"*Computational Analysis of Post Translational Modifications in the Pathogenesis of Alzheimer's Disease*"

A dissertation
submitted in partial fulfilment of the requirements for the degree of
Master of Technology

BIOMEDICAL ENGINEERING

BY

Mehar Sahu
2K19/BME/06

UNDER THE SUPERVISION OF

Prof. Pravir Kumar

Department of Biotechnology
Delhi Technological University
(Formerly Delhi College of Engineering)
Shahbad Daulatpur, Bawana Road, Delhi-110042. India

Delhi Technological University

Shahbad Daulatpur, Main Bawana Road, Delhi-110042. India

DECLARATION

I, **Mehar Sahu**, 2K19/BME/06 student of M. Tech. Biomedical Engineering, hereby declare that the Dissertation Project entitled "**Computational analysis of post translational modifications in the pathogenesis of Alzheimer's Disease**" is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology. This work is original and not copied from any source without paper citation. I have honoured the principles of academic integrity and have upheld the normal student code of academic conduct in the completion of this work.

Place: Delhi

Date: 02-07-2021

Mehar Sahu

Delhi Technological University

Shahbad Daulatpur, Main Bawana Road, Delhi-110042. India

CERTIFICATE

This is to certify that the Dissertation Project titled "**Computational analysis of post translational modifications in the pathogenesis of Alzheimer's Disease**" which is being submitted by **Ms Mehar Sahu**, 2K19/BME/06, 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 of the work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part of full for any Degree or Diploma to this University or elsewhere.

Place: DTU, Delhi

Date: 02.07.2021

Prof. Pravir Kumar

Head of Department
Delhi Technological University

ACKNOWLEDGEMENT

At the time of submission of my M. Tech. Dissertation, I am grateful to the almighty God who has bestowed upon the wisdom, strength and patience to take up this endeavour. Apart from the effort, the success of this project depends largely on the encouragement and guidelines of many others. I, therefore, take this opportunity to express my gratitude to the people who have been instrumental in the successful completion of this project.

My initial thank is addressed to my mentor Prof Pravir Kumar, Head of the Department, Department of Biotechnology, Delhi Technological University, who gave me this opportunity to work in a project under him. It was his enigmatic supervision, constant encouragement and expert guidance which enabled me to complete this work. I humbly seize this opportunity to express my gratitude to him.

I would like to extend my sincere gratitude to Dr Rashmi Ambasta for her keen observation and continuous advice. Her thoughtful inputs on the project issues have been invaluable for the productive progress of the project.

Words are inadequate in offering thanks to Mr Rohan Gupta and Mr Devesh Srivastava who like a family, have shown confidence in me and helped me in my project.

I extend my thanks to technical staff Mr Jitender Singh and Mr C.B. Singh who have been an aid whenever required. Lastly, I wish to extend my thanks to my family and friends who have supported me through the entire process.

Mehar Sahu
2K19/BME/06

CONTENTS

1. **Introduction** 10
2. **Literature Review** 10
   - **2.1 Neurodegenerative Disease** 10
   - **2.2 Alzheimer's Disease** 11
   - **2.3 Post-Translational Modifications** 12
   - **2.4 Role of PTMs in AD and other NDDs pathogenesis** 12
   - **2.5 Acetylation and Ubiquitination as significant pathways in pathogenesis of AD** 16
   - **2.6 Implication of PTM on signaling transduction** 16
     - **2.6.1 APMK Pathway** 16
     - **2.6.2 PI3K/Akt/GSK3β Pathway** 17
     - **2.6.3 Apoptosis and Autophagy** 18
     - **2.6.4 Mitochondrial Dysfunction** 19
   - **2.7 PTM as therapeutic targets in AD treatment** 20
   - **2.8 Role of artificial intelligence in drug discovery** 20
3. **Methodology** 21
   - **3.1 Extraction and pre-processing data** 21
   - **3.2 Protein-Protein Interaction network of extracted proteins** 23
   - **3.3 Identification of critical Acetylation and Ubiquitination sites** 23
   - **3.4 Structural analysis of protein** 23
   - **3.5 Pathway analysis** 23
   - **3.6 Impact of lysine mutations on acetylation and ubiquitination** 23
   - **3.7 Identification of drug molecule** 23
4. **Results and Discussion** 23
   - **4.1 Data collection and differential gene expression analysis** 23
   - **4.2 HUB genes in the pathogenesis of AD** 24
   - **4.3 Critical lysine residues involved in AD** 25
   - **4.4 Protein secondary structure analysis** 26
   - **4.5 YWHAZ as critical protein involved in the pathogenesis of AD** 26
   - **4.6 Impact of lysine mutation YWHAZ** 28
   - **4.7 Impact of drug on YWHAZ** 28
5. **Conclusion** 29

References 30

LIST OF FIGURES

S. No.	Name of figure	Page number
1.	Domain architectures and positions of PTMs in proteins of different NDDs	14
2.	Volcano plot, normalize sample and heat map of GSE1297	22
3.	Protein-Protein Interaction network of DEGs	25
4.	Fold enrichment and p-values of biological pathways related to NEDD8, ITGB1 and YWHAZ	27
5.	Putative binding sites on YWHAZ with Phenethyl Isothiocyanate	29

LIST OF TABLES

S. No.	Name of table	Page Number
1.	A consolidated list of different PTMs and their target genes along with their respective modified amino acid residues that are involved in different NDDs	15
2.	Shortlisted DEGs indicating 13 downregulated and 353 upregulated genes between AD and healthy conditions	24
3.	Common lysine residues for ubiquitination and acetylation of HUB genes	26
4.	List of PTM and Non-PTM sites of NEDD8, YWHAZ, ITGB1 and ATP5F1B	26
5.	Functional enrichment analysis (biological pathways)	27
6.	Impact of YWHAZ's 'K' putative mutation to either 'R' or 'D' on disease susceptibility predicted with the help of PMut, SNAP2 and PANTHER	28
7.	Results of CB Docking of YWHAZ protein with Phenethyl Isothiocyanate drug	28

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
Aβ	Amyloid β
NFT	Neurofibrillary Tangles
HDAC	Histone Deacetylase
TRIM29	Tripartite Motif Containing 29
GSK3β	Glycogen Synthase Kinase 3 Beta
APP	Amyloid Peptide Protein
PTM	Post Translational Modification
NO	Nitric Oxide
KPI	Kunitz Proteases Inhibitor
CDC2	Cell Division Cycle
CDK5	Cyclin-dependent Kinase
AMPK	Adenosine Monophosphate activated protein Kinase
PI3K	Phosphatidylinositol Kinases
SMILES	Simplified molecular input line entry system
MMP	Matched molecular pair
GBM	Gradient boosting machine
PPI	Protein-Protein interaction
PLMD	Protein lysine modification database

ABSTRACT

Aim: Post-translational modifications like acetylation and ubiquitination share a common feature that they both act on lysine residue. Acetylation is responsible for transcriptional deregulation which further leads to mitochondrial dysfunction, autophagic pathway problems and DNA damage which ultimately leads to cell death. On the other hand, ubiquitination aids in degrading the accumulated toxic proteins. Thus, we aim to investigate the potential acetylation and ubiquitination sites in YWHAZ which is responsible for the pathogenesis of AD. Moreover, we aim to identify the impact of these PTMs on the structural features of YWHAZ and also the influence of putative lysine mutation on disease susceptibility. Lastly, we also aim to identify possible drugs and their impact on YWHAZ protein.

Result: Herein, we found 13 downregulated genes and 35 upregulated genes between AD and healthy conditions. Further, protein-protein interaction (PPI) network and PTMs integration helped us identify HUB genes namely, YWHAZ, ATP5B, MRPS16, MRPL15, NEDD8, KLHL22, COPS8, ITGB1, PTFAR, and LAMTOR2 with 20 potential lysine modified sites. Moreover, 43% of PTM sites in NEDD8, YWHAZ, ITGB1 and ATP5F1B fall in coiled and none of the four regulatory proteins had any ordered region. Added, 7 common putative lysine sites, K3, K9, K27, K68, K85, K115 and K138 of YWHAZ are crosstalk hotspots for acetylation and ubiquitination.

Conclusion: The loss of acetylated hotspots results in more loss of ubiquitination function than gain of function.

1. Introduction

Neurodegenerative diseases (NDDs) like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Multiple sclerosis (MS) and Amyotrophic lateral sclerosis (ALS) are caused due to progressive loss of neuronal cells which further causes synaptic disfunction and memory impairment (1). Out of all the NDDs, AD is the most prevalent disease amongst older people to which there is no cure so far. Many studies have demonstrated post-translational modifications (PTMs) to play a crucial role in the pathogenesis of NDDs. There are more than fifty types of PTMs and phosphorylation, ubiquitination, acetylation, SUMOylation and methylation are some of the common PTMs. These PTMs are responsible for transcriptional alterations that further leads to mitochondrial dysfunctions, DNA damage, autophagy and apoptosis of the cell which are pathological characteristics off AD. Acetylation is one of the major PTM which promotes euchromatin structure which leads to transcriptional activation that further reverses the impairment of cellular processes that reinstates synaptic functions. On the other hand, histone deacetylases (HDACs) reverse the process of acetylation and result in transcriptional repression that further leads to neurodegeneration. Besides acetylation, ubiquitination also plays a crucial role in removing toxic protein accumulated in brain via ubiquitin proteosome system (UPS). In this study, we found AD related HUB genes via protein-protein interaction (PPI) network. Moreover, we investigated biological pathways in which these shared genes were involved. The most important feature of ubiquitination and acetylation is the involvement of lysine (K) residues. Added, we identified critical acetylation and ubiquitination sites. Furthermore, we investigated the impact of lysine mutation on acetylation and ubiquitination, where lysine residues were replaced by arginine and aspartic acid. Lastly, we also identified a drug molecule named Phenethyl isothiocyanate in the drug bank database which shows putative binding sites on YWHAZ which is one of the HUB gene involved in the pathogenesis of AD.

2. Review of Literature

2.1. Neurodegenerative Disease

Neurodegenerative disease (NDD) is an umbrella term for a variety of conditions that primarily affects the neurons in the human brain. Neurons are the building blocks of the nervous system which includes the brain and spinal cord. Body cannot reproduce or replace the damaged neurons. This further causes problem with movement called "ataxia", or problem with functioning called "dementia". The disease can be anywhere in brain, spinal cord, cranial nerves, neuromuscular junction, nerve roots and muscles. The development of human brain begins during the stage of pregnancy and continues through infancy, childhood and adolescence. The disorder can be acquired not only at these stages but can be by birth or can be acquired at adult stage also. There are basically three types of neurological disorders, firstly, Congenital, disorders present at the time of birth; Acquired, disorders developed after birth and Idiopathic, disorders due to some unknown reasons. If a person is suffering from neurological disorder and shows symptoms that are physical, related to thoughts, behavior or emotions, then the person must seek professional assistance. Treatment given to such patient include Acupuncture and Oriental medicines which have been found to be effective as conjunctive therapy for neurological disorders; Yoga and Physical exercises also helps to cure disorders to some extent. Some technologically related treatments are also there such as Brain mapping which is an attempt

to picture out the brain structure particularly its centers and functional lobes. The mapping done is converted into data which is further analyzed by experts; Cyber knife, a robotic radiosurgery system which is usually used to treat tumors and is an alternative method to surgeries; Deep brain stimulation, it is used to treat tremors and movement problems. Another treatment option is Gamma knife, it is a type of radiation therapy used to treat tumors. Moreover, neurons and glial cells have been generated successfully from stem cells *in vitro* to treat neurological disorders. Common NDDs are Alzheimer's disease, Parkinson's disease, Huntington's disease, Spinocerebellar ataxia, Multiple sclerosis and Amyotrophic lateral sclerosis. The death of neuronal cells causes improper functioning of the brain cellular machinery which further results in loss of memory, synaptic dysfunction, and cognitive problems (2).

2.2. Alzheimer's Disease

Alzheimer's disease (AD) is a neurological disorder. In this disease brain cells are destroyed which further leads to memory loss and dysfunction of brain functions. By the time brain cells decline, they wither and die, thus, the brain function becomes worse. That's why AD is considered fatal and till date we have no cure to it. AD is a global health challenge now a day. It has affected many areas of the world including Europe, Bulgaria, Spain, Poland, Netherland, Scotland and England etc. In United States, AD is the 6^{th} leading cause of the death. The recent survey tells that people are dying more by AD than by breast cancer and prostate cancer. AD affects people belonging to an age group of 60 or above. But, some of the symptoms may appear during middle age also. One cannot detect AD by just looking at some of the symptoms. On an average, a person suffering from AD can survive only 4 to 8 years after diagnosis. Health tools have also been designed for early detection of AD like giving education and spreading awareness materials. Family questionnaire can be done to prevent AD in a family. AD is the most common form of Dementia. Dementia is a general term for decline in mental ability. Under dementia, AD accounts for 60 to 80% of cases. There are different types of dementia which are associated with particular type of brain cells and that too in a particular part of the brain. It characterized by progressive cognitive decline and the pathological markers are extracellular senile plaques made up of beta-amyloid protein and intracellular neurofibrillary tangles. When a person suffers from AD, the hippocampus (center of thoughts and memory) is likely to be affected first that's why it is said that memory loss is the one of the earliest symptoms. Damage to hippocampus leads to oxygen starvation (hypoxia) which further leads to Anterograde Amnesia, it is a condition in which one cannot retain or form new memories. As the disorder becomes severe, there are some observable symptoms like, serious memory loss, disorientation in space, mood swings, body balancing problems, speech problems and difficulty in remembering about time, place and events. The precise number of stages of AD are somewhere arbitrary. Some expert uses the simple three phase model (early, moderate and severe), while others have found a granular breakdown to be more useful aid to understand the progression of the illness. The most common system developed by Dr Barry Reisberg of New York University breaks the progression of AD into 7 stages namely, Stage 1: Normal outward behavior; Stage 2: Very mild changes; Stage 3: Mild decline; Stage 4: Moderate decline; Stage 5: Moderately severe decline; Stage 6: Severe decline; Stage 7: Very severe decline (3).

2.3.Post-Translational Modifications

Post-Translational Modification (PTM) is a phenomenon in which the ribosome uses the genetic code to translate the mRNA molecule into polypeptides. Once the polypeptide is synthesized, it is usually modified before it actually becomes a mature and active protein. Such modifications are known as PTMs. Different types of PTMs are Methylation, Acetylation, Glycosylation, Lipidation, Ubiquitination, SUMOylation, Phosphorylation and Proteolysis.

Methylation: Methyl group (-CH3) can be added onto the amino acid by an enzyme called methyltransferase. Methylation usually increases the hydrophobic character of the amino acid. Methylation is usually utilized in epigenetic regulation, which is the regulation of gene expression.

Acetylation: N-Acetylation is the transfer of an acetyl group onto the nitrogen of an amino acid. This process can take place when ribosome is still translating the polypeptide chain. N-Acetylation plays a crucial role in gene expression. Histone, the protein that assists in condensing DNA into chromatids can be acylated, which reduces their ability to fold and open up the DNA for transcription.

Glycosylation: This is one of the major ways in which polypeptides are modified. This process involves adding sugar components to the proteins. Thin affects the protein conformation and folding. One example of proteins is glycosylated is membrane proteins that act as receptor for important biological molecules. Example: Neurotransmitter.

Lipidation: it is a process by which lipid components are added into polypeptides. Usually, those proteins that are destined to be in membranes, such as the ER membrane, mitochondrial membrane undergoes this process. It increases the proteins hydrophobic character, which in turn increases the protein affinity to membranes.

Ubiquitination: Misfolded/ defective proteins undergo PTM by ubiquitination. Ubiquitin is a cytosolic globular non-enzymatic protein. Glycine residue of ubiquitin covalently attaches to the ammonia group of lysine of target protein. Ubiquitin proteins are degraded by cytosolic proteases/proteasomes. It is an irreversible process.

Phosphorylation: Amino acids such as serine, threonine and tyrosine found on the polypeptide chain can be modified via phosphorylation by enzymes called protein kinases. This type of modification plays a crucial role in cell cycle, signal transduction and apoptosis. It is a reversible process.

Proteolysis: Certain proteins are synthesized in their inactive form (zymogen). In order to activate them, enzymes called proteases must break certain peptide bonds. Many of the digestive enzymes in the small intestine uses this type of PTM.

