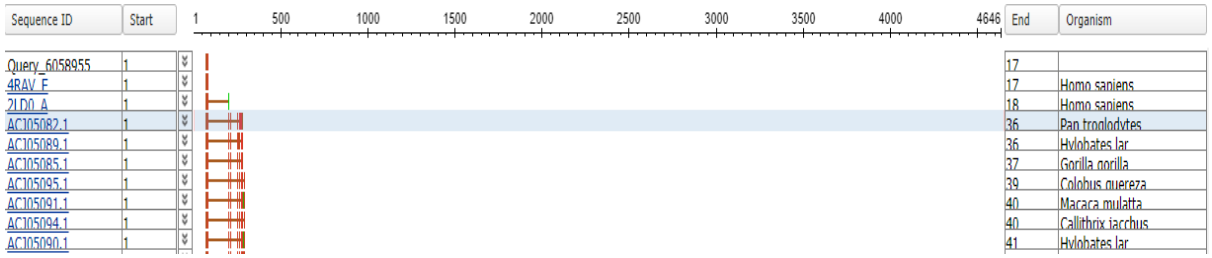


Figure 3.10: Membrane preference in cobalt (red for low membrane and green for high membrane).

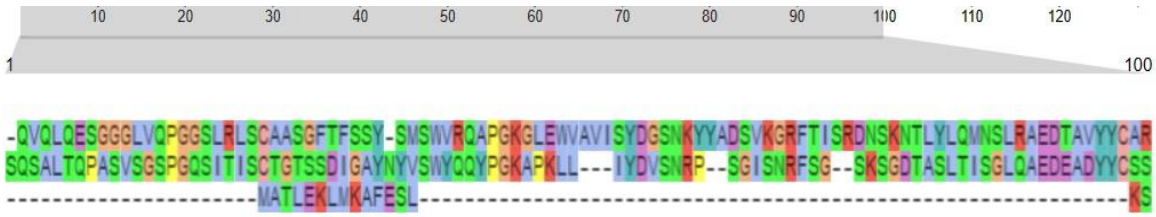


Figure 3.11: Representing different color-coded amino acid by using Clustal Omega.

3.4 Visualization and Attribute Manipulation:

PyMol software was used to determine the active site for ligand binding with the sample chain, its RMSD score, and the potential binding site for the ligand molecule.

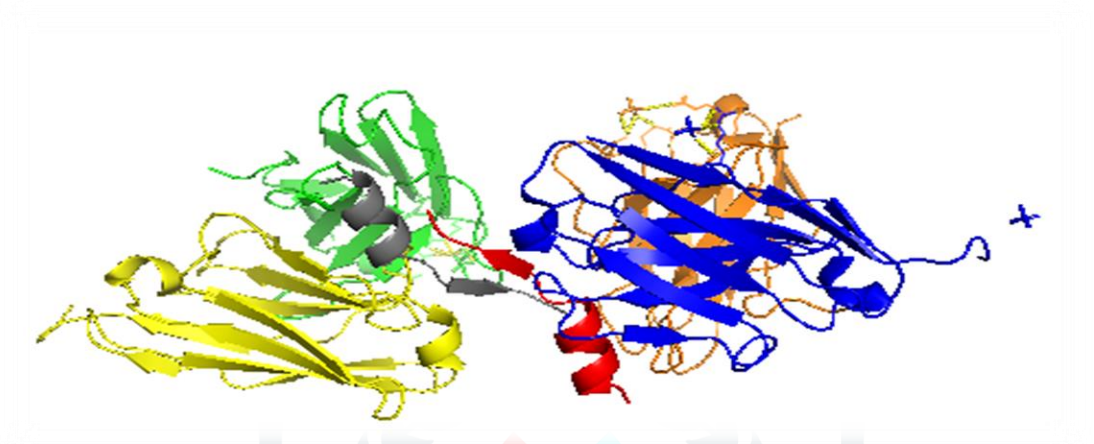


Figure 3.12: Representing each chain with different colors Chain A(yellow), Chain B(Green), Chain C(Blue), Chain D(Orange), Chain E(gray), Chain F(red).

