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"Computational Analysis of Post-Translational Modifications in Major Neurodegenerative Diseases"

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Submitted by:

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CANDIDATE'S DECLARATION

I, Harshita Goswami, 2K20/BIO/01 hereby certify that the work which I presented in the Major Project entitled **"Computational Analysis of Post-Translational Modifications in Major Neurodegenerative Diseases"** in fulfilment of the requirement for the award of the Degree of Masters of Technology in Bioinformatics and submitted to the Department of Biotechnology, Delhi Technological University, Delhi is an authentic record of my own, carried out during a period from 7-Jan-2022 to 27-May-2022, under the supervision of HOD & Prof. Pravir Kumar.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other University. The work has been communicated in IEEE indexed journal with the following details:

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SUPERVISOR'S CERTIFICATE

I hereby certify that the Project dissertation titled **"Computational Analysis of Post-Translational Modifications in Major Neurodegenerative Diseases"** which is submitted by Harshita Goswami, 2K20/BIO/01, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology is a record for the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

Date: 27 May 2022

Prof. Pravir Kumar

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ABSTRACT

AIM: Post-translational modifications like acetylation and ubiquitination share a common feature that they both act on lysine residue. Acetylation is accountable for transcriptional deregulation which additionally causes mitochondrial dysfunction, autophagic pathway problems, and DNA damage which causes cell death. On the other hand, ubiquitination assists in degrading toxic proteins. Thus, we aim towards the investigation of ubiquitination sites & potential acetylation in SNRPD1 which is responsible for the pathogenesis of AD, PD, ALS, HD, MS, and SCZ. Moreover, we aim towards the identification of impact by these Post- translational modifications on the formational features of SNRPD1 & also the influence upon susceptibility of disease by putative lysine alteration. Lastly, we also focus to identify possible drugs and their impact on SNRPD1 protein.

RESULT: 123 DEGs were shortlisted based on the adjusted p-value. PPI network was constructed to analyze the interaction between regulatory proteins in all six diseases. Studying this network gave us HUB genes namely, SNRNP70, SF3B4, and SNRPD1. Critical lysine residues involved were analyzed for SNRNP70, SF3B4, and SNRPD1. Thereafter, protein secondary structure analysis showed SNRPD1 has 9 PTM sites in the helix region while only 1 PTM site in the coiled region. Further, pathway analysis showed that SNRPD1 is involved in the top 13 enriched pathways, whereas, SNRNP70 and SF3B4 are involved in 4 and 5 enriched pathways respectively. Mutation of lysine residues with arginine and aspartic acid indicated that all sites have an effect on disease susceptibility, however, some showed a high confidence score. Lastly, it was found that Artemether is the best drug for SNRPD1 the putative binding site where the CB Dock tool shows that Q24, K44, H26, T16, V15, T14, I69, L70, P71, D72, S97, I96, Y95, and R94.

CONCLUSION: The results show that more than the gain of function, there is depletion of ubiquitination function due to loss of acetylated hotspots.

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Harshita Goswami

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CONTENT **Page No.**

LIST OF TABLES

LIST OF FIGURES

CHAPTER - 1
INTRODUCTION

Most cases of disability and death are caused due to neurodegenerative diseases worldwide. Advanced neuron atrophy, the main cause of neurodegeneration causes neuronal connectivity issues and its final demise, thus, causing adverse effects on brain functioning (1). Even with such advancements in technology and research work, scientists have failed to reverse brain disease degeneration. As neurodegeneration prevails silently in the body for years before showing actual symptoms (2,3).

Protein post- functional modulations are referred to as the particular amino acids which are attached to proteolytic cleavage or utilitarian groups through its covalent extension by chemical modulations of protein post their bio-synthesis (3,4). Being reversible or its opposite through mediation by enzymatic and its opposite means, is the primary feature of Protein post- functional modulation and due to this feature, there have been experiments of demonstrations of over 600 different protein post- functional modulations and thus, diversification of proteomes by modulation of functional & structural properties of proteins happens due to this plethora of protein post- functional modulations (5,6).

The protein PTMs act as a pivot in the regulation of cellular procedure and aging roles and due to this, PTMs shall be controlled or its usage be restricted so that its de-regulation can have a hand in the contribution to the progression of disease pathogenesis (7). It is pertinent to note that the Neurotoxicity, aggregation or protein misfolding may be ensued due to anomalous modulation of credulous proteins as a person ages and as the probability of de- regulation of PTM increases. Against this backdrop, due to genesis of toxic protein aggregates, a therapeutic pathway may be proffered that may obviate through the recognition of PTMs (8).

CHAPTER - 2
REVIEW OF LITERATURE

2.1 Neurodegenerative Diseases

With continuous advancements in technology in the process of sequencing, we have been able to witness the mapping of metabolomic patterns in various Neurodegenerative Disorders in brain tissues of the human post-mortem which included in vitro cells, and in vivo cells as well as animal models. The investigations regarding these have also promoted the revelation of traditional neurodegeneration paths & unearthed novel objectives which even included synaptic degeneration in the preponderance of Neurodegenerative diseases which also share divergent perplexing characteristics. For instance, despite the performance of fervent genetic gauging in major patient populations, apart from few studies of neuro-pathophysiology recognizing defective genes and mutation of genes, there has been no familiar genetic origin in a considerable proportion of Neurodegenerative episodes. Exposure to alcohol, various social factors, abuse of drugs, nutritional deficiency, chemicals, and toxins have all contributed to advertising economic conditions which have led to an embodiment of behavioral and pathology shortcomings, as recognized by a significant number of neurodegenerative studies The need for novel treatments used in preventing the advancement of Neurodegenerative Diseases and ameliorating the symptoms have been at an all-time high because of medications and therapies showing very poor results while being evaluated for these diseases (9).

Characterization of neurodegenerative diseases is done by dysfunction and loss in the functioning of neurons. Different disorders have varying functional systems and thus, showcase a broad range of clinical symptoms. Proteins with changed physicochemical properties which are deposited pose an actual issue and these are called misfolded proteins. These proteins containing physiologic modifications often result in reformed toxic functioning. Most neurodegenerative diseases are categorized by the deposition of these proteins.

For an instance, in spastic paraplegia and spinocerebellar ataxia, no such deposition has been reported, although, encoding genes are the main target of protein mutations (10).

Neurodegenerative Diseases have been the subject matter of a considerable number of investigations in the past decade. Even though many advancements have been made in this field, the fact that these ailments continue to be much staggering and mortal, in turn, stresses the fact that there is still a lot of scope for development for a lot more efficacious treatment. The epigenetic alterations portray a prospective site for pharmaceutical interceding due to being highly suitable targets, as suggested by recent progress. The emergence of anomalous epigenetic alterations related to Neuro-degenerative disorders has started and the demand for assessing recent progress in epigenetic apparatus in Neuro-degenerative Diseases' research is also being emphasized (11,12)

2.2 Alzheimer's Disease (AD)

Alzheimer's disease is the first cause of dementia and is the most common neurodegenerative disease. Moreover, there are currently approximately 46.8 million people which are suffering from Alzheimer's worldwide and this number is likely to double every two decades. The constitution of 1% of all cases of Alzheimer's, is from genetics, as has been proven while researching the familial forms of this disorder and it has also been seen that in most patients of Alzheimer's disease, idiopathy is the foremost cause. Talking about the early onset of this disease, it has been linked to mutations in 4 genes, namely the genes encoding amyloid precursor protein (APP), presenilin 1, presenilin 2, & tau protein (12,13).

Spatial and memory consciousness stultification, movement affliction, delusion, depression, hallucination, and dementia (and anomic aphasia, acalculia, and apathy in some rare cases) are some of the classic symptoms of Alzheimer's disease (14). Despite there being a considerable advancement in the research describing AD-related changes, still many cases leading to Alzheimer's remain ambiguous (15). The Amyloid Cascade, which comprises

the agglomeration of amyloid beta-amyloid-beta genetical defection (i.e., APP, presenilin 1, presenilin 2), environmental elements, and other factors, is the most extensively welcomed hypothesis. An immune reaction is triggered by feeble plaques which in turn leads to tau hyperphosphorylation, tenderness, and conglomeration in tangles which further leads to neuron degeneration and impaired neurotransmission in varied brain regions and even death in some cases. Acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil), which enhance the acetylcholine at synapses, and NMDA receptor antagonist memantine which modifies the ingress of the calcium channel are the main symptomatic treatments for Alzheimer's (16).

2.3 Parkinson's Disease (PD)

Parkinson's disease is the second most common Neuro-degenerative disease and the most generally seen movement disorder. Moreover, around 1% of people aged more than 60 years and around 5% of the people aged 80 years and above suffer from Parkinson's. This disease is identified by an intensifying deprivation of dopaminergic neurons in the subcortical basal ganglia which is inside the SNpc. Hence, due to this midbrain region playing a critical role in refining motor circuits and clearing the way for movement, Parkinson's demonstrates clinically with a pathognomonic triad of resting tremor and rigidity (17).