2.4.Role of Post-Translational Modification in AD and other NDDs Pathogenesis

PTMs such as acetylation, phosphorylation, glycosylation, amidation, methylation, ubiquitination, and hydroxylation are prominently involved in the progression of NDDs (Table 1). In AD, the first neuropathological hallmark is the formation of senile plaques and Aβ peptide deposits (4). APP, a type 1 membrane glycoprotein, undergoes an amyloidogenic pathway where it is cleaved by β- and γ- secretase and forms soluble fragment of sAPPβ and short Aβ peptide. Alternatively, a non-amyloidogenic pathway occurs where α-secretase cleaves the Aβ sequence to prevent the formation of toxic peptides, generating sAPPα and p3 peptides (5). APP is a multi-domain membrane protein that consists of signal peptide, cysteine-rich region, acidic domain, Kunitz proteases

inhibitor (KPI)/OX2 and Aβ peptide. Multiple PTMs have been observed, like oxidation of M35 to methionine sulfoxide, which leads to the formation of Aβ protofibrils (6), whereas, cell division cycle protein 2 (cdc2) kinase generates phosphorylation at S26. In the same manner, nitration of Y10 because of nitric oxide (NO) can lead to aggregation of Aβ, whereas, glycosylation of Y10 changes the γ-secretase cleavage due to the proximity of this PTM to the transmembrane domain (7). Polyglutamylation of E11 can give rise to increased aggregation and formation of β-sheet in-vitro. Furthermore, racemization of D1 is higher in plaques, whereas, S26 shows an increased tendency to form fibrils (8). Similarly, the O-GlcNAcylation of APP at T576 regulates APP trafficking and processing, which increases its toxic aggregates (9). Furthermore, in AD, NFTs, which are intraneuronal aggregates of abnormally phosphorylated tau protein, is a major cause of neuronal cell death. Tau protein is subdivided into four domains, i.e., N-terminal, a proline-rich domain, microtubule-binding domain, and C-terminal. Phosphorylation is the most common PTM as it decreases the affinity for microtubule binding, which leads to neuronal cytoskeleton destabilization. Phosphorylation by casein kinase 1 (CK1) can be taken as the most significant kinase of tau. Tau phosphorylation at S262, S293 and S356 decrease tau binding to microtubules, whereas, phosphorylation at S235 and S262 has been shown to dissociate Tau microtubule (4,10). Glycosylation in the presence of kinases like protein kinase A (PKA), cyclin-dependent kinase 5 (CDK5), and glycogen synthase kinase 3β (GSK3β) reduces phosphorylation, which is expected to prevent NFT formation. Truncation at D13, E391, and D421 results in tau aggregation, whereas, only a single site of O-GlyNAcylation at S400 showed an inverse relationship with hyper-phosphorylation (11). However, oxidation at C322 gives no certainty, whether it takes part in tau lesion or not (12). Moreover, aberrant palmitoylation at C186 or C187 results in decreased neuronal plasticity and increased misfolded protein aggregates (13).

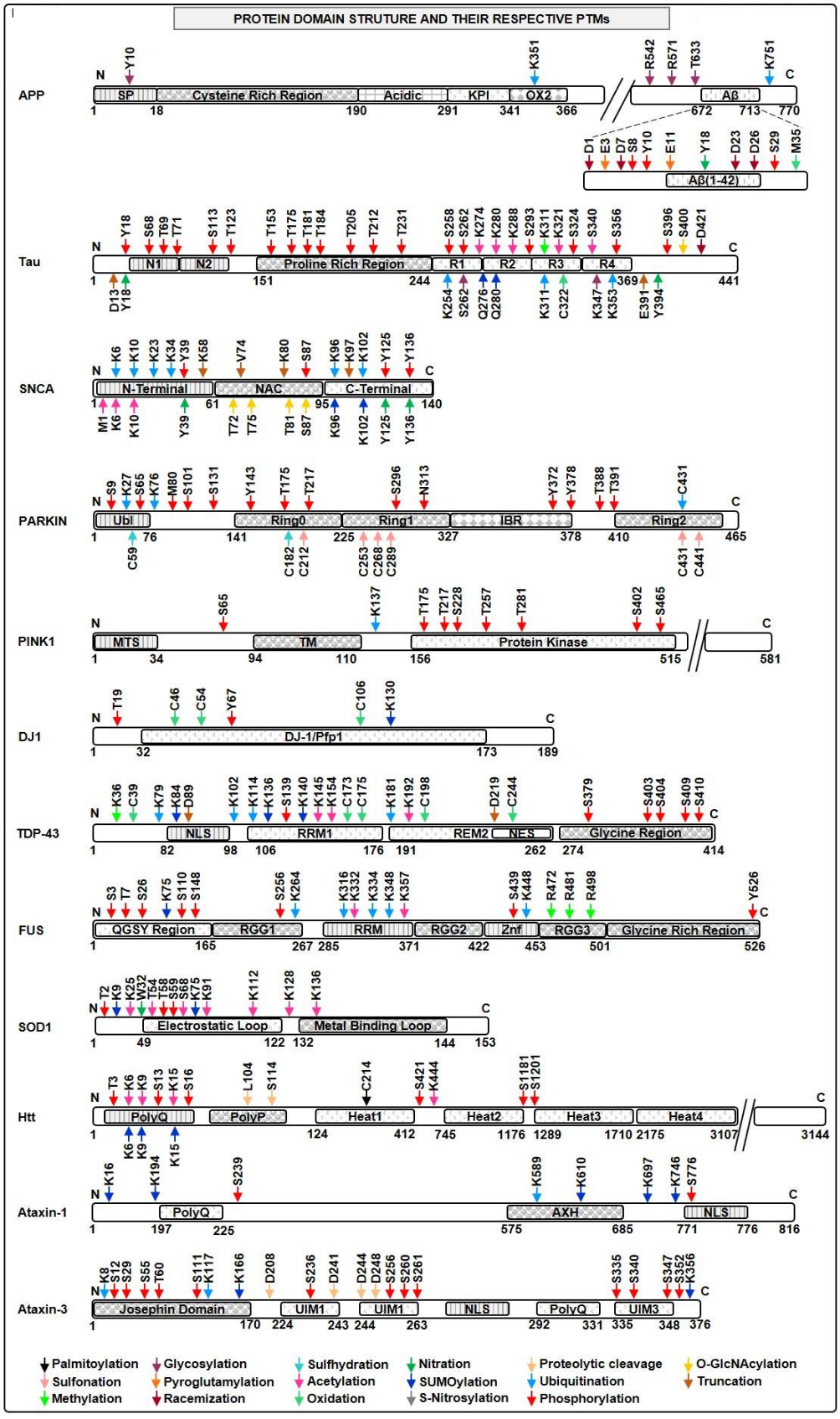


Figure 1: Domain architectures and position of post-translational modifications in proteins of different neurodegenerative diseases

Table 1: A consolidated list of different PTMs and their target genes along with their respective modified amino acid residue that are involved in the different neurodegenerative disorders (shaded in grey)

PTM	Protein	Residue	AD	PD	ALS	HD	MDD	SCA	References
Acetylation	GFAP	K153 and K189							(14)
	PPP1R3B	G57							(15)
	Tau	K280, K281,							(16)
	Tau	K163, K174, K190, K224, K234, K240, K254, K280, K281, K290, K311, K375, K385, K395							(17)
	TDP-43	K145							(18)
	α-synuclein	K6, K10							(19)
	Ataxin-7	K257							(20)
	htt	K6, K9, K15							(21)
Glycosylation	APP	T576							(9)
	APOE	R212							(22)
	MUC5B	V144							(23)
	MAPT	N.A							(24)
	OGT	N.A							(25)
	α-synuclein	K6, K10, K12, K21, K23, K32, K34, K43, K45							(26)
Adenylation	α-synuclein	T33, T54, T75							(27)
Carbonylation	Tau	K163, K280, K281, K311							(28)(29)
Citrullination	FUS, EWS, and TAF15	RG/RGG motif							(30)
	GFAP	R270, R416							(31)
	MBP	R41, R47, R63, R96, R129							(32)
	NRGN	R68							(32)
Crotonylation	NEAT1	H3K27							(33)
Methylation	MAPT	K44							(34)
	MAPT	K163, K174, K180, K254, K267, K290							(35)
	MAPT	K24, K67, K190							(36)
	PPP2CA	L309							(36)
	PINK1	K27							(37)
	UBTF	K231/K254							(38)
Nitration	amyloid β	Y10							(39)
	amyloid β(1-40)	Y10							(40)
	Tau	Y18, Y394							(41)
	α-synuclein	H50							(42)
	α-synuclein	Y39, Y125, Y133/Y136							(43)
Phosphorylation	ABI3	S210, S213, and S216							(22)
	APOE	C147							(44)
	APOE	R212							(22)
	LRRK2	G2023							(45)
	MORN2	E38							(46)
	Ataxin-1	S776, S239							(47,48)
	Ataxin-3	S12, S29, S256, S236 S340, S352							(49–52)
	MUC5B	V144							(23)
S-Nitrosylation	IDE	C178, C789, C819, C966							(53)
	GOSPEL	C47							(54)
	CDK5	C83, C157							(55)
	Drp1	C644							(56)
Succinylation	PDHA1	K77, K244, K344							(57)
	APP	K687							(57)
	α-secretase	K16							(57)
	Tau	K280, K311							(57)
Ubiquitination	ATP5F1C	112							(22)
	FASN	R1927							(23)
	PPC2C	T2709, T2710, T2712							(58)
	TRAF6	K63							(59)

	Ataxin-1	K589	(60)
	Ataxin-3	K117	(61)
	SOD1	N.A	(62)
	BAG2	N.A	(63)
	PINK1	C431	(64)
	PARKIN	K27, K48, K76	(65)
SUMOylation	α-synuclein	K102	(66)
	DJ1	K130	(67)
	PARKIN	N.A	(65)
	Amyloid-β	K11	(68)
	Tau	K340	(69)
	BACE1	Dileucine motif	(69)
	Rhes-htt	K14, K49, K153	(70)
	Ataxin-1	K16, K194, K610, K697, K746	(71)
	Ataxin-3	K166, K356	(72,73)
	Ataxin-7	K257	(74)
	SOD1	K75	(69)
	EAAT2	K570	(69)
Palmitoylation	APP	C186 and C187	(75)
	PSD-95	C3, C5	(76)

2.5.Acetylation and Ubiquitination as Significant Pathway in Pathogenesis of AD

Memory loss is one of the main features of AD. Epigenetic mechanisms, particularly histone acetylation controls plasticity and memory processes which gets hampered in case of the dysfunction of the process (77). Improper functioning of histone acetylation is involved in different types of signal transduction pathways like differentiation, cell apoptosis, vascular remodeling, inflammation reaction, immune responses, neuronal plasticity and metabolic reprogramming (78). Moreover, change in acetylation of both nuclear and cytoplasmic non-histone protein has also been associated with AD, with NF-κB, p53, α-tubulin and tau, affecting more regulatory pathways involved in AD (78). There are evidences that relates protein acetylation to AD and this further suggests that it plays an important role in cognitive problem in AD patients. Acetylase p300 acetylate K122, K123, K218, K221 and K310 residues of NF-κB. Moreover, PFAC acetylates at K122 which results in Aβ induced activation of NF-κB. Other deacetylase like sirtuin SIRT1 also regulates NF-κB in *in vitro* models of AD (78–80). It is also known that tau acetylation suppresses degradation of phosphorylated tau. Acetylase p300 also regulates acetylation of tau, whereas, deacetylase SIRT1 mediates deacetylation of tau (78,81). Moreover, acetylated tau may contribute to tau mediated neurodegeneration by decreasing the solubility and microtubule assembly and , thereby, increasing tau fibrillation (78,82). There are numerous studies which states that both ubiquitination and proteosome plays an important role in producing and handling APP, Aβ and Tau proteins. APP maturation is halted by ubiquitination at K63 which is stimulated by ubiquitin 1 (83). CHIP facilitates alternative ubiquitination during the involvement of Hsp90 due to which phosphorylated tau gets accumulated. It has also been observed that FBXW7 facilitates ubiquitination of γ-secretase which unexpectedly increases Aβ production (83). Conjugation of lysine residues of APP (K724, K725, K726, K751 and K763) with ubiquitin in mouse brain and its damage leads to accumulation of both intracellular and secreted Aβ40 (84).

2.6.Implication of Post-Translational Modification on Signaling Transduction

2.6.1. AMPK Pathway

Adenosine monophosphate-activated protein kinase (AMPK) is a serine/threonine kinase regulating cellular energy metabolism (85). AMPK, a heterotrimer protein kinase, comprises of three subunits, namely α, β and γ (86). Here, α acts as a catalytic

subunit, whereas, β and γ are regulatory subunits. All these three subunits have several isoforms such as α1-α2, β1-β2, γ1-γ2-γ3, respectively (87). Further, the γ subunit is comprised of four nucleotide-binding cystathionine-beta-synthase (CBS) domains, which act as binding sites for adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP) (87). During the conditions of energy scarcity, when the AMP:ATP ratio is increased, AMP is allosterically attached to the γ domain of AMPK, resulting in conformational changes in AMPK through phosphorylation of its α subunit at T172 by various kinases like liver kinase B1 (LKB1), transforming growth factor-beta activated kinase 1 (Tak1), Calmodulin dependent protein kinase kinase-β (CaMKKβ) (88). Phosphorylation of AMPK at T172 amplifies its activity, resulting in fully activated AMPK, which then regulates downstream substrates like acetyl CoA carboxylase (ACC), unc-51 like autophagy activating kinase 1 (ULK1), tuberous sclerosis complex 1/2 (TSC1/2), and sterol regulatory element-binding protein (SREBP) via phosphorylation (88). By regulating these downstream substrates, AMPK switches off all energy-consuming anabolic pathways and amplifies all energy releasing catabolic pathways (89). It has been observed that the myristoylation of the AMPK β subunit promotes allosteric binding between AMP/AMPK and phosphorylation of the T172 site of α subunit during ATP depletion conditions (90). Likewise, another study has shown that SUMOylation of the AMPKβ2 subunit through SUMO2 amplifies the total activity of AMPK (91). Besides, H2O2 mediated oxidation of α and β subunit's cysteine residues of AMPK increases the kinase activity of AMPK (92). Interestingly it has also been reported that H2O2 mediated S-glutathionylation at C299 and C304 of AMPK α subunit facilitates AMPK activation (93,94). Conversely, it has been observed that α and γ subunits undergo O-GlcNAcylation, and inhibition of O-GlcNAcylation suppresses AMPK activation (95). Likewise, one study reported that ubiquitin ligase cidea suppresses AMPK activity by ubiquitin-dependent proteasomal degradation of the AMPK β subunit (96). Moreover, the AMPK pathway has been implicated in many NDDs. Tau acetylation promotes neurofibrillary tangle formation in AD. One study reported that AMPK reduces tau acetylation by activating SIRT1. In this study, AMPK activated SIRT1 by enhancing nicotinamide adenine dinucleotide (NAD+) concentration, followed by deacetylation of tau by SIRT1 (97,98).

2.6.2. PI3K/Akt/GSK3β Pathway

Phosphatidylinositol 3-kinase (PI3K)-AKT signaling pathway is a significant regulator of a plethora of cellular processes like cell proliferation, apoptosis, cell survival, autophagy, metabolism and cell growth (99–101). In the PI3K-AKT pathway, binding of ligands (cytokines, growth factors, hormones) to their specific cell-surface receptors leads to receptor activation, which then recruits and activates the lipid kinase PI3K. Activated PI3K then phosphorylates membrane lipid phosphatidylinositol 4, 5-bisphosphate (PIP2), converting it into phosphatidylinositol (3,4, 5)-trisphosphate (PIP3), which acts as a second messenger, mediating remaining intracellular signaling (102). Further, PIP3 mobilizes AKT to the plasma membrane and docks with AKT via the pleckstrin homology (PH) domain of AKT (102). This binding of AKT leads to conformational changes in AKT, which allows phosphorylation of AKT at T308 by phosphoinositide-dependent kinase 1 (PDK1) and at S473 by mammalian target of

rapamycin complex 2 (mTORC2), resulting in full activation of AKT (103). This fully activated AKT then further regulates desired cellular processes via phosphorylation of downstream substrates like GSK3, mammalian target of rapamycin complex 1 (mTORC1), FOXOs. It has been reported that O-GlcNAcylations of AKT at T305 and T312 can thwart interaction between PDK1 and AKT, thereby inhibiting phosphorylation of AKT at T308, resulting in the reduced biological activity of AKT (97). Conversely, AKT SUMOylation at K276, amplifies its kinase activity (104). Likewise, it has been observed that oxidation of AKT at C60 and C77 of its PH domain amplifies the affinity of AKT towards PIP3 and facilitates AKT translocation to the plasma membrane (105). Another study reported that K63 ubiquitination of AKT by E3 ligase TRAF6 promotes AKT membrane translocation and amplifies its phosphorylation (106). Moreover, PI3K-AKT signaling has been implicated in various NDDs. We know that GSK3β is the major kinase responsible for tau hyperphosphorylation, and it is also a downstream substrate for AKT. AKT can downregulate GSK3β by phosphorylating GSK3β at S9. One study showed that tau hyperphosphorylation was decreased by activating the PI3K-AKT pathway, which downregulated the activity of GSK3β (107). Conversely, another study on AD has shown that sulfhydration of AKT at C77 thwarts phosphorylation of GSK3β by AKT, thereby promoting tau phosphorylation by GSK3β (108). Additionally, a study on human neuronal cells showed that acetylation of AKT at K163, K377, under an HDAC6 inhibitor's presence impairs AKT's kinase activity (109). Interestingly, it has been reported that SIRT1 promoted axon development by deacetylation of AKT, which activated the AKT pathway, leading to GSK3β inhibition (110). Further in AD, AGEs can also stimulate tau hyperphosphorylation by suppressing the AKT pathway, thus activating GSK3 through upregulation of receptors for advanced glycation end products (RAGE) (111). Additionally, it has been observed that the S-nitrosylation of PTEN leads to its inactivation, resulting in elevation of PI3K-AKT, which can protect against Aβ neurotoxicity (112). Furthermore, myristoylated AKT has been reported to promote neuroprotection by preventing axonal degeneration (113).

