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RESEARCH ARTICLE
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IDENTIFICATION OF COMMON DIFFERENTIALLY EXPRESSED GENES (DEGS) AND HUB GENES IN NEURODEGENERATIVE DISEASES: A COMPARATIVE STUDY OF ALZHEIMER'S AND PARKINSON'S USING EXTENSIVE DATA MINING

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Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most prevalent neurodegenerative disorders, sharing overlapping pathophysiological mechanisms. This study aims to identify common differentially expressed genes (DEGs) and hub genes between AD and PD using publicly available datasets from the Gene Expression Omnibus (GEO). We utilized datasets GSE5281 for AD and GSE49036 for PD to conduct a comparative analysis. After normalization and differential expression analysis, common DEGs were identified, followed by protein-protein interaction (PPI) network construction using the STRING database. Hub genes were extracted through Cytoscape's cytoHubba plugin based on centrality measures. The results highlight shared molecular pathways and key hub genes, including MAPT, SNCA, APP, and KLHL2, which may serve as potential therapeutic targets for both diseases. These findings contribute to a better understanding of the common molecular landscape in neurodegenerative diseases and open avenues for novel treatment strategies.

Keyword: Neurodegenerative Diseases, Hub genes, Biomarker, Treatment

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders worldwide, significantly impacting aging populations [1, 2]. Both diseases are characterized by progressive neuronal degeneration, which leads to cognitive and motor impairments [3]. Despite their clinical differences—AD primarily affects memory and cognition, while PD predominantly impacts motor function—the two diseases share overlapping pathophysiological mechanisms [4]. These shared mechanisms include protein misfolding, oxidative stress, mitochondrial dysfunction, and neuroinflammation [5]. As a result, there has been growing interest in uncovering common molecular pathways and biomarkers that contribute to both AD and PD, which may ultimately aid in the development of more effective therapeutic strategies.

Gene expression profiling has emerged as a powerful tool for identifying molecular alterations in neurodegenerative diseases [6]. Differentially expressed genes (DEGs) in particular have been instrumental in shedding light on the genes that are upregulated or downregulated in disease states compared to healthy controls [7]. The identification of common DEGs between AD and PD could reveal shared molecular underpinnings that drive neurodegeneration in both conditions [8]. Moreover, hub genes—those that play central roles in molecular networks—are often critical for disease progression and may serve as potential therapeutic targets.

In this study, we aim to identify common DEGs and hub genes between AD and PD using publicly available transcriptomic datasets from the Gene Expression Omnibus (GEO). We focused on datasets GSE5281 for AD and GSE49036 for PD, which contain gene expression profiles from brain tissues of patients with AD and PD, respectively. Through a comparative analysis of these datasets, we sought to uncover overlapping molecular signatures that could provide insights into shared pathological processes and identify key hub genes that may be crucial for the development and progression of both diseases.

By utilizing bioinformatics approaches to analyze these datasets, we aim to contribute to the growing body of knowledge surrounding the molecular connections between AD and PD. Identifying common DEGs and hub genes not only enhances our understanding of the shared biology between these diseases but also holds promise for the discovery of novel biomarkers and therapeutic targets that could be relevant across multiple neurodegenerative disorders.

Methodology

Dataset Selection

Publicly available gene expression datasets were sourced from the GEO database (https://www.ncbi.nlm.nih.gov/geo/), which provides curated high-throughput gene expression data. The datasets used for AD and PD were selected based on several criteria, including sample size, availability of data from brain tissues, and the inclusion of both diseased and control samples.

1. AD Dataset: The dataset GSE5281 was selected for AD. This dataset contains gene expression data derived from post-mortem brain tissue of AD patients and non-demented control subjects.

2. PD Dataset: The dataset GSE49036 was selected for PD. It includes transcriptomic data from various regions of the brain from individuals diagnosed with PD and healthy controls.

Data Preprocessing

Data preprocessing steps were performed to ensure the quality and reliability of the analysis.

