Article

Network-based investigation to identify the common gene-disease linkage between Alzheimer's disease, Parkinson's disease, and epilepsy

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Abstract
Neurological illnesses such as Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy (EP) have a significant impact on worldwide health. This study uses network pharmacology and genomic analysis to find shared genes and pathways linked to various illnesses.The STRING database was used to identify shared genes between AD, PD, and EP. Associated proteins of common genes were obtained and imported into Cytoscape to design and analyze networks. Gene enrichment analysis was performed using ShinyGO V0.77. AD, PD, and EP share three genes: KIF5A, NDUFB9, and MT-ND1. Network analysis showed relationships between these genes and their associated proteins. Pathway enrichment study revealed major pathways, including Alzheimer's, Parkinson's disease, Neurodegeneration, and oxidative phosphorylation pathways.The current study revealed genetic interconnectivity of AD, PD, and EP, underlining the role of mitochondrial failure, oxidative stress, and synaptic dysfunction in their development. KIF5A, NDUFB9, and MT-ND1 play critical roles in these pathways, making them attractive therapeutic targets. Indirect interactions between these genes via common proteins such as SNCA and MAPT indicate complicated regulatory networks. Identifying common genes and pathways sheds light on shared mechanisms underlying AD, PD, and EP. Drug repurposing opportunities targeting key proteins like SNCA and MAPT may offer novel therapeutic avenues.

Keywords Alzheimer's disease (AD); Parkinson's disease (PD); Epilepsy (EP); neurological disorders, network pharmacology; associated proteins.

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1 Introduction

A significant burden of neurological disorders exists on global health. In developing nations, epilepsy (EP), Parkinson's disease (PD), and Alzheimer's disease (AD) are the most prevalent neurological disorders among

older adults.

The seventh most common cause of death, according to the World Health Organization, is dementia. AD accounts for 60–70% of dementia cases; it is the most prevalent type of dementia. Over one-third of the population about 85 years old is affected by AD dementia, which affects an estimated 55 million people globally. The development of intracellular tau neurofibrillary tangles and extracellular amyloid (Aβ) plaque are the hallmarks of AD (Cacace, 2016). The most prevalent type of motor disorder is PD, which affects 1-2% of people over 60, with an increasing prevalence as people age. The accumulation of α-synuclein in neurons in the form of Lewy bodies is the main neuropathological sign of PD (Kalinderi, 2016).

Globally, Epilepsy is considered the second most prevalent neurological disorder with an estimated 50 million people worldwide (Cano, 2021a). It is characterized by an electrical imbalance in neurons which leads to recurrent seizures (Fisher, 2014).

Growing evidence suggests that the pathophysiology and clinical significance of these neurological disorders may be similar. Numerous studies have determined that 80% of PD patients will experience dementia, with an average onset time of 10 years following PD diagnosis (Anang, 2017). Additionally, patients who have cognitive impairments are more likely to experience seizures. According to Zhang, 2022, individuals with AD and PD have a 10-fold increased risk of developing epilepsy compared to those without AD, and a 2.5-fold increased risk compared to those without PD over the age of 65.

According to certain neuropathological studies, epilepsy may be the root cause of neurodegenerative diseases (Cano, 2021b). Hyperexcitability of nervous tissue is mainly responsible for the activation of seizures. Recent studies suggest that neuronal hyperexcitability might play a significant role in promoting cognitive impairment in AD. Thus, the increase in amyloid plaque and tau protein levels might be related to the molecular pathways that trigger seizures (Kang, 2021). Similarly, neuronal excitability due to the accumulation of abnormal α-synuclein promotes membrane depolarization, oxidative stress, and massive influx of Ca++ via mitochondrial dysfunction and Lewy body formation which in turn increase the neurodegeneration process and vice versa (Badawy, 2009). Generally, in AD, the role of Aβ and hyperphosphorylated tau, the modulation of NMDA receptors in neuroinflammation and neurodegeneration results in neuronal hyperexcitability that precedes seizures. Likewise, a rise in intracellular Ca++, oxidative stress, and accumulation of Lewy bodies contribute to neuronal hyperexcitability (Estrada-Sanchez, 2017). All these mechanisms indicate the common molecular linkage between AD, PD, and EP. There is the possibility that the common mechanisms of these diseases include the common genes. The genetic correlation between AD, PD, and EP has not yet been found. Hence, the identification of disease genes and disease pathways could offer better targets for drug development.