2.6.3. Apoptosis and Autophagy

Autophagic/lysosomal degradation is a significant cellular response to stress where autophagosomes containing cytosolic constituents are transported into the lysosome for degradation, which is essential for protein homeostasis and cell health. The degradation of long-lived protein aggregates is majorly carried out by autophagy, but many different PTMs are implemented to deregulate this process, leading to NDDs. In AD, Autophagy is the primary pathway for the degradation of APP and APP cleavage products, including Aβ (114). In tau protein, autophagy dysfunction leads to tau aggregates' formation, which significantly affects Tau phosphorylation. In addition, tau hyperphosphorylation causes uncertainty in microtubule, which further halt autophagosome-lysosome fusion, leading to aggregation of immature autophagosomes (115). The primary suppressor of autophagy initiation is the mTOR protein kinase, which is heavily autophosphorylated at S2481 in AD (116). Furthermore, inhibition of BCL-2 on beclin 1 is weakened by either phosphorylation of BCL-2 by JNK-1 or by phosphorylation of beclin 1 by DAPK1, thus promoting autophagy (117). Experimental evidence showed a direct link between proteolytic cleavage of beclin 1 and apoptotic

cell loss in the AD brain, where they indicated that the cleavage state of beclin 1 determines the functional involvement in both neurodegeneration and neuroprotection (118). A study found that SIRT2, HDAC6 and p300 stimulate Tau phosphorylation and autophagic flux in AD, and the results also included that HDAC4 and p300 modulate Tau acetylation (119). Another finding demonstrated that tau accumulation suppresses IST1 transcription, where the mechanism involves ANP32A-regulated mask of histone acetylation, which further represses autophagosome-lysosome fusion (120). A finding directs that SUMOylation might be involved in the autophagy-lysosome pathway in tauopathies. In progressive supranuclear palsy (PSP) brain tissues, SUMO1 colocalizes within perinuclear tau-positive inclusions in oligodendrocytes and label lysosomes oligodendrocytes containing tau inclusions, in contrast to those where tau aggregates are absent (121). Moreover, the Oxidation of Aβ at M35 inhibits the autophagy pathway (98,122).

2.6.4. Mitochondrial Dysfunction

Several decades of studies have realized that mitochondrial dysfunction plays an essential role in the pathomechanism of several NDDs (123). Mitochondrial dysfunction under any pathological conditions will increase nitroxidative stress, stimulating the PTMs of mitochondrial protein and might also cause oxidative damage to mitochondrial DNA (124). In AD, Aβ translocates to the mitochondrial membrane, where it encourages intracellular calcium ion release and promotes excess accumulation of these ions to open the mPTP and damage the structure of mitochondria (125). These opening further leads to a drop in the electrochemical gradient causing activation of apoptosis-inducing factors and caspases, which finally results in AD progression (126). Many PTMs are responsive to the stressful and changing environment in which mitochondria exerts functions like phosphorylation, acetylation, ubiquitination and succinylation (127). Likewise, SUMOylation has been implicated in impaired mitochondrial function and high-stress conditions. Interaction of SUMO1 with Aβ and phosphorylated Tau causes an increase in oligomers' formation, whereas interaction with SUMO2/3 increases their solubility (128). However, studies suggest that N-acetylcysteine may decrease mitochondrial-related oxidative stress in AD patients. Oxidative stress at some sites may facilitate tau phosphorylation, which may be modified in AD patients. Tau protein is involved in the axonal transport of organelles like mitochondria; the hyperphosphorylated Tau might block the mitochondrial transport leading to energy deprivation and causing neurodegeneration. Moreover, abnormal communication of hyperphosphorylated tau and mitochondrial fission protein dynamin-like protein 1 (Drp-1suggests a relationship with mitochondrial dynamics alternation (129). Furthermore, a study states that Drp1 S616 phosphorylation is likely to be involved in mitochondrial fragmentation and Drp1 over activation in AD (130). It is important to note that certain proteins aid in mitochondrial transport like motor protein (kinesin 1 and dynein) and mitochondrial protein adaptors (RhoT1/T2, syntaphilin, and TRAK2). Interestingly, truncated tau expression significantly increases the association of TRAK2 with mitochondria, expressing full-length tau, and caspase-cleaved tau may affect mitochondrial transport due to an increase of TRAK2-mitochondria binding and therefore reducing the ATP production available for the transportation of mitochondria (98,131).

2.7. Post-Translational Modifications as Therapeutic Targets in AD Treatment

Data suggests that enzymes of PTMs shows advantageous therapeutic activity in neuronal dysfunction. Recent studies also suggests that insinuations of drugs and natural biomolecules targets different enzymes of various PTMs in AD therapeutics (132). In AD, hyperphosphorylation of Tau at S396 residue by GSK-3 results in the formation of neural fibrils accumulate, leading to tau aggregation. SAR502250 (133), curcumin (134), 6-hydroxydopamine (135) have been reported to downregulate GSK3 activity, thus reducing tau aggregation. Similarly, BACE1 is an exciting target for AD therapeutics, which phosphorylates Aβ with the help of enzymes such as γ-secretase and β-secretase that cleaves APP, and thus, results in the aggregation and formation of Aβ plaques. Likewise, palmitoylation of APP leads to enhanced APP cleavage by BACE1, leading to amyloidogenesis. However, inhibition of Sterol O-acyltransferase (ACAT) with CP-113818 reduces the APP palmitoylation level and can be used in AD therapeutics (75,136). A recent experiment demonstrated the involvement of conformation-sensitive anti-Aβ oligomers (AβOs) intrabodies in the process of Aβ oligomerization, which serves as a therapeutic target (137). The succinylation of APP at K687 residue hampers its degradation and escalates Aβ aggregation. It was observed that the succinylated APP, along with Aβ agglomerates, was present in the hippocampus of a transgenic mouse for AD due to diminished brain glucose regulation (138). Further, Aβ nitration at Y10 is a bit contradictory. An early study reported that Y10 nitration by peroxynitrite enhances aggregate formation, which was found in amyloid plaque core in the AD mice model (39). However, a recent experiment showed that Y10 nitration notably curbed amyloid aggregation. The aggregates formed in the former study, when treated with L-NIL, accounted for reduced 3NTyr10-Aβ in APP/PS1 mice (139).

2.8. Role of Artificial Intelligence in Drug Discovery

Today AI has come out as a very successful and demanding technology because it saves time and is cost-efficient (140). In general, cell classification, cell sorting, calculating properties of small molecules, synthesizing organic compounds with the help of computer programs, designing new compounds, developing assays, and predicting the 3D structure of target molecules are some time-consuming and tiresome tasks which with the help of AI can be reduced and can speed up the process of drug discovery (141,142). The primary drug screening includes the classification and sorting of cells by image analysis through AI technology. Many ML models using different algorithms recognize images with great accuracy but become incompetent when analysing big data. To classify the target cell, firstly, the ML model needs to be trained so that it can identify the cell and its features, which is basically done by contrasting the image of the targeted cells, which separates it from the background (143). Images with varying textured features like wavelet-based texture features and Tamura texture features are extracted, which is further reduced in dimensions through principal component analysis (PCA). A study suggests that least-square SVM (LS-SVM) showed the highest classification accuracy of 95.34% (144,145). Regarding cell sorting, the machine needs to be fast to separate out the targeted cell type from the given sample. Evidence suggests that image-activated cell sorting (IACS) is the most advanced device that could measure the optical, electrical, and mechanical properties of the cell (146). The secondary drug screening includes analysing the physical properties,

bioactivity, and toxicity of the compound. Melting point and partition coefficient are some of the physical properties that govern the compound's bioavailability and are also essential to design new compounds (147), while designing a drug, molecular representation can be done using different methods like molecular fingerprinting, simplified molecular-input line-entry system (SMILES), and Coulomb matrices (148). These data can be used in DNN, which comprises two different stages, namely generative and predictive stage. Though both the stages are trained separately through supervised learning, when they are trained jointly, bias can be applied to the output, where it is either rewarded or penalized for a specific property. This whole procedure can be used for reinforcement learning (149). Matched molecular pair (MMP) has been extensively used for QSAR studies. MMP is associated with a single change in a drug candidate, which further influences the bioactivity of the compound (150). Along with MMP, other ML methods are used like DNN, RF, and gradient boosting machines (GBM) to get modifications. It has been observed that DNN can predict better than RF and GBM (151). With the increase in databases, which are publicly available like ChEMBL, PubChem, and ZINC, we have access to millions of compounds annotating information like their structure, known targets and purchasability; MMP plus ML can predict bioactivity like oral exposure, intrinsic clearance, ADMET, and method of action (145,152,153). Optimizing the toxicity of a compound is the most time-consuming and expensive task in drug discovery and is a crucial parameter as it adds significant value to the drug development process (132).

3. Methodology

3.1. Extraction and Pre-processing of Data

Herein, we took AD related gene expression database GSE1297, from National Center for Biotechnology Information (NCBI) Gene expression omnibus (GEO). This dataset is deposited by Blalock *et al*., and contains 22 AD disease samples along with 9 healthy control samples. For this dataset, the microarray analysis was performed using Affymetrix Human Genome U133A Array.

For differential gene expression analysis, we downloaded .CEL files from this dataset. We used Limma package in R studio for differential gene expression analysis. Firstly, read.celfiles function was used to input AD and control's .CEL files in r studio. Afterwards, normalizeQuantiles was used to normalize AD and control samples. Further, we used ebayes and toptable functions in order to obtain differentially expressed genes (DEGs) between AD samples and healthy control samples. The DEGs were shortlisted based on adjusted p-value being less than and equal to .05 in order to remove the false positives.

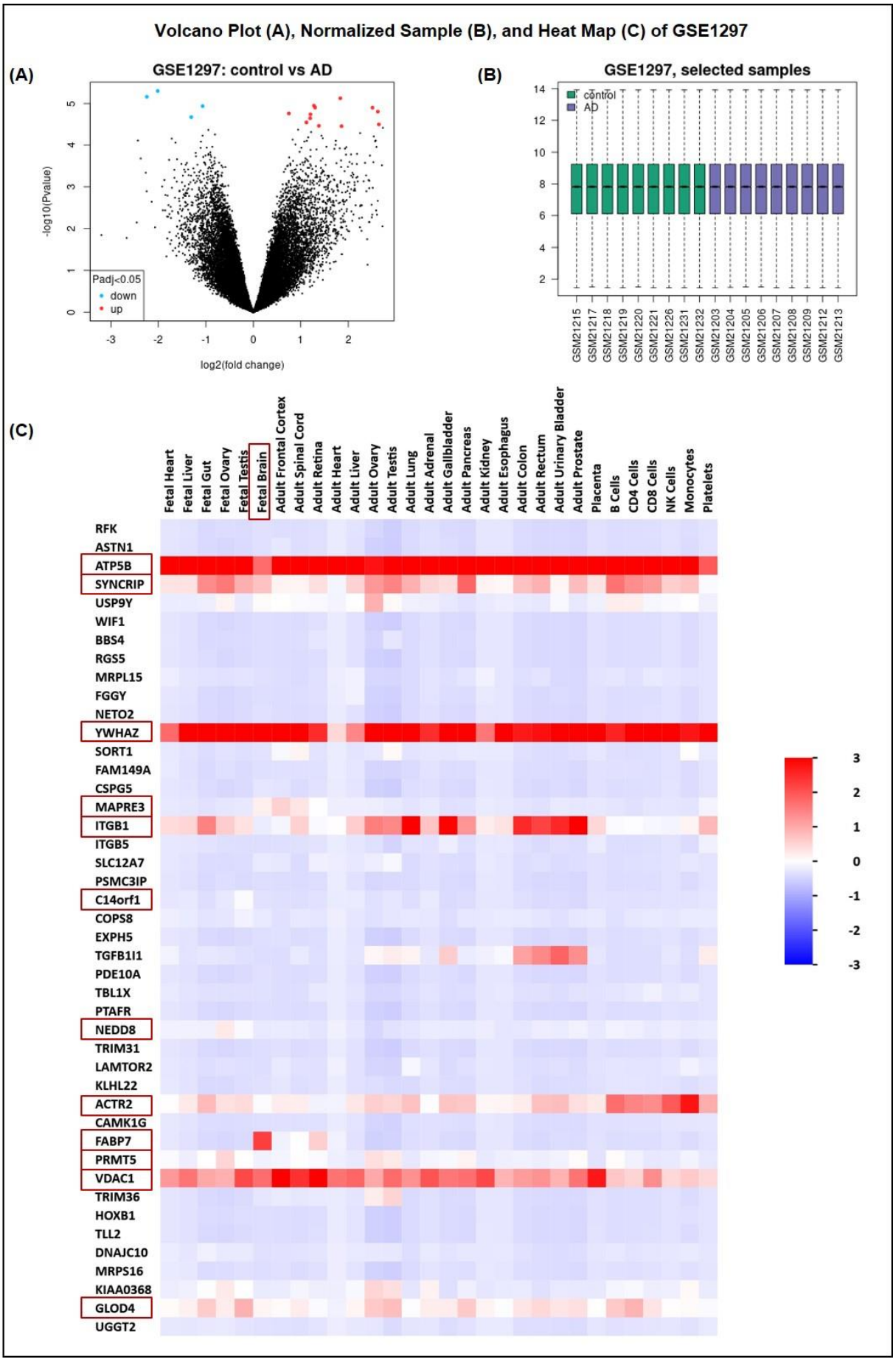


Figure 2: Volcano plot, Normalized sample and Heat map of GSE1297

3.2.Protein-Protein Interaction Network of Extracted Proteins

After identification of DEG's, the different genes were mapped to their corresponding proteins and protein-protein interaction network were identified through STRING database and the Cytoscape. PPI network were constructed to analyze the interaction between regulatory protein in AD. After PPI network, HUB genes of the network were identified through CytoHubba and MCODE.

3.3.Identification of Critical Acetylation and Ubiquitination Sites

Ubiquitination and acetylation are considered as important post-translational modifications involved in the pathogenesis of the AD. The most important feature of ubiquitination and acetylation is the involvement of lysine (K) residues. Protein lysine modification database (PLMD) was used to analyze the critical lysine residue involved in the pathogenesis of AD on HUB genes.

3.4.Structural Analysis of Protein

As we know that PTMs have an influence on secondary structure which in turn effects its biological properties. Hence, we decided to analyse the effects of PTMs on secondary structure of regulatory proteins. We used publicly available PSIPRED and Disopred tools (http://bioinf.cs.ucl.ac.uk/psipred/) to obtain structure information of regulatory proteins on both PTM and non PTM sites. We used PLMD database (http://plmd.biocuckoo.org/) in order to obtain PTM sites on lysine residues of regulatory proteins. Our structural analysis was divided into helix, coiled and strand categories.

3.5.Pathway Analysis

Biological pathway is the most important feature of a protein, which identifies the pathway in which a protein is involved. The HUB genes, namely NEDD8, YWHAZ, and ITGB1 were imported in the FUNRICH R to analyze the enriched biological pathways followed by the said proteins.

3.6.Impact of Lysine Mutations on Acetylation and Ubiquitination

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

3.7.Identification of Drug Molecules

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

4. Results and Discussion

4.1.Data collection and differential gene expression analysis

The obtained DEGs between AD and healthy control samples is shown in the **supplementary file 1**. The negative value of logFC denotes downregulated genes where positive value of logFC indicates upregulated genes in AD conditions. Further, DAVID tool (https://david.ncifcrf.gov/) was used to annotate the DEGs with their official gene names. All of the DEGs were shortlisted based on their adjusted p values being less than

and equal to .05. Herein, we obtained 13 downregulated genes and 35 upregulated genes between AD and healthy conditions.