1. Normalization: Both datasets were normalized to reduce technical variability and adjust for differences in data distribution between samples. This was done using the Robust Multi-Array Average (RMA) method in the R environment.

2. Removal of Batch Effects: If datasets were generated from different platforms or contained batch effects due to technical variations, we used the "ComBat" function from the R package sva to correct for these effects.

3. Log Transformation: Where necessary, log2 transformation of the gene expression values was applied to normalize the distribution of the data.
4. Probe Annotation: For datasets with probes instead of gene symbols, probe IDs were mapped to corresponding gene symbols using the appropriate platform annotation files. Probes with multiple mappings were excluded to avoid ambiguity.
5. Filtering: Genes with low expression values across all samples or those with no significant variability were filtered out to focus on the most biologically relevant genes.

Identification of Differentially Expressed Genes (DEGs)
To identify DEGs between AD and PD patients compared to their respective controls, we performed statistical analysis using the limma (Linear Models for Microarray Analysis) package in R.
1. Statistical Testing: Differential expression was determined using the moderated t-test, which is part of the limma package. Genes with an adjusted p-value < 0.05 and a log fold change (logFC) > 1 or < -1 were considered significant DEGs.
2. Benjamini-Hochberg Correction: To control for the false discovery rate (FDR) due to multiple testing, we applied the Benjamini-Hochberg method. The adjusted p-values were used to identify significantly differentially expressed genes.
3. Comparative Analysis: The DEGs identified from the AD dataset (GSE5281) were compared with those identified from the PD dataset (GSE49036) to find common DEGs that are differentially expressed in both diseases.
Functional Enrichment Analysis
To gain insights into the biological processes and pathways associated with the identified DEGs, we performed Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Pathways with a p-value < 0.05 were considered significantly enriched.

Protein-Protein Interaction (PPI) Network Construction
To explore the interactions between the common DEGs, a PPI network was constructed using data from the STRING database (https://string-db.org/), which provides known and predicted protein-protein interactions.
1. Network Construction: The common DEGs were input into the STRING database, and a PPI network was generated with a confidence score cutoff of 0.7 (high confidence). Only interactions supported by experimental evidence or strong predictions were included.
2. Network Visualization: The resulting PPI network was visualized using Cytoscape software (v3.8.2). Nodes represented proteins (encoded by the DEGs), and edges represented interactions between these proteins.
3. Hub Gene Identification: Hub genes were identified based on the number of connections (degree centrality) within the PPI network. Genes with the highest degree of centrality were considered hub genes, as they likely play key roles in the underlying molecular mechanisms of AD and PD.

Statistical Analysis
All statistical analyses, including the identification of DEGs and functional enrichment analysis, were conducted in the R environment. Statistical significance was defined as an adjusted p-value < 0.05 unless otherwise stated. Descriptive statistics, including mean, standard deviation, and fold change, were calculated to summarize the expression profiles of key genes.

Ethical Considerations
As this study utilized publicly available datasets, no ethical approval was required. All datasets used were anonymized and freely accessible for research purposes from the GEO repository.

Results

We used two datasets to identify DEGs and hub genes in AD and PD. Venn diagram in Figure 1A shows the overlap of DEGs between the two datasets, GSE5281 (AD) and GSE49036 (PD). The GSE5281 dataset contains 796 unique DEGs, while the GSE49036 dataset has 716 unique DEGs. The overlap between these two datasets reveals 41 common DEGs, which are hypothesized to play roles in the pathophysiology shared by both AD and PD. These 41 genes represent potential candidates for further investigation into the common molecular mechanisms underlying these neurodegenerative diseases. Figure 1B-C illustrates the PPI network of the 41 common DEGs identified between AD and PD. The nodes in the network represent the proteins encoded by the DEGs, and the edges represent interactions between these proteins. The highly interconnected nodes suggest potential hub genes that may have a critical role in both AD and PD. Genes like APP (Amyloid Precursor Protein), MAPT (Microtubule-Associated Protein Tau), KLHL2, and SNCA (Alpha-Synuclein) are likely key