The presence of intraneuronal proteinaceous inclusions termed LBs which mainly comprise α-synuclein is the main pathological feature of Parkinson's, apart from nigral degeneration. The α-synuclein, a cytosolic 140 amino acid protein encoded by the SNCA gene on chromosome 4q21 while being plentiful at presynaptic terminals, is significantly exhibited within neurons. The dominant familial forms of Parkinson's are usually triggered by multiple rare SNA point mutations and, the microtubular forms of α-synuclein, within LBs, have been identified which accrue in irregular and genetical forms of Parkinson's (18).

2.4 Amyotrophic lateral sclerosis (ALS)

One of the most deadly and incurable neurodegenerative diseases which is indicated by loss of both upper and lower motor neurons is known by the name Amyotrophic lateral sclerosis (ALS). The symptoms of this disease usually include wasting and muscle weakness, spinal and bulbar affliction, and in some cases even paralysis and death due to failure of the respiratory system (19). The Ubiquitination form of TDP-43 and SOD1 by degenerating neurons that are conglomerated by marked cytoplasmic protein are the characteristics of both familial and sporadic Amyotrophic lateral sclerosis. TDP-43, a 414 amino acid protein is normally a nuclear resident which is intricated completely in the injunction of RNA metabolism and is encoded by the TARDBP gene (20).

Ubiquitinated, truncated, and cytoplasmic forms of TDP-43 amass as protein agglomerates in Amyotrophic lateral sclerosis. Moreover, these protein agglomerates, which are neurotoxic, generate phenotypes like ALS which further furnish a loss of nuclear TDP 43. Superoxide dismutase, a 153 amino acid zinc & copper-dependent metalloenzyme, and predominantly lysosomal, cytoplasmic, although nuclear, operates to forage extremely instinctual superoxide radicals by converting them to molecular oxygen and hydrogen peroxide. The protein is rendered prone to the development of neuronal incorporated bodies, conglomeration, and misfolding due to the effect in the post-translational processing which in turn comes from mutations in the SOD1 gene sequence in SOD1 mediated familial Amyotrophic lateral sclerosis (21). Experts have even suggested a regular pathophysiological apparatus for idiopathic and inherited Amyotrophic lateral sclerosis after misfolded SOD1 has been found in patients with sporadic ALS (22).

2.5 Huntington's disease (HD)

Huntington’s Disease, which is caused by expansion of CAG repeat in the Huntingtin gene on chromosome 4p16.3, is a rare neurodegenerative disease that is autosomal dominant with an average onset age of 40 years (23). The hallmark of this disease is the development of conglomerated Huntingtin gene

inside the intranuclear inclusion bodies. Moreover, the degeneration of neurons in the stratum which in turn projects to other areas of basal ganglia and thereby modulates central motor circuitries is the central pathology of Huntingtin's disease and in turn, this is reflected by patients with dreadful motoric malformation which includes involuntary muscle movements also known as chorea, in the clinical picture of this disease (24).

Due to the further development of the disease, another related array of cognitive, behavioral, and psychiatric symptoms emerge as other brain regions also undergo degeneration. Htt, a large 3144 amino acid, which commands a significant no. of cytoplasmic and nuclear homeostatic functions, is a monomeric protein that is importantly needed for embryonic neurogenesis and controls and regulates much of the synaptic activity (25). The N-terminal Htt particles which are vulnerable to misfolding or forming an amyloid-like structure, are generated by induction of enlarged polyQ stretch of protein. Moreover, the accumulation tendency of Htt is increased because of the anatomy change by the formation of β-pleated sheets from the polyQ tracts and thus, these changes ensue in the congregation of oligomeric formations and hence forming Htt positive intracellular inclusion bodies that in turn convulses the cellular homeostasis and triggers neuronal degeneration (26).

2.6 Multiple sclerosis (MS)

Generally caused by autoimmune triggered axonal demyelination within the central nervous system, Multiple Sclerosis is classified as a neuroinflammatory disease (27). But, the diagnostic procedure is established on an amalgamation of brain imaging, blood screening, and clinical history only because of the variation in the clinical presentation solely due to the reason being the focal inflammatory lesion affecting the central nervous system structure. The types of Multiple Sclerosis include progressive relapsing (PRMS), relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS), and each type of this disease, has a distinctive curative outlook and forecast (28).

In neuroinflammatory disease, 85% of the patients are detected with relapsing-remitting at the early symptomatic stage and it's most likely that the majority of patients will advance the progression of extremely debilitating secondary progressive (29). Moreover, it has been found that a connection between neurodegeneration and neurotoxicity in Multiple Sclerosis may be represented by the recognition of oligomeric, proteinaceous agglomerations that would include sediments of neuronal somata constituting accumulated Bsn protein, as well as APP, tau & Aβ. Bsn, a large 3926 amino acid localized in Multiple Sclerosis and assemblages in neuronal cells to trigger neurodegeneration and neurotoxicity, has numerous functions in settling synaptic purposes and functions and is a scaffold protein that is also a part of the presynaptic cytoskeletal matrix (30).

2.7 Schizophrenia (SZN)

With a percentage of patients all-round the globe of 1%, Schizophrenia is a psychiatric disorder in which people usually experience hallucinations or phantasmagoria which are characterized by wrong perceptions about certain things, smells, or sounds, that, in reality, do not exist or are not present at that particular point of time. As mentioned above, three types of hallucinations only target the human body's four senses: ears, eyes, nose, and skin. These four types of hallucinations in Schizophrenia are named Auditory hallucination, Visual hallucination, Olfactory & Gustatory hallucination, and Tactile hallucination. Amongst these four types of hallucination, Auditory hallucination is the most common and is characterized by voices running inside a person's head which might be soft or harsh voices either demanding a person to act against something or to abstain from doing something. Talking Visual hallucination is characterized by situations wherein the patient sees people, objects, certain lights or patterns flying or floating near or above or in front of him, and in a significant number of cases, the visuals are related to certain people who are no longer alive.

Visual hallucination also makes the patient difficult to sagaciousness of distance or depth. Now, Olfactory & Gustatory hallucination is characterized by

situations wherein the patient feels like there is a bad smell or taste that is getting emitted by objects around him or in the food he is eating that usually makes him believe that he is being poisoned. The last type of hallucination, the Tactile hallucination is usually characterized by feelings or sensations of certain things moving on or inside the body of the patient. Apart from hallucinations, delusion is just another symptom experienced by the patient with Schizophrenia and this symptom is identified by having a lot of beliefs inside the mind of the patient simultaneously which might include the belief that the police or army is looking for the person or some parent or guardian is trying to control the brain of the patient with remote control, and in a variety of cases, it also makes the patient believe that he is being stalked or framed in a conspiracy or even he is some superhuman or god or a famous personality. Now, delusions that are experienced by the patient are of multiple types, namely Somatic delusion, Referential delusion, Persecutory delusion, Grandiose delusion, Religious delusion, Erotomatic delusion, etc.

Apart from hallucination and delusion, poor hygiene, declined motivation, struggle in communicating emotions, muddled speech, and deteriorating interest in socialization with family & friends are some of the other secondary symptoms of Schizophrenia. A big chunk of patients with this disease also undergo symptoms of anxiety and depression and subsequently the symptoms of Schizophrenia worsen when either coupled with other psychiatric disorders or linked with the use of illicit drugs or toxins, which in turn leads to worsening the symptoms of Schizophrenia (31).

2.8 Post-Translational Modifications in NDDs

Amongst the most pivotal regulators of protein properties, are the Post-translational modulations (PTMs) which include nitrosylation, methylation, glycosylation & phosphorylation, and other forms as well which can modulate the activity, localization, yield, and reciprocity of proteins which in turn plays a critical role in tuning of several cellular pathways (32). Modifications of the activity-based process for complicated brain functions which include memory and learning, in the adult brain & neurodevelopment are the key functions by

Post-translational modifications of proteins, among other functions and hence, it has been explained in the issue “Post-translational modulations in brain health and disease” about the role of PTMs in various brain disorders (33).