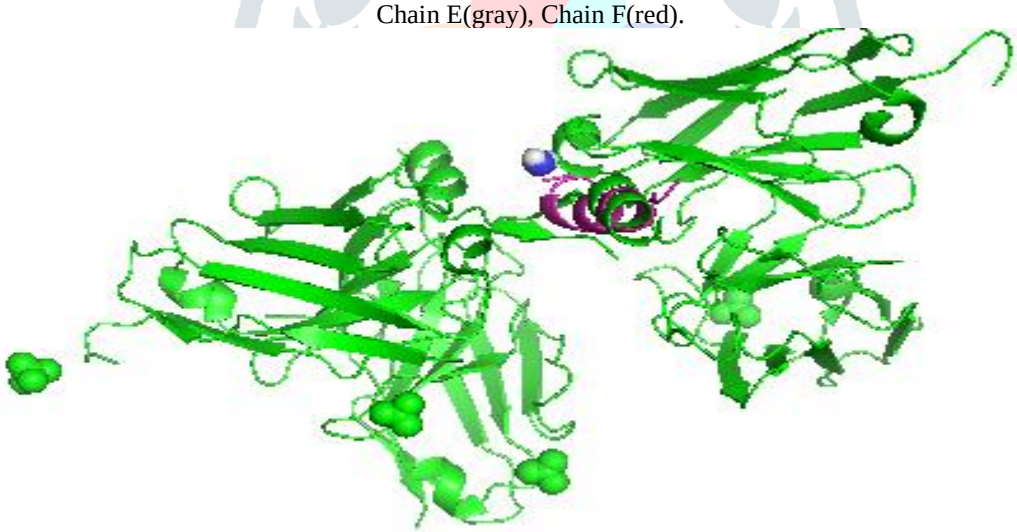


Figure 3.13: Representing alignment of 4rav chain & 2ld0 in PyMol RMSD = 3.870.

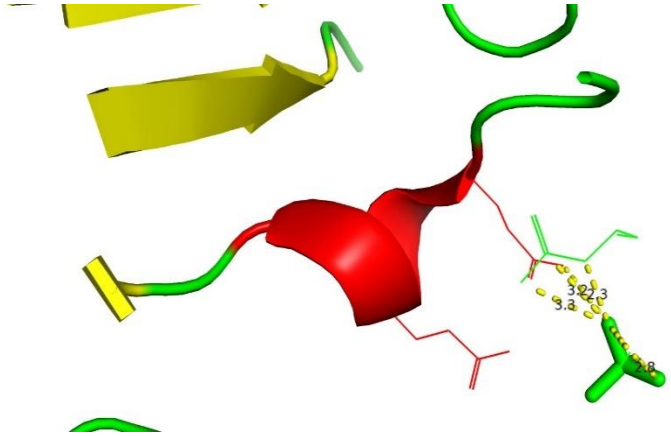


Figure 3.14: Measurement of SO_4in PyMol interaction with protein sample.

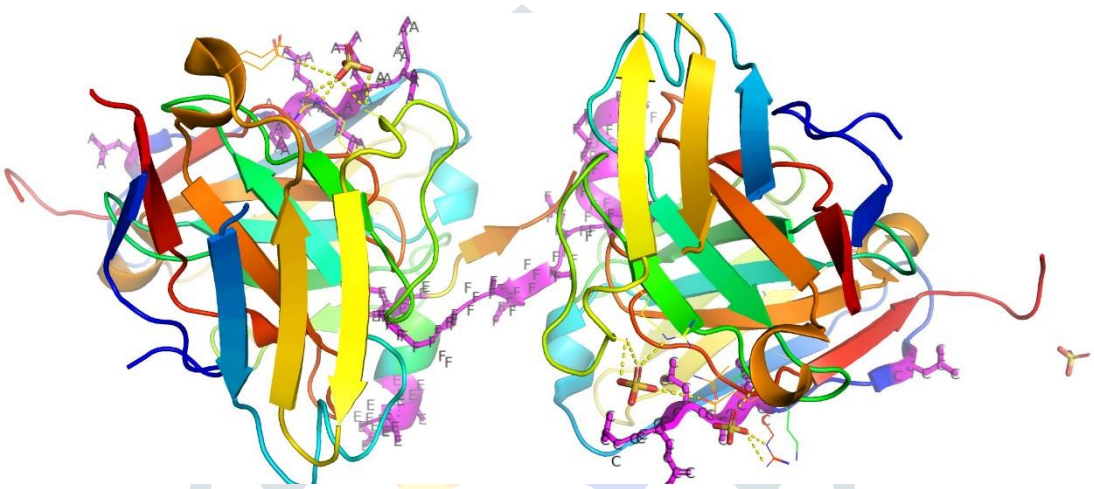


Figure 3.15: Active site identification of the protein 4RAV by using Python-based software.

