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RESEARCH ARTICLE
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COMPARATIVE ANALYSIS OF ALZHEIMER'S DISEASES: IDENTIFICATION OF HUBS TO FORECAST DIAGNOSIS THROUGH COMPREHENSIVE DATA MINING

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Abstract
Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders, often sharing overlapping molecular mechanisms. This study seeks to identify common differentially expressed genes (DEGs) and hub genes between AD and PD using gene expression data from publicly available datasets. We analyzed the GSE122063 dataset for AD and GSE20141 dataset for PD, both sourced from the Gene Expression Omnibus (GEO). After preprocessing, normalization, and differential expression analysis, common DEGs were identified and a protein-protein interaction (PPI) network was constructed using the STRING database. Hub genes were determined using the cytoHubba plugin in Cytoscape based on various centrality measures. The key findings of this study reveal shared pathways involving cellular stress response, neuroinflammation, and synaptic dysfunction. Significant hub genes, including APP, SNCA, MAPT, and TP53, may represent novel therapeutic targets for both AD and PD. These results contribute to understanding the shared molecular landscape between these neurodegenerative disorders and open new avenues for the development of therapeutic interventions.

Keywords: Neurodegeneration, Transcriptomics, Hub genes, Alzheimer’s, Parkinson’s, Bioinformatics

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are two of the most prominent neurodegenerative diseases, together affecting millions of people globally [1, 2]. Both diseases primarily affect the elderly, posing substantial public health challenges as global life expectancy rises [1]. AD is the leading cause of dementia, marked by progressive cognitive decline, memory loss, and impaired reasoning, eventually leading to complete loss of independence [3]. At the cellular level, AD is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein, which contribute to synaptic dysfunction and widespread neuronal death [4].

In contrast, PD primarily manifests with motor dysfunction, including symptoms such as bradykinesia (slowness of movement), muscle rigidity, resting tremors, and postural instability [5]. Non-motor symptoms like cognitive decline and mood disorders also become apparent in the later stages. The hallmark pathological features of PD include the loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, intracellular inclusions mainly composed of alpha-synuclein aggregates [6]. Both diseases are progressive and currently lack curative treatments, which necessitates continued research into their underlying mechanisms to identify potential therapeutic targets.

Despite the distinct clinical presentations of AD and PD, emerging evidence suggests that these two neurodegenerative diseases share several fundamental pathological processes. Key overlapping mechanisms include:

1. Protein Aggregation: Both AD and PD are marked by the accumulation of misfolded proteins (amyloid-beta and tau in AD; alpha-synuclein in PD), which impair cellular homeostasis and contribute to neuronal death [7].
2. Mitochondrial Dysfunction: Mitochondria, the powerhouse of the cell, exhibit diminished function in both diseases, leading to increased oxidative stress and energy deficits that further exacerbate neurodegeneration [8].
3. Neuroinflammation: Chronic activation of microglia, the brain’s resident immune cells, leads to a sustained inflammatory response that is toxic to neurons in both AD and PD [9].
4. Oxidative Stress: Imbalance between the production of reactive oxygen species (ROS) and the cell’s antioxidant defenses is another common feature, resulting in damage to cellular components, including proteins, lipids, and DNA [10].

Given these shared mechanisms, studying the molecular underpinnings common to both AD and PD offers the potential to uncover novel biomarkers and therapeutic targets that could be beneficial in treating both disorders.

Methodology

Dataset Selection

We sourced publicly available transcriptomic data from the GEO database (https://www.ncbi.nlm.nih.gov/geo/), focusing on datasets derived from post-mortem brain tissue samples of AD and PD patients, along with healthy controls.

1. AD Dataset: GSE122063 was chosen, which contains microarray data from the prefrontal cortex of AD patients and age-matched healthy controls.
2. PD Dataset: GSE20141 was selected, providing microarray data from the substantia nigra of PD patients and controls.

Data Preprocessing

We employed the following preprocessing steps to ensure consistency and robustness in our analysis:

1. Normalization: Both datasets were normalized using the Robust Multi-Array Average (RMA) method to reduce technical variability and standardize expression values across samples.

