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BIOCHEMICAL PATHWAYS IN NEURODEGENERATIVE DISORDERS: A MOLECULAR PERSPECTIVE

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ABSTRACT

Neurodegenerative disorders involve progressive neuronal dysfunction driven by complex molecular changes. Alzheimer's disease and Parkinson's disease differ clinically and anatomically, yet both are associated with mitochondrial impairment, lipid dysregulation, inflammatory signaling, and cellular stress. This study aimed to identify disease-specific and shared biochemical pathways in Alzheimer's disease and Parkinson's disease using comparative transcriptomic analysis. Publicly available human microarray datasets from Alzheimer's disease hippocampal tissue and Parkinson's disease substantia nigra neurons were analyzed. Expression data were log2 transformed, quality assessed, and examined using principal component analysis. Differentially expressed genes were identified using Welch's t-test with false discovery rate correction. Shared genes were annotated and evaluated through Gene Ontology biological process and KEGG pathway enrichment analyses. Alzheimer's disease showed predominant downregulation of genes associated with neuronal signalling and metabolic regulation, whereas Parkinson's disease displayed stronger transcriptomic activation. Comparative analysis identified 57 shared differentially expressed probes, including genes linked to mitochondrial transport, lipid handling, phospholipid signaling, and cellular stress regulation. Enrichment analysis highlighted cholesterol homeostasis, fatty acid oxidation, mitochondrial protein import, PPAR signaling, HIF-1 signaling, cAMP signaling, autophagy, and glycerophospholipid metabolism as common pathway-level disturbances. The findings indicate that Alzheimer's disease and Parkinson's disease share convergent molecular mechanisms involving mitochondrial dysfunction, lipid metabolism, inflammatory signaling, and cellular stress responses. These pathway-level alterations may provide useful targets for future biomarker and therapeutic investigations.

KEYWORDS: Alzheimer's disease, Parkinson's disease, transcriptomics, mitochondrial dysfunction, lipid metabolism

1. INTRODUCTION

Neurodegenerative diseases are a major health challenge worldwide, because they develop over time, are becoming more common and are untreatable. These disorders involve a slow progressive deterioration of neurons, which is associated with a loss of neural integrity and, eventually, cognitive dysfunction, behavioral abnormalities and motor impairment. Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders and together contribute a significant part of disability associated with old age. Although the main clinical features differ between the two disorders, there are complex changes at the molecular level linked to mitochondrial dysfunction, oxidative stress, neuroinflammation, protein homeostasis dysfunction, and metabolic regulation in both disorders (Lamptey et al., 2022). The main hallmarks of Alzheimer's disease are progressive cognitive decline, loss of synapses, extracellular deposition of amyloid-β (Aβ) and intraneuronal formation of neurofibrillary tangles (NFT) of hyperphosphorylated tau protein. Strong association with disease has been seen with neuronal loss in the hippocampus and cerebral cortex, which leads to impaired memory and executive dysfunction (Scheltens et al., 2021). Neuropathological studies have shown that, throughout the course of Alzheimer's disease, there are widespread changes in neuronal signalling, inflammatory activation and disruption of cellular metabolism, all of which lead to progressive neurodegeneration (DeTure & Dickson, 2019). Parkinson's disease, in contrast, is mainly characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies that contain α-synuclein. The clinical manifestations consist of tremor, rigidity, bradykinesia, and postural instability, but more recently, non-motor symptoms are being recognized as important

parts of the disease (Bloem et al., 2021). In recent mechanistic studies, the roles of mitochondrial dysfunction, proteostasis and inflammatory signaling in Parkinsonian neurodegeneration have been highlighted (Morris et al., 2024).

In the past few years, there have been major advances in the technology and application of transcriptomic (genetic) methods that have greatly facilitated the understanding of changes at the molecular level in neurodegenerative disease. Dysregulated pathways that have been identified by gene expression profiling include those for neuronal survival, immune activation, synaptic signaling, and energy metabolism. There is growing evidence that several neurodegenerative diseases are not completely independent pathological processes, but have common molecular abnormalities. The large-scale transcriptomic meta-analyses have shown a strong consistency in the presence of inflammation of the nervous system, mitochondrial dysfunction, and proteostasis deficits in the pathogenesis of several different neurodegenerative diseases (Noori et al., 2021). These results have led the focus to pathway-level dysregulation as opposed to disease-specific biomarkers.