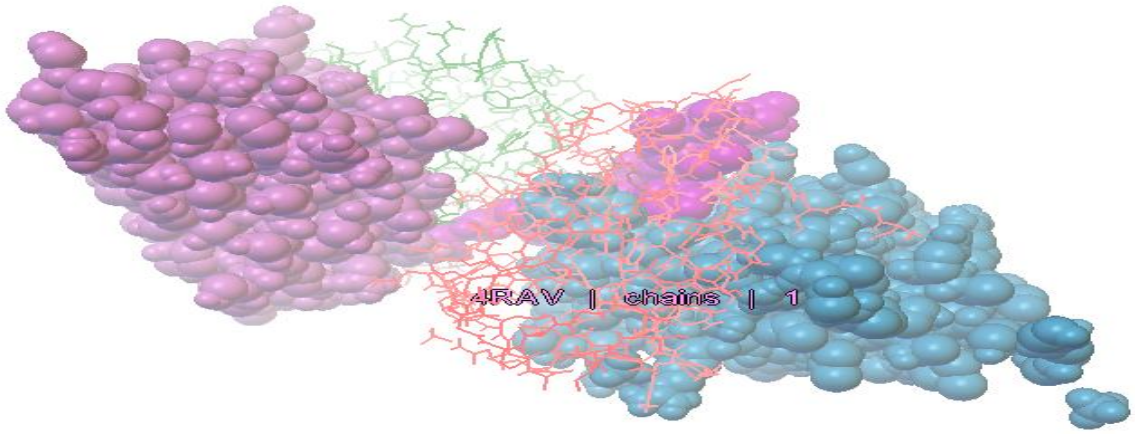
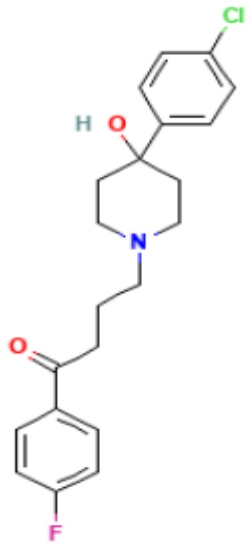


Figure 3.16: Prepared Protein sample for protein-ligand interaction.

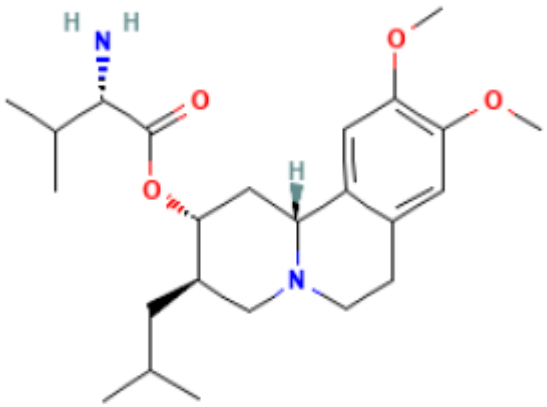
3.5 Protein-Ligand Docking:

Now, PubChem was used to determine the 2D and 3D structure of the potential drug of Huntington protein sample to determine structural activity and relationship of a compound or ligand with the sample so that we can prioritize candidates for our study. For this study, only two potential drugs named Ingrezza (Valbenazine) and Haloperidol are used, and their auto-blind Docking results and scores are as follows:



(A)

Haloperidol



(B)

Ingrezza (Valbenazine)