The environmental risk factors such as toxins, chemicals, etc, in the context of Parkinson’s disease, also impact the occurrence of abnormal Post-translation modifications which can be understood by justifying PTMs’ role of αsynuclein and LRRK2 in the said disease’s said pathogenesis. (34). It was found in a study that Post-translation modifications ubiquitination, phosphorylation, and SUMOylation have been shown to impact Parkinson’s related proteins while putting pivot over mitochondria. The demonstration of acetylation of α-synuclein and tau protein has also been shown to affect the microtube-sustained autophagy in Alzheimer’s and Parkinson’s. It was also found that murine tau proteins and humans show dissimilarities in purpose and structure and it has also been reported that due to the modulation of creatine kinase B by oxidation, there has never likely been a situation in Alzheimer’s, wherein the human tau protein’s N- terminal would bind the creatine kinase of mitochondria (35). Death due to neural degeneration because of protein phosphorylation’s involvement and its further coherent decline in mild cognitive impairment and preclinical Alzheimer’s been discussed in various studies and the significance of mass spectrometry has also been accentuated in the multiple stages of Alzheimer’s during the study of Post-translational modulations (36).

The association of mitochondrial incongruity with dropped levels of O-linked N-acetyl-glucosamine glycosylation in Alzheimer’s has been demonstrated in a study by Pinho and subsequently, restoration of a physiological degree of metabolites which in turn leads to neuroprotection by therapeutic outlook which is affected by reperfusion triggered changes in acetyl-coenzyme and metabolic transitional nicotinamide adenine dinucleotide, have been debated by Klimova and its subsequent collaborators (37).

2.9 Ubiquitination and Acetylation in NDs

Ubiquitination, a reversible process, necessitates the involvement of three types of enzymes, namely ubiquitin-conjugating enzyme, ubiquitin-activating enzyme, and ubiquitin-protein ligase activities whose involvements are triggered by the binding of ubiquitin to K remnants of a protein and catalyzation of enzymes with de- ubiquitinating activities are used for the eradication of the ubiquitin chain. The indicator for deterioration, mainly through autophagy and UPS, is known as the process of Polyubiquitination. Its inclusions represent species constricted to subcellular chambers, known as ubiquitinated and ubiquitin proteins, which are destined to deteriorate through autophagy and UPS. On the other hand, alteration of protein quality standard machinery which adds up to neurodegeneration happens in the inclusion of proteasome and ubiquitin components in sequestration.

Acetylation, maneuverer by histone acetyltransferase enzymes, is the product of an acetyl group to a lysine (K) remnant of a protein and the acetyl groups are removed by catalyzation of Histone Deacetylase Enzymes, and this particular process is known to be reversible and henceforth, there is are a various number of evidences that show that the modification of motor neuron disorders and poly happening through pathogenesis, is done by acetylation.

CHAPTER – 3
METHODOLOGY

3.1. Extraction and Pre-processing of Data

We took gene expression database GSE26927, from National Centre for Biotechnology Information (NCBI) Gene expression omnibus (GEO) using key words ((Parkinson's disease) AND genes) AND "Homo sapiens"[porgn]. This dataset is deposited by Durrenberger et al., and it contains –

Table 1: Number of Control and Disease in GSE26927

CONDITION	CONTROL	DISEASE
AD	11	7
PD	12	8
ALS	10	10
HD	10	10
MS	10	10
SCZ	10	10

For this dataset, the microarray analysis was performed using GEO2R. We obtained the following data –