Neuroinflammation has recently become an important factor in the neurodegenerative progression. Activated microglia and astrocytes persist in their inflammatory response, leading to chronic inflammatory signaling, excessive levels of oxidative stress and injury of neurons in the affected brain areas. Recent research has shown that inflammatory responses and metabolic dysfunction are closely intertwined, with inflammatory processes exacerbating neurodegenerative pathology, along with mitochondrial dysfunction (Cohen et al., 2024). There is also growing interest in the role of disturbances of lipid metabolism on membrane stability, on the transmission of the synapse and on the regulation of cellular energy. Experimental evidence has demonstrated that defective mitochondrial fatty acid degradation can directly lead to inflammatory activation and neurodegeneration, thus reinforcing the connection between metabolic imbalance and neuronal damage (Mi et al., 2023).

A number of transcriptomic studies have been conducted on the separate molecular changes related to AD and PD. Meta-analytical studies in AD have identified dysregulated genes that are involved in immune signaling, which are also involved in the synaptic function and metabolic pathways (Su et al., 2019). Transcriptomic and proteomic studies have also shown alterations in functional molecular networks in neuronal communication and intracellular transport in the brains of AD (Canchi et al., 2019). Transcriptomic profiling studies in PD have identified gene changes specific to each stage of the disease related to mitochondrial activity, oxidative phosphorylation, and inflammatory signalling pathways (Cappelletti et al., 2023). Molecular studies have also shown that during the neurodegenerative process, energy homeostasis pathways such as AMPK/SIRT1/PGC-1α signaling play a role in regulating mitochondrial function and the survival of neurons (Chen et al., 2025).

While there has been significant work done to describe the individual neurodegenerative diseases, few studies have focused on common transcriptomic changes between AD and PD in an integrated analysis. Most disease-specific studies have been focused on the pathology of the diseases, and limited effort has been spent on uncovering common biochemical and molecular pathways that could underlie a generalized neurodegenerative pathway. While there is currently a large amount of evidence that points to this, there is still a lack of transcriptomic overlap that has been fully characterized between AD and PD, with there being some overlapping features of mitochondrial dysfunction, lipid regulation, inflammatory signaling, and proteostasis (Sanghai & Tranmer, 2023). Comparative bioinformatics analysis can thus be useful to find common molecular signatures and biological processes that could be therapeutic targets for multiple neurodegenerative diseases.

Thus, the current study was aimed at exploring biochemical and molecular pathways involved in AD and PD by comparative transcriptomic analysis of human microarray data. The genes that were differentially expressed in both disorders were first identified separately for each disorder, after which a gene analysis was done to find the common genes, and functional enrichment analysis was performed to identify the significant biological processes and signaling pathways. Specific focus was given to molecular mechanisms for the mitochondrial, lipid, inflammatory and cellular stress control. The intent of the study was to get a bigger picture of the common molecular architecture of neurodegenerative diseases and find out what pathways might be involved in common neurodegenerative progression through the integrated approach.

2. METHODOLOGY

2.1 Research Design

In this study, a comparative transcriptomic bioinformatics approach was used to explore common molecular mechanisms between AD and PD. Differential expression analysis of publicly available human microarray datasets from post-mortem brain tissues identified the up-regulated and down-regulated genes, common molecular signatures, as well as the enriched biological pathways related to neurodegeneration. Data was preprocessed, normalized, subjected to differential gene expression analysis, shared gene identification and functional enrichment analysis.

2.2 Data Source

Blalock et al. (2004) examined post-mortem human brain tissue samples for AD-associated changes in the transcription of genes in the early stage of the disease, and the AD dataset was gathered from that study. There were 22 AD samples and 9 controls analyzed with the Affymetrix Human Genome U133A Array platform. The PD dataset was acquired from the study that was conducted by Zheng et al. (2010), in which they investigated genome-wide expression changes in laser-dissected substantia nigra neurons from PD patients and neurologically healthy controls. Ten PD samples and 8 controls were analyzed with the Affymetrix Human Genome U133 Plus 2.0 Array platform.