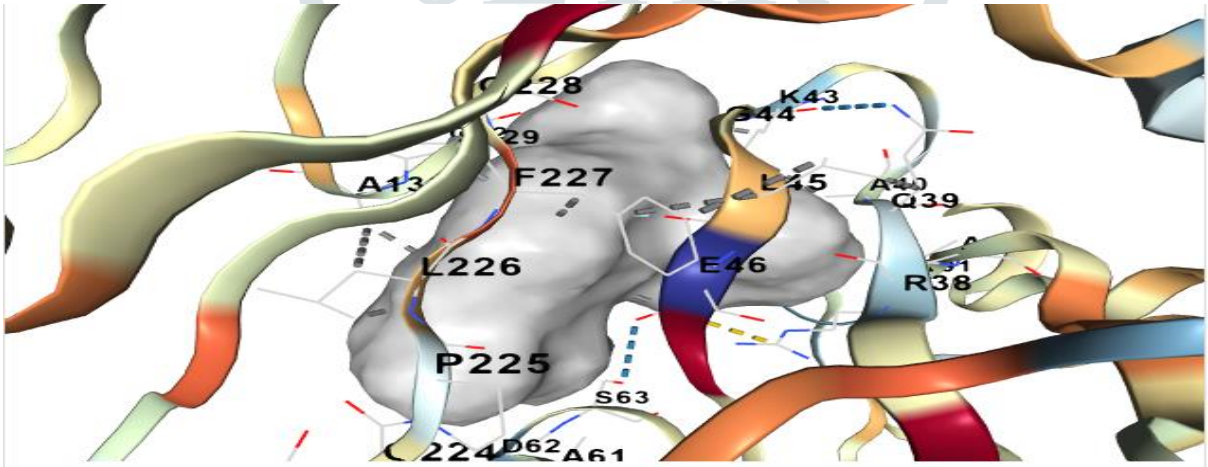


Figure 3.17: Representing auto-blind docking between sample (4rav) and Ingrezza (Valbenazine).

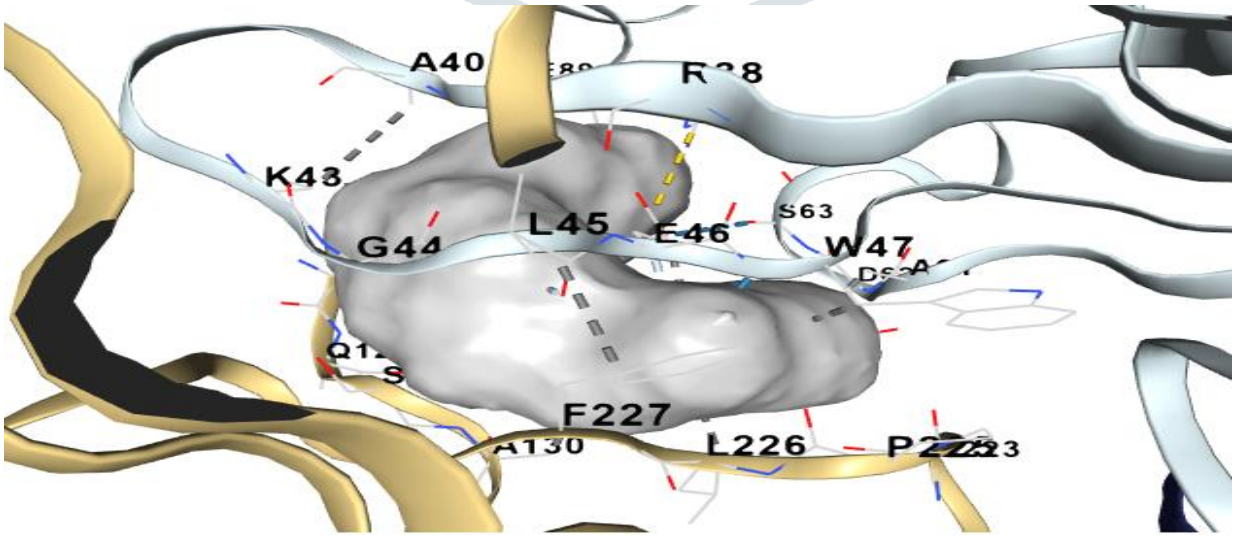


Figure 3.18: Representing auto-blind docking between 4rav & Haloperidol.

Table 3.1: Docking Scores of effective drugs.

S.No.	Drug name	Vina Score	Cavity Volume (A^3)	Centre			Docking Size		
				x	y	z	x	y	z
1.	Ingrezza (Valbenazine)	-7	457	29	-12	70	23	23	23
2.	Haloperidol	-8	800	70	19	-61	25	25	25

3.6 Structural Classification with CATH:

CATH Classification:

Level	CATH Code	Description
	2	Mainly Beta
	2.60	Sandwich
	2.60.40	Immunoglobulin-like
	2.60.40.10	Immunoglobulins

Figure 3.19: Representing structural diversity in protein sample 4rav, each class, architecture, topology & hierarchy is represented by a distinct code.

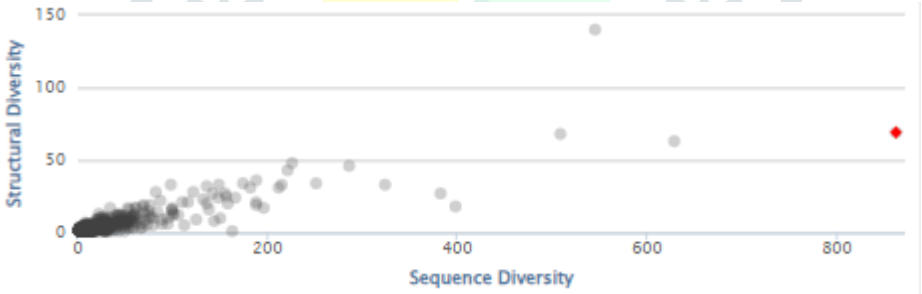


Figure 3.20: Analysis of structure Diversity in CATH.