Table 2: Shortlisted DEGs indicating 13 downregulated genes and 35 upregulated genes between AD and healthy conditions

ID	adj.P.Val	P.Value	logFC	Gene.symbol	Gene.title
208224_at	0.0404	0.00000504	-2.013	HOXB1	homeobox B1
206278_at	0.0404	0.00000696	-2.243	PTAFR	platelet activating factor receptor
215008_at	0.0404	0.00000754	1.832	TLL2	tolloid like 2
219718_at	0.0404	0.00001133	1.277	FGGY	FGGY carbohydrate kinase domain containing
213400_s_at	0.0404	0.0000116	-1.069	TBL1X	transducin (beta)-like 1X-linked
212428_at	0.0404	0.00001252	1.301	KIAA0368	KIAA0368
209070_s_at	0.0404	0.00001271	2.51	RGS5	regulator of G-protein signaling 5
205344_at	0.0407	0.00001572	2.624	CSPG5	chondroitin sulfate proteoglycan 5
218291_at	0.0407	0.00001741	0.748	LAMTOR2	late endosomal/lysosomal adaptor, MAPK and MTOR activator 2
201840_at	0.0407	0.00001828	1.204	NEDD8	neural precursor cell expressed, developmentally down-regulated 8
218046_s_at	0.0422	0.00002272	1.198	MRPS16	mitochondrial ribosomal protein S16
221580_s_at	0.049	0.00002856	1.119	MIR1304	microRNA 1304///small nucleolar RNA, C/D box 5///small nucleolar RNA, H/ACA box 32///small nucleolar RNA, H/ACA box 40///small nucleolar RNA, H/ACA box 18///small nucleolar RNA, H/ACA box 1///small nucleolar RNA, H/ACA box 8///TATA-box binding protein associated factor, RNA polymerase I subunit D
212797_at	0.049	0.00003198	2.646	SORT1	sortilin 1
200729_s_at	0.049	0.00003452	1.381	ACTR2	ARP2 actin related protein 2 homolog
216190_x_at	0.049	0.00003517	1.859	ITGB1	integrin subunit beta 1
215161_at	0.0505	0.00003852	2.73	CAMK1G	calcium/calmodulin dependent protein kinase IG
218027_at	0.0508	0.00004265	0.944	MRPL15	mitochondrial ribosomal protein L15
201125_s_at	0.0508	0.00004333	-0.947	ITGB5	integrin subunit beta 5
205501_at	0.0508	0.00004856	1.217	PDE10A	phosphodiesterase 10A
221781_s_at	0.0508	0.00005161	2.251	DNAJC10	DnaJ heat shock protein family (Hsp40) member C10
205956_x_at	0.0508	0.00005546	-0.807	PSMC3IP	PSMC3 interacting protein
218066_at	0.0508	0.00005909	-1.069	SLC12A7	solute carrier family 12 member 7
221837_at	0.0508	0.00005942	1.437	KLHL22	kelch like family member 22
203841_x_at	0.0508	0.00006159	2.538	MAPRE3	microtubule associated protein RP/EB family member 3
201322_at	0.0508	0.0000648	1.156	ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide
218888_s_at	0.0508	0.00006862	1.464	NETO2	neuropilin and tolloid like 2
214950_at	0.0508	0.00006979	-1.719	IL9R	interleukin 9 receptor
209025_s_at	0.0508	0.00007369	0.829	SYNCRIP	synaptotagmin binding cytoplasmic RNA interacting protein
222196_at	0.0508	0.00007746	-2.431	LOC389906	zinc finger protein 839 pseudogene
217786_at	0.0508	0.00007769	2.579	PRMT5	protein arginine methyltransferase 5
202143_s_at	0.0508	0.00007849	1.737	COPS8	COP9 signalosome subunit 8
205030_at	0.0508	0.0000791	1.126	FABP7	fatty acid binding protein 7
206624_at	0.0508	0.0000806	2.566	USP9Y	ubiquitin specific peptidase 9, Y-linked
213197_at	0.0508	0.00008161	1.077	ASTN1	astrotactin 1
209651_at	0.0508	0.0000821	-1.104	TGFB1I1	transforming growth factor beta 1 induced transcript 1
210159_s_at	0.0524	0.00008708	-1.638	TRIM31	tripartite motif containing 31
218801_at	0.0561	0.00009684	0.887	UGGT2	UDP-glucose glycoprotein glucosyltransferase 2
200638_s_at	0.0561	0.0000983	1.733	YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta
203224_at	0.0561	0.00010965	1.541	RFK	riboflavin kinase
213929_at	0.0561	0.00010991	-0.863	EXPH5	exophilin 5
217188_s_at	0.0561	0.000111	2.595	C14orf1	chromosome 14 open reading frame 1
204712_at	0.0561	0.0001124	1.958	WIF1	WNT inhibitory factor 1
37796_at	0.0561	0.00011467	-0.983	SAP25	Sin3A associated protein 25///leucine rich repeats and calponin homology domain containing 4
209092_s_at	0.0561	0.00011539	1.013	GLOD4	glyoxalase domain containing 4
222291_at	0.0561	0.00011642	-1.111	FAM149A	family with sequence similarity 149 member A
212745_s_at	0.0561	0.00011925	1.821	BBS4	Bardet-Biedl syndrome 4
201939_at	0.0561	0.00012186	1.93	PLK2	polo like kinase 2
219736_at	0.0561	0.00012344	1.709	TRIM36	tripartite motif containing 36
217140_s_at	0.0568	0.00012744	1.33	VDAC1	voltage dependent anion channel 1

4.2. HUB genes in the pathogenesis of AD

PPI network analysis identified that 19 nodes and 17 edges were involved in the core PPI network, where NEDD8, KLHL22, and COPS8 have high node degree. The core network suggests another isolated interaction between TRIM31, PTAFR, and LAMTOR2. Further,

the PPI network suggests that YWHAZ, ATP5B, MRPS16, MRPL15, NEDD8, KLHL22, COPS8, ITGB1, PTFAR, and LAMTOR2 were HUB genes in the network.

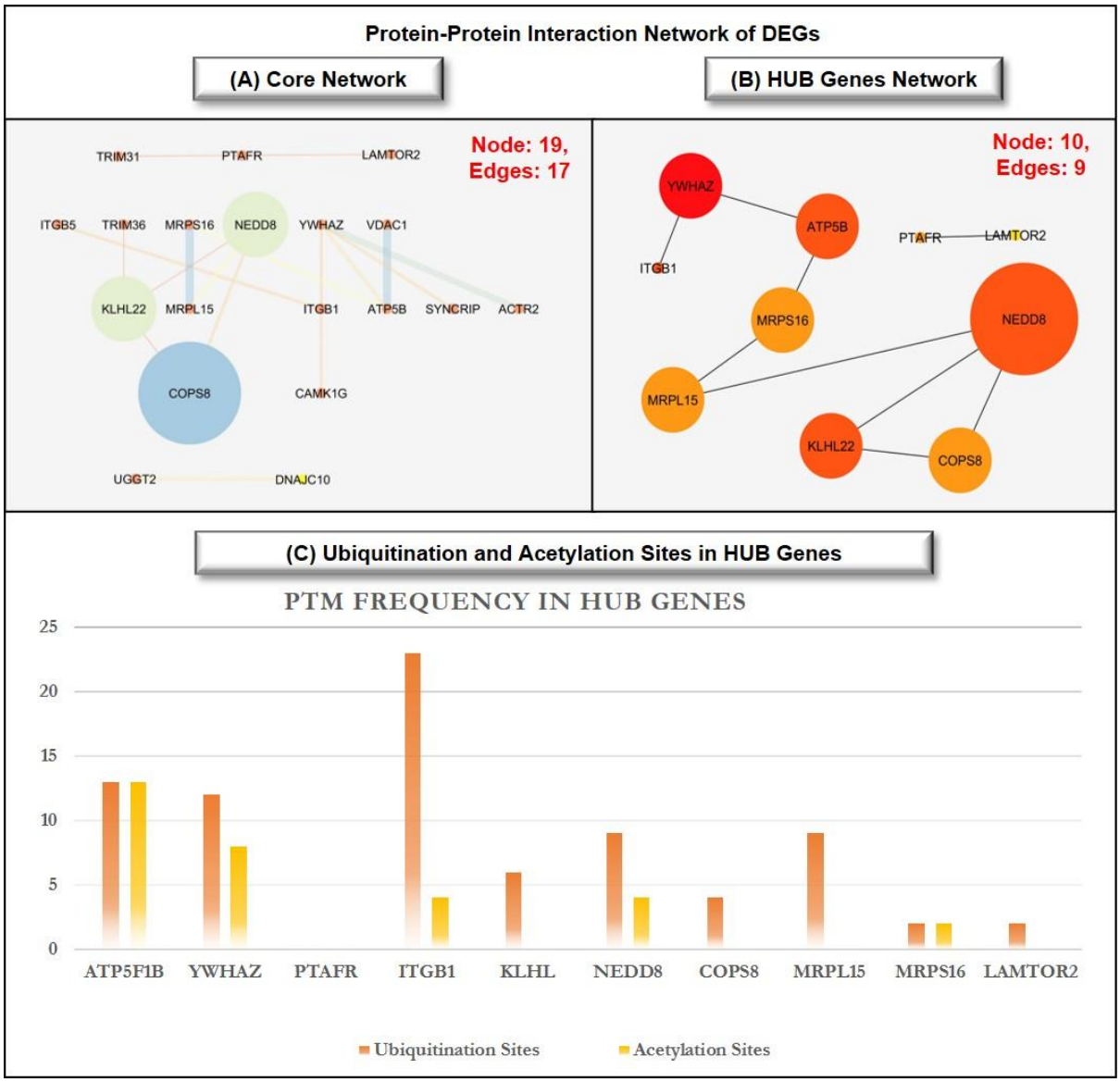


Figure 3: Protein-protein interaction network of DEGs
(PPI network of cluster represents 10 proteins extracted from the core PPI network after clustering analysis. The stack bar representation shows lysine modified sites.)

4.3.Critical lysine residues involved in AD

HUB genes, such as YWHAZ, ATP5F1B, ITGB1, NEDD8, and MRPS16 were analyzed for identification of common ubiquitination and acetylation sites. The results indicated that YWHAZ have 7 common acetylation and ubiquitination sites, whereas, ATP5F1B have 9 common ubiquitination and acetylation sites. Further, ITGB1 and NEDD8 have 4 ubiquitination and acetylation sites. Similarly, MRPs16 have only 1 common ubiquitination and acetylation site.

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

	UniProt ID	Ubiquitination	Acetylation	Common
YWHAZ	P63104	**K3**, **K9**, K11, **K27**, **K68**, K74, K75, **K85**, K103, **K115**, **K138**, K139	**K3**, **K9**, **K27**, **K68**, **K85**, **K115**, **K138**, K157	K3, K9, K27, K68, K85, K115, K138
ATP5F1B	P06576	K55, K124, **K133**, **K159**, K161, **K198**, **K201**, **K259**, **K264**, K351, **K426**, **K480**, **K485**	**K133**, **K159**, **K198**, **K201**, K212, **K259**, **K264**, **K426**, K432, K451, **K480**, **K485**, K522	K133, K159, K198, K201, K259, K264, K426, K480, K485
ITGB1	P05556	K87, K107, K134, K163, K190, K202, K228, K238, K346, K398, K518, K551, K575, **K619**, K672, **K678**, K692, K765, K768, **K774**, K784, **K794**, K798	**K619**, **K678**, **K774**, **K794**	K619, K678, K774, K794
NEDD8	Q15843	K4, K6, **K11**, **K22**, K27, K33, **K48**, **K54**, K60	**K11**, **K22**, **K48**, **K54**	K11, K22, K48, K54
MRPS16	Q9YD3	K40, **K64**	**K64**, K85	K64

4.4.Protein secondary structure analysis

From protein secondary structure analysis, we observed that coiled structure had most of the PTM sites in NEDD8, ITGB1 and ATP5F1B compared to their helix and strand structure. In ITGB1 9 PTM sites fall in coiled region, compared to 5 PTMs and 4 PTMs in coiled region of ATP5F1B and NEDD8 respectively. Only YWHAZ had most of the PTMs in helix structure. YWHAZ has 9 PTM sites in helix region while only 1 PTM site in coiled region. Many studies have reported that coiled structure is responsible for protein interactions and aggregation propensity. Frequency of PTMs in helix structure was maximum in YWHAZ followed by ITGB1. Frequency of PTM in helix region was least in ATP5F1B as it had only 1 PTM in helix region. Strikingly, YWHAZ didn't show any presence of strand structure, whereas ITGB1 had 5 PTM sites in strand region. Intriguingly, none of the four regulatory proteins had any ordered region. In NEDD8 no PTM lysine site fell in the ordered or disordered region. Likewise, even in ITGB1 none of the PTMs lysine sites fell in ordered or disordered region. Similarly, YWHAZ and ATP5F1B also showed no PTM sites in ordered or disordered region.

Table 4: List of PTM and Non PTM sites of NEDD8, YWHAZ, ITGB1 and ATP5F1B in coiled, helix and strand regions

	NEDD8		YWHAZ		ITGB1		ATP5F1B	
	PTM	Non PTM	PTM	Non PTM	PTM	Non PTM	PTM	Non PTM
Helix	3	0	9	11	5	8	1	10
Coiled	4	0	1	0	9	24	5	4
Strand	2	0	0	0	5	6	3	0

4.5.YWHAZ as critical protein involved in the pathogenesis of AD

Pathway analysis of YWHAZ, NEDD8, and ITGB1 demonstrated that YWHAZ is involved in top 19 enriched pathways (p-value ≤ 0.05). Further, the results demonstrated that NEDD8 and ITGB1 are involved in 11 and 13 enriched pathways respectively as shown in table.

Table 5: Functional enrichment analysis (Biological pathways)

S. No.	Biological Pathway	P-value	Protein
1.	Class I PI3K signaling events	0.0358	NEDD8; ITGB1; YWHAZ;
2.	Class I PI3K signaling events mediated by Akt	0.0358	NEDD8; ITGB1; YWHAZ;
3.	mTOR signaling pathway	0.0358	NEDD8; ITGB1; YWHAZ;
4.	Insulin Pathway	0.0358	NEDD8; ITGB1; YWHAZ;
5.	IGF1 pathway	0.0363	NEDD8; ITGB1; YWHAZ;
6.	CDC42 signaling events	0.0258	ITGB1; YWHAZ;
7.	GP1b-IX-V activation signaling	0.0282	YWHAZ;
8.	Rap1 signaling	0.0313	YWHAZ;
9.	Syndecan-1-mediated signaling events	0.0377	NEDD8; ITGB1; YWHAZ;
10.	GMCSF-mediated signaling events	0.0364	NEDD8; ITGB1; YWHAZ;
11.	Nectin adhesion pathway	0.0369	NEDD8; ITGB1; YWHAZ;
12.	TRAIL signaling pathway	0.0423	NEDD8; ITGB1; YWHAZ;
13.	a4b7 Integrin signaling	0.0282	ITGB1;
14.	ATR signaling pathway	0.0429	NEDD8; YWHAZ;
15.	Canonical Wnt signaling pathway	0.0122	YWHAZ;
16.	Noncanonical Wnt signaling pathway	0.0189	YWHAZ;
17.	Glypican 3 network	0.0035	YWHAZ;
18.	Plasma membrane estrogen receptor signaling	0.0379	NEDD8; ITGB1; YWHAZ;
19.	Alpha4 beta1 integrin signaling events	0.0047	ITGB1; YWHAZ;
20.	N-cadherin signaling events	0.0433	YWHAZ;