2. Batch Effect Removal: Since the datasets may originate from different platforms or technical conditions, we corrected for potential batch effects using the "ComBat" function from the sva R package.
3. Log Transformation: Expression values were log2 transformed where necessary to stabilize variance across the data.
4. Gene Mapping: Probes from both datasets were mapped to corresponding gene symbols using the appropriate platform annotation files. Probes mapping to multiple genes or without annotations were excluded.
5. Filtering: Low-expression genes were removed to focus on the most biologically relevant signals, ensuring reliable identification of DEGs.

Differential Expression Analysis

We utilized the limma (Linear Models for Microarray Analysis) package to identify DEGs between diseased and control samples in both datasets.

1. Statistical Testing: A moderated t-test was applied to assess differential gene expression. Genes with an adjusted p-value < 0.05 and an absolute log fold change > 1 were considered significant.
2. False Discovery Rate (FDR) Correction: To account for multiple testing, we employed the Benjamini-Hochberg procedure to adjust p-values and minimize the risk of false positives.
3. Cross-disease DEG Comparison: DEGs identified from the AD dataset (GSE122063) were compared with those from the PD dataset (GSE20141) to identify overlapping DEGs between the two diseases.

Functional Enrichment Analysis

To better understand the biological roles of the common DEGs, we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis using the ClusterProfiler R package. Pathways and processes with a p-value < 0.05 were considered significantly enriched.

PPI Network Construction and Hub Gene Identification

We constructed a protein-protein interaction (PPI) network of the common DEGs using the STRING database, setting a confidence score cutoff of 0.7 to ensure high-quality interactions.

1. Network Visualization: The PPI network was visualized using Cytoscape, where nodes represented proteins and edges denoted protein interactions.
2. Hub Gene Identification: Hub genes were identified using the cytoHubba plugin in Cytoscape based on degree centrality and other network metrics (closeness, betweenness). Genes with the highest centrality scores were considered hub genes due to their critical roles in network connectivity.

Statistical Analysis

All statistical analyses were conducted in R, and results were visualized using ggplot2.

Results

Identification of Common DEGs

A total of 845 DEGs were identified in the AD dataset (GSE122063), and 678 DEGs were found in the PD dataset (GSE20141) (Figure 1A). Comparative analysis revealed 54 overlapping DEGs between the two datasets (Figure 1A). A PPI network was constructed using the 54 common DEGs, revealing a highly interconnected network of proteins involved in neuroinflammation, protein degradation, and synaptic plasticity. Key hub genes identified include: APP, SNCA, MAPT, and TP53 (Figure 1B).

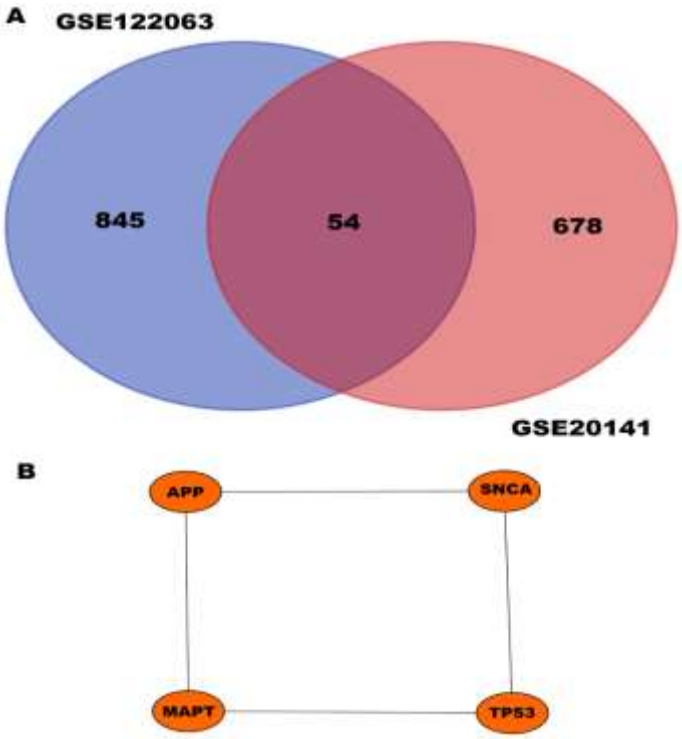

Figure 1: Identification of DEGs and Hub genes in AD and PD datasets. (A) Number of DEGs. (B) Hub genes.