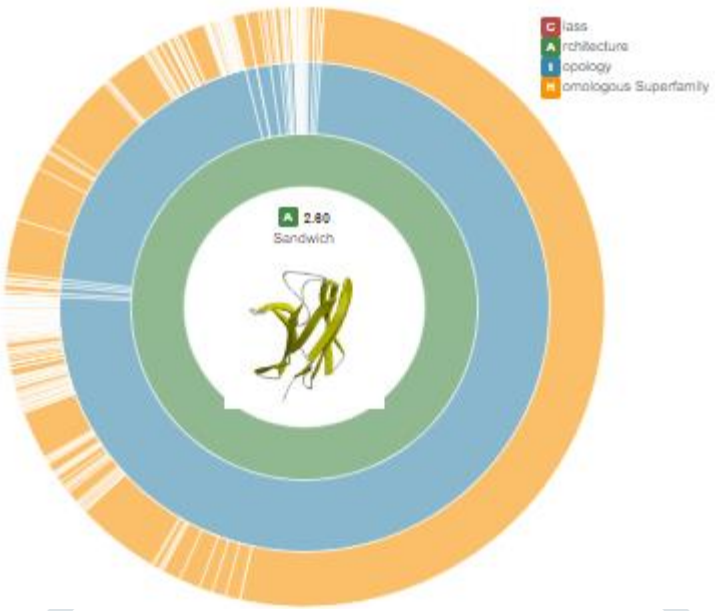


Figure 3.21: Representing Architecture of the protein sample (4rav) by distinct code.

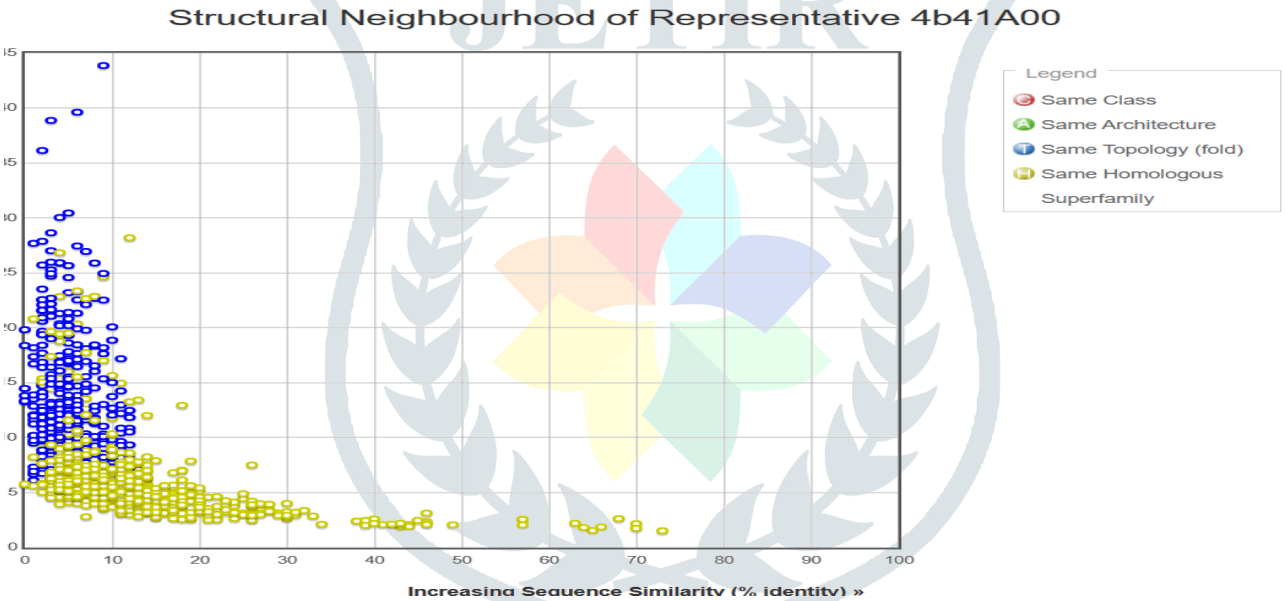


Figure 3.22: Graph representing the structural neighborhood of protein sample 4rav with increasing sequence similarity in which yellow colour represents the same homologous superfamily with our sample and blue represents the same topology with our sample.