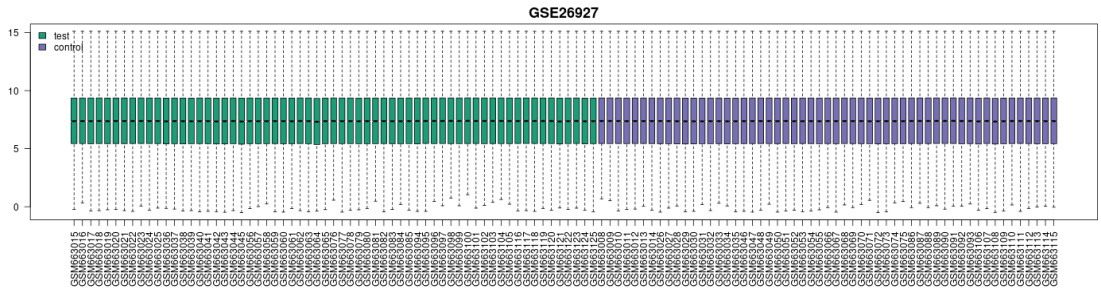


Figure 1: Box Plot

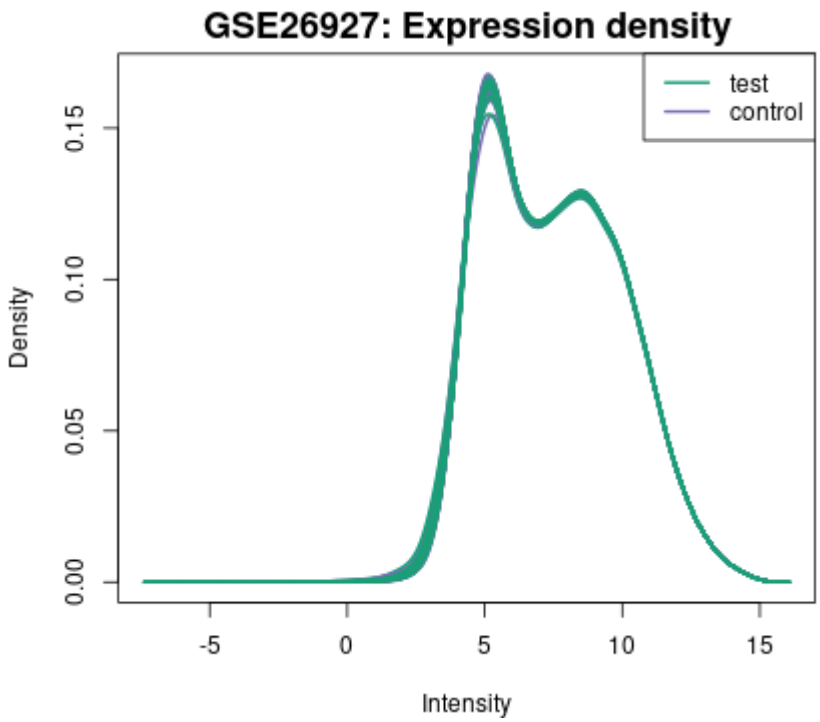


Figure 2: Expression Density Plot

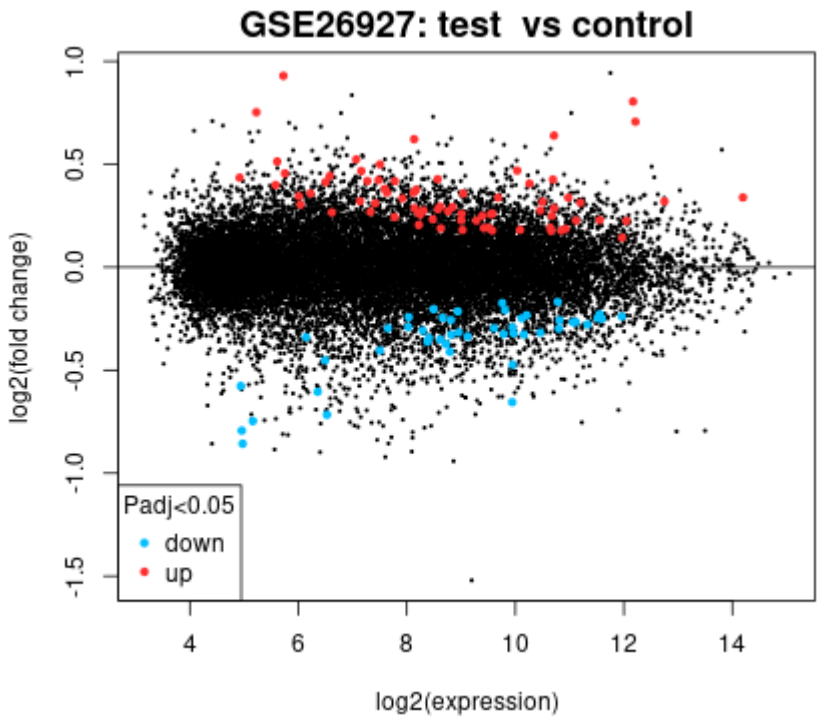


Figure 3: Mean-Difference Plot

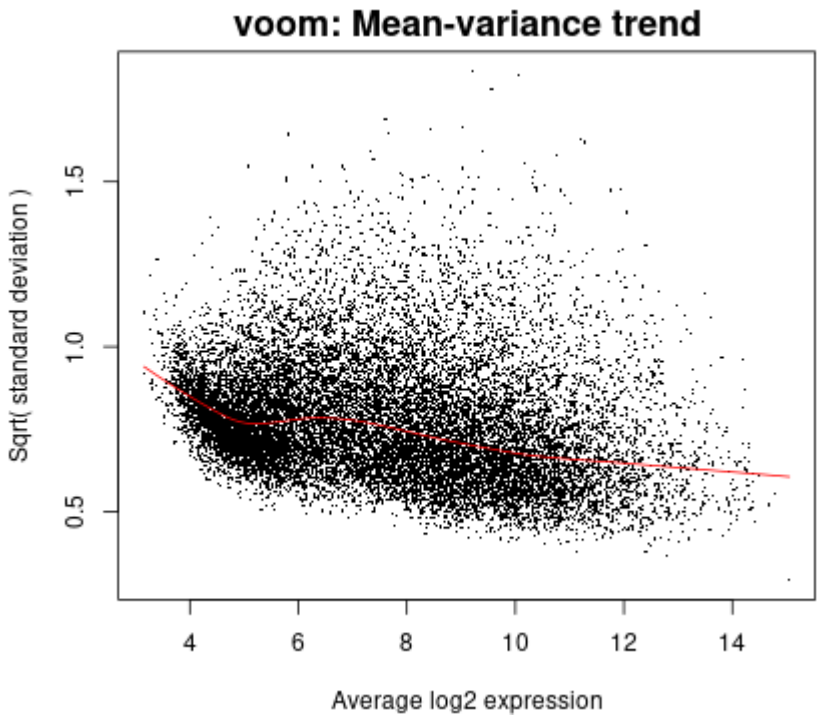


Figure 4: Mean Variance-Trend Plot

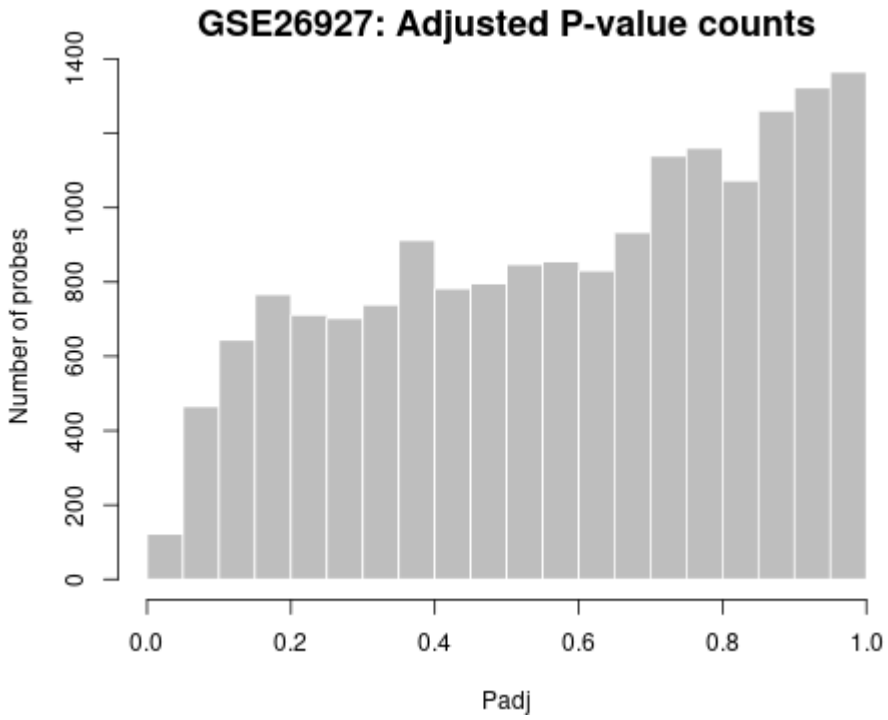


Figure 5: P-Value Histogram

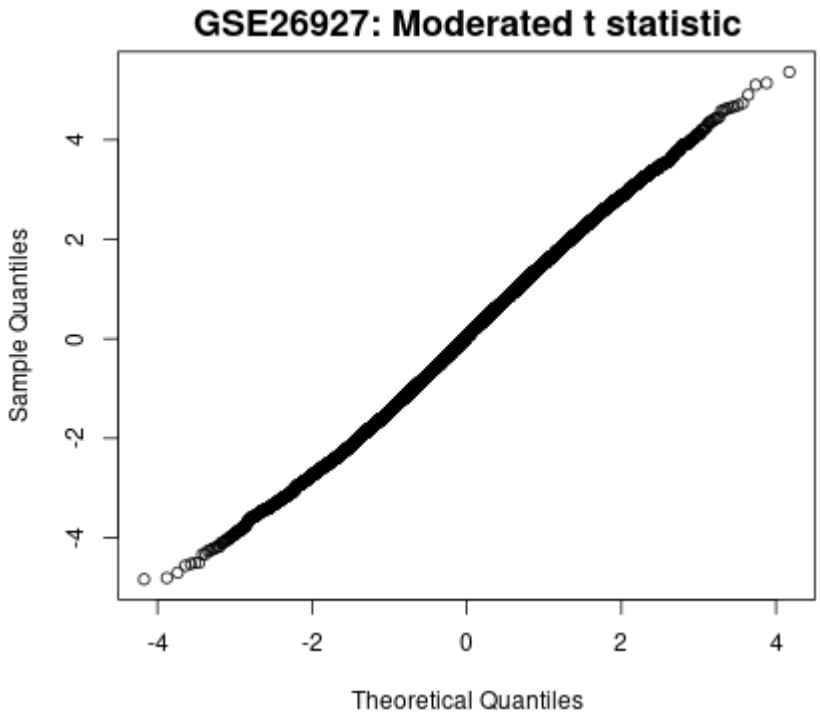


Figure 6: T-Statistic Quantile-Quantile Plot

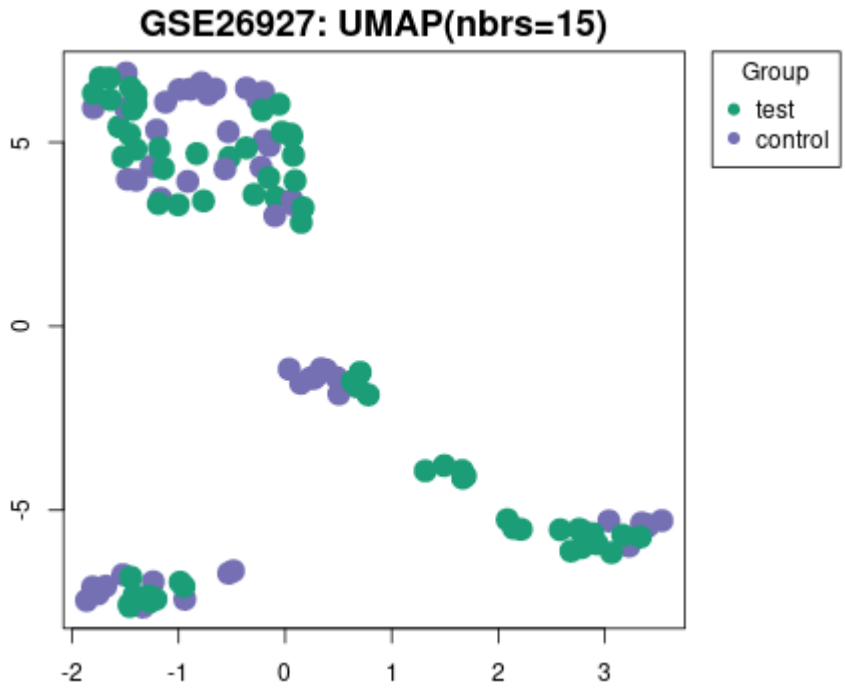


Figure 7: UMAP Plot

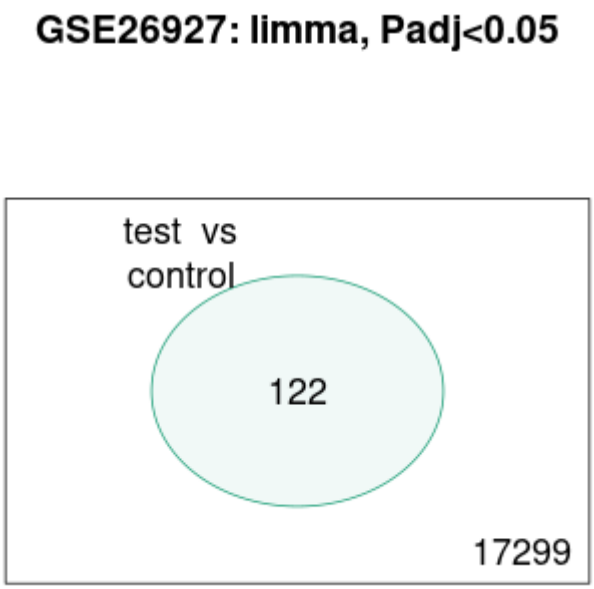


Figure 8: Venn Diagram

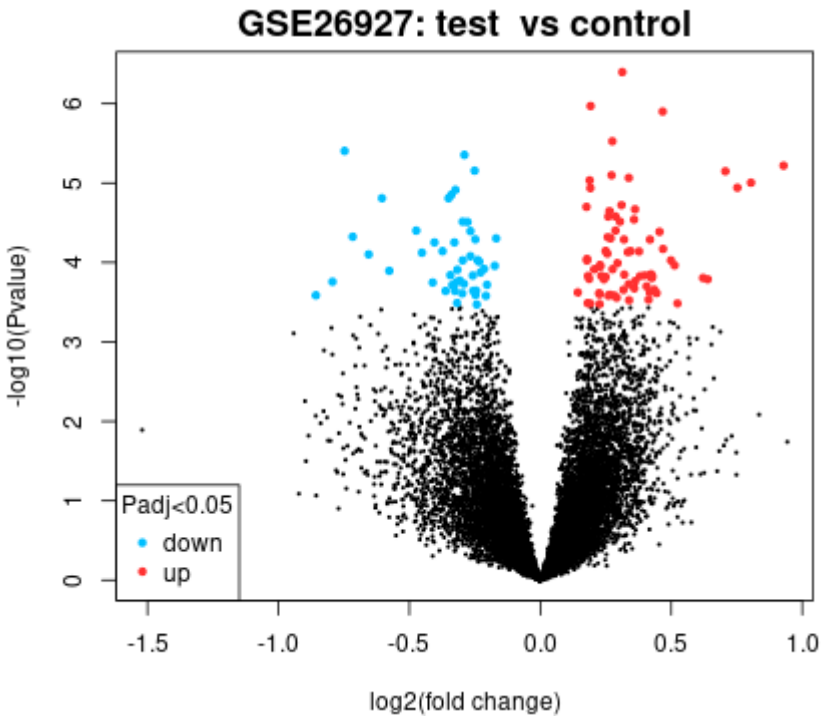


Figure 9: Volcano Plot

3.2 Protein-Protein Interaction Network of Extracted Proteins

After the identification of DEGs, the different genes were mapped to their corresponding proteins, and the PPI network was identified through the Cytoscape & STRING database. PPI networks were constructed to analyze the interaction between regulatory proteins in all six diseases. After the PPI network, HUB genes of the network were identified through CytoHubba.

3.3 Identification of Critical Acetylation and Ubiquitination Sites

Ubiquitination and acetylation are important PTMs in the pathogenesis of all six diseases. The most important feature is the participation of lysine (K) residues. A protein lysine modulation database was used to analyze the critical lysine residue of HUB genes in all six diseases.

3.4 Structural Analysis of Protein

PTMs are known to have an impact on a secondary structure, and further affect its biological properties. Hence, we decided to analyze the effects of PTMs on the secondary structure of regulatory proteins. We used publicly available PSIPRED to acquire structural information of regulatory proteins on both PTM and non-PTM sites on lysine residues.

3.5 Pathway Analysis

The biological pathway is the most important feature of a protein, which identifies the pathway in which a protein is involved. The HUB genes, namely SNRNP70, SF3B4, and SNRPD1 were imported into the Reactome Pathway Database (https://reactome.org/) to analyze the enriched biological pathways.

3.6 Impact of Lysine Mutations on Acetylation and Ubiquitination

The vulnerability of disease of putative lysine (K) mutation, either with arginine (R) or aspartic acid (D) was studied with the help of mutational analysis by using tools like PMut, and SNAP2.

3.7 Identification of Drug Molecules

FASTA sequence of SNRPD1 is extracted from PDB in .pdb file format. The sequence is uploaded as a target in the drug bank database to identify the possible drugs and we got 5 drugs. Further, we did protein-ligand docking using CB Dock to identify its binding site on YWHAZ.

CHAPTER - 4
RESULTS AND DISCUSSION

4.1 Data Collection and Differential Gene Expression Analysis

The DEGs were shortlisted based on the adjusted p-value being less than and equal to .05 to remove the false positives and we shortlisted 123 DEGs out of 17422 genes.

Table 2: All 123 DEGs

ID	Adj P Val	P-Value	Gene Symbol	Gene Title
ILMN_3876	0.00698	0.0000004	SPEN	spen family transcriptional repressor