Pathway Enrichment Analysis

The enrichment analysis of hub genes reveals several key pathways that are significantly overrepresented, indicating potential roles in diverse biological processes and diseases. Notably, thyroid cancer emerged as the most enriched pathway, with the highest fold enrichment, suggesting that the hub genes may be heavily involved in oncogenic processes linked to thyroid malignancies. Following closely is the ferroptosis pathway, which has gained increasing attention for its role in regulated cell death through iron-dependent lipid peroxidation (Figure 2 and 3). This process has implications not only in cancer but also in neurodegenerative diseases, hinting at a broader relevance of the hub genes in cell death mechanisms. Other cancer-related pathways, such as those involving endometrial, pancreatic, colorectal, and prostate cancers, are also highly enriched, pointing to a strong connection between the hub genes and various types of cancer (Figure 2 and 3).

Furthermore, pathways like mitophagy (animal) and longevity-regulating pathways suggest that mitochondrial health and cellular longevity mechanisms may be centrally involved in the pathogenesis driven by these hub genes (Figure 2 and 3). This aligns with the well-documented role of mitochondrial dysfunction in both Alzheimer's disease and Parkinson's disease, which also appear on the list with significant enrichment. The presence of p53 signaling, a critical pathway in tumor suppression and DNA repair, reinforces the role of these hub genes in cellular stress responses, which could be a shared mechanism between cancer and neurodegenerative conditions (Figure 2 and 3). The inclusion of the pathways of neurodegeneration-multiple diseases, specifically enriched in both Alzheimer's and Parkinson's disease, highlights that the hub genes are not only involved in oncogenesis but also play central roles in neurodegenerative disease pathways, particularly through mechanisms like protein aggregation, oxidative stress, and neuroinflammation. These findings suggest that the identified hub genes may be key players in the intersection of cancer biology and neurodegeneration, offering potential insights for targeted therapies in both fields.

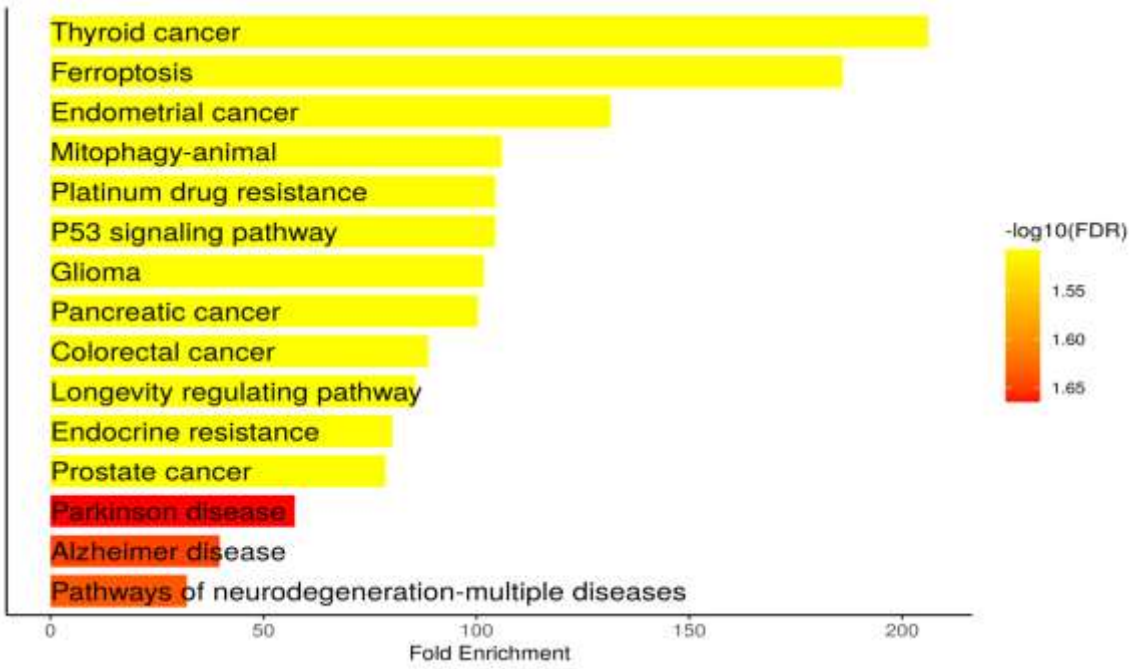

Figure 2: KEGG pathways associated with Hub genes.