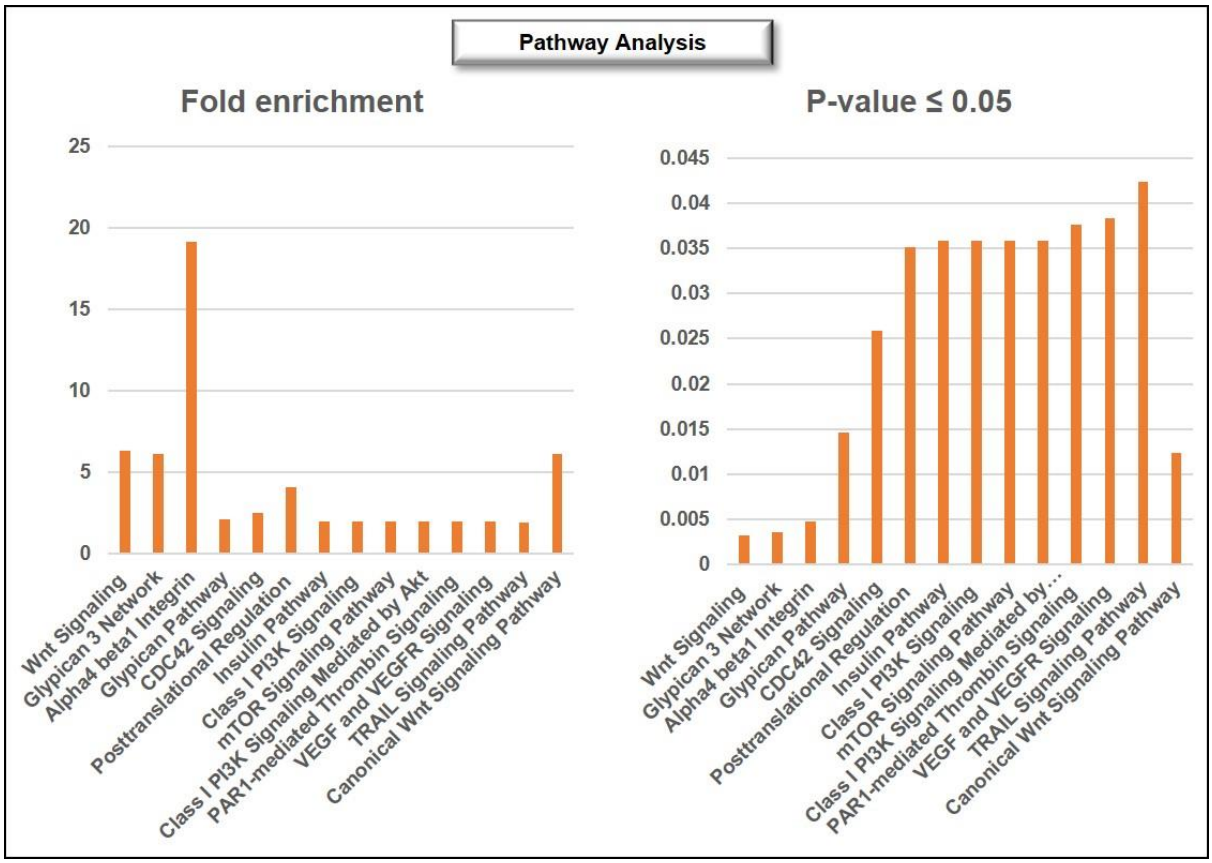


Figure 4: Fold enrichment and p-values of biological pathways related to NEDD8, ITGB1 and YWHAZ

4.6.Impact of lysine mutation on YWHAZ

The observed results indicates that all sites have an effect on disease susceptibility. However, K3D, K9D, K27, K68D, K85, K115D and K138D have high confidence score. High intolerant mutations that are susceptible to disease are shown in the table given below.

Table 6: Impact of YWHAZ's 'K' putative mutation to either 'R' or 'D' on disease susceptibility predicted with the help of PMut, SNAP2 and PANTHER

Residue	PMut	PANTHER	SNAP2	Confidence
K3R	0.26	0.57	0	0.83
K3D	0.54	0.57	1	2.11
K9R	0.3	0.57	0	0.87
K9D	0.78	0.57	1	2.35
K27R	0.61	0.89	1	2.5
K27D	0.75	0.89	1	2.64
K68R	0.4	0.89	0	1.29
K68D	0.87	0.89	1	2.76
K85R	0.41	0.85	1	2.26
K85D	0.84	0.85	1	2.69
K115R	0.46	0.85	0	1.31
K115D	0.85	0.85	1	2.7
K138R	0.24	0.57	0	0.81
K138D	0.57	0.57	1	2.14

4.7.Impact of drug on YWHAZ

Phenethyl Isothiocyanate is the only drug for YWHAZ that has been identified in drug bank database. CB Dock tool shows that I106, L119, A148, E102, K122, Q144, S145, Y126, L129, L98 and I141 are the putative binding sites on YWHAZ where Phenethyl Isothiocyanate may bind. Vina score of -4.6 shows stable system and thus, a likely binding interaction.

Table 7: **Results of CB Docking of YWHAZ protein with Phenethyl Isothiocyanate drug**

Vina Score	Cavity Size	Center			Size		
		x	y	z	x	y	z
-4.6	278	-29	-14	63	18	18	18
-4.3	234	-26	1	61	18	18	18
-4.2	264	-16	-2	54	18	18	18
-3.9	574	-33	22	35	18	18	29
-3.6	382	-34	29	52	18	18	18

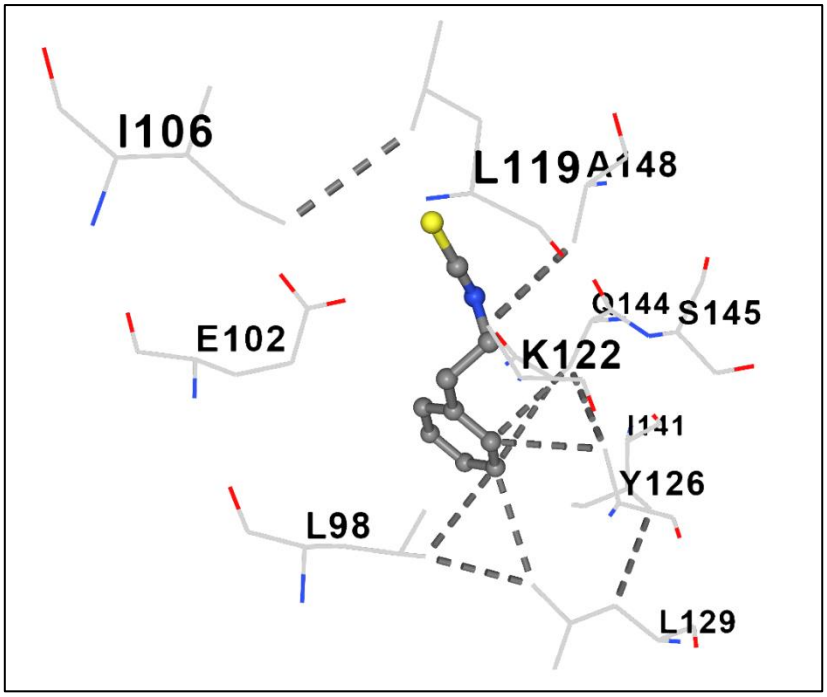


Figure 5: Putative binding sites on YWHAZ with Phenethyl Isothiocyanate

5. Conclusion

Alzheimer's disease is one of the most prevalent neurodegenerative disease. It is the 6th leading cause of death. However, recent data suggests that it might rank as high as 3rd, just behind cancer and heart diseases for older people. Evidences suggests that involvement of post-translational modifications are possible in the pathogenesis of AD. In this study, we target involvement of two PTMs i.e., acetylation and ubiquitination. The common feature shared by both the PTMs is that both act on the lysine residue and thereby, crosstalk between acetylation and ubiquitination becomes an enthralling topic of research. Here, we first extracted and pre-processed the data for which microarray analysis was performed using Affymetrix human genome U133A array. Further, 13 downregulated and 35 upregulated DEGs were shortlisted based on adjusted p-value. PPI network was constructed to analyze the interaction between regulatory protein in AD. Studying this network gave us HUB genes namely, YWHAZ, ATP5B, MRPS16, MRPL15, NEDD8, KLHL22, COPS8, ITGB1, PTFAR, and LAMTOR2. Critical lysine residues involved were analyzed for YWHAZ, ATP5F1B, ITGB1, NEDD8, and MRPS16; it was found that YWHAZ had 7 common ubiquitination and acetylation sites. Thereafter, protein secondary structure analysis showed YWHAZ has 9 PTM sites in helix region while only 1 PTM site in coiled region. Many studies have reported that coiled structure is responsible for protein interactions and aggregation propensity. Further, pathway analysis showed that YWHAZ is involved in top 19 enriched pathways, whereas, NEDD8 and ITGB1 are involved in 11 and 13 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 high confidence score. Lastly, it was found that Phenethyl Isothiocyanate is the only drug for YWHAZ that has been identified in drug bank and the putative binding site were I106, L119, A148, E102, K122, Q144, S145, Y126, L129, L98 and I141 that was observed using CB Dock.

References

1. Gupta R, Kumar P. Computational Analysis Indicates That PARP1 Acts as a Histone Deacetylases Interactor Sharing Common Lysine Residues for Acetylation, Ubiquitination, and SUMOylation in Alzheimer's and Parkinson's Disease. ACS Omega [Internet]. 2021 Mar 2 [cited 2021 Jun 26];6(8):5739–53. Available from: https://dx.doi.org/10.1021/acsomega.0c06168

2. Biroccio A, Del Boccio P, Panella M, Bernardini S, Di Ilio C, Gambi D, et al. Differential post-translational modifications of transthyretin in Alzheimer's disease: A study of the cerebral spinal fluid. Proteomics. 2006;

3. Alzheimer's Disease: The 7 Stages of the Disease [Internet]. [cited 2021 Jun 19]. Available from: https://www.webmd.com/alzheimers/guide/alzheimers-disease-stages

4. Martin L, Latypova X, Terro F. Neurochemistry International Post-translational modifications of tau protein : Implications for Alzheimer ' s disease. Neurochem Int. 2011;58(4):458–71.

5. Coburger I, Hoefgen S, Than ME. The structural biology of the amyloid precursor protein APP – a complex puzzle reveals its multi-domain architecture. 2014;395(5):485–98.

6. Kummer MP, Heneka MT. Truncated and modified amyloid-beta species. 2014;1–9.

7. Warmack RA, Boyer DR, Zee C Te, Richards LS, Sawaya MR, Cascio D, et al. Structure of amyloid-β (20-34) with Alzheimer's-associated isomerization at Asp23 reveals a distinct protofilament interface. Nat Commun. 2019;

8. Warmack RA, Boyer DR, Zee C, Richards LS, Sawaya MR, Cascio D, et al. reveals a distinct proto fi lament interface. Nat Commun. 2019;1–12.

9. Chun YS, Kwon OH, Chung S. O-GlcNAcylation of amyloid-β precursor protein at threonine 576 residue regulates trafficking and processing. Biochem Biophys Res Commun. 2017;

10. Ercan-Herbst E, Ehrig J, Schöndorf DC, Behrendt A, Klaus B, Gomez Ramos B, et al. A post-translational modification signature defines changes in soluble tau correlating with oligomerization in early stage Alzheimer's disease brain. Vol. 7, Acta Neuropathologica Communications. 2019.

11. Morris M, Knudsen GM, Maeda S, Trinidad JC, Ioanoviciu A, Burlingame AL, et al. Tau post-translational modifications in wild-type and human amyloid precursor protein transgenic mice. 2015;(July).

12. Tang H, Wu Y, Wang D, Razak YA, Wei N, Almansob YAM, et al. Un co rre cte d Au tho r P roo f Tau Abnormalities and the Potential Un co rre cte d Au tho r P roo f. 2018;

13. Zaręba-Kozioł M, Figiel I, Bartkowiak-Kaczmarek A, Włodarczyk J. Insights into protein S-palmitoylation in synaptic plasticity and neurological disorders: Potential and limitations of methods for detection and analysis. Frontiers in Molecular Neuroscience. 2018.

14. Liu D, Liu C, Li J, Azadzoi K, Yang Y, Fei Z, et al. Proteomic analysis reveals differentially regulated protein acetylation in human amyotrophic lateral sclerosis spinal cord. PLoS One. 2013;8(12).

15. Manuscript A, Genes BTM. Alzheimer ' s Disease. 2012;1(2):191–8.

16. Trzeciakiewicz H, Tseng JH, Wander CM, Madden V, Tripathy A, Yuan CX, et al. A dual pathogenic mechanism links tau acetylation to sporadic tauopathy. Sci Rep. 2017;7(February):1–13.

17. Ferreon JC, Jain A, Choi KJ, Tsoi PS, Mackenzie KR, Jung SY, et al. Acetylation disfavors tau phase separation. Int J Mol Sci. 2018;19(5):1–12.

18. Wang P, Wander CM, Yuan CX, Bereman MS, Cohen TJ. Acetylation-induced TDP-43 pathology is suppressed by an HSF1-dependent chaperone program. Nat Commun [Internet]. 2017 Dec 1 [cited 2021 Feb 20];8(1):1–15. Available from: www.nature.com/naturecommunications

19. de Oliveira RM, Vicente Miranda H, Francelle L, Pinho R, Szegö ÉM, Martinho R, et al. The mechanism of sirtuin 2–mediated exacerbation of alpha-synuclein toxicity in models of Parkinson disease. PLoS Biol. 2017;15(3):1–27.

20. Duncan CE, An MC, Papanikolaou T, Rugani C, Vitelli C, Ellerby LM. Histone deacetylase-3 interacts with ataxin-7 and is altered in a spinocerebellar ataxia type 7 mouse model. Mol Neurodegener. 2013;8(1):1–14.

21. Chaibva M, Jawahery S, Pilkington AW, Arndt JR, Sarver O, Valentine S, et al. Acetylation within the First 17 Residues of Huntingtin Exon 1 Alters Aggregation and Lipid Binding. Biophys J. 2016;111(2):349–62.

22. Sims R, Van Der Lee SJ, Naj AC, Bellenguez C, Badarinarayan N, Jakobsdottir J, et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nat Genet. 2017;49(9):1373–84.

23. Wong ML, Arcos-Burgos M, Liu S, Vélez JI, Yu C, Baune BT, et al. The PHF21B gene is associated with major depression and modulates the stress response. Mol Psychiatry. 2017;22(7):1015–25.

24. Diwu Y, Tian J, Shi J. Effect of Xixin decoction on O-linked N-acetylglucosamine Glycosylation of tau proteins in rat brain with sporadic Alzheimer disease. J Tradit Chinese Med. 2013;33(3):367–72.

25. Kumar A, Singh PK, Parihar R, Dwivedi V, Lakhotia SC, Ganesh S. Decreased O-linked GlcNAcylation protects from cytotoxicity mediated by huntingtin exon1 protein fragment. J Biol Chem [Internet]. 2014 May 9 [cited 2020 Oct 17];289(19):13543–53. Available from: http://www.jbc.org/

26. Vicente Miranda H, Szego ÉM, Oliveira LMA, Breda C, Darendelioglu E, De Oliveira RM, et al. Glycation potentiates α-synuclein-associated neurodegeneration in synucleinopathies. Brain. 2017;140(5):1399–419.

27. Mattoo S, Sanyal A, Dutta S, Chandran A, Koller A, Camara A, et al. Alpha-Synuclein is a Target of Fic-mediated Adenylylation/AMPylation: Implications for Parkinson's Disease. bioRxiv. 2019;525659.

28. Guru KrishnaKumar V, Baweja L, Ralhan K, Gupta S. Carbamylation promotes amyloidogenesis and induces structural changes in Tau-core hexapeptide fibrils. Biochim Biophys Acta - Gen Subj. 2018;1862(12):2590–604.

29. Cohen TJ, Guo JL, Hurtado DE, Kwong LK, Mills IP, Trojanowski JQ, et al. The

acetylation of tau inhibits its function and promotes pathological tau aggregation. Nat Commun. 2011;2(1):252–9.

30. Tanikawa C, Ueda K, Suzuki A, Iida A, Nakamura R, Atsuta N, et al. Citrullination of RGG Motifs in FET Proteins by PAD4 Regulates Protein Aggregation and ALS Susceptibility. Cell Rep. 2018;22(6):1473–83.

31. Ishigami A, Masutomi H, Handa S, Nakamura M, Nakaya S, Uchida Y, et al. Mass spectrometric identification of citrullination sites and immunohistochemical detection of citrullinated glial fibrillary acidic protein in Alzheimer's disease brains. J Neurosci Res. 2015;93(11):1664–74.

32. L. Sheng, M. Christopher AM. 乳鼠心肌提取 HHS Public Access. Physiol Behav. 2016;176(1):100–106.

33. Wang Z, Zhao Y, Xu N, Zhang S, Wang S, Mao Y, et al. NEAT1 regulates neuroglial cell mediating Aβ clearance via the epigenetic regulation of endocytosis-related genes expression. Cell Mol Life Sci. 2019;76(15):3005–18.

34. Funk KE, Thomas SN, Schafer KN, Cooper GL, Liao Z, Clark DJ, et al. Lysine methylation is an endogenous post-translational modification of tau protein in human brain and a modulator of aggregation propensity. Biochem J. 2014;462(1):77–88.

35. Thomas SN, Funk KE, Wan Y, Liao Z, Davies P, Kuret J, et al. Dual modification of Alzheimer's disease PHF-tau protein by lysine methylation and ubiquitylation: A mass spectrometry approach. Acta Neuropathol. 2012;123(1):105–17.