Currently, various treatment options are available for AD, PD, and EP. However, no preventive or curative treatment exists for neurological disorders at present, putting a massive burden on public health and society. Also, the new methods are still in their development stage and facing failure in the clinical trial phase.The successful drug development strategy is limited due to the lack of drug efficacy and selection ofsignificant drug targets for complex diseases.The traditional drug strategy is based on the poor efficacy of highly selective single-target drugs. Generally, complex diseases are multi-genic or multi-protein and can be managed with a multi-targeted approach (Patwardhan, 2005). Network pharmacology is a new paradigm that focuses on a multi-target strategy. Recently more attention has been directed towards molecular drug targets in cellular signaling networks (Zhang, 2019). Network analysis is an attractive field in proteomics and bioinformatics which provides a deeper understanding of genes, and cellular and molecular processes in the case of diseases (Kim, 2022; Zhang, 2016, 2018, 2021, 2023).

Identifying disease-gene associations is essential for finding disease-causing genes and understanding the

mechanism of disease. Recently, network-based techniques have received attention for their effectiveness in predicting disease-gene associations (Zhang, 2013).

Hence, the present study aims to explore the network-based approach to identify the common genes and disease pathways in AD, PD, and EP.

2 Methods

2.1 Identification of common genes involved in AD, PD, and EP

The genes involved in AD, PD, and EP were retrieved from the STRING database (STRING: functional protein association networks (string-db.org)). All genes were obtained specifically by filtering the organism as “Homo sapiens”. All unique sets of genes for each disease were imported to Venny 2.1.0 to find common genes between AD & PD, AD & EP, PD & EP, and AD, PD & EP.

2.2 Identification of associated proteins of common genes

The associated proteins of each common gene involved in AD, PD & EP were retrieved from the STRING database. Duplicates of all associated proteins were removed to obtain distinct sets of associated proteins for each of three common genes.

2.3 Network Construction and Analysis

The total unique associated genes for each common gene were imported to Cytoscape 3.2.0 software to construct the network and were analyzed using analyzer tool (Yang and Zhang, 2022).

Software/ Web tools/ Databases used:

String: STRING: functional protein association networks (string-db.org)

Cytoscape: Cytoscape: An Open Source Platform for Complex Network Analysis and Visualization

ShinyGO 0.77: ShinyGO 0.77 (sdstate.edu)

KEGG Database: KEGG: Kyoto Encyclopedia of Genes and Genomes

3 Results

3.1 Identification of common genes involved in AD, PD, and EP

The genes involved in AD, PD, and EP were retrieved from the STRING database (10 December 2023). About 354 genes were found to beinvolved in AD, 236 genes in PD, and 306 genes in EP.The three genes namely KIF5A, MT-ND1, and NDUFB9 were found common among AD, PD, and EP. 181 genes were found to be common in AD and PD. Similarly, only one gene, i.e., HTRA2 is common in PD & EP. 9 genes were found to be common between AD and EP (Fig. 1).

3.2 Identification of associated proteins of common genes

The STRING database was used to retrieve the associated protein targets for the three common genes. All associated proteins of each of the three common genes were compiled for each disease by removing duplicates to obtain a unique set of associated protein targets for each common gene i.e. KIF5A, MT-ND1 & NDUFB9 (Table 1).