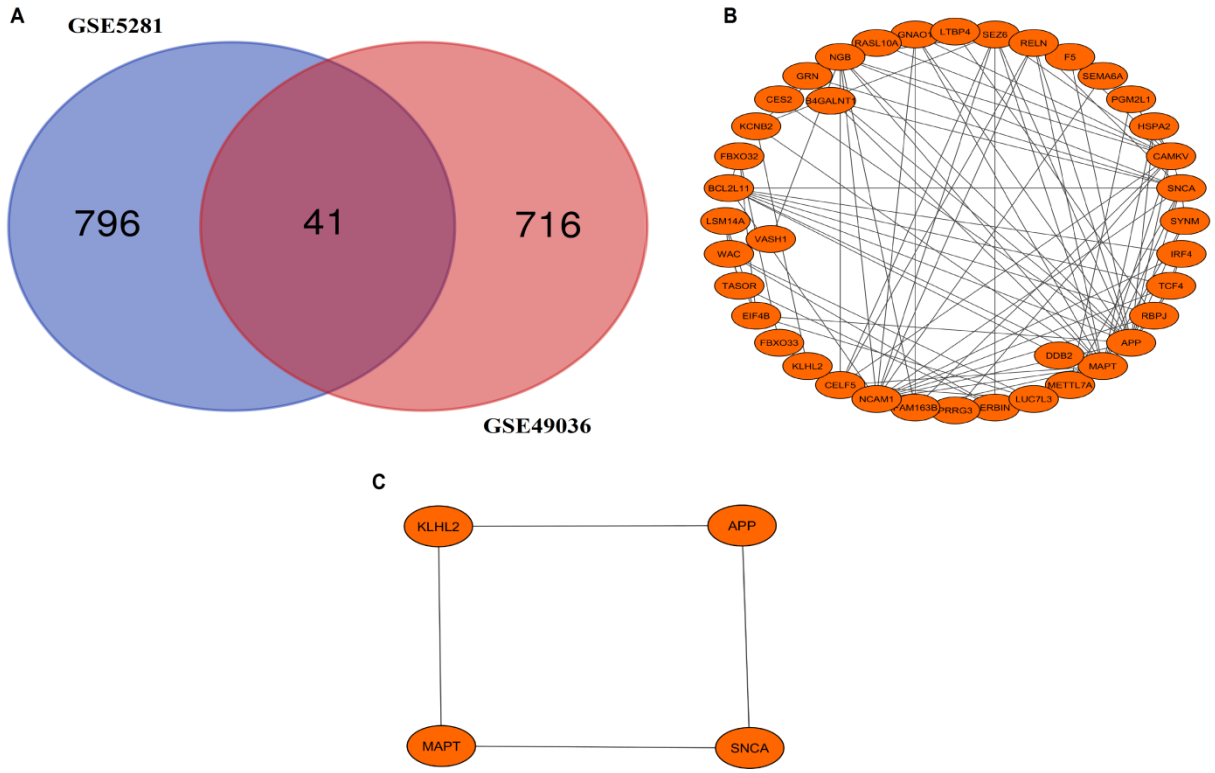

Figure 1: Identification of DEGs and hub genes in AD and PD. (A) Venn diagram. (B) PPI network of common DEGs. (C) PPI network of hub genes.

Pathway enrichment analysis

Figures 2 and 3 illustrate pathway enrichment analysis of hub genes identified in the study, with the pathways listed on the y-axis and fold enrichment values on the x-axis. Among the pathways, the colorectal cancer pathway shows the highest fold enrichment, indicating a strong association of these hub genes with colorectal cancer. This suggests that certain molecular mechanisms linked to these genes might be shared between neurodegenerative diseases, such as AD and PD, and colorectal cancer. This connection may reflect underlying oncogenic or tumor-suppressive processes common to both cancer and neurodegenerative pathology. Additionally, the serotonergic synapse pathway is significantly enriched, highlighting the involvement of these genes in neurotransmitter signaling, particularly serotonin. This is particularly relevant as disruptions in serotonergic signaling are commonly associated with neurodegenerative conditions, including AD and PD, where they contribute to cognitive deficits and mood disorders. Furthermore, the toxoplasmosis pathway's enrichment suggests a potential link between immune responses to infections, such as Toxoplasma