36. Sontag JM, Sontag E. Protein phosphatase 2A dysfunction in Alzheimer's disease. Front Mol Neurosci. 2014;7(MAR):1–10.

37. Pulido R. Retraction for Berthier et al., PINK1 regulates histone H3 trimethylation and gene expression by interaction with the polycomb protein EED/WAIT1. Proc Natl Acad Sci U S A. 2014;111(45):16225.

38. Hwang YJ, Han D, Kim KY, Min SJ, Kowall NW, Yang L, et al. ESET methylates UBF at K232/254 and regulates nucleolar heterochromatin plasticity and rDNA transcription. Nucleic Acids Res. 2014;42(3):1628–43.

39. Kummer MP, Hermes M, Delekarte A, Hammerschmidt T, Kumar S, Terwel D, et al. Nitration of tyrosine 10 critically enhances amyloid β aggregation and plaque formation. Neuron. 2011;71(5):833–44.

40. Zhao J, Wang P, Li H, Gao Z. Nitration of Y10 in Aβ1-40: Is It a compensatory reaction against oxidative/nitrative stress and Aβ aggregation? Chem Res Toxicol. 2015;28(3):401–7.

41. Reynolds MR, Berry RW, Binder LI. Site-specific nitration differentially influences τ assembly in vitro. Biochemistry. 2005;44(42):13997–4009.

42. Xiang W, Menges S, Schlachetzki JCM, Meixner H, Hoffmann AC, Schlötzer-Schrehardt U, et al. Posttranslational modification and mutation of histidine 50 trigger alpha synuclein aggregation and toxicity. Mol Neurodegener. 2015;10(1):1–16.

43. Burai R, Ait-Bouziad N, Chiki A, Lashuel HA. Elucidating the role of site-specific nitration of α-synuclein in the pathogenesis of Parkinson's disease via protein semisynthesis and mutagenesis. J Am Chem Soc. 2015;137(15):5041–52.

44. Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, Foroud T, et al. Genome-wide association study of CSF biomarkers Aβ1-42, t-tau, and p-tau181p in the ADNI cohort. Neurology. 2011;76(1):69–79.

45. Do CB, Tung JY, Dorfman E, Kiefer AK, Drabant EM, Francke U, et al. Web-based genome-wide association study identifies two novel loci and a substantial genetic component for parkinson's disease. PLoS Genet. 2011;7(6).

46. Landers JE, Melki J, Meininger V, Glass JD, Van Den Berg LH, Van Es MA, et al. Reduced expression of the Kinesin-Associated Protein 3 (KIFAP3) gene increases survival in sporadic amyotrophic lateral sclerosis. Proc Natl Acad Sci U S A. 2009;106(22):9004–9.

47. Jorgensen ND, Andresen JM, Lagalwar S, Armstrong B, Stevens S, Byam CE, et al. Phosphorylation of ATXN1 at Ser776 in the cerebellum. J Neurochem. 2009;110(2):675–86.

48. Ju H, Kokubu H, Todd TW, Kahle JJ, Kim S, Richman R, et al. Polyglutamine disease toxicity is regulated by nemo-like kinase in spinocerebellar ataxia type 1. J Neurosci. 2013;33(22):9328–36.

49. Matos CA, Nóbrega C, Louros SR, Almeida B, Ferreiro E, Valero J, et al. Ataxin-3 phosphorylation decreases neuronal defects in spinocerebellar ataxia type 3 models. J Cell Biol. 2016;212(4):465–80.

50. Pastori V, Sangalli E, Coccetti P, Pozzi C, Nonnis S, Tedeschi G, et al. CK2 and GSK3 phosphorylation on S29 controls wild-type ATXN3 nuclear uptake. Biochim Biophys Acta - Mol Basis Dis. 2010;1802(7–8):583–92.

51. Fei E, Jia N, Zhang T, Ma X, Wang H, Liu C, et al. Phosphorylation of ataxin-3 by glycogen synthase kinase 3β at serine 256 regulates the aggregation of ataxin-3. Biochem Biophys Res Commun. 2007;357(2):487–92.

52. Mueller T, Breuer P, Schmitt I, Walter J, Evert BO, Wüllner U. CK2-dependent phosphorylation determines cellular localization and stability of ataxin-3. Hum Mol Genet. 2009;18(17):3334–43.

53. Ralat LA, Ren M, Schilling AB, Tang WJ. Protective role of Cys-178 against the inactivation and oligomerization of human insulin-degrading enzyme by oxidation and nitrosylation. J Biol Chem. 2009;284(49):34005–18.

54. Sen N, Hara MR, Ahmad AS, Cascio MB, Kamiya A, Ehmsen JT, et al. GOSPEL: a neuroprotective protein that binds to GAPDH upon S-nitrosylation. Neuron. 2009;63(1):81–91.

55. Qu J, Nakamura T, Holland EA, McKercher SR, Lipton SA. S-nitrosylation of Cdk5. Prion. 2012;6(4):364–70.

56. Soonpaa MH, Field LJ, Spalding K, Bhardwaj RD, Buchholz B, Druid H, et al. S-Nitrosylation of Drp1 Mediates b -Amyloid – Related Mitochondrial Fission and Neuronal Injury. 2009;(April):102–6.

57. Yang Y, Tapias V, Acosta D, Xu H, Chen H, Bhawal R, et al. Succinylation Links Metabolic Reductions to Amyloid and Tau Pathology. bioRxiv. 2019;764837.

58. Sherva R, Tripodis Y, Bennett DA, Chibnik LB, Crane PK, De Jager PL, et al. Genome-

wide association study of the rate of cognitive decline in Alzheimer's disease. Alzheimer's Dement. 2014;10(1):45–52.

59. Yan R, Farrelly S, McCarthy J V. Presenilins are novel substrates for TRAF6-mediated ubiquitination. Cell Signal. 2013;25(9):1769–79.

60. Hong S, Lee S, Cho SG, Kang S. UbcH6 interacts with and ubiquitinates the SCA1 gene product ataxin-1. Biochem Biophys Res Commun. 2008;371(2):256–60.

61. Todi S V., Scaglione KM, Blount JR, Basrur V, Conlon KP, Pastore A, et al. Activity and cellular functions of the deubiquitinating enzyme and polyglutamine disease protein ataxin-3 are regulated by ubiquitination at lysine 117. J Biol Chem. 2010;285(50):39303–13.

62. Novoselov SS, Mustill WJ, Gray AL, Dick JR, Kanuga N, Kalmar B, et al. Molecular Chaperone Mediated Late-Stage Neuroprotection in the SOD1G93A Mouse Model of Amyotrophic Lateral Sclerosis. PLoS One. 2013;8(8).

63. Che X, Tang B, Wang X, Chen D, Yan X, Jiang H, et al. The BAG2 protein stabilises PINK1 by decreasing its ubiquitination. Biochem Biophys Res Commun. 2013;441(2):488–92.

64. Koyano F, Okatsu K, Ishigaki S, Fujioka Y, Kimura M, Sobue G, et al. The principal PINK1 and Parkin cellular events triggered in response to dissipation of mitochondrial membrane potential occur in primary neurons. Genes to Cells. 2013;18(8):672–81.

65. Junqueira SC, Centeno EGZ, Wilkinson KA, Cimarosti H. Post-translational modifications of Parkinson's disease-related proteins: Phosphorylation, SUMOylation and Ubiquitination. Biochim Biophys Acta - Mol Basis Dis. 2019;1865(8):2001–7.

66. Abeywardana T, Pratt MR. Extent of inhibition of α-synuclein aggregation in vitro by SUMOylation is conjugation site- and SUMO isoform-selective. Biochemistry. 2015;54(4):959–61.

67. Shinbo Y, Niki T, Taira T, Ooe H, Takahashi-Niki K, Maita C, et al. Proper SUMO-1 conjugation is essential to DJ-1 to exert its full activities. Cell Death Differ. 2006;13(1):96–108.

68. Emerson JP, Cabelli DE, Donald M, Erbayraktar S, Grasso G, Sfac- A, et al. Positive and negative regulation of APP amyloidogenesis by sumoylation. 2003;100(15):4–10.

69. Mukhopadhyay D, Dasso M. The Role of SUMO in Mitosis. Adv Exp Med Biol. 2017;963(March 2018):171–84.

70. Subramaniam S, Mealer RG, Sixt KM, Barrow RK, Usiello A, Snyder SH. Rhes, a physiologic regulator of sumoylation, enhances cross-sumoylation between the basic sumoylation enzymes E1 and Ubc9. J Biol Chem. 2010;285(27):20428–32.

71. Ju H, Kokubu H, Lim J. Beyond the Glutamine Expansion: Influence of Posttranslational Modifications of Ataxin-1 in the Pathogenesis of Spinocerebellar Ataxia Type 1. Mol Neurobiol. 2014;50(3):866–74.

72. Zhou YF, Liao SS, Luo YY, Tang JG, Wang JL, Lei LF, et al. SUMO-1 Modification on K166 of PolyQ-Expanded aTaxin-3 Strengthens Its Stability and Increases Its Cytotoxicity. PLoS One. 2013;8(1):1–9.

73. Almeida B, Abreu IA, Matos CA, Fraga JS, Fernandes S, Macedo MG, et al. SUMOylation of the brain-predominant Ataxin-3 isoform modulates its interaction with p97. Biochim Biophys Acta - Mol Basis Dis. 2015;1852(9):1950–9.

74. Janer A, Werner A, Takahashi-Fujigasaki J, Daret A l., Fujigasaki H, Takada K, et al. SUMOylation attenuates the aggregation propensity and cellular toxicity of the polyglutamine expanded ataxin-7. Hum Mol Genet. 2009;19(1):181–95.

75. Bhattacharyya R, Barren C, Kovacs DM. Palmitoylation of amyloid precursor protein regulates amyloidogenic processing in lipid rafts. J Neurosci. 2013;

76. Parsons MP, Kang R, Buren C, Dau A, Southwell AL, Doty CN, et al. Bidirectional control of Postsynaptic Density-95 (PSD-95) clustering by Huntingtin. J Biol Chem. 2014;289(6):3518–28.

77. Schueller E, Paiva I, Blanc F, Wang X-L, Cassel J-C, Boutillier A-L, et al. Dysregulation of histone acetylation pathways in hippocampus and frontal cortex of Alzheimer's disease patients. [cited 2021 Jun 20]; Available from: https://hal.archives-ouvertes.fr/hal-03049269

78. Lu X, Wang L, Yu C, Yu D, Yu G. Histone acetylation modifiers in the pathogenesis of alzheimer's disease. Front Cell Neurosci [Internet]. 2015 Jun 16 [cited 2021 Jun 20];9(June):1–8. Available from: /pmc/articles/PMC4468862/

79. Chen LF, Fischle W, Verdin E, Greene WC. Duration of nuclear NF-κB action regulated by reversible acetylation. Science (80-) [Internet]. 2001 Aug 31 [cited 2021 Jun 20];293(5535):1653–7. Available from: https://pubmed.ncbi.nlm.nih.gov/11533489/

80. Marwarha G, Raza S, Meiers C, Ghribi O. Leptin attenuates BACE1 expression and amyloid-β genesis via the activation of SIRT1 signaling pathway. Biochim Biophys Acta - Mol Basis Dis [Internet]. 2014 [cited 2021 Jun 21];1842(9):1587–95. Available from: https://pubmed.ncbi.nlm.nih.gov/24874077/

81. Min SW, Cho SH, Zhou Y, Schroeder S, Haroutunian V, Seeley WW, et al. Acetylation of tau inhibits its degradation and contributes to tauopathy. Neuron [Internet]. 2010 Sep [cited 2021 Jun 21];67(6):953–66. Available from: https://pubmed.ncbi.nlm.nih.gov/20869593/

82. Irwin DJ, Cohen TJ, Grossman M, Arnold SE, Xie SX, Lee VMY, et al. Acetylated tau, a novel pathological signature in Alzheimer's disease and other tauopathies. Brain [Internet]. 2012 [cited 2021 Jun 21];135(3):807–18. Available from: https://pubmed.ncbi.nlm.nih.gov/22366796/

83. Atkin G, Paulson H. Ubiquitin pathways in neurodegenerative disease [Internet]. Vol. 7, Frontiers in Molecular Neuroscience. Frontiers Research Foundation; 2014 [cited 2021 Jun 21]. Available from: /pmc/articles/PMC4085722/

84. Watanabe Y, Taguchi K, Tanaka M. Ubiquitin, Autophagy and Neurodegenerative Diseases. Cells. 2020;9(9):1–15.

85. Assefa BT, Tafere GG, Wondafrash DZ, Gidey MT. The Bewildering Effect of AMPK Activators in Alzheimer's Disease: Review of the Current Evidence. Biomed Res Int. 2020;2020.

86. Curry DW, Stutz B, Andrews ZB, Elsworth JD. Targeting AMPK signaling as a neuroprotective strategy in Parkinson's disease. J Parkinsons Dis. 2018;8(2):161–81.

87. Yan Y, Zhou XE, Xu HE, Melcher K. Structure and physiological regulation of AMPK. Int J Mol Sci. 2018;19(11).

88. Peixoto CA, Oliveira WH de, Araújo SM da R, Nunes AKS. AMPK activation: Role in the signaling pathways of neuroinflammation and neurodegeneration. Experimental Neurology. 2017.

89. Sanz P, Rubio T, Garcia-Gimeno MA. AMPKbeta subunits: More than just a scaffold in the formation of AMPK complex. FEBS J. 2013;280(16):3723–33.

90. Oakhill JS, Chen ZP, Scott JW, Steel R, Castelli LA, Linga N, et al. β-Subunit myristoylation is the gatekeeper for initiating metabolic stress sensing by AMP-activated protein kinase (AMPK). Proc Natl Acad Sci U S A. 2010;107(45):19237–41.

91. Rubio T, Vernia S, Sanz P. Sumoylation of AMPKβ2 subunit enhances AMP-activated protein kinase activity. Mol Biol Cell. 2013;24(11):1801–11.

92. Cardaci S, Filomeni G, Ciriolo MR. Redox implications of AMPK-mediated signal transduction beyond energetic clues. J Cell Sci. 2012;125(9):2115–25.

93. Klaus A, Zorman S, Berthier A, Polge C, Ramirez S, Michelland S, et al. Glutathione S-Transferases Interact with AMP-Activated Protein Kinase: Evidence for S-Glutathionylation and Activation In Vitro. PLoS One. 2013;8(5):1–10.

94. Zmijewski JW, Banerjee S, Bae H, Friggeri A, Lazarowski ER, Abraham E. Exposure to hydrogen peroxide induces oxidation and activation of AMP-activated protein kinase. J Biol Chem. 2010;285(43):33154–64.

95. Bullen JW, Balsbaugh JL, Chanda D, Shabanowitz J, Hunt DF, Neumann D, et al. Cross-talk between two essential nutrient-sensitive enzymes O-GlcNAc Transferase (OGT) and Amp-Activated Protein Kinase (AMPK). J Biol Chem. 2014;289(15):10592–606.

96. Zungu M, Schisler JC, Essop MF, McCudden C, Patterson C, Willis MS. Regulation of AMPK by the ubiquitin proteasome system. Am J Pathol. 2011;178(1):4–11.

97. Wang Z, Liang L, Yin Z, Lin J. Improving chemical similarity ensemble approach in target prediction. J Cheminform. 2016;

98. Gupta R, Sahu M, Srivastava D, Tiwari S, Ambasta RK, Kumar P. Post-translational modifications: Regulators of neurodegenerative proteinopathies [Internet]. Vol. 68, Ageing Research Reviews. Elsevier Ireland Ltd; 2021 [cited 2021 Jun 11]. Available from: https://pubmed.ncbi.nlm.nih.gov/33775891/

99. Heras-Sandoval D, Pérez-Rojas JM, Hernández-Damián J, Pedraza-Chaverri J. The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. Cell Signal. 2014;26(12):2694–701.

100. Song G, Ouyang G, Bao S. The activation of Akt/PKB signaling pathway and cell survival. J Cell Mol Med. 2005;9(1):59–71.

101. Xu F, Na L, Li Y, Chen L. Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. Cell Biosci. 2020;10(1):1–12.

102. Rai SN, Dilnashin H, Birla H, Singh S Sen, Zahra W, Rathore AS, et al. The Role of PI3K/Akt and ERK in Neurodegenerative Disorders. Neurotox Res. 2019;35(3):775–95.

103. Chan CH, Jo U, Kohrman A, Rezaeian AH, Chou PC, Logothetis C, et al.

Posttranslational regulation of Akt in human cancer. Cell Biosci. 2014;4(1):1–9.

104. Lin CH, Liu SY, Lee EHY. SUMO modification of Akt regulates global SUMOylation and substrate SUMOylation specificity through Akt phosphorylation of Ubc9 and SUMO1. Oncogene. 2016;35(5):595–607.