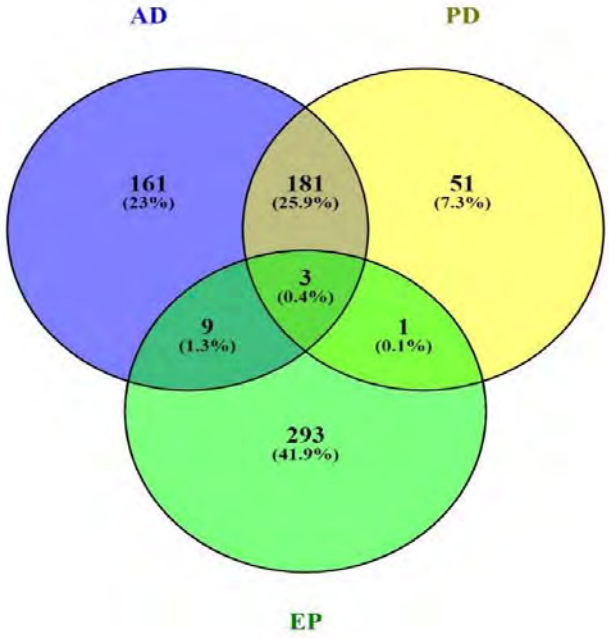

Fig. 1 Venn Diagram showing the genes that overlap in AD, PD, and EP Target genes for AD are represented by the blue circle (161), PD target genes by the yellow circle (51), and EP target genes by the green circle (293). The coincident section displays the target genes that AD, PD, and EP have in common.

Table 1 Unique associated protein targets for KIF5A, MT-ND1 & NDUFB9.

Common Genes	No of associated proteins			Unique associated proteins After duplicate removal
	AD	PD	EP	
KIF5A	23	18	09	32
NDUFB9	96	101	04	99
MT-ND1	92	93	07	103
Total	211	212	20	**234 (149 After duplicate removal)**

The unique sets of associated protein targets for each common gene namely KIF5A, MT-ND1 and NDUFB9, were imported tocytoscape to construct a network. The network obtained was analyzed by the Network analyzer tool.The network consisted of total 149 nodes and 234 edges with average degree value of 1.6 and 87 nodes in total with degree values higher than the average degree value.The network was further analyzedbased on centrality measures and clustering coefficient (Fig. 2).

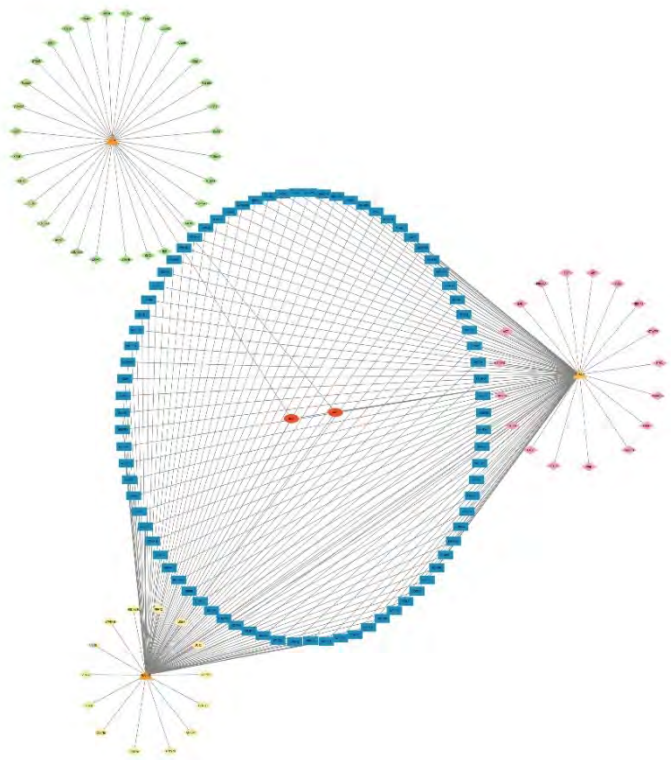

Fig. 2 Common disease genes target protein network. The network represents the interrelation among the 3 common genes and associated target proteins. a) orange color triangle nodes represent 3 common genes between AD, PD & EP. b) Oval red nodes indicate the intersecting associated proteins between 3 common genes. c) Blue square nodes represent 82 common target proteins between MT-ND1 & NDUFB9. d) The pink diamond nodes are the associated proteins of MT-ND1. e) yellow diamond nodes represent associated proteins of NDUFB9. f) green color diamond nodes indicate the associated proteins of KIF5A.