gondii, and the progression of neurodegenerative diseases. Inflammatory responses triggered by such infections may exacerbate AD or PD pathology. The FoxO signaling pathway, which is enriched in these hub genes, is crucial for regulating cellular processes such as oxidative stress response, apoptosis, and longevity. This pathway's involvement underscores the significance of oxidative stress and programmed cell death in neurodegenerative diseases, where cellular damage and neuronal loss are central features. The enrichment of the Epstein-Barr virus (EBV) infection pathway further points to the role of viral infections and immune responses in the shared mechanisms underlying AD and PD. EBV infection has been previously associated with neurological disorders, suggesting that viral reactivation or immune dysregulation may contribute to neurodegeneration.

Other pathways, such as the estrogen signaling pathway, spinocerebellar ataxia, and PI3K-Akt signaling pathway, are also significantly enriched. The estrogen signaling pathway is particularly interesting due to its role in neuroprotection and its implications in both AD and PD, where estrogen may modulate neuroinflammation and neurodegeneration. Spinocerebellar ataxia highlights the role of these hub genes in motor function and cerebellar degeneration, which can overlap with motor symptoms observed in PD. Finally, the PI3K-Akt signaling pathway is known for its critical role in cell survival and proliferation, suggesting that disruptions in this pathway could be central to the neurodegenerative processes observed in both AD and PD. Together, these findings reveal the complex interplay of genetic, immune, and cellular survival mechanisms underlying neurodegeneration and emphasize the relevance of these hub genes in various biological pathways related to both neurodegenerative diseases and cancer.

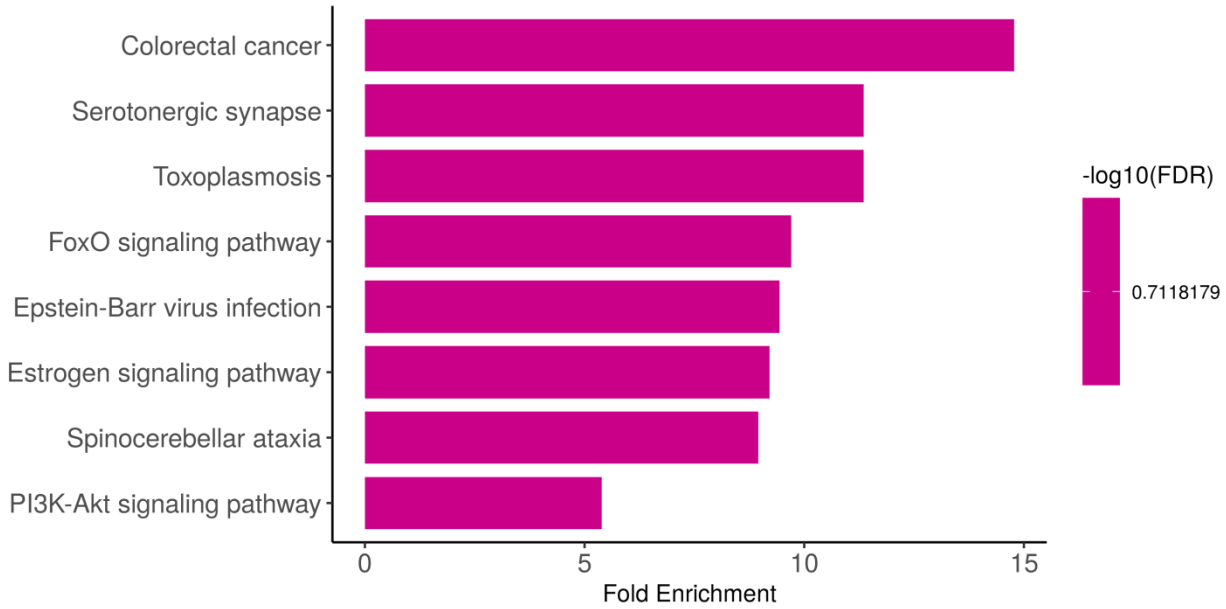

Figure 2: Pathway enrichment analysis of hub genes. P-values < 0.05.