3.7 DNA Analysis with Nebcutter:

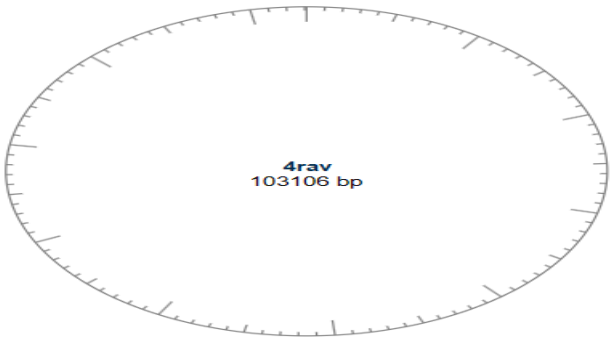


Figure 3.23: Finding possible recognition site for a specific restriction enzyme using Nebcuttercircular with103106 bp, having GC content 49% and AT 53%.

3.8Pathway Analysis:

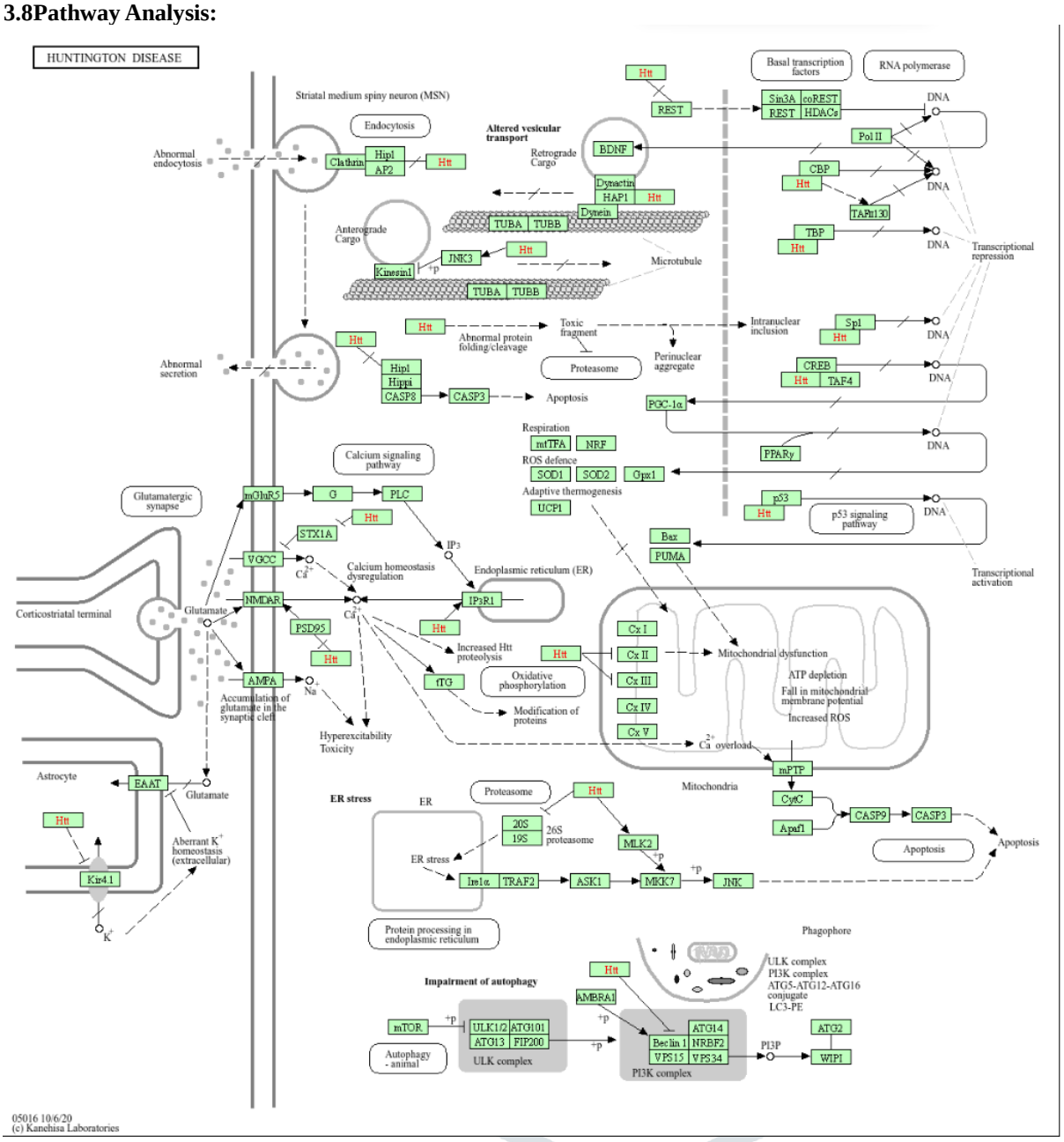


Figure 3.24: Pathway analysis of Huntington's Disease.

STRING- used for determining functional analysis of protein in which network nodes represent protein in which various interactions of protein are visualized.