Further it was observed that NDUFB9 and MT-ND1 interact with each other directly. However, KIF5A have no direct interaction with NDUFB9 and MT-ND1. All the three common genes KIF5A, MT-ND1 & and NDUFB9 were observed to interact with each other indirectly either through two common proteins i.e. SNCA and/or MAPT. In addition, network analysis revealed that, of 149 nodes in the network, only five nodesnamely MAPT, SNCA, KIF5A, NDUFB9, MT-ND1were found to have a higher betweenness and closeness centrality. The betweenness and closeness centrality of MT-ND1 is the highest. MAPT & SNCA have a higher clustering coefficient suggesting that these genes are directly connected with three common genes namely KIF5A, MT-ND1 & and NDUFB9and thus are involved in regulating the functions of these common genes via the commonpathways associated between AD, PD and EP (Table 2).

Gene set enrichment analysis was carried using ShinyGO V0.77 tool to identify top 10 pathways associated with common genes. The order of the top 10 pathways associated with common genes was: Amyotropic lateral sclerosis > Alzheimer's disease > Parkinson's disease > Pathways of neurodegeneration > prion disease > Huntington's disease > Oxidative phosphorylation > retrograde endocannabinoid signaling > Diabetic cardiomyopathy > Thermogenesis, as indicated by darker color intensity of green dots in Figs 3 & 4.

Table 2 Parameters of network analysis.

Genes	Betweenness Centrality	Closeness Centrality	Clustering Coefficient
MAPT	0.1652	0.5051	0.3333
SNCA	0.1652	0.5051	0.3333
KIF5A	0.3654	0.3915	0.00
NDUFB9	0.4578	0.6519	0.0173
MT-ND1	0.5062	0.6636	0.0159

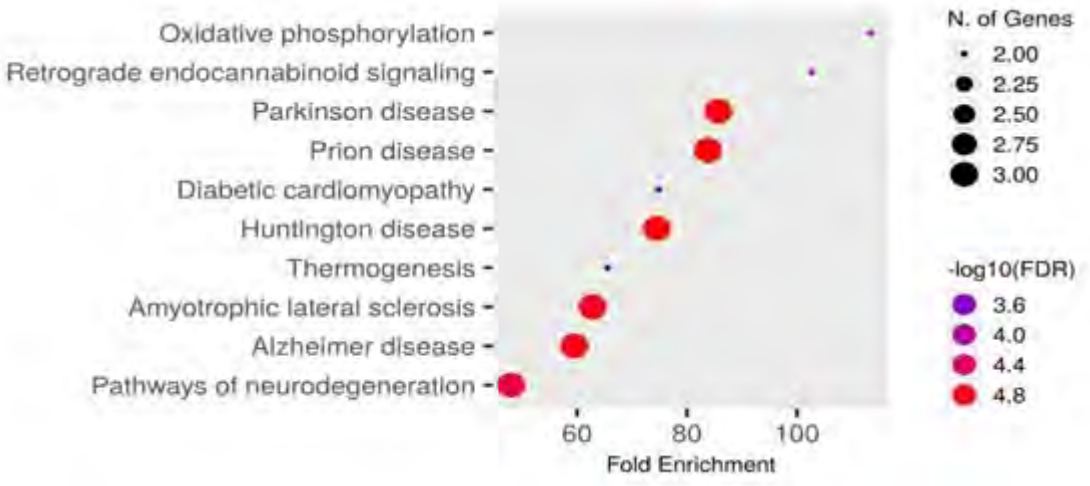

Fig. 3 Pathway enrichment analysis of the common genes.