2.3 Data Preprocessing and Normalization

Data matrices of gene expression and the associated metadata were imported for pre-processing and analysis. Sample labels were associated with expression profiles to define disease and control groups for each data set. To reduce the

technical variability and ensure that the distribution of the expression intensity values is consistent across samples, the values were Log2 transformed. Boxplots and principal component analysis (PCA) were used to evaluate the dataset quality and efficiency of normalization before carrying out statistical analysis downstream.

2.4 Differential Gene Expression Analysis

Independent differential expression analysis was done for the AD and PD datasets. To determine log2 fold change values for each gene, mean expression values for the disease and control groups were analyzed. Welch's t-test was used to assess statistical significance, and the false discovery rate was used via the Benjamini–Hochberg method to correct for multiple testing. Genes with P-values < 0.05 were considered statistically significant.

2.5 Shared Gene Identification and Functional Enrichment Analysis

Comparative analysis of the significant transcripts of both datasets was performed to identify shared DEGs between AD and PD. Probe identifiers were annotated to corresponding gene symbols and gene descriptions for biological interpretation. Functional enrichment analysis (FEA) was then conducted to determine if there were any biological processes or signaling pathways significantly associated with them. Gene Ontology biological process analysis and Kyoto Encyclopedia of Genes and Genomes pathway analysis were performed to assess the molecular functions involved in the neurodegenerative process, such as inflammatory signaling, cellular stress responses, mitochondrial activity and lipid metabolism.

3. RESULTS

3.1 Transcriptomic Variation and Sample Clustering

To assess the difference in transcriptomic variability between disease and control samples in both neurodegenerative datasets, principal component analysis (PCA) was performed. The PCA distribution of samples from the hippocampus of the AD data set is illustrated in Fig. 1A. Significant, but diverse, transcriptional changes are associated with Alzheimer's pathology, as evidenced by the moderate separation between the disease and control groups along the principal components. Biological heterogeneity of hippocampal neurodegeneration was observed since several AD samples showed overlap with controls. The clustering pattern obtained by PCA for the PD data is presented in Figure 1B. When compared to AD, PD samples showed a higher segregation from control substantia nigra samples, indicative of greater transcriptomic remodeling in dopaminergic neuronal populations. The wider spread of PD samples also suggested a substantial molecular variation with the progression of the disease.

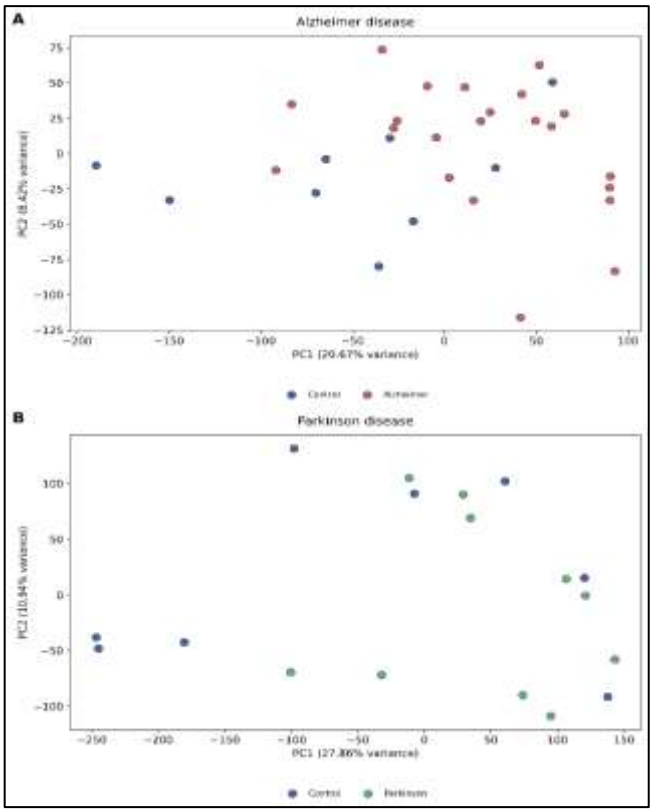

Figure 1. Principal component analysis of transcriptomic profiles in neurodegenerative disorders. (A) PCA clustering of hippocampal samples from AD and control groups. (B) PCA clustering of substantia nigra samples from PD and control groups.