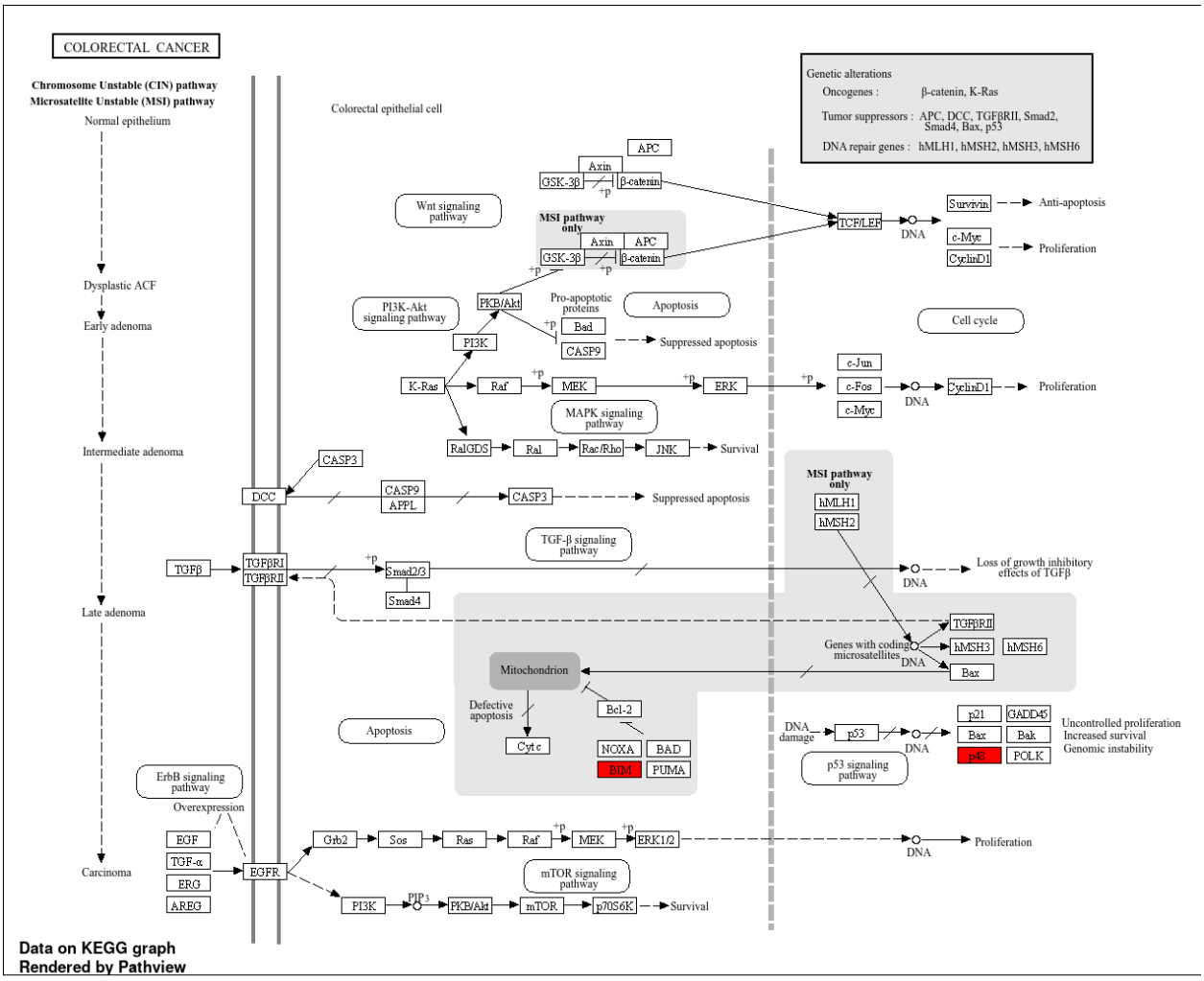

Figure 3: Top most pathway of hub genes. P-values < 0.05.