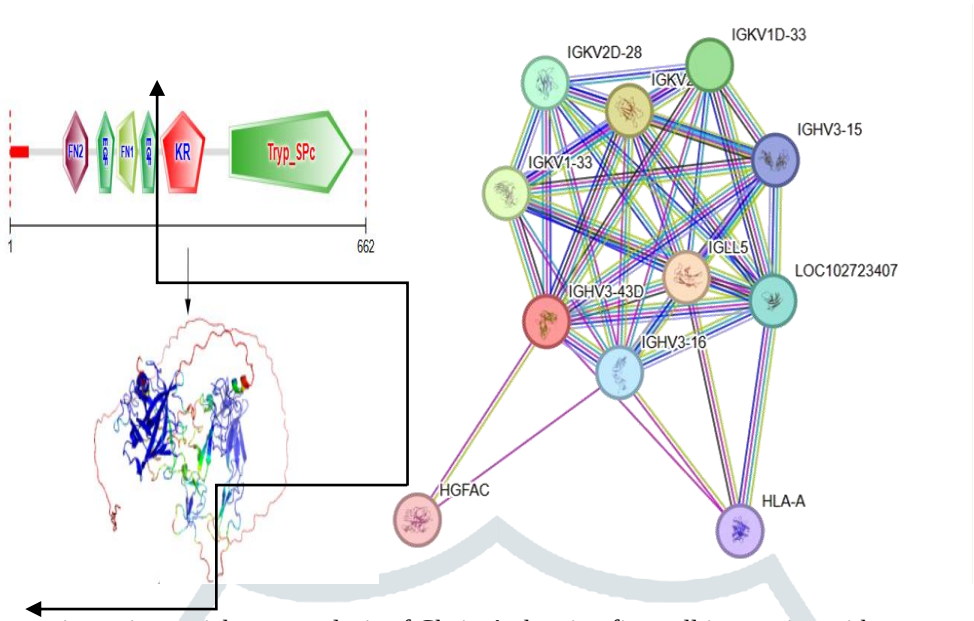


Figure 3.25: Representing string enrichment analysis of Chain A showing first cell interaction with sequence identity 98.9%. The metrics provided pertain to a String Enrichment Analysis conducted for Chain A within a protein-protein interaction (PPI) network. This analysis reveals that Chain A consists of 11 nodes representing proteins, interconnected by 42 edges denoting interactions between these proteins.