105. Su Z, Burchfield JG, Yang P, Humphrey SJ, Yang G, Francis D, et al. Global redox proteome and phosphoproteome analysis reveals redox switch in Akt. Nat Commun. 2019;10(1):1–18.

106. Yang W-L, Wang J, Chan C-H, Lee S-W, Campos AD, Lamothe B, et al. The E3 ligase TRAF6 regulates Akt ubiquitination and activation. Science. 2009 Aug;325(5944):1134–8.

107. Baki L, Shioi J, Wen P, Shao Z, Schwarzman A, Gama-Sosa M, et al. PS1 activates PI3K thus inhibiting GSK-3 activity and tau overphosphorylation: Effects of FAD mutations. EMBO J. 2004;23(13):2586–96.

108. Sen T, Saha P, Jiang T, Sen N. Sulfhydration of AKT triggers Tau-phosphorylation by activating glycogen synthase kinase 3β in Alzheimer's disease. Proc Natl Acad Sci U S A. 2020;117(8):4418–27.

109. Iaconelli J, Lalonde J, Watmuff B, Liu B, Mazitschek R, Haggarty SJ, et al. Lysine Deacetylation by HDAC6 Regulates the Kinase Activity of AKT in Human Neural Progenitor Cells. ACS Chem Biol. 2017;

110. Li XH, Chen C, Tu Y, Sun HT, Zhao ML, Cheng SX, et al. Sirt1 promotes axonogenesis by deacetylation of akt and inactivation of GSK3. Molecular Neurobiology. 2013.

111. Chen Y, Guan Y, Zhang Z, Liu H, Wang S, Yu L, et al. Wnt signaling pathway is involved in the pathogenesis of amyotrophic lateral sclerosis in adult transgenic mice. Neurol Res. 2012;34(4):390–9.

112. Kwak YD, Ma T, Diao S, Zhang X, Chen Y, Hsu J, et al. NO signaling and S-nitrosylation regulate PTEN inhibition in neurodegeneration. Mol Neurodegener. 2010;

113. Cheng HC, Kim SR, Oo TF, Kareva T, Yarygina O, Rzhetskaya M, et al. Akt suppresses retrograde degeneration of dopaminergic axons by inhibition of macroautophagy. J Neurosci. 2011;31(6):2125–35.

114. Sun M, Asghar SZ, Zhang H. The polarity protein Par3 regulates APP trafficking and processing through the endocytic adaptor protein Numb. Neurobiol Dis [Internet]. 2016 Sep 1 [cited 2020 Sep 24];93:1–11. Available from: /pmc/articles/PMC4930744/?report=abstract

115. Li Q, Liu Y, Sun M. Autophagy and Alzheimer's Disease [Internet]. Vol. 37, Cellular and Molecular Neurobiology. Springer New York LLC; 2017 [cited 2020 Sep 24]. p. 377–88. Available from: https://pubmed.ncbi.nlm.nih.gov/27260250/

116. Díaz-Troya S, Pérez-Pérez ME, Florencio FJ, Crespo JL. The role of TOR in autophagy regulation from yeast to plants and mammals [Internet]. Vol. 4, Autophagy. Taylor and Francis Inc.; 2008 [cited 2020 Sep 24]. p. 851–65. Available from: https://pubmed.ncbi.nlm.nih.gov/18670193/

117. Ribarič S, Milisav Ribarič I. Autophagy and Cell Death in Alzheimer's, Parkinson's and Prion Diseases. In: Programmed Cell Death [Internet]. IntechOpen; 2020 [cited 2020

Sep 24]. Available from: www.intechopen.com

118. Bieri G, Lucin KM, O'Brien CE, Zhang H, Villeda SA, Wyss-Coray T. Proteolytic cleavage of Beclin 1 exacerbates neurodegeneration. Mol Neurodegener [Internet]. 2018 Dec 29 [cited 2020 Oct 17];13(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30594228/

119. Esteves AR, Palma AM, Gomes R, Santos D, Silva DF, Cardoso SM. Acetylation as a major determinant to microtubule-dependent autophagy: Relevance to Alzheimer's and Parkinson disease pathology. Biochim Biophys Acta - Mol Basis Dis [Internet]. 2019 Aug 1 [cited 2020 Oct 8];1865(8):2008–23. Available from: https://pubmed.ncbi.nlm.nih.gov/30572013/

120. Feng Q, Luo Y, Zhang XN, Yang XF, Hong XY, Sun DS, et al. MAPT/Tau accumulation represses autophagy flux by disrupting IST1-regulated ESCRT-III complex formation: a vicious cycle in Alzheimer neurodegeneration. Autophagy [Internet]. 2020 Apr 2 [cited 2020 Oct 8];16(4):641–58. Available from: https://pubmed.ncbi.nlm.nih.gov/31223056/

121. Kontaxi C, Piccardo P, Gill AC. Lysine-directed post-translational modifications of tau protein in Alzheimer's disease and related tauopathies [Internet]. Vol. 4, Frontiers in Molecular Biosciences. Frontiers Media S.A.; 2017 [cited 2020 Sep 24]. p. 56. Available from: www.frontiersin.org

122. Nixon RA. Autophagy, amyloidogenesis and Alzheimer disease [Internet]. Vol. 120, Journal of Cell Science. J Cell Sci; 2007 [cited 2020 Sep 24]. p. 4081–91. Available from: https://pubmed.ncbi.nlm.nih.gov/18032783/

123. Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. Journal of Pharmacology and Experimental Therapeutics. 2012.

124. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006.

125. Moreira PI, Carvalho C, Zhu X, Smith MA, Perry G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2010.

126. Reddy PH. Amyloid beta, mitochondrial structural and functional dynamics in Alzheimer's disease [Internet]. Vol. 218, Experimental Neurology. NIH Public Access; 2009 [cited 2020 Sep 25]. p. 286–92. Available from: /pmc/articles/PMC2710427/?report=abstract

127. Gómez-Serrano M, Camafeita E, Loureiro M, Peral B. Mitoproteomics: Tackling mitochondrial dysfunction in human disease. Vol. 2018, Oxidative Medicine and Cellular Longevity. Hindawi Limited; 2018.

128. Henley JM, Carmichael RE, Wilkinson KA. Extranuclear SUMOylation in Neurons. Trends in Neurosciences. 2018.

129. García-Escudero V, Martín-Maestro P, Perry G, Avila J. Deconstructing mitochondrial dysfunction in alzheimer disease [Internet]. Vol. 2013, Oxidative Medicine and Cellular Longevity. Hindawi Limited; 2013 [cited 2020 Sep 25]. p. 13. Available from: /pmc/articles/PMC3693159/?report=abstract

130. Dowding JM, Song W, Bossy K, Karakoti A, Kumar A, Kim A, et al. Cerium oxide

nanoparticles protect against Aβ-induced mitochondrial fragmentation and neuronal cell death. Cell Death Differ [Internet]. 2014 Oct 1 [cited 2020 Oct 17];21(10):1622–32. Available from: https://pubmed.ncbi.nlm.nih.gov/24902900/

131. Quintanilla RA, Tapia-Monsalves C, Vergara EH, Pérez MJ, Aranguiz A. Truncated Tau Induces Mitochondrial Transport Failure Through the Impairment of TRAK2 Protein and Bioenergetics Decline in Neuronal Cells. Front Cell Neurosci [Internet]. 2020 Jul 30 [cited 2020 Oct 17];14. Available from: https://pubmed.ncbi.nlm.nih.gov/32848607/

132. Gupta R, Srivastava D, Sahu M, Tiwari S, Ambasta RK, Kumar P. Artificial intelligence to deep learning: machine intelligence approach for drug discovery. Mol Divers. 2021 Apr 12;

133. Griebel G, Stemmelin J, Lopez-Grancha M, Boulay D, Boquet G, Slowinski F, et al. The selective GSK3 inhibitor, SAR502250, displays neuroprotective activity and attenuates behavioral impairments in models of neuropsychiatric symptoms of Alzheimer's disease in rodents. Sci Rep. 2019;9(1):1–15.

134. Sathya S, Devi KP. The use of polyphenols for the treatment of alzheimer's disease. Role Mediterr Diet Brain Neurodegener Dis. 2017;239–52.

135. Morales-García JA, Susín C, Alonso-Gil S, Pérez DI, Palomo V, Pérez C, et al. Glycogen synthase kinase-3 inhibitors as potent therapeutic agents for the treatment of Parkinson disease. ACS Chem Neurosci. 2013;4(2):350–60.

136. Hutter-Paier B, Huttunen HJ, Puglielli L, Eckman CB, Kim DY, Hofmeister A, et al. The ACAT inhibitor CP-113,818 markedly reduces amyloid pathology in a mouse model of Alzheimer's disease. Neuron. 2004;44(2):227–38.

137. Meli G, Visintin M, Cannistraci I, Cattaneo A. Direct in Vivo Intracellular Selection of Conformation-sensitive Antibody Domains Targeting Alzheimer's Amyloid-β Oligomers. J Mol Biol. 2009;

138. Wang H, Lu J, Gao WC, Ma X, Li N, Ding Z, et al. Donepezil down-regulates propionylation, 2-hydroxyisobutyrylation, butyrylation, succinylation, and crotonylation in the brain of bilateral common carotid artery occlusion-induced vascular dementia rats. Clin Exp Pharmacol Physiol. 2020;0–2.

139. Zhao J, Wu J, Yang Z, Li H, Gao Z. Nitration of Tyrosine Residue Y10 of Aβ1-42 Significantly Inhibits Its Aggregation and Cytotoxicity. Chem Res Toxicol. 2017;30(4):1085–92.

140. Davenport TH, Ronanki R. Artificial intelligence for the real world. Harv Bus Rev. 2018;

141. Zhavoronkov A, Vanhaelen Q, Oprea TI. Will Artificial Intelligence for Drug Discovery Impact Clinical Pharmacology? [Internet]. Vol. 107, Clinical Pharmacology and Therapeutics. Nature Publishing Group; 2020 [cited 2021 Jan 16]. p. 780–5. Available from: https://pubmed.ncbi.nlm.nih.gov/31957003/

142. Watson O, Cortes-Ciriano I, Taylor A, Watson JA. A decision theoretic approach to model evaluation in computational drug discovery. arXiv. 2018.

143. Tripathy RK, Mahanta S, Paul S. Artificial intelligence-based classification of breast cancer using cellular images. RSC Adv [Internet]. 2014 Jan 28 [cited 2021 Jan

15];4(18):9349–55. Available from: https://pubs.rsc.org/en/content/articlehtml/2014/ra/c3ra47489e

144. Samui P, Kothari DP. Utilization of a Least Square Support Vector Machine (LSSVM) for slope stability analysis. Sci Iran. 2011 Feb 1;18(1 A):53–8.

145. Chan HCS, Shan H, Dahoun T, Vogel H, Yuan S. Advancing Drug Discovery via Artificial Intelligence [Internet]. Vol. 40, Trends in Pharmacological Sciences. Elsevier Ltd; 2019 [cited 2021 Jan 15]. p. 592–604. Available from: http://www.cell.com/article/S016561471930135X/fulltext

146. Ho CWL, Soon D, Caals K, Kapur J. Governance of automated image analysis and artificial intelligence analytics in healthcare. Vol. 74, Clinical Radiology. W.B. Saunders Ltd; 2019. p. 329–37.

147. Andrysek T. Impact of physical properties of formulations on bioavailability of active substance: Current and novel drugs with cyclosporine. In: Molecular Immunology. Elsevier Ltd; 2003. p. 1061–5.

148. Elton DC, Boukouvalas Z, Butrico MS, Fuge MD, Chung PW. Applying machine learning techniques to predict the properties of energetic materials. Sci Rep [Internet]. 2018 Dec 1 [cited 2021 Jan 16];8(1):9059. Available from: www.nature.com/scientificreports

149. Popova M, Isayev O, Tropsha A. Deep reinforcement learning for de novo drug design. Sci Adv [Internet]. 2018 Jul 25 [cited 2021 Jan 15];4(7):eaap7885. Available from: http://advances.sciencemag.org/

150. Tyrchan C, Evertsson E. Matched Molecular Pair Analysis in Short: Algorithms, Applications and Limitations. Vol. 15, Computational and Structural Biotechnology Journal. Elsevier B.V.; 2017. p. 86–90.

151. Turk S, Merget B, Rippmann F, Fulle S. Coupling Matched Molecular Pairs with Machine Learning for Virtual Compound Optimization. J Chem Inf Model [Internet]. 2017 Dec 26 [cited 2021 Jan 15];57(12):3079–85. Available from: https://pubs.acs.org/doi/abs/10.1021/acs.jcim.7b00298

152. Carpenter KA, Huang X. Machine Learning-based Virtual Screening and Its Applications to Alzheimer's Drug Discovery: A Review. Curr Pharm Des [Internet]. 2018 Dec 3 [cited 2021 Jan 15];24(28):3347–58. Available from: https://pubmed.ncbi.nlm.nih.gov/29879881/

153. Schyman P, Liu R, Desai V, Wallqvist A. vNN Web Server for ADMET Predictions. Front Pharmacol [Internet]. 2017 Dec 4 [cited 2021 Jan 15];8(DEC):889. Available from: http://journal.frontiersin.org/article/10.3389/fphar.2017.00889/full

Ageing Research Reviews 68 (2021) 101336

IF 10.616

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Post-translational modifications: Regulators of neurodegenerative proteinopathies

Rohan Gupta [1], Mehar Sahu [1], Devesh Srivastava [1], Swati Tiwari [1], Rashmi K. Ambasta, Pravir Kumar [*]

Molecular Neuroscience and Functional Genomics Laboratory, Department of Biotechnology, Delhi Technological University (Formerly DCE), Delhi 110042, India

ARTICLE INFO

Keywords:
Post-translational modifications
Neurodegenerative disease
Proteinopathies
Protein aggregation

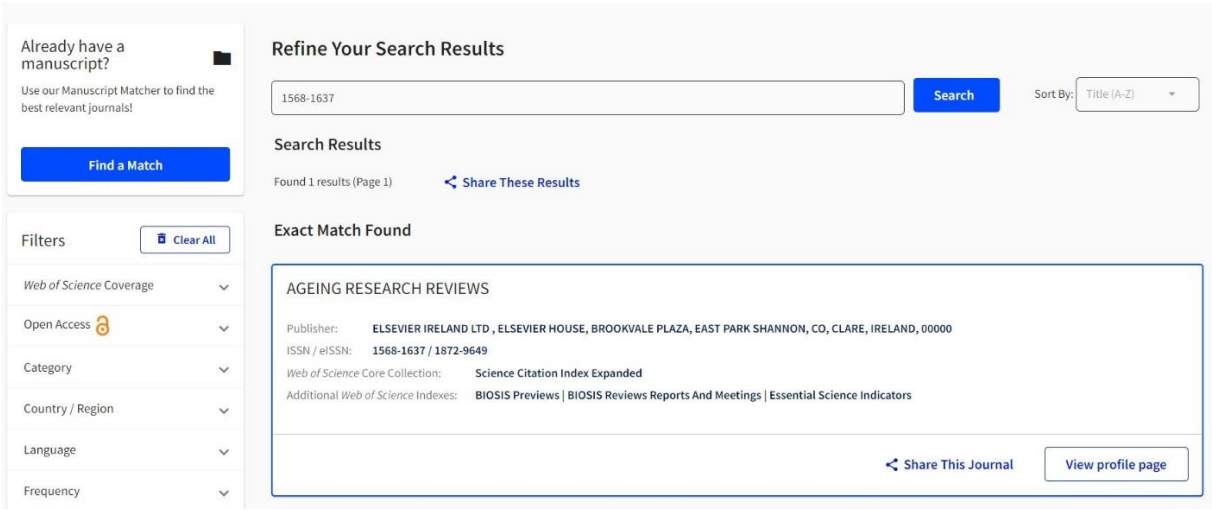
ABSTRACT

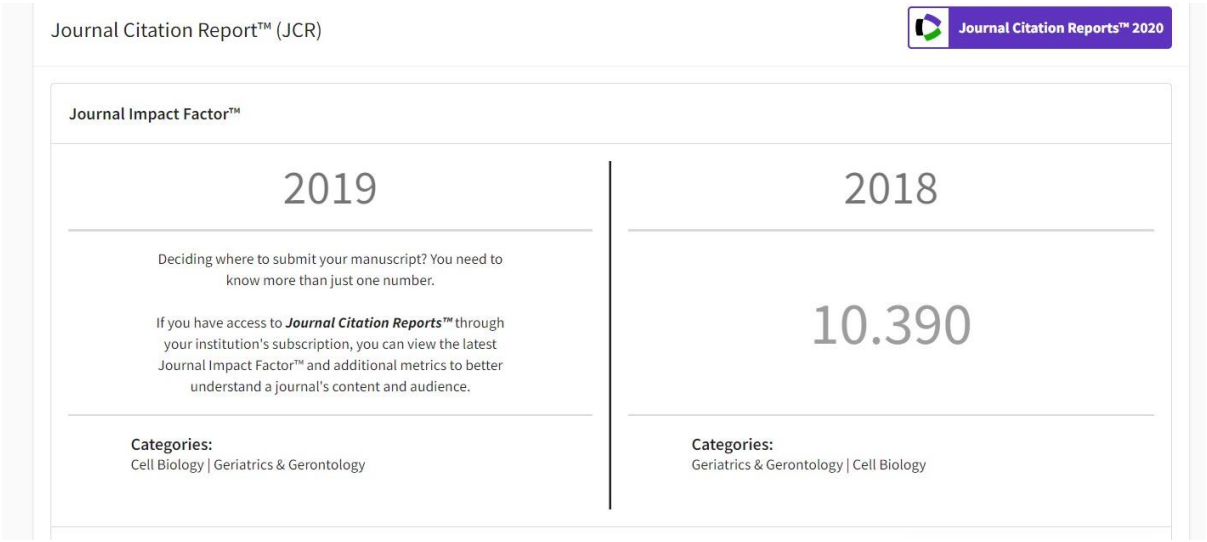
One of the hallmark features in the neurodegenerative disorders (NDDs) is the accumulation of aggregated and/or non-functional protein in the cellular milieu. Post-translational modifications (PTMs) are an essential regulator of non-functional protein aggregation in the pathogenesis of NDDs. Any alteration in the post-translational mechanism and the protein quality control system, for instance, molecular chaperone, ubiquitin-proteasome system, autophagy-lysosomal degradation pathway, enhances the accumulation of misfolded protein, which