ILMN_11046	0.00731	0.00000126	CALML4	Calmodulin-like 4
ILMN_3952	0.01284	0.00000442	ANAPC15	Anaphase-promoting complex subunit 15
ILMN_22745	0.01323	0.00000697	THOC7	THO complex 7
ILMN_21370	0.01323	0.0000071	MT1F	metallothionein 1F
ILMN_21104	0.01323	0.00000604	OTOS	otospiralin
ILMN_13075	0.01323	0.00000861	RBM6	RNA binding motif protein 6
ILMN_22362	0.01323	0.00000924	FAM193A	family with sequence similarity 193-member A
ILMN_22286	0.01323	0.00000988	MT1G	metallothionein 1G
ILMN_9701	0.01326	0.00001157	C7orf26	chromosome 7 open reading frame 26
ILMN_25187	0.01326	0.00001218	TCEB1	transcription elongation factor B subunit 1
ILMN_18546	0.01326	0.00001145	BNIPL	BCL2 interacting proteins-like
ILMN_18443	0.01428	0.00001412	BRCC3	BRCA1/BRCA2-containing complex subunit 3
ILMN_17701	0.01428	0.00001553	MKKS	McKusick-Kaufman syndrome
ILMN_5571	0.01695	0.0000214	TCF3	transcription factor 3
ILMN_18019	0.01707	0.00002253	USP21	ubiquitin specific peptidase 21
ILMN_14076	0.01841	0.00002627	SAFB2	scaffold attachment factor B2
ILMN_6274	0.01841	0.00002642	AXIN1	axin 1
ILMN_24988	0.01858	0.00002877	ROBO3	roundabout guidance receptor 3

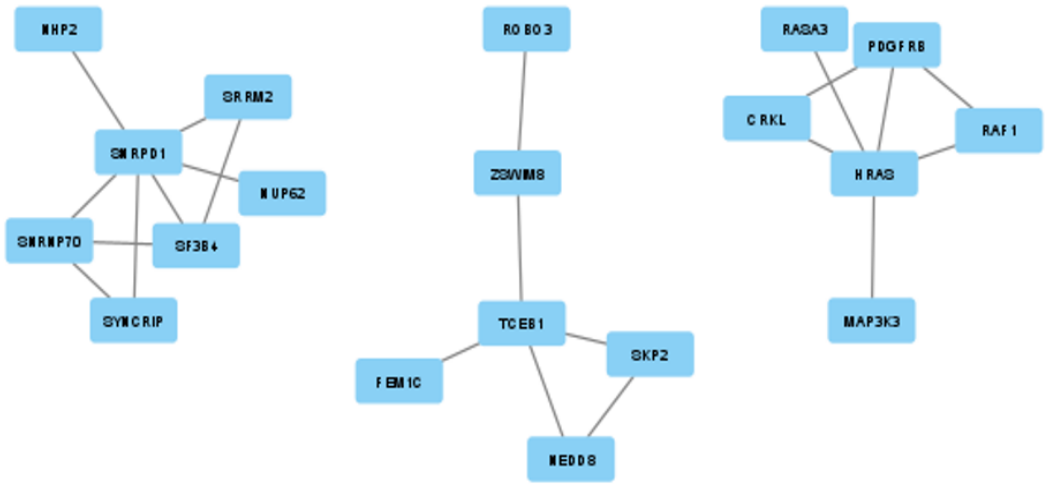
ILMN_137433	0.01858	0.00003093	BOLA3	bolA family member 3
ILMN_25959	0.01858	0.00003066	C12orf45	chromosome 12 open reading frame 45
ILMN_426	0.01858	0.00003062	MAP3K3	mitogen-activated protein kinase kinase kinase 3
ILMN_22997	0.02171	0.00004031	MRPL1	mitochondrial ribosomal protein L1
ILMN_19460	0.0224	0.00004795	KIAA0556	KIAA0556
ILMN_18776	0.0224	0.00004975	STX12	syntaxin 12
ILMN_14673	0.0224	0.00005119	NHP2	NHP2 ribonucleoprotein
ILMN_24430	0.0224	0.00004745	MACROD2	MACRO domain containing 2
ILMN_139203	0.0224	0.00004963	ZNF384	zinc finger protein 384
ILMN_22035	0.0224	0.00005142	RAB12	RAB12, member RAS oncogene family
ILMN_24280	0.02325	0.00005603	MDP1	Magnesium-dependent phosphatase 1
ILMN_10742	0.02325	0.00005604	SMPD1	sphingomyelin phosphodiesterase 1
ILMN_16257	0.02681	0.00007167	ZSWIM8	zinc finger SWIM-type containing 8
ILMN_21714	0.02681	0.0000721	RNFT2	ring finger protein, transmembrane 2
ILMN_11890	0.02681	0.00007391	CRYGS	crystallin gamma S
ILMN_5379	0.02681	0.00007198	SGF29	SAGA complex associated factor 29
ILMN_13003	0.02691	0.00007723	BTBD7	BTB domain containing 7
ILMN_20932	0.02707	0.00007926	EGR1	early growth response 1
ILMN_24619	0.02681	0.0000754	HS3ST5	heparan sulfate-glucosamine 3-sulfotransferase 5
ILMN_28470	0.02888	0.00009426	SYNCRIP	synaptotagmin binding cytoplasmic RNA interacting protein
ILMN_675	0.02888	0.0000945	NUP62	nucleoporin 62
ILMN_1785	0.02888	0.00009416	STH	saitohin
ILMN_3366	0.02946	0.00009809	NDUFAF2	NADH: ubiquinone oxidoreductase complex assembly factor 2
ILMN_24708	0.03015	0.00010211	RAVER1	ribonucleoprotein, PTB binding 1
ILMN_1519	0.03099	0.0001078	ZNFX1	zinc finger NFX1-type containing 1
ILMN_12170	0.03099	0.00011029	MRPS9	mitochondrial ribosomal protein S9
ILMN_21088	0.03112	0.00011255	SRRM2	serine/arginine repetitive matrix 2
ILMN_2342	0.03099	0.00010872	PSME1	proteasome activator subunit 1
ILMN_11181	0.03211	0.00012067	HRAS	HRas proto-oncogene, GTPase

