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A BIOINFORMATICS-BASED NETWORK STUDY TO UNDERSTAND GENES AND PATHWAYS INVOLVED IN PARKINSONISM

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Abstract:

Parkinsonism is a progressive neurodegenerative disorder characterized by dopaminergic neuron loss, mitochondrial dysfunction, protein aggregation, oxidative stress, and neuroinflammation. Current treatments are mainly symptomatic and do not prevent disease progression, highlighting the need to identify key molecular regulators. This study employed an integrated bioinformatics approach to analyse Parkinsonism-associated genes using DisGeNET, STRING, Network Analyst, KEGG, Reactome, Gene MANIA, GEO2R, DESeq2, and DGIdb. Hub genes identified included SNCA, LRRK2, PRKN, PINK1, and TNF. Differential expression analysis revealed upregulation of SNCA, LRRK2, TNF, and IL6 and downregulation of PRKN, PINK1, and TH. Enriched pathways were mainly related to dopaminergic signalling, mitochondrial quality control, apoptosis, and inflammatory responses. These findings provide mechanistic insights and highlight potential therapeutic targets in Parkinsonism.

Keywords: *Parkinsonism, Bioinformatics, Gene Network, Hub Genes, Pathway Analysis.*

Introduction

Parkinsonism is a progressive neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as bradykinesia, rigidity, tremor, and postural instability, along with non-motor complications (1,2). Parkinson's disease (PD), the most common form of parkinsonism, involves complex and interconnected molecular mechanisms including mitochondrial dysfunction, abnormal protein aggregation, synaptic dysregulation, oxidative stress, and neuroinflammation, which collectively contribute to progressive neuronal loss (3,4). Although current therapeutic strategies provide symptomatic relief, they do not prevent neuronal degeneration or halt disease progression, highlighting the need for deeper molecular-level understanding (2, 29).

Given the multifactorial nature of Parkinsonism, investigation of isolated genes or single pathways is insufficient to fully explain disease pathology. Systems biology and network-based approaches enable comprehensive analysis of disease-associated genes and their molecular interactions. Protein–protein interaction (PPI) network analysis facilitates identification of hub genes and central regulatory nodes, while functional enrichment and pathway analyses reveal dysregulated biological processes and signalling pathways involved in disease progression (14,22). Integration of transcriptomic datasets further strengthens these findings by validating disease-associated gene expression changes under pathological conditions (33, 34).

Therefore, the present study applies an integrated bioinformatics workflow combining disease gene mining, PPI network construction, hub gene identification, functional and pathway enrichment analysis, differential gene expression evaluation, and drug–gene interaction screening to systematically investigate the molecular basis of Parkinsonism. This systems-level strategy aims to identify key molecular regulators and prioritize potential biomarkers and therapeutic targets for future disease-modifying interventions.

Materials and Methods

1. Gene collection using DisGeNET

Parkinsonism-associated genes were retrieved from the DisGeNET database using the keyword "Parkinsonism". DisGeNET is a comprehensive platform that integrates gene–disease associations from curated repositories, genome-wide association studies, animal models, and scientific literature. Retrieved genes were ranked based on the DisGeNET association score, which reflects the strength and reliability of evidence supporting each gene–disease relationship (14). High-confidence genes were selected for further analysis. Duplicate entries were removed, and gene symbols were standardized according to official nomenclature guidelines. The curated gene set was subsequently used as the input for all downstream bioinformatics analyses.

2. Protein–protein interaction analysis using STRING

The curated gene list was uploaded into STRING, selecting Homo sapiens as the reference organism. Interactions with a confidence score of 0.4 or higher were considered... The resulting PPI network consisted of nodes (proteins) and edges (functional associations) (6, 11).

Gene Ontology (GO) Biological Process enrichment was performed within STRING. Statistical significance was evaluated using false discovery rate (FDR) correction, and terms with FDR < 0.05 were considered significantly enriched [6, 40]. The network was exported for topology analysis (11, 12).