3.2 Differential Gene Expression Analysis

Much transcriptional variation was revealed in both neurodegenerative diseases by differential expression analysis. The volcano plot was created from the AD data set, as shown in Figure 2A. Most of the genes that showed large fold changes

were negatively regulated, and indicated general downregulation of transcripts in the hippocampus. A number of genes, including the following ones that are related to neuronal signaling and metabolic regulation, were significantly downregulated: *OPRM1, NFATC4, GRIN2C,* and *CES1*. Conversely, very few genes, such as *UBE4B*, were found to be significantly up-regulated. The most prominently dysregulated genes that were found in the AD samples are listed in Table 1. As can be seen in the table, some of the most highly altered genes were involved in neuronal communication, phospholipid metabolism, transcription regulation and intracellular signaling pathways.

Table 1. Top differentially expressed genes identified in AD hippocampal samples.

Gene Symbol	Gene Name	Log2 Fold Change	P-value	Expression Status
PTTG3P	Pituitary tumour-transforming 3 pseudogene	-1.783	4.874E-06	Downregulated
OPRM1	Opioid receptor mu 1	-1.982	6.514E-06	Downregulated
UBE4B	Ubiquitination factor E4B	1.746	1.931E-05	Upregulated
NFATC4	Nuclear factor of activated T cells 4	-1.521	2.840E-05	Downregulated
ZNF710	Zinc finger protein 710	-1.259	1.423E-04	Downregulated
CTTN	Cortactin	-1.075	1.800E-04	Downregulated
GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C	-1.074	2.130E-04	Downregulated
PLA2G5	Phospholipase A2 group V	-1.327	2.324E-04	Downregulated
HNRNPM	Heterogeneous nuclear ribonucleoprotein M	-1.138	2.370E-04	Downregulated
CES1	Carboxylesterase 1	-1.645	2.722E-04	Downregulated

The volcano plot is created using the PD dataset and shown in Figure 2B. Compared to AD, PD samples showed a wider spectrum of significantly dysregulated transcripts with a higher number of strongly upregulated genes. *INSL3, THAP3, SNTB2, MIR7-3HG* and *LINC01588* showed significant upregulation while *INTS14* and *SH3GL3* were significantly downregulated.