Discussion

Alzheimer's disease (AD) and Parkinson's disease (PD) are two of the most common neurodegenerative disorders, characterized by progressive neuronal loss, cognitive decline, and motor dysfunction [9]. Although the two diseases exhibit distinct clinical manifestations—AD primarily affecting memory and cognitive function, while PD predominantly affects motor control—they share several pathophysiological features, including protein misfolding, mitochondrial dysfunction, oxidative stress, and neuroinflammation [10]. Both conditions are associated with abnormal protein aggregates: beta-amyloid plaques and tau tangles in AD, and Lewy bodies containing alpha-synuclein in PD [11]. Recent advances in transcriptomics have revealed molecular overlaps between these diseases, suggesting shared genetic and signaling pathways [11, 12]. In this study, we utilized two publicly available datasets from the Gene Expression Omnibus (GEO)—GSE5281 for AD and GSE49036 for PD—to identify common differentially expressed genes (DEGs) and hub genes, aiming to provide insight into the shared molecular mechanisms underlying these neurodegenerative diseases.

We began by identifying DEGs in each dataset, which revealed 796 unique DEGs in the AD dataset (GSE5281) and 716 in the PD dataset (GSE49036). A Venn diagram showed an overlap of 41 DEGs between the two datasets (Figure 1A), indicating common gene expression changes in both diseases. These shared DEGs may represent molecular players involved in both AD and PD pathophysiology. Proteins encoded by these 41 common DEGs were further analyzed using protein-protein interaction (PPI) network analysis, revealing several highly interconnected hub genes, including APP (Amyloid Precursor Protein), MAPT (Microtubule-Associated Protein Tau), SNCA (Alpha-Synuclein), and

KLHL2 (Kelch-like Protein 2) (Figure 1B-C). These hub genes are well-documented in the literature for their role in AD and PD, strengthening their significance as key molecular players in both diseases. The identification of APP and MAPT as hub genes is consistent with their established roles in AD. APP **is** cleaved to produce beta-amyloid, the primary component of amyloid plaques, while MAPT encodes tau protein, whose hyperphosphorylation leads to the formation of neurofibrillary tangles [13]. Both plaques and tangles are pathological hallmarks of AD, contributing to neuronal damage and cognitive decline. Similarly, the identification of SNCA, encoding alpha-synuclein, as a hub gene is unsurprising given its central role in PD pathogenesis [14]. Alpha-synuclein aggregates form Lewy bodies, the main pathological hallmark of PD, which contribute to neuronal death, particularly in the substantia nigra, resulting in the motor symptoms characteristic of PD [15].

Interestingly, KLHL2, a lesser-known gene in the context of neurodegeneration, emerged as a potential hub gene in this study. While its role in AD and PD is not as well characterized as APP, MAPT, or SNCA, KLHL2 has been implicated in regulating protein degradation and may contribute to the clearance of misfolded proteins, a process that is defective in both AD and PD. This finding opens avenues for future research into the role of KLHL2 in neurodegeneration and its potential as a therapeutic target.

To further explore the biological significance of these hub genes, we performed pathway enrichment analysis, which revealed several enriched pathways. The colorectal cancer pathway showed the highest fold enrichment, suggesting an intriguing link between neurodegenerative diseases and cancer. Previous studies have reported inverse relationships between cancer and neurodegenerative diseases, where patients with AD or PD are often at a lower risk of developing cancer, and vice versa [16, 17]. This may reflect opposing cellular mechanisms: while cancer is characterized by uncontrolled cell proliferation, neurodegenerative diseases involve excessive cell death. However, the shared molecular mechanisms identified in our study may indicate common genetic vulnerabilities, such as dysregulation of cell cycle pathways or DNA repair mechanisms, which could predispose individuals to either disease under different conditions.