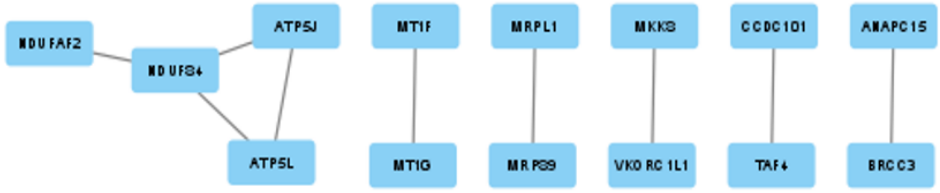
ILMN_4860	0.03211	0.00012155	CEBPG	CCAAT/enhancer-binding protein gamma
ILMN_21859	0.03211	0.00012166	KMT5A	lysine methyltransferase 5A
ILMN_11023	0.03214	0.00012359	NIT2	nitrilase family member 2
ILMN_6413	0.03264	0.00012741	TMEM27	transmembrane protein 27
ILMN_1868	0.03327	0.00013402	SLC30A9	solute carrier family 30 members 9
ILMN_17501	0.03327	0.00014422	TATDN1	TatD DNase domain containing 1
ILMN_8602	0.03327	0.00014082	CTSH	cathepsin H
ILMN_29960	0.03327	0.00014615	C12orf10	chromosome 12 open reading frame 10
ILMN_19501	0.03327	0.00014203	RASA3	RAS p21 protein activator 3
ILMN_12460	0.03327	0.00014829	SF3B4	splicing factor 3b subunit 4
ILMN_17046	0.03327	0.00014886	DIDO1	death inducer-obliterator 1
ILMN_27794	0.03327	0.00014549	SEPT6	septin 6
ILMN_1462	0.03343	0.00015162	ZFYVE26	zinc finger FYVE-type containing 26
ILMN_22649	0.03327	0.00014896	ZNF692	zinc finger protein 692
ILMN_6862	0.03375	0.00015684	SLC7A2	solute carrier family 7 members 2
ILMN_12588	0.03375	0.00015693	LAMA5	laminin subunit alpha 5
ILMN_12468	0.03379	0.0001627	ITPKB	inositol-trisphosphate 3-kinase B
ILMN_137712	0.03379	0.00016291	GATAD1	GATA zinc finger domain containing 1
ILMN_24124	0.03469	0.00016925	VRK1	vaccinia related kinase 1
ILMN_29134	0.03509	0.00017724	RPA3	replication protein A3
ILMN_11905	0.03509	0.00017925	DHX36	DEAH-box helicase 36
ILMN_14355	0.03502	0.0001749	SV2C	synaptic vesicle glycoprotein 2C
ILMN_21135	0.03593	0.00018572	HABP4	hyaluronan binding protein 4
ILMN_2297	0.03593	0.00018771	CTDSP2	CTD small phosphatase 2
ILMN_10532	0.03593	0.00019105	SLC27A5	solute carrier family 27 members 5
ILMN_23906	0.03593	0.0001918	MTMR7	myotubularin related protein 7
ILMN_25767	0.03705	0.00019994	PDGFRB	Platelet-derived growth factor receptor beta
ILMN_8459	0.03889	0.00021208	MICALL2	MICAL like 2
ILMN_8310	0.03943	0.00022129		
ILMN_16269	0.03943	0.00022618	PDCD2	programmed cell death 2
ILMN_28397	0.03943	0.00022007	CCR2	C-C motif chemokine receptor 2
ILMN_28971	0.03943	0.0002278	DYNLL2	dynein light chain LC8-type 2
ILMN_839	0.03943	0.00022859	GPATCH4	G-patch domain containing 4

ILMN_24287	0.03943	0.0002284	SC5D	sterol-C5-desaturase
ILMN_767	0.04028	0.00023696		
ILMN_4848	0.04028	0.00023817	CRKL	CRK like proto-oncogene, an adaptor protein
ILMN_7162	0.04028	0.0002451	BEX3	brain expressed X-linked 3
ILMN_10698	0.04028	0.00024252	GALM	galactose mutarotase
ILMN_21168	0.04059	0.00025097	GCC1	GRIP and coiled-coil domain containing 1
ILMN_21253	0.04028	0.00024376	SNRNP70	small nuclear ribonucleoprotein U1 subunit 70
ILMN_9044	0.04059	0.00025973	DUSP18	dual specificity phosphatase 18
ILMN_137162	0.04059	0.00026177	SDCCAG3	serologically defined colon cancer antigen 3
ILMN_1167	0.04059	0.0002568	NDUFS4	NADH: ubiquinone oxidoreductase subunit S4
ILMN_3617	0.04059	0.00026325	RPP40	ribonuclease P/MRP subunit p40
ILMN_28461	0.04059	0.00025892	TDRD5	Tudor domain containing 5
ILMN_7722	0.04243	0.00027767	ZNF264	zinc finger protein 264
ILMN_19110	0.04454	0.00029404	ABHD15	abhydrolase domain containing 15
ILMN_18028	0.04492	0.00029911	FAM107A	family with sequence similarity 107-member A
ILMN_22764	0.04783	0.00032567	ZNF319	zinc finger protein 319
ILMN_29701	0.04783	0.00032946	ZNF318	zinc finger protein 318
ILMN_14594	0.04783	0.00032741	EHD2	EH domain containing 2
ILMN_807	0.04844	0.0003392	SNRPD1	small nuclear ribonucleoprotein D1 polypeptide
ILMN_20161	0.048	0.00033342	FEM1C	fem-1 homolog C

4.2 HUB Genes in the Pathogenesis of all Six Diseases

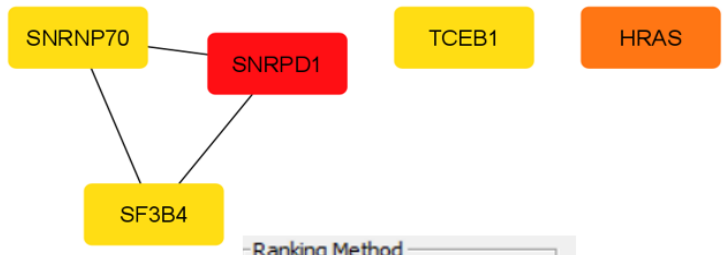
PPI network analysis identified that 33 nodes and 31 edges were involved in the core PPI network. The core network suggests another isolated interaction between MT1F-MT1G, MRPL1-MRP89, MKK8-VKORC1L1, CCDC1O1-TAF4, and ANAPC15-BRCC3. Further, the CytoHubba analysis suggests that SNRNP70, SF3B4, and SNRPD1 were HUB genes in the network.





Summary Statistics	
Number of nodes	33
Number of edges	31
Avg. number of neighbors	1.879
Network diameter	2
Network radius	1
Characteristic path length	1.268
Clustering coefficient	0.165
Network density	0.029
Connected components	9
Multi-edge node pairs	0
Number of self-loops	0
Analysis time (sec)	0.052

CYTOHUBBA ANALYSIS



Ranking Method: MCC

Rank	Node
1	SNRPD1
2	HRAS
3	TCEB1
3	SF3B4
3	SNRNP70

Figure 10: PPI Network of HUB Genes

4.3 Critical lysine residues involved in AD

HUB genes, such as SNRNP70, SNRPD1, and SF3B4 were analyzed for common ubiquitination and acetylation sites. The results indicated that SNRNP70 has 7 common acetylation and ubiquitination sites, whereas, SF3B4 has 1 common ubiquitination and acetylation site. Further, SNRPD1 has zero common ubiquitination and acetylation site.