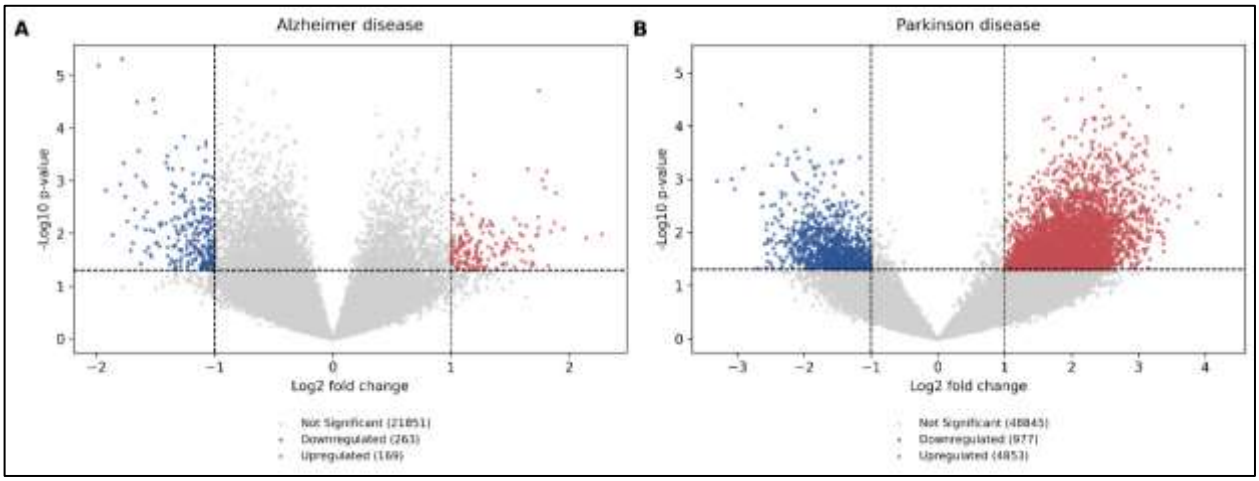

Figure 2. Volcano plot representation of differential gene expression profiles in neurodegenerative disorders. (A) Differentially expressed genes identified in AD samples relative to controls. (B) Differentially expressed genes identified in PD samples relative to controls.

The more important PD-related genes are listed in Table 2. These genes were mainly related to RNA-associated processes, non-coding regulatory activity, transcriptional regulation, and neuronal signaling.

Table 2. Top differentially expressed genes identified in PD substantia nigra samples.

Gene Symbol	Gene Name	Log2 Fold Change	P-value	Expression Status
INSL3	Insulin-like 3	2.334	5.517E-06	Upregulated
THAP3	THAP domain containing 3	2.421	1.999E-05	Upregulated
SNTB2	Syntrophin beta 2	2.151	3.103E-05	Upregulated
INTS14	Integrator complex subunit 14	-2.943	3.925E-05	Downregulated
EGFLAM-AS2	EGFLAM antisense RNA 2	3.137	4.308E-05	Upregulated

SH3GL3	SH3 domain containing GRB2 like 3, endophilin A3	-1.836	5.073E-05	Downregulated
WDR35-DT	WDR35 divergent transcript	2.320	7.058E-05	Upregulated
MIR7-3HG	MIR7-3 host gene	2.351	7.077E-05	Upregulated
LINC01588	Long intergenic non-protein coding RNA 1588	2.496	7.347E-05	Upregulated
PIN1P1	Peptidylprolyl cis/trans isomerase pseudogene	2.343	7.581E-05	Upregulated

3.3 Hierarchical Clustering of Significant Genes

To assess expression patterns associated with disease, most significantly dysregulated genes from each data set were subjected to hierarchical clustering analysis. The heatmap from the AD data is displayed in Figure 3A. Several genes were found to be downregulated and clustered together among the disease samples, including genes involved in neuronal signaling, phospholipid metabolism and intracellular regulatory processes. However, while there was some overlap between disease and control groups, the heatmap revealed disease-related transcriptional suppression in several hippocampal samples. A heatmap is created from the PD data set, as shown in Figure 3B. The clustering separation of PD samples from controls was greater than that of AD samples from controls. Multiple transcripts were coordinately upregulated in disease samples, suggesting that the transcriptional remodeling was extensive in the substantia nigra neurons impacted by disease.