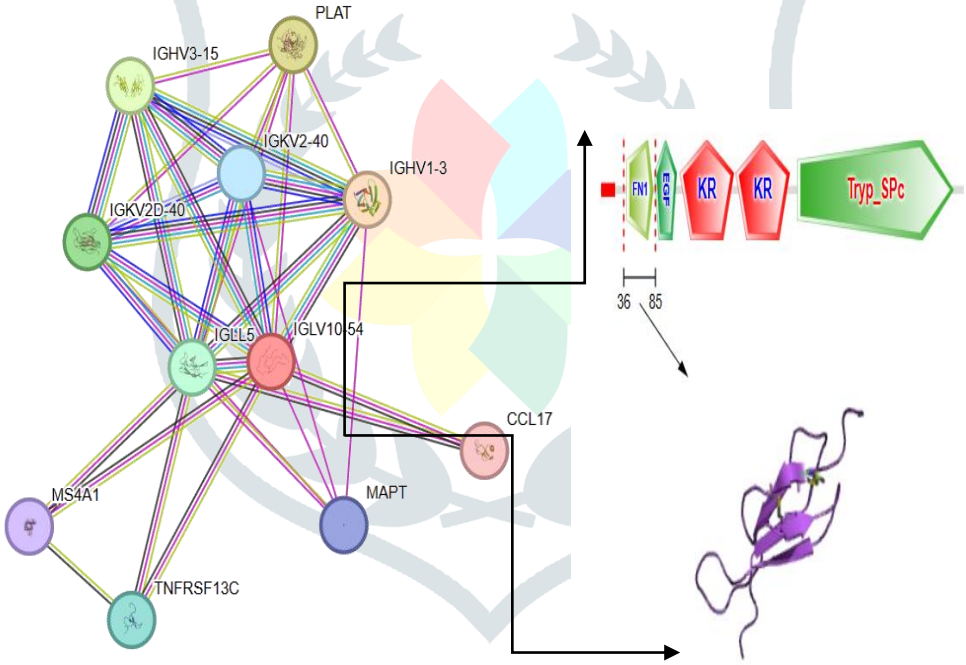


Figure 3.26: String Enrichment Analysis Of Chain B showing first cell interaction with immunoglobulin lambda variable 10-54 having identity 80.8%.

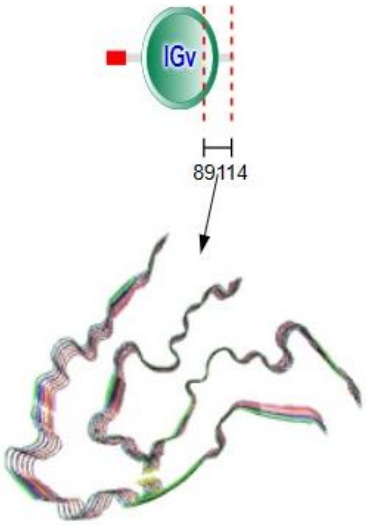


Figure 3.27: Representing sequence identity of PLAT with chain B which is 100%.

Figure 3.28: Representation of "Nodes" by using string analysis.

Figure 3.29: Representation of "Edges" by using string analysis.

4. DISCUSSION

The results indicate significant protein interactions, suggesting biological connections among the proteins. Understanding the misfolding of Huntington's fragment is crucial for diagnosing the disease earlier and developing targeted therapies. Our study aims to computationally analyze the misfolding huntingtin fragment protein 4RAV isolated from human blood.We validated the protein sample's suitability using ERRAT and PROCHECK on the SAVES server. The score indicated suitability for further analysis. We then analyzed the 4RAV structure in RASMOL and PyMol software. RASMOL provided graphical representation and insights into the 3D structure, while PyMol helped identify active and binding sites.Sequence similarity between various protein chains was analyzed using NCBI BLAST and COBALT. PubChem aided in identifying ligand structures for Huntington's treatment. Ligand docking with 4RAV was performed using CB Dock 2 to assess binding efficiency.CATH classified the protein, KEGG identified potential disease pathways, and Clustal Omega and InterPro Scan revealed evolutionary relationships. STRING analysis unveiled protein-protein interactions.In summary, our study offers insights into Huntington's disease mechanisms, potential therapeutic targets, and protein-protein interactions through computational analysis of the 4RAV protein fragment.

5. CONCLUSION

In conclusion, our research provided a comprehensive exploration of the structural and functional aspects of a protein linked to Huntington's Disease using an integrated bioinformatics approach. Through meticulous validation and analysis of molecular interactions, we uncovered key insights into disease mechanisms. Our study extended beyond structural analyses to decipher genetic blueprints, revealing potential therapeutic targets. Innovative methodologies like Nebcutter provided novel perspectives on disease regulation. Furthermore, our research transcended traditional boundaries, embracing innovative methodologies such as the adaptation of Nebcutter for DNA analysis. This unconventional approach unearthed surprising insights into the genetic landscape associated with Huntington's Disease, challenging existing paradigms and providing novel perspectives on disease regulation at the genetic level. As we reflect on the culmination of our research journey, it becomes evident that our endeavours have far-reaching implications for both scientific understanding and clinical practice. By elucidating the structural and functional intricacies of proteins associated with Huntington's Disease, we pave the way for the development of novel treatments and interventions aimed at halting or even reversing disease progression. Moreover, our findings contribute to the broader landscape of neurodegenerative research, offering insights that may extend beyond Huntington's Disease to other related conditions, thus broadening the scope of potential therapeutic targets and strategies.Our findings have significant implications for understanding and treating Huntington's Disease and other neurodegenerative conditions. Moving forward, interdisciplinary collaboration and innovation will continue to drive progress towards effective treatments and a healthier future for all.

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