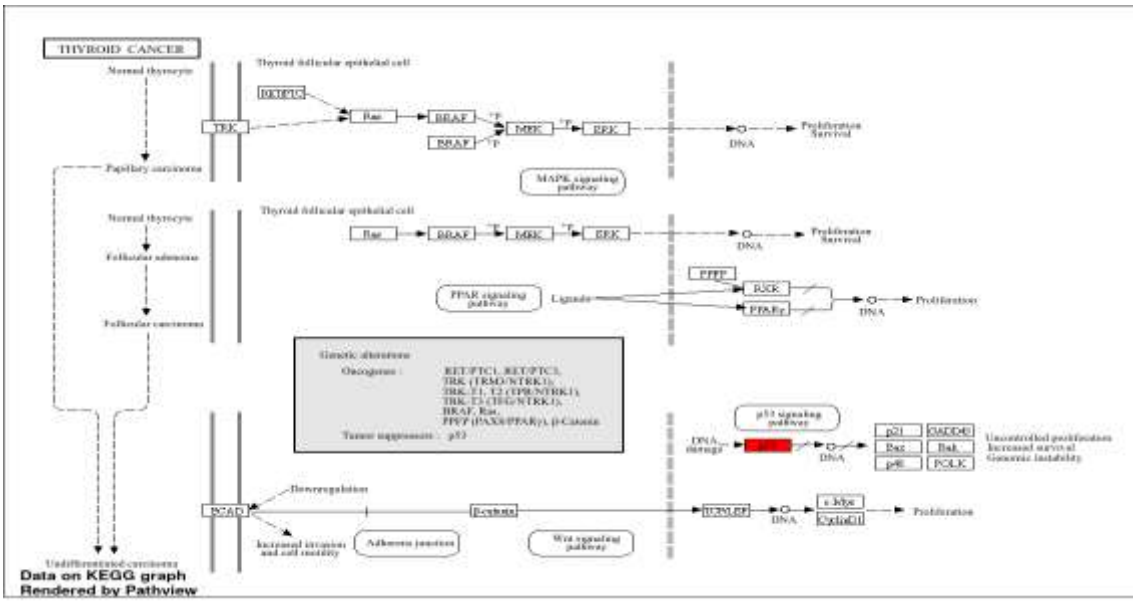

Figure 3: Most relevent pathway to hub genes.

Discussion

In this study, we performed a comparative analysis of differentially expressed genes (DEGs) between Alzheimer's disease (AD) and Parkinson's disease (PD), two of the most prevalent neurodegenerative disorders. By identifying shared DEGs and constructing protein-protein interaction (PPI) networks, we pinpointed several key hub genes that may play pivotal roles in the pathogenesis of both diseases. These hub genes, due to their high connectivity in the PPI network, are likely to be master regulators of essential cellular processes affected in both AD and PD.

Hub Gene 1: APP (Amyloid Precursor Protein)

Among the identified hub genes, APP stands out as a critical player in the pathogenesis of both AD and PD. APP is well known for its role in AD, where its abnormal cleavage leads to the accumulation of amyloid-beta (Aβ) peptides, forming extracellular plaques that are toxic to neurons [11]. However,

recent studies have highlighted a broader role for APP in other neurodegenerative diseases, including PD. Evidence suggests that amyloid-beta may not only contribute to cognitive decline in AD but also to the dopaminergic neuron loss seen in PD [12]. APP's function extends to synaptic formation and plasticity, meaning that its dysregulation can affect neuronal communication in both diseases. The presence of APP as a shared hub gene underscores the convergence of protein aggregation pathways in AD and PD, making it a promising therapeutic target. Drugs targeting the processing of APP, such as beta- or gamma-secretase inhibitors, have been investigated in AD and may have potential therapeutic value in PD as well.