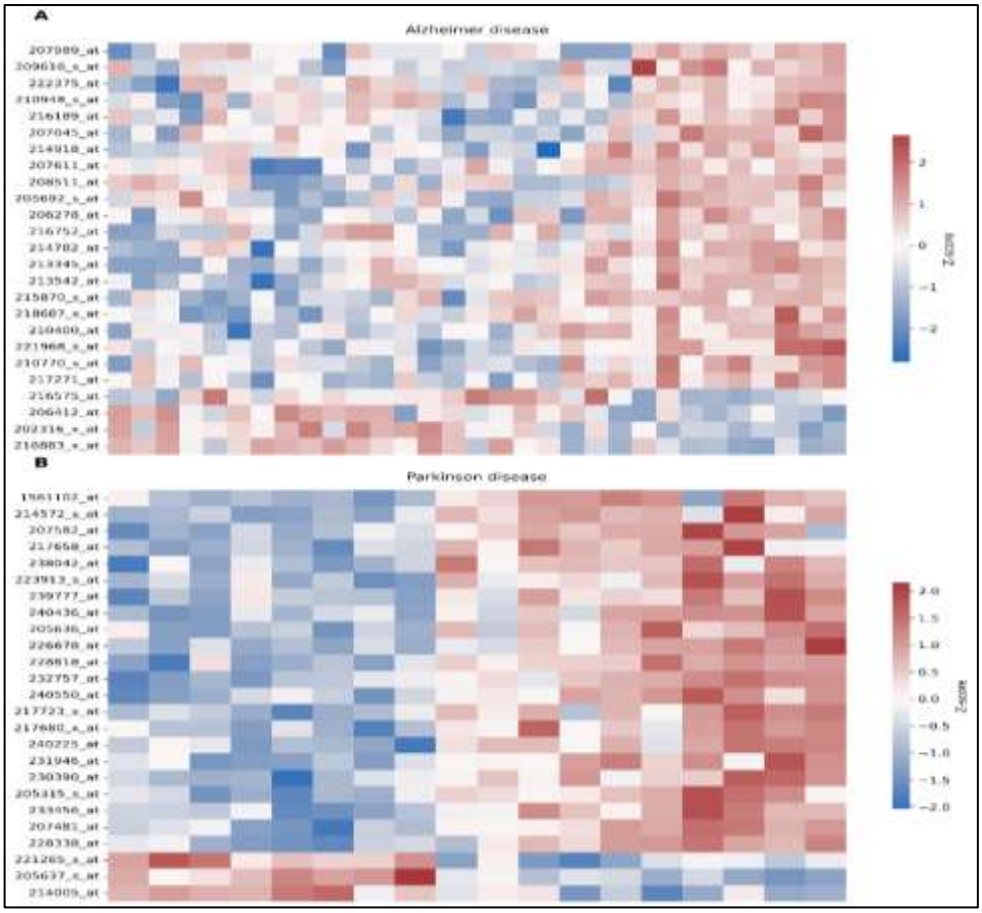

Figure 3. Heatmap analysis of top differentially expressed genes in neurodegenerative disorders. (A) Hierarchical clustering of significant genes in AD samples. (B) Hierarchical clustering of significant genes in PD samples.

3.4 Shared Molecular Signatures and Functional Enrichment Analysis

Comparative transcriptomic analysis revealed 57 common probes between the AD and PD datasets that were also found to be significantly differently expressed. Pathway enrichment of shared genes revealed that pathways related to mitochondrial transport, lipid metabolism, inflammatory signaling and cellular stress responses were enriched. The shared genes of representatives are listed in Table 3. Several genes are functionally related to mitochondrial homeostasis,

phospholipid metabolism, and regulation of intracellular stress, such as *TIMM23, PIK3R4, LCAT, FABP3*, and *DNAJB9*, pointing to convergent molecular mechanisms for the neurodegenerative progression.

Table 3. Representative shared genes identified across AD and PD datasets.

Gene Symbol	Gene Name
EBP	EBP cholestenol delta-isomerase
TIMM23B	Translocase of inner mitochondrial membrane 23B
TIMM23	Translocase of inner mitochondrial membrane 23
ITM2A	Integral membrane protein 2A
PIK3R4	Phosphoinositide-3-kinase regulatory subunit 4
ARHGDIA	Rho GDP dissociation inhibitor alpha
LCAT	Lecithin-cholesterol acyltransferase
DNAJB9	DnaJ heat shock protein family member B9
SRGN	Serglycin
FABP3	Fatty acid binding protein 3

The Gene Ontology biological process enrichment analysis of shared differentially expressed genes is shown in Figure 4A. Pathways in cholesterol homeostasis, fatty acid oxidation, reverse cholesterol transport and mitochondrial protein import were significantly enriched. The results indicate that there is a significant level of metabolic and mitochondrial dysfunction common to both AD and PD. The results of KEGG pathway enrichment analysis are shown in Figure 4B. Several pathways related to neurodegeneration were enriched in these shared genes, such as the PPAR signaling pathway, the HIF-1 signaling pathway, the cAMP signaling pathway, the autophagy pathway, and the glycerophospholipid metabolism pathway. As a whole, these enrichment profiles point to mitochondrial dysfunction, lipid regulation, metabolic stress signaling, and disturbed cellular homeostasis being core molecular characteristics shared by both neurodegenerative disorders.