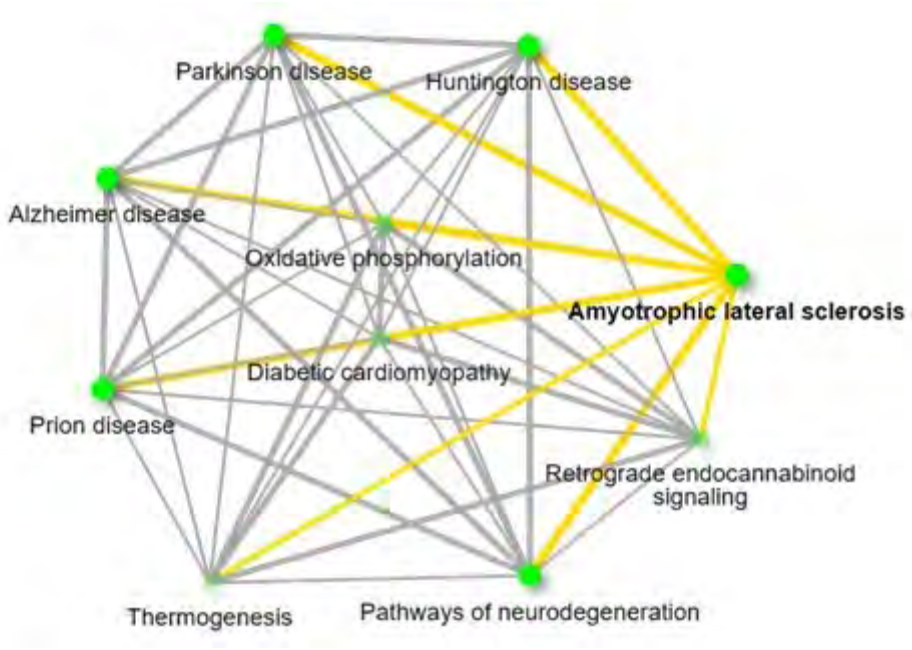

Fig. 4 Pathway network.

4 Discussion

Understanding the genetic overlap between different neurological disorders is crucial for elucidating shared molecular mechanisms and potential therapeutic targets. In the study conducted, a comprehensive analysis of genes implicated in AD, PD, and EP revealed interesting commonalities and intersections, focusing on the interconnectedness of these disorders at a genetic level. According to scientific observations AD, PD, and EP have distinctly different clinical and pathological characteristics. Still, they share many common mechanisms including α-synuclein protein, tau protein, oxidative stress, and mitochondrial dysfunction (Xie, 2014). Numerous studies have suggested that these neurological disorders can be prevented or treated by blocking the tau and α-synuclein proteins, as well as by building up and activating the antioxidant system, reducing oxidative stress, and altering mitochondrial activities (Van Bulck, 2019). However, this mechanical approach has only preventive actions that failed to prove complete curative treatment. Thus, there is continuous need to develop curative therapies for these neurological disorders. Hence, in the current study, in order to explorenew treatment alternatives, we focused on network pharmacology tool to identify shared common genes and pathway linkages and thereby identify new target for drug development for these neurological disorders viz, AD, PD, and EP.

Network analysis results has identified KIF5A, MT-ND1, and NDUFB9 as the common genes between AD, PD, and EP. This finding suggests the existence of shared genetic pathways or biological processes underlying these seemingly distinct neurological conditions. KIF5A, Kinesin family member 5A protein is a microtubule-dependent protein that controls basic neuronal processes including survival, morphogenesis, and plasticity (Miki, 2005). KIF5A gene encodes a motor protein involved in intracellular transport, including the transport of mitochondria and mitochondrial components, assembly and maintenance of mitochondrial respiratory chain complexes, which are crucial for cellular energy production. Dysfunction of these complexes has been implicated in various neurological disorders, suggesting a potential link between KIF5A and neurological conditions (Campbell, 2014). Further KIF5Ais essential for the trafficking of GABAA receptors to the cell surface and synaptic sites. Aberrant KIF5A function may lead to defects in the transport

of GABAA receptors, affecting their localization and availability at synapses. This disruption in GABAA receptors trafficking could contribute to altered inhibitory neurotransmission and neuronal dysfunction (Lorenz, 2018). In neurons, KIF5A is involved in transporting various cargoes, including mitochondria, synaptic vesicles, and protein complexes, along axons to maintain neuronal function and viability. The KIF5A gene can lead to defects in axonal transport and neuronal degeneration, like the pathology observed in PD (Kreft, 2014). Along with that, there is a reported inverse correlation between Amyloid-beta precursor protein (APP) expression and soluble hyperphosphorylated tau levels & KIF5A (Hares, 2021).