Table 3: Common lysine residues for ubiquitination and acetylation on HUB genes

GENES	UNIPROT ID	UBIQUITINATION	ACETYLATION	COMMON
SNRNP70	P08621	K103, K118, K130, K138, K167, K27, K32, K346, K87	K103, K118, K130, K162, K27, K32, K346, K87	K103, K118, K130, K27, K32, K346, K87
SNRPD1	P62314	K48, K9	K41, K44	-
SF3B4	Q15427	K78	K78, K82	K78

4.4 Protein Secondary Structure Analysis

From protein secondary structure analysis, we observed that the coiled structure had most of the PTM sites in SNRNP70 and SF3B4 compared to their helix and strand structure. Only SNRPD1 had most of the PTMs in helix structure. SNRPD1 has 9 PTM sites in the helix region while only 1 PTM site in the coiled region. Many studies have reported that coiled structure is responsible for protein interactions and aggregation propensity. The frequency of PTMs in helix structure was maximum in SNRPD1 followed by SF3B4. The frequency of PTM in the helix region was least in SNRNP70 as it had only 3 PTM in the helix region. Amazingly, SNRPD1 didn't show any presence of strand structure, whereas SF3B4 had 5 PTM sites in the strand region. Fascinatingly, none of the three regulatory proteins had any ordered region. In SNRNP70 no

PTM lysine site fell in the ordered or disordered region. Likewise, even in SF3B4 none of the PTM lysine sites fell in the ordered or disordered region. Similarly, SNRPD1 also showed no PTM sites in the ordered or disordered regions.

Table 4: List of PTM and Non-PTM sites of SNRNP70, SNRPD1, & SF3B4 in helix, coiled & strand forms.

STRUCTURE	**SNRNP70**		**SNRPD1**		**SF3B4**	
	PTM	NON-PTM	PTM	NON-PTM	PTM	NON-PTM
Helix	3	0	9	11	5	8
Coiled	4	0	1	0	9	24
Strand	2	0	0	0	5	6

4.5 Pathway Analysis

Pathway analysis of SNRNP70, SNRPD1, and SF3B4 demonstrated that SNRPD1 is involved in the top 13 enriched pathways. Further, the results demonstrated that SNRNP70 and SF3B4 are involved in 4 and 5 enriched pathways respectively as shown in the table.

Table 5: Input HUB Genes and their UniProt IDs.

INPUT	**UniProt ID**	**INPUT**	**UniProt ID**	**INPUT**	**UniProt ID**
SF3B4	Ql5427	SNRNP70	P08621	SNRPDl	P62314, P62316

Table 6: Functional enrichment analysis (Biological pathways)

Pathway name	**Proteins found**	**Entities p-Value**
mRNA Splicing - Major Pathway	SNRNP70, SNRPD1, SF3B4	6.05E-8
mRNA Splicing	SNRNP70, SNRPD1, SF3B4	7.18E-8
Processing of Capped Intron-Containing Pre-mRNA	SNRNP70, SNRPD1, SF3B4	2.05E-7
mRNA Splicing - Minor Pathway	SNRPD1, SF3B4	3.58E-7
Metabolism of RNA	SNRNP70, SNRPD1, SF3B4	1.16E-5
SARS-CoV-2 modulates host translation machinery	SNRPD1	1.24E-4
snRNP Assembly	SNRPD1	1.49E-4
Metabolism of non-coding RNA	SNRPD1	1.49E-4
SARS-CoV-2-host interactions	SNRPD1	3.57E-3
SARS-CoV-2 Infection	SNRPD1	5.84E-3
SARS-CoV Infections	SNRPD1	8.82E-3
Infectious disease	SNRPD1	7.37E-2
Disease	SNRPD1	1.67E-1

4.6 Impact of Lysine Mutation on SNRPD1

The observed results indicate that all sites affect disease susceptibility. However, K44D has the highest confidence score. High intolerant mutations that are susceptible to the disease are shown in the table given below.

Table 7: Impact of SNRPD1 'K' putative mutation to 'R' or 'D' on vulnerability of disease prognosticated with the aid of SNAP2 & PMUT

RESIDUE	SNAP2	PMUT	CONFIDENCE
K48D	0.54	0.5661	1.1061
K9D	0.75	-	
K41D	0.74	-	
K44D	0.87	0.5431	1.4131

4.7 Impact of Drugs on SNRPD1

From Protein Bank Data, we got Artenimol and 4 of its similar structures. We used Artenimol as control and Artemether had the Vina score of -6.4 showing a stable system and thus, a likely binding interaction. CB Dock tool shows that Q24, K44, H26, T16, V15, T14, I69, L70, P71, D72, S97, I96, Y95, and R94 are the putative binding sites on SNRPD1 where Artemether may bind.

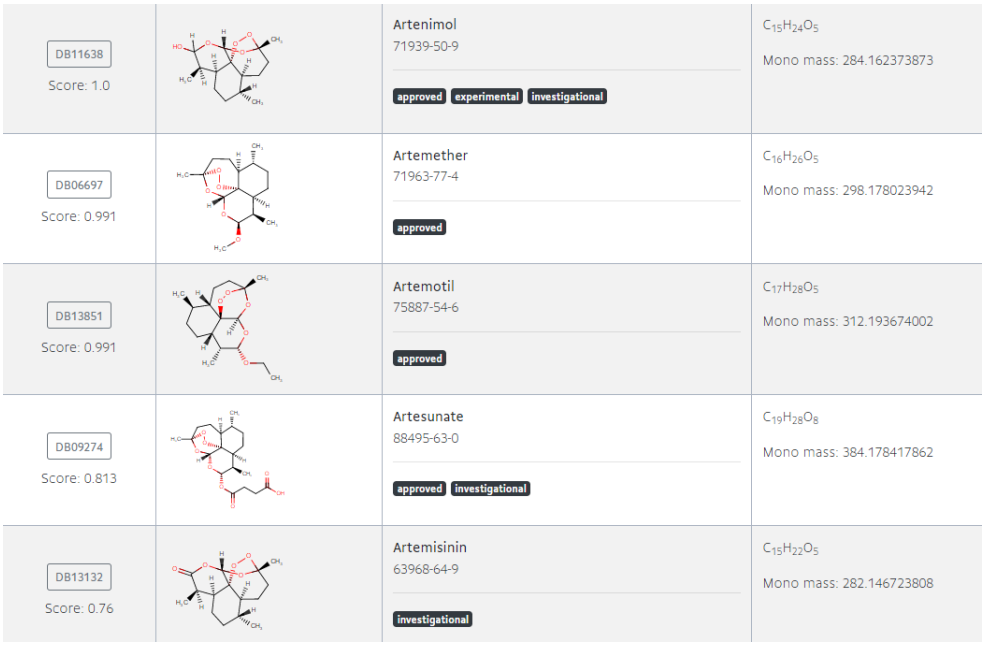


Figure 11: Artenimol and 4 of its similar structures on Drug Bank Database.

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-6.4	91	45	39	-8	19	19	19
-6.2	760	32	40	11	19	25	19
-6.1	221	44	26	-6	19	19	19
-5.5	62	47	43	8	19	19	19
-5.3	65	36	25	0	19	19	19