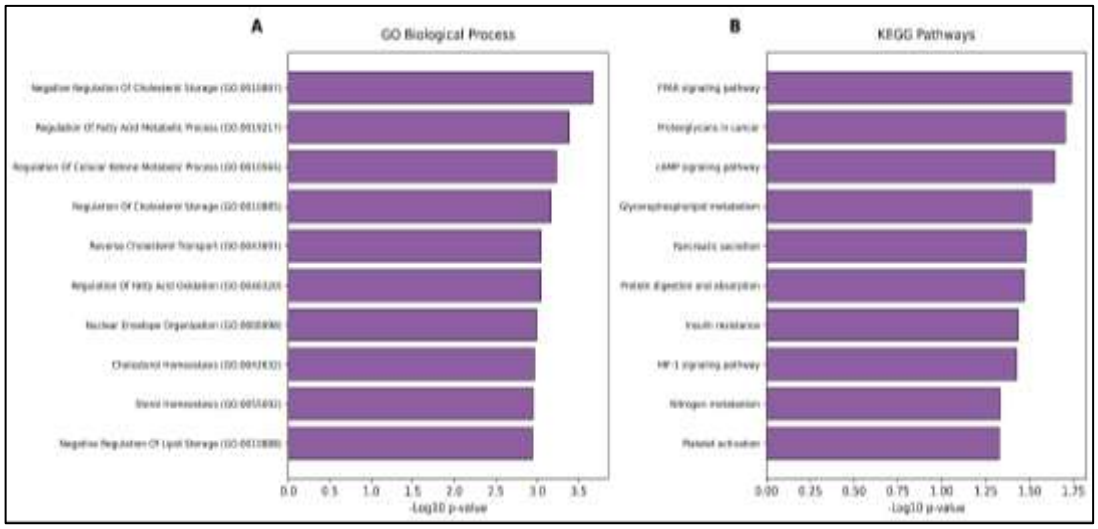

Figure 4. Functional enrichment analysis of shared differentially expressed genes. (A) Gene Ontology biological process enrichment analysis. (B) KEGG pathway enrichment analysis.

4. DISCUSSION

The comparison of the transcriptomic profiles showed that, although AD and PD affect different parts of the brain and clinical manifestations of the diseases, there is a shared molecular disturbance. Partial disease-control separation was observed using PCA in AD, and greater separation was observed in PD, indicating that the extent of transcriptional remodeling was greater in the substantia nigra dataset as compared to the hippocampal dataset. This trend was similar to that of the differential expression burden in PD, with a higher percentage of differential expressions being upregulated. The AD dataset had an overrepresentation of downregulated genes, such as genes involved in neuronal signaling, phospholipid metabolism, transcriptional regulation, and intracellular signaling. This indicates inhibition of neuronal communication and metabolic regulatory processes of the hippocampal tissue. We found that PD exhibited higher upregulation of disease-associated genes, reflecting increased transcriptional activity of disease genes in affected dopaminergic neurons associated with stress response, cellular remodeling, and regulatory RNA activity.

Both disorders had overlapping molecular signatures as revealed by the shared gene analysis. The genes *TIMM23, PIK3R4, LCAT, FABP3* and *DNAJB9* point to commonality in the areas of mitochondrial protein import, lipid handling, phosphoinositide signaling and cellular stress regulation. In addition, functional enrichment analysis was performed, and the main biological pathways included cholesterol homeostasis, fatty acid oxidation, reverse cholesterol transport, mitochondrial protein import, PPAR signaling, HIF-1 signaling, cAMP signaling, autophagy and glycerophospholipid metabolism. These results all suggest that neurodegenerative processes do not restrict themselves to just individual protein aggregation, but also include the synchronisation of metabolic, mitochondrial and inflammatory pathways.