The network analysis results in current study revealed a total of 23, 18, and 9 associated proteins for KIF5A in AD, PD, and EP, respectively. These associated proteins encompass diverse functional categories, including synaptic transmission, cytoskeletal organization, and vesicle trafficking, providing convincing evidence for the involvement of the KIF5A gene in several pathways associated with these neurological disorders.

Similarly, MT-ND1, a subunit of mitochondrial complex I, which is essential for cellular respiration and ATP production Complex-I. Some studies reported deficiency of Complex I and Complex II (succinate dehydrogenase, SDH) in SN neurons from PD patients (Grunewald, 2016). The Parkinson's disease pathway shows increased Ca+2 overload due to mitochondrial dysfunction and increased ROS from complex I deficiency, which in turn causes ATP depletion (Yusnita, 2010). The brain is highly energy-demanding, and ATP produced by mitochondria is essential for neuronal function. Mitochondrial dysfunction, including impaired complex I activity, has been implicated in the accumulation and toxicity of beta-amyloid peptides, further exacerbating neuronal damage in AD (Cavalcante, 2022). Similarly, mitochondria are involved in regulating calcium homeostasis and neuronal excitability. Dysfunction of complex I, including MT-ND1, may disrupt these processes, potentially leading to hyperexcitability and seizure activity (Zsurka, 2010).

The results of current study revealed a total of 92, 93, and 7 associated proteins for MT-ND1 in AD, PD, and EP, respectively. These associated proteins focus on mitochondrial function, neuroprotection, and synaptic transmission. Along with this, the expression of MT-ND1 in all the top 10 pathways analyzed by pathway enrichment analysis supports the role of MT-ND1 in neurological disorders.

NDUFB9 another common gene belongs to NADH: ubiquinone oxidoreductase (complex I) family protein. The ubiquinone and cytochrome c together constitute the mitochondrial respiratory chain that encodes an iron-sulfur protein (IP) component of complex I. NDUFB9 is the protagonist in maintaining the assembly of complex I. Any cleavage of NDUFB9 that results in altered ROS levels, reduced ATP production, and impaired mitochondrial function contributes to neuronal damage (Gowthami, 2019). Some emerging evidence suggests that APOE4 may also interact with components of the mitochondrial respiratory chain, including NDUFB9, to modulate mitochondrial function and contribute to AD pathogenesis. APOE4 is a well-established genetic risk factor for AD. Both APOE4 and NDUFB9 alterations have been associated with increased oxidative stress in AD. APOE4 may promote oxidative stress through various mechanisms, including impairing antioxidant defenses and mitochondrial function. NDUFB9 alterations may further enhance oxidative stress, leading to neurodegeneration (Mahley, 2023). The analysis in present study identified a total of 96, 101, and 4 associated proteins for NDUFB9 in AD, PD, and EP, respectively. These associated proteins emphasize on mitochondrial function, energy metabolism, and oxidative stress response pathways. The present study highlights the involvement of NDUFB9 in all top 10 KEGG pathways based on the pathway enrichment analysis.

The network analysis parameters, including betweenness centrality, closeness centrality, and clustering coefficient, provided valuable insights into the functional importance and connectivity of common genes implicated in Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy (EP). Betweenness centrality