Abbreviations: PTMs, Post-translational modifications; NDDs, Neurodegenerative diseases; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, Amyotrophic lateral sclerosis; HD, Huntington's disease; TDP-43, Transactivation response DNA binding protein-43; Aβ, β-amyloid; NFTs, Neurofibrils tangles; SNpc, Substantia nigra pars compacta; polyQ, Polyglutamine; LBs, Lewy bodies; htt, Huntingtin protein; SOD1, Superoxide dismutase 1; UPS, Ubiquitin-proteasome system; CMA, Chaperone mediated autophagy; HSPs, Heat shock proteins; PSEN2, Presenilin-2; IT15, Interesting transcript 15; TARDBP, TAR DNA Binding Protein; NO, Nitric oxide; CK1, Casein kinase 1; GSK-3β, Glycogen synthase kinase 3β; PKA, Protein kinase A; CDK5, Cyclin-dependent kinase 5; DYRK1A, Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A; REP, Repressor element of PARKIN; MTS, Mitochondrial targeting sequence; TM, Transmembrane; FUS, Fused in sarcoma; NLS, Nuclear localization sequence; RRMs, RNA recognition motif; NES, Nuclear export sequence; ER, Endoplasmic reticulum; UPR, Unfolded protein response; IRE1α, Inositol-requiring enzyme 1 α; PERK, Protein kinase R like endoplasmic reticulum kinase; ATF6α, Activating transcription factor 6 α; DR5, Death receptor 5; eIF2α, Eukaryotic initiation factor 2 α; XBP1, X-box binding protein 1; ASK1-JNK, apoptosis signal-regulating kinase 1/ c-Jun N-terminal kinases; TRAF2, TNF receptor-associated factor 2; PAD4, Protein arginase deaminase 4; SP1, Specificity protein 1; SP2, Specificity protein 2; PARP16, poly ADP ribose polymerase 16; Umf1, ubiquitin fold modifier 1; CHOP, C/EBP homologous protein; ERAD, endoplasmic reticulum-associated degradation; APP, Amyloid precursor protein; PSEN1, Presenilin-1; BACE1, Beta-secretase 1; BiP, Binding immunoglobulin protein; PARKIN, E3 ubiquitin-protein ligase parkin; PINK1, PTEN-induced kinase 1; PDI, Protein disulfide isomerase; GADD34, Growth arrest and DNA damage-inducible protein; DJ1, Protein deglycase; ATFS1, Cyclic AMP-dependent transcription factor; PDR1, Pleiotropic drug resistance 1; CSMNs, Corticospinal motor neurons; FOXO1, Forkhead box protein O1; FTLD, frontotemporal lobar degeneration; ASK1, Signal-regulating kinase 1; PI3K, Phosphatidylinositol 3-kinase; PIP2, Phosphatidylinositol 4,5-bisphosphate; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; PH domain,

* Corresponding author.
E-mail address: pravirkumar@dtu.ac.in (P. Kumar).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.arr.2021.101336
Received 28 October 2020; Received in revised form 10 March 2021; Accepted 22 March 2021
Available online 26 March 2021


Already have a manuscript?
Use our Manuscript Matcher to find the best relevant journals!
Find a Match
Refine Your Search Results
1568-1637
Search
Sort By: Title (A-Z)
Search Results
Found 1 results (Page 1)
Share These Results
Filters
Clear All
Web of Science Coverage
Open Access
Category
Country / Region
Language
Frequency
Exact Match Found
AGEING RESEARCH REVIEWS
Publisher: ELSEVIER IRELAND LTD , ELSEVIER HOUSE, BROOKVALE PLAZA, EAST PARK SHANNON, CO, CLARE, IRELAND, 00000
ISSN / eISSN: 1568-1637 / 1872-9649
Web of Science Core Collection: Science Citation Index Expanded
Additional Web of Science Indexes: BIOSIS Previews | BIOSIS Reviews Reports And Meetings | Essential Science Indicators
Share This Journal
View profile page


Journal Citation Report™ (JCR)
Journal Citation Reports™ 2020
Journal Impact Factor™
2019
Deciding where to submit your manuscript? You need to know more than just one number.
If you have access to Journal Citation Reports™ through your institution's subscription, you can view the latest Journal Impact Factor™ and additional metrics to better understand a journal's content and audience.
Categories:
Cell Biology | Geriatrics & Gerontology
2018
10.390
Categories:
Geriatrics & Gerontology | Cell Biology

Molecular Diversity
https://doi.org/10.1007/s11030-021-10217-3

IF 2.013

Artificial intelligence to deep learning: machine intelligence approach for drug discovery

Rohan Gupta[1] · Devesh Srivastava[1] · Mehar Sahu[1] · Swati Tiwari[1] · Rashmi K. Ambasta[1] · Pravir Kumar[1]

Received: 29 January 2021 / Accepted: 22 March 2021

Abstract

Drug designing and development is an important area of research for pharmaceutical companies and chemical scientists. However, low efficacy, off-target delivery, time consumption, and high cost impose a hurdle and challenges that impact drug design and discovery. Further, complex and big data from genomics, proteomics, microarray data, and clinical trials also impose an obstacle in the drug discovery pipeline. Artificial intelligence and machine learning technology play a crucial role in drug discovery and development. In other words, artificial neural networks and deep learning algorithms have modernized the area. Machine learning and deep learning algorithms have been implemented in several drug discovery processes such as peptide synthesis, structure-based virtual screening, ligand-based virtual screening, toxicity prediction, drug monitoring and release, pharmacophore modeling, quantitative structure–activity relationship, drug repositioning, polypharmacology, and physiochemical activity. Evidence from the past strengthens the implementation of artificial intelligence and deep learning in this field. Moreover, novel data mining, curation, and management techniques provided critical support to recently developed modeling algorithms. In summary, artificial intelligence and deep learning advancements provide an excellent opportunity for rational drug design and discovery process, which will eventually impact mankind.

Graphic abstract

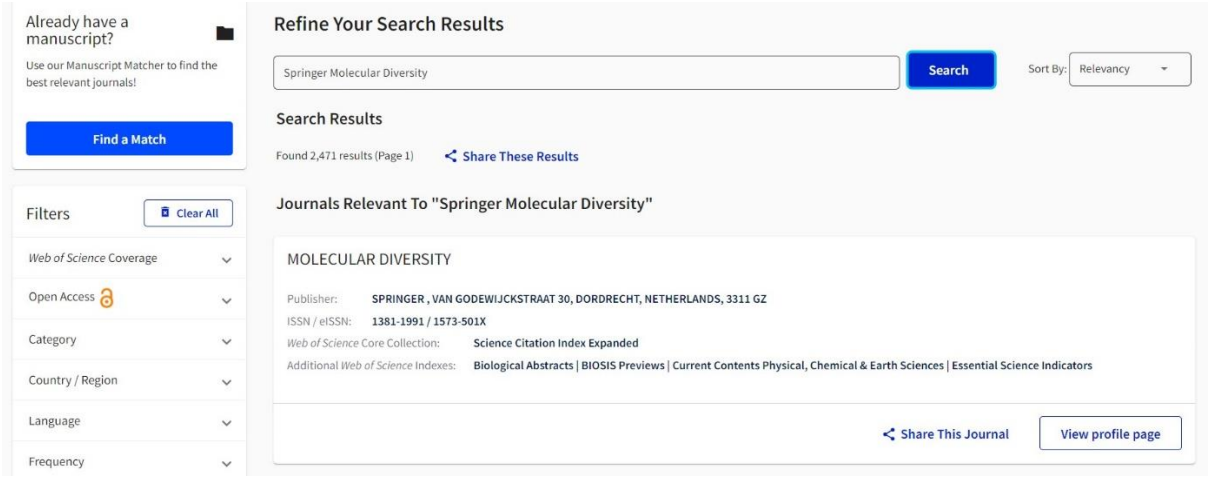
The primary concern associated with drug design and development is time consumption and production cost. Further, inefficiency, inaccurate target delivery, and inappropriate dosage are other hurdles that inhibit the process of drug delivery and development. With advancements in technology, computer-aided drug design integrating artificial intelligence algorithms can eliminate the challenges and hurdles of traditional drug design and development. Artificial intelligence is referred to as superset comprising machine learning, whereas machine learning comprises supervised learning, unsupervised learning, and reinforcement learning. Further, deep learning, a subset of machine learning, has been extensively implemented in drug design and development. The artificial neural network, deep neural network, support vector machines, classification and regression, generative adversarial networks, symbolic learning, and meta-learning are examples of the algorithms applied to the drug design and discovery process. Artificial intelligence has been applied to different areas of drug design and development process, such as from peptide synthesis to molecule design, virtual screening to molecular docking, quantitative structure–activity relationship to drug repositioning, protein misfolding to protein–protein interactions, and molecular pathway identification to polypharmacology. Artificial intelligence principles have been applied to the classification of active and inactive, monitoring drug release, pre-clinical and clinical development, primary and secondary drug screening, biomarker

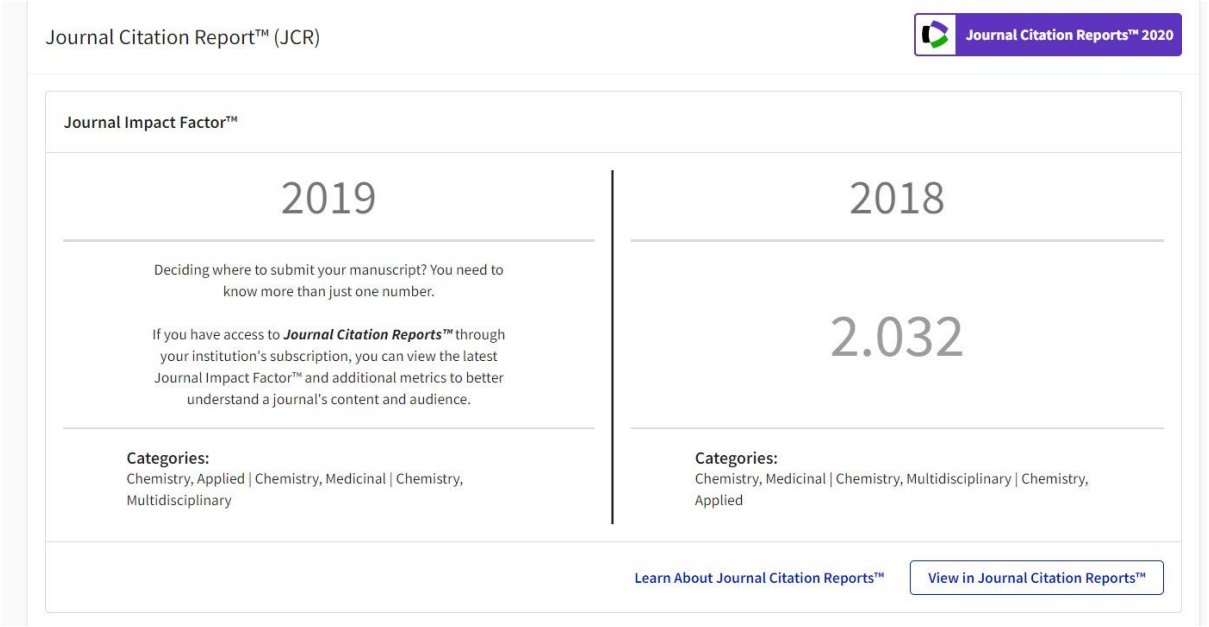
Rohan Gupta, Devesh Srivastava, Mehar Sahu, and Swati Tiwari contributed equally to this work.

✉ Pravir Kumar
pravirkumar@dtu.ac.in; kpravir@gmail.com

[1] Molecular Neuroscience and Functional Genomics Laboratory, Department of Biotechnology, Delhi Technological University (Formerly DCE), Shahbad Daulatpur, Bawana Road, Delhi 110042, India

Published online: 12 April 2021


Already have a manuscript?
Use our Manuscript Matcher to find the best relevant journals!
Find a Match
Refine Your Search Results
Springer Molecular Diversity
Search
Sort By: Relevancy
Search Results
Found 2,471 results (Page 1)
Share These Results
Filters
Clear All
Web of Science Coverage
Open Access
Category
Country / Region
Language
Frequency
Journals Relevant To "Springer Molecular Diversity"
MOLECULAR DIVERSITY
Publisher: SPRINGER , VAN GODEWIJCKSTRAAT 30, DORDRECHT, NETHERLANDS, 3311 GZ
ISSN / eISSN: 1381-1991 / 1573-501X
Web of Science Core Collection: Science Citation Index Expanded
Additional Web of Science Indexes: Biological Abstracts | BIOSIS Previews | Current Contents Physical, Chemical & Earth Sciences | Essential Science Indicators
Share This Journal
View profile page


Journal Citation Report™ (JCR)
Journal Citation Reports™ 2020
Journal Impact Factor™
2019
Deciding where to submit your manuscript? You need to know more than just one number.
If you have access to Journal Citation Reports™ through your institution's subscription, you can view the latest Journal Impact Factor™ and additional metrics to better understand a journal's content and audience.
Categories:
Chemistry, Applied | Chemistry, Medicinal | Chemistry, Multidisciplinary
2018
2.032
Categories:
Chemistry, Medicinal | Chemistry, Multidisciplinary | Chemistry, Applied
Learn About Journal Citation Reports™
View in Journal Citation Reports™

29th June 2021

Letter Of Acceptance

Abstract id: ICETSEM_2806129835

Abstract Title: Computational Analysis of Post Translational Modifications in the Pathogenesis of Alzheimer's Disease

Author: Mehar Sahu

Co-Authors: Pravir Kumar

Dear Mr/Ms Mehar Sahu,

Congratulations!!

The scientific research paper reviewing committee of "**2nd International Conference on Emerging Trends in Science, Engineering and Management-2021**" (ICETSEM-2021) scheduled to take place on the **15th and 16th July 2021** organized by GM Institute of Technology, Davangere, Karnataka & IFERP is pleased to inform your research paper titled "**Computational Analysis of Post Translational Modifications in the Pathogenesis of Alzheimer's Disease"** has been accepted after our double-blind peer review process for presenting paper at ICETSEM 2021. Authors and speakers are recommended to proceed for registration to confirm their slots in relevant scientific sessions by following the link: https://icetsem.net/conference-registration.php

Acceptance Status: Yes

For further details and other affiliated journals feel free to contact us,

***Additional Charges Applicable for publications in Scopus and Web of Science indexed Journals**

Registration Guidelines: https://icetsem.net/conference-registration-guidelines.php

No of authors per paper is limited, only 5 authors per paper. If Exceeds have to pay Rs.200 per head

Share your payment document after registering at https://icetsem.net/conference-registration.php and email the payment document to info@icetsem.net

Regards,
Dr.Praveen.J.,
IQAC Director, Professor & Head(ECE),
Convener, ICETSEM 2021,
GM Institute of Technology, Davnagere,Karnataka

K.Gomathi,
Conference Coordinator, IFERP,
+918122268465.