The enrichment of metabolic and mitochondrial pathways in the AD dataset aligns with findings that insulin resistance and mitochondrial dysfunction are associated with neurodegeneration in Alzheimer's disease (Lanzillotta et al., 2026). The decreased expression of genes involved in neuronal signaling further supports the findings that amyloid-β affects neuronal communication and/or synaptic functioning in AD (Zhang et al., 2022). The inflammatory and mitochondrial signatures are also consistent with the observation of microglial mitochondrial dysfunction playing a significant role in the pathogenesis of AD (Li et al., 2022). The marked transcriptomic dysregulation observed in SN samples in PD is consistent with SN mitochondrial dysfunction as a hallmark of the disease and a therapeutic target (Henrich et al., 2023). The enrichment of oxidative stress and inflammatory pathways also agrees with evidence showing that dopamine oxidation products contribute to neuroinflammation and neuronal injury in PD (Chakrabarti & Bisaglia, 2023). Additionally, findings that neuronal PGC-1α is involved in regulating brain metabolism and vulnerability to aging further support the involvement of energy-related pathways, such as PPAR and HIF-1 signaling (Souder et al., 2025).

Enrichment of common lipid and cholesterol pathways is aligned with evidence that lipid metabolism of the neuroglia plays a role in the development of the brain, regulation of inflammation, and progression of neurodegenerative diseases (Yang et al., 2022). The overlap between AD and PD also aligns with the broader understanding that metabolic dysfunction is a shared underlying mechanism in the degeneration of the nervous system in various diseases (Maiese, 2023). The relevance of metabolic pathway disruption in neurodegeneration is further substantiated by recent evidence of systemic metabolic dysregulation found in RNA sequencing in AD (Villegas-Trujillo et al., 2026). Finally, transcriptomic results from spatial analyses of AD have also highlighted mitochondrial stress signaling and region-specific molecular vulnerability, which further corroborate the mitochondrial themes found in the current analysis (Navarro et al., 2020). PD transcriptomic models also showed changes in the regulation of dopaminergic genes and stress-induced molecular responses that align with the significant changes in expression observed in this study (Kim et al., 2025). The inflammatory component identified in the pathway analysis has also been reported in peripheral immune transcriptomic studies in PD, which also revealed inflammatory and oxidative stress signatures (Thome et al., 2025).

These results point towards pathway-level analysis providing a better understanding of the shared neurodegenerative mechanisms than single-gene interpretation alone. There is an overlap between lipid metabolism, mitochondrial import, autophagy, and inflammatory signaling pathways, and this suggests possible molecular hubs that can lead to disease in both AD and PD. Pathways that link energy regulation, adaptation to cellular stress and neuronal survival, like PPAR signaling and mitochondrial protein import, are particularly important for future therapeutic exploration. Results also confirm the utility of comparative transcriptomics in the discovery of cross-disease biomarkers. The commonalities in genes including *TIMM23, FABP3, LCAT* and *PIK3R4* could point the way for future research into common molecular vulnerabilities in neurodegenerative diseases.

There are some restrictions that must be taken into consideration. Microarray datasets with relatively small sample sizes were used. The results were also obtained by computational analysis and need to be validated experimentally. Future studies will require expanding RNA sequencing cohorts, cell type-specific distinction and protein level verification. Pairing transcriptomics with a combination of proteomics, metabolomics and clinical metadata would enhance interpretation and further determine whether the common pathways found here are indicators of common disease mechanisms or unique responses to neuronal injury in different regions.

5. CONCLUSION

Comparing the transcriptomes of AD and PD identified both disease-specific and common molecular changes. There was a trend toward decreased expression of genes associated with neuronal signaling and metabolic regulation in AD, and increased expression in the transcriptomes of PD in the substantia nigra. Common genes revealed convergent disruption of mitochondrial function, lipid metabolism, phospholipid regulation, autophagy and inflammatory signaling despite the tissue origins and the disease phenotypes. Functional enrichment analysis revealed that central pathways linked to both disorders are cholesterol homeostasis, fatty acid oxidation, mitochondrial protein import, PPAR signaling, HIF-1 signaling, cAMP signaling and glycerophospholipid metabolism. These results indicate that neurodegeneration is associated with a coordinated disruption of biochemical pathways, not just changes at the level of individual genes. Some of the genes shared between the diseases, including *TIMM23, FABP3, LCAT* and *PIK3R4*, may be molecular markers for future cross-disease studies. The study highlights the utility of comparative transcriptomics for identifying shared molecular mechanisms among neurodegenerative diseases and offers a roadmap of pathways for new biomarker identification and therapeutic investigation.

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