measures the extent to which a gene lies on the shortest paths between other genes in the network. Higher values indicate greater influence or importance of the gene in mediating interactions between other genes (Koschutzki, 2008a; Yang and Zhang, 2022). In this analysis, MT-ND1 exhibited the highest betweenness centrality, followed by NDUFB9 and KIF5A, which indicates its pivotal position in mediating communication and signal transmission between different genes or protein complexes. This finding underscores the significance of mitochondrial dysfunction and energy metabolism dysregulation in the pathogenesis of AD, PD, and EP. Closeness centrality measures how close a gene is to all other genes in the network. Genes with higher closeness centrality values are more efficiently connected to other genes and exert greater influence over the network dynamics (Koschutzki, 2008b). In this analysis, MT-ND1 and NDUFB9 exhibited higher closeness centrality compared to other genes, suggesting their proximity to other genes and efficient communication within the network. These two genes may serve as central nodes for coordinating cellular processes associated with neurodegeneration and synaptic dysfunction in AD, PD, and EP. The clustering coefficient measures the degree to which genes in the network tend to cluster together. A clustering coefficient close to 1 indicates a highly clustered network, whereas a value close to 0 suggests a more dispersed network structure (Zhong, 2021). In this analysis, all genes exhibited low clustering coefficients, indicating dispersed connectivity and minimal clustering of genes into functional modules or complexes. This finding implies a modular and distributed organization of molecular interactions underlying neurodegenerative processes in these disorders.

Pathway enrichment analysis identified the top 10 pathways associated with common genes in AD, PD, and EP, providing insights into the biological processes and molecular pathways dysregulated in these disorders. The identified pathways, including amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and pathways of neurodegeneration, underscore the shared pathophysiological mechanisms and molecular pathways underlying AD, PD, and EP. These pathways encompass various biological processes, including protein misfolding, oxidative stress, mitochondrial dysfunction, and synaptic transmission abnormalities, which are hallmark features of neurological disorders. Targeting key pathways associated with common genes may offer novel therapeutic avenues for the development of disease-modifying treatments and neuroprotective interventions.

By employing network analysis tools such as Cytoscape and Network Analyzer, the interplay between common genes and associated target proteins was elucidated, shedding light on the molecular interactions underlying processes. NDUFB9 and MT-ND1 were found to interact directly with each other, suggesting a direct functional relationship between these common genes. Conversely, KIF5A did not exhibit direct interactions with NDUFB9 or MT-ND1, indicating potential indirect mechanisms of interaction. Despite the lack of direct interactions, all three common genes (KIF5A, MT-ND1, and NDUFB9) were observed to interact indirectly through two common proteins, SNCA and/or MAPT. SNCA is a synuclein alpha neuronal protein responsible for synaptic activation and neurotransmission. While MAPT is the microtubule-associated protein tau plays a crucial role in microtubule stabilization. This indirect connectivity highlights the presence of shared pathways or regulatory mechanisms involving these common genes in these neurological disorders.
According to the KEGG pathway database, Cinpanemab, Prasinezumab, and Minzasolmin are the drugs linked with SNCA protein reported as anti-Parkinson’s agents. We discovered that SNCA is connected to every common gene involved in AD, PD, and EP. Therefore, the current study recommends attempting to repurpose these drugs for the treatment of epilepsy and Alzheimer's disease. Similarly, in the case of MAPT protein also, Bepranemab, Flortaucipir, Gosuranemab, Hydromethylthionine, Hydromethylthioninemesylate, Posdinemab, Semorinemab, Tilavonemab, and Zagotenemab are reported as drugs in Alzheimer’s disease treatment which may be repurposed for Parkinson’s disease and epilepsy. Since these two proteins were

linked to the discovered common genes, repurposing these drugs would be an appealing potential for these three neurological disorders.

5 Conclusion

Neurological illnesses such as epilepsy (EP), Parkinson's disease (PD), and Alzheimer's disease (AD) provide serious obstacles to global health, particularly in aging populations. Even though these illnesses have different clinical manifestations, there is growing evidence that they share molecular underpinnings. In order to find shared genes and pathways linked to epilepsy (EP), Parkinson's disease (PD), and Alzheimer's disease (AD), this study used network pharmacology and genomic analyses. Important genes that have been linked with Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy (EP) include KIF5A, NDUFB9, and MT-ND1, which were observed to interact indirectly through two common proteins, SNCA and/or MAPT. Therefore, possible drug repurposing options targeting SNCA and MAPT may present new therapeutic options for the treatment of AD, PD, and EP, based on complex gene-protein interactions. The results of the current study advanced our knowledge of neurological conditions and opened new avenues for innovative treatment approaches.

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