The significant enrichment of the serotonergic synapse pathway underscores the importance of neurotransmitter signaling in both AD and PD. Disruptions in serotonergic signaling are known to contribute to both cognitive deficits and mood disorders commonly observed in AD and PD patients. Previous studies have shown reduced serotonin levels in the brains of individuals with AD and PD, and serotonergic neurons are among the earliest affected in PD [18]. The involvement of the serotonergic pathway in our study highlights its role in the non-motor symptoms of PD, such as depression and anxiety, as well as cognitive decline in AD.

The enrichment of the toxoplasmosis pathway in our analysis points to a possible link between infections and neurodegeneration. Toxoplasma gondii, the causative agent of toxoplasmosis, has been suggested to play a role in triggering neuroinflammation, which is a key feature of both AD and PD. This finding aligns with the growing body of evidence that infections may exacerbate or even trigger neurodegenerative processes by activating the immune system [19]. Similarly, the Epstein-Barr virus (EBV) infection pathway was enriched, further suggesting that viral infections may be involved in the shared pathology of AD and PD. Previous studies have implicated EBV in multiple sclerosis and other neurological disorders, and our findings support the hypothesis that viral infections could contribute to neurodegenerative disease progression by inducing chronic inflammation and immune responses [20].

Another enriched pathway of interest is the FoxO signaling pathway, which regulates oxidative stress response, apoptosis, and cellular longevity. The FoxO transcription factors are critical regulators of cellular homeostasis, and their dysregulation has been linked to both aging and neurodegeneration [21]. Oxidative stress is a well-established feature of both AD and PD, contributing to neuronal damage and death. Our finding that the FoxO pathway is enriched in the shared hub genes supports its central role in the neurodegenerative process, particularly in regulating the response to oxidative damage.

The enrichment of the estrogen signaling pathway is also noteworthy, given the neuroprotective effects of estrogen. Estrogen has been shown to modulate neuroinflammation and promote synaptic plasticity, and its decline during aging has been linked to increased risk of both AD and PD [21]. The involvement of this pathway in our analysis suggests that estrogen signaling may play a protective role in both diseases, potentially offering therapeutic avenues for hormone replacement therapy or estrogen receptor modulators.

Lastly, the PI3K-Akt signaling pathway, known for its role in promoting cell survival and inhibiting apoptosis, was enriched in the hub genes. This pathway is crucial for maintaining neuronal survival, and its dysregulation has been implicated in both AD and PD [22]. Inhibition of PI3K-Akt signaling leads to increased apoptosis and neurodegeneration, making it a potential therapeutic target for preventing neuronal loss in these diseases [23].

Our results are consistent with previous studies that have identified shared molecular mechanisms between AD and PD, particularly in relation to protein aggregation, oxidative stress, and neuroinflammation. However, the identification of pathways such as colorectal cancer and toxoplasmosis in our analysis offers new insights into potential links between neurodegeneration, cancer, and infections that have not been extensively explored in the past. Previous studies have primarily focused on well-known pathways like amyloid processing and synaptic dysfunction, but our analysis broadens the scope to include immune responses and cell survival mechanisms. Additionally, our study highlights the role of lesser-known genes like KLHL2, which have not been as widely studied in the context of AD and PD, offering new potential targets for research and therapeutic intervention.

Conclusion

In conclusion, this study provides a comprehensive analysis of common DEGs and hub genes between AD and PD, revealing shared molecular mechanisms that may contribute to the pathogenesis of both diseases. Our findings underscore the complex interplay between genetic, immune, and signaling pathways in neurodegeneration, offering new insights into potential therapeutic targets for these devastating disorders.

Conflict of interest

None

Acknowledgement

None

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