Figure 12: Results of CB Docking of SNRPD1 with Artemether

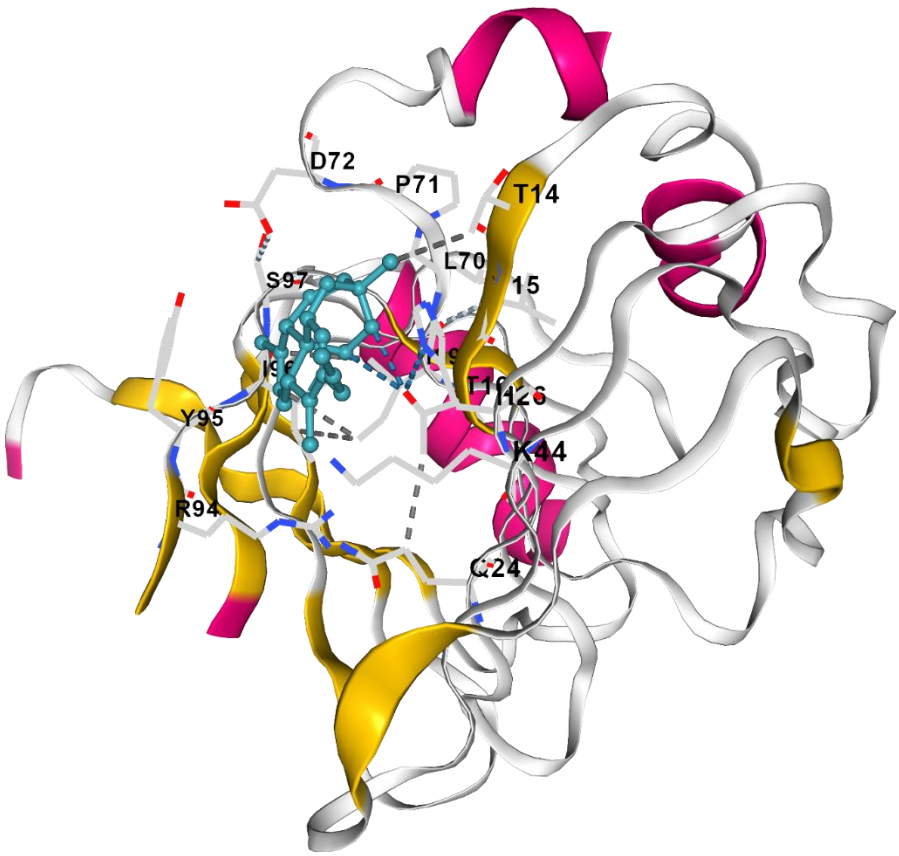


Figure 13: Putative binding sites on SNRPD1 with Artemether

CHAPTER – 5

CONCLUSION

In this study, we performed an analysis of two PTMs i.e., acetylation and ubiquitination. Here, we first extracted and pre-processed the data for which microarray analysis was performed using the GEO2R. Further, 123 DEGs were shortlisted based on the adjusted p-value. PPI network was constructed to analyze the interaction between regulatory proteins in all six diseases. Studying this network gave us HUB genes namely, SNRNP70, SF3B4, and SNRPD1. Critical lysine residues involved were analyzed for SNRNP70, SF3B4, and SNRPD1; it was found that SNRPD1 had no common ubiquitination and acetylation sites. Thereafter, protein secondary structure analysis showed SNRPD1 has 9 PTM sites in the helix region while only 1 PTM site in the coiled region. Many studies have reported that coiled structure is responsible for protein interactions and aggregation propensity. Further, pathway analysis showed that SNRPD1 is involved in the top 13 enriched pathways, whereas, SNRNP70 and SF3B4 are involved in 4 and 5 enriched pathways respectively. Mutation of lysine residues with arginine and aspartic acid indicated that all sites have an effect on disease susceptibility, however, some showed a high confidence score. Lastly, it was found that Artemether is the best drug for SNRPD1 the putative binding site where the CB Dock tool shows that Q24, K44, H26, T16, V15, T14, I69, L70, P71, D72, S97, I96, Y95, and R94.

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LIST OF PUBLICATIONS

1. H. Goswami and P. Kumar, "Is Artificial Intelligence a Helping Hand for the Future of Neurosurgery?" 2021 5th International Conference on Information Systems and Computer Networks (ISCON), 2021, pp. 1-6, DOI: 10.1109/ISCON52037.2021.9702473.

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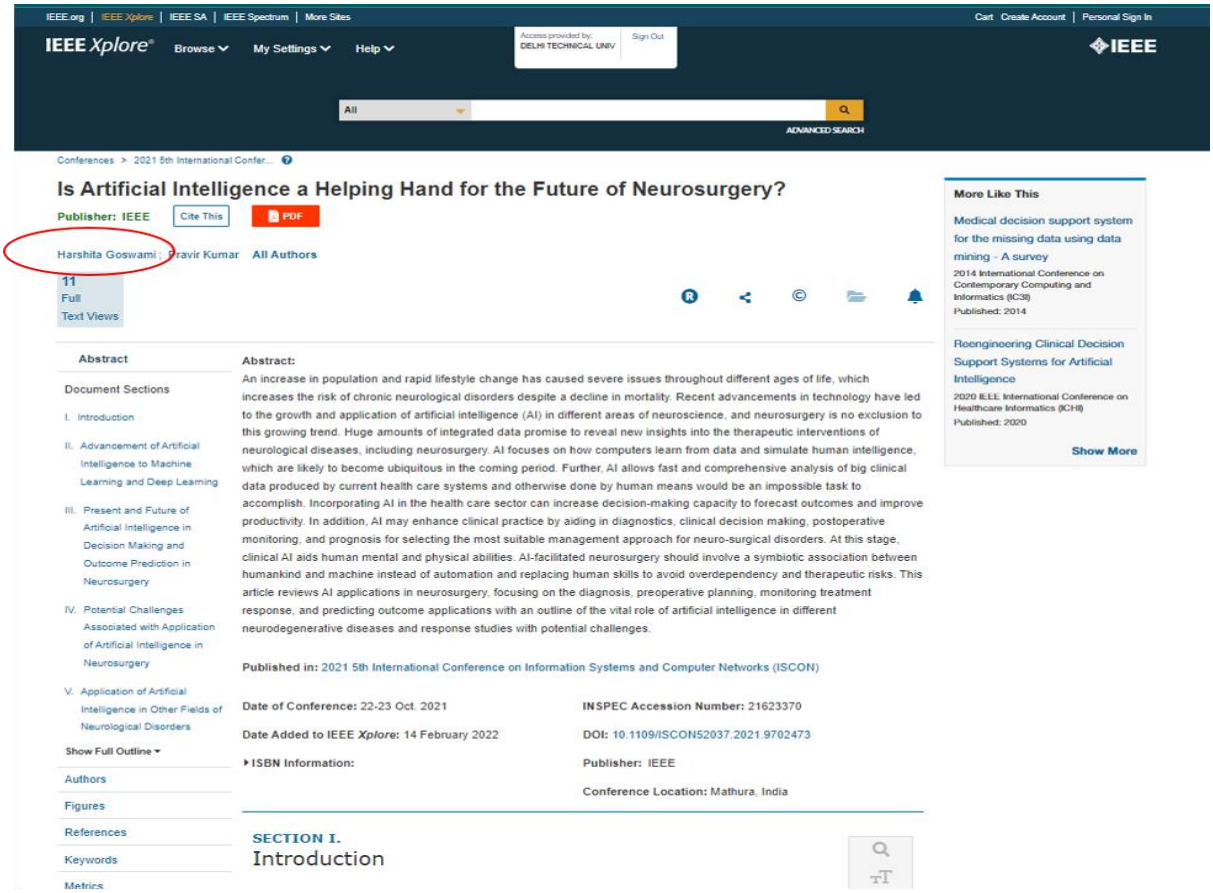

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I. Introduction

II. Advancement of Artificial Intelligence to Machine Learning and Deep Learning

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Abstract:

An increase in population and rapid lifestyle change has caused severe issues throughout different ages of life, which increases the risk of chronic neurological disorders despite a decline in mortality. Recent advancements in technology have led to the growth and application of artificial intelligence (AI) in different areas of neuroscience, and neurosurgery is no exclusion to this growing trend. Huge amounts of integrated data promise to reveal new insights into the therapeutic interventions of neurological diseases, including neurosurgery. AI focuses on how computers learn from data and simulate human intelligence, which are likely to become ubiquitous in the coming period. Further, AI allows fast and comprehensive analysis of big clinical data produced by current health care systems and otherwise done by human means would be an impossible task to accomplish. Incorporating AI in the health care sector can increase decision-making capacity to forecast outcomes and improve productivity. In addition, AI may enhance clinical practice by aiding in diagnostics, clinical decision making, postoperative monitoring, and prognosis for selecting the most suitable management approach for neuro-surgical disorders. At this stage, clinical AI aids human mental and physical abilities. AI-facilitated neurosurgery should involve a symbiotic association between humankind and machine instead of automation and replacing human skills to avoid overdependency and therapeutic risks. This article reviews AI applications in neurosurgery, focusing on the diagnosis, preoperative planning, monitoring treatment response, and predicting outcome applications with an outline of the vital role of artificial intelligence in different neurodegenerative diseases and response studies with potential challenges.

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A Dissertation

Submitted in Partial Fulfilment of The

Requirements for The Award of The Degree

Of

MASTER OF TECHNOLOGY

IN

BIOINFORMATICS

Submitted by:

HARSHITA GOSWAMI

2K20/BIO/01

Under the supervision of

HOD & PROF. PRAVIR KUMAR

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I, Harshita Goswami, 2K20/BIO/01 hereby certify that the work which I presented in the Major Project entitled **"Computational Analysis of Post-Translational Modifications in Major Neurodegenerative Diseases"** in fulfilment of the requirement for the award of the Degree of Masters of Technology in Bioinformatics and submitted to the Department of Biotechnology, Delhi Technological University, Delhi is an authentic record of my own, carried out during a period from 7-Jan-2022 to 27-May-2022, under the supervision of HOD & Prof. Pravir Kumar.

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Supervisor & HOD

Department of Biotechnology

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