Hub Gene 2: SNCA (Alpha-synuclein)

SNCA, which encodes alpha-synuclein, is a hallmark gene in PD but also appears as a hub gene in our analysis of AD. The aggregation of alpha-synuclein in Lewy bodies is a primary pathological feature of PD, contributing to the degeneration of dopaminergic neurons [13]. However, accumulating evidence suggests that alpha-synuclein may also play a role in AD pathology. Alpha-synuclein has been detected in amyloid plaques and tau tangles, implicating it in the protein aggregation processes common to both diseases [14]. Additionally, it has been suggested that alpha-synuclein may exacerbate amyloid-beta toxicity in AD, further driving neurodegeneration [14]. The identification of SNCA as a hub gene indicates that targeting alpha-synuclein aggregation and its interactions with other misfolded proteins could be a therapeutic strategy relevant to both diseases. This also highlights the shared mechanisms of protein aggregation and neurotoxicity in AD and PD.

Hub Gene 3: MAPT (Microtubule-Associated Protein Tau)

MAPT, encoding the tau protein, is another hub gene identified in both AD and PD. While tau pathology is a hallmark of AD, where hyperphosphorylated tau forms neurofibrillary tangles, tau abnormalities have also been linked to PD, particularly in tauopathies like frontotemporal dementia and parkinsonism [15]. The role of tau in microtubule stabilization is critical for maintaining neuronal structure and function, and its dysregulation can lead to cytoskeletal breakdown, axonal transport deficits, and synaptic dysfunction [16]. MAPT's central role in both diseases highlights the importance of tau as a shared molecular target. Tau-directed therapies, including tau aggregation inhibitors and anti-tau immunotherapies, are currently under investigation in AD and may also hold potential for PD treatment.

Hub Gene 4: TP53 (Tumor Protein P53)

TP53, a well-known tumor suppressor gene, emerged as a hub gene with significant roles in both AD and PD [17]. TP53 is involved in regulating cellular stress responses, apoptosis, and DNA repair mechanisms [17]. In the context of neurodegenerative diseases, TP53 activation has been linked to neuronal apoptosis and oxidative stress, which are prominent features in both AD and PD. Overactivation of TP53 can lead to excessive cell death in the brain, contributing to neurodegeneration. Interestingly, oxidative stress and mitochondrial dysfunction, both of which are upstream activators of TP53, are common pathogenic processes in AD and PD [18, 19]. Targeting the TP53 pathway to prevent excessive neuronal apoptosis could be a viable therapeutic strategy in both diseases, especially considering the role of oxidative stress in their progression.

The identification of these shared hub genes, including APP, SNCA, MAPT, TP53, highlights common molecular pathways underlying the pathogenesis of AD and PD, despite their differing clinical presentations. These hub genes provide critical insights into the shared mechanisms of protein aggregation, mitochondrial dysfunction, neuroinflammation, and oxidative stress, offering potential biomarkers and therapeutic targets for both diseases. Future research should focus on the development of multitarget therapeutic strategies that address these overlapping pathways. By targeting common pathological processes, we may be able to develop more effective treatments that not only alleviate symptoms but also slow the progression of neurodegeneration in both AD and PD.

Conclusion

This study identified a set of common DEGs and hub genes shared between AD and PD, revealing significant overlaps in the molecular pathways involved in both neurodegenerative disorders. Key hub genes, including APP, SNCA, MAPT, TP53, were highlighted as potential targets for therapeutic intervention due to their central roles in neuronal survival, plasticity, and stress response. The functional enrichment of pathways related to neuroinflammation, synaptic dysfunction, and mitochondrial health underscores the shared molecular mechanisms between AD and PD. Our findings suggest that therapeutic strategies targeting these common pathways could potentially benefit patients suffering from both diseases. Further experimental validation of these hub genes and pathways is essential to confirm their roles in neurodegeneration. Additionally, expanding this analysis to larger, multi-omic datasets could provide a more comprehensive understanding of the molecular overlap between AD and PD, potentially leading to the discovery of novel biomarkers and treatments.

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None

Conflict of interest

None

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