3. Network analysis and hub gene identification, and enrichment using NetworkAnalyst

The STRING-derived PPI network was imported into NetworkAnalyst for topology analysis. Degree centrality and betweenness centrality were calculated to identify hub genes, defined as nodes ranking in the top percentile for these measures (11, 12).

Functional enrichment analysis was performed for Gene Ontology (GO) Biological Process and KEGG pathways using over-representation analysis. Statistical significance was determined using hyper geometric testing with FDR correction, and terms with FDR < 0.05 were considered significant (6, 40).

4. Gene–gene interaction network construction using GeneMANIA

The selected gene set was analysed using GeneMANIA, with Homo sapiens selected as the reference organism. Networks were generated based on co-expression, physical interactions, shared pathways, co-localization, and

protein domain similarity. Default weighting parameters were applied. Additional related genes predicted by the algorithm were recorded (25, 26).

5. KEGG Pathway Analysis

The Parkinsonism-associated gene set was analysed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) Mapper, with Homo sapiens selected as the reference organism. Genes were mapped to human disease and signaling pathways, and pathways with $p < 0.05$ were considered significantly enriched (17, 19).

6. Pathway Analysis using Reactome

Pathway enrichment was conducted using the Reactome Analyse Data tool with Homo sapiens selected (32). Over-representation analysis was performed using hyper geometric testing with Benjamini–Hochberg false discovery rate (FDR) correction (33). Pathways with FDR < 0.05 were considered statistically significant (34).

7. Differential gene expression analysis using GEO (GEO2R and DESeq2)

The transcriptomic dataset GSE120746 was obtained from the Gene Expression Omnibus (GEO) (35). Initial screening was performed using GEO2R (36). Differential expression analysis was further validated using DESeq2 (37). Log_2 fold change (log_2FC) and adjusted p-values (Padj) were calculated. Genes with Padj < 0.05 were considered significantly differentially expressed.

Significant differentially expressed genes (DEGs) were cross-compared with identified hub genes to prioritize targets showing both topological centrality and transcriptional dysregulation (37).

8. Drug–gene interaction analysis using DGIdb

Hub genes and significant DEGs were submitted to the Drug–Gene Interaction Database for interaction screening (38). Documented drug–gene interactions, interaction types (inhibitor, agonist, antagonist, antibody), and interaction counts were extracted to evaluate therapeutic relevance and druggability (38).

Results

1. DisGeNET – Gene collection

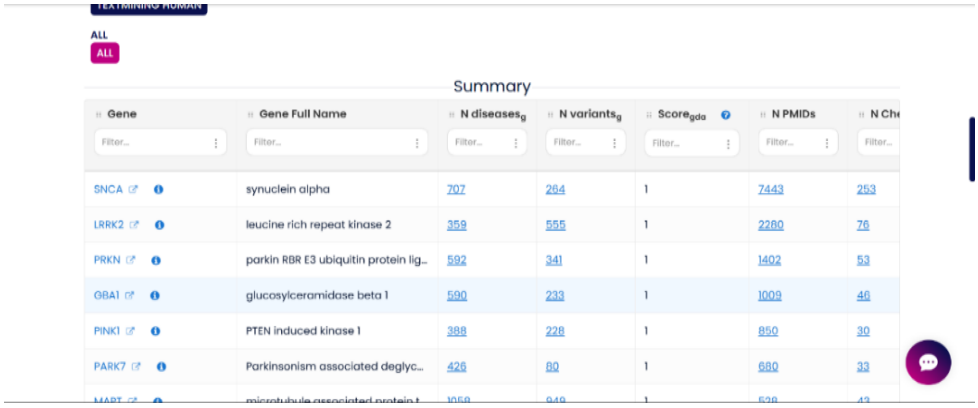

Figure 1: DisGNET gene-disease association table for Parkinsonism – associated genes

The DisGeNET query for Parkinson's disease (CUI: C0030567) identified 3,516 associated genes and 5,161 single-nucleotide polymorphisms (SNPs), indicating extensive genetic evidence linked to the disorder [15]. Gene–Disease Association (GDA) scores reflected varying levels of supporting evidence [15]. From this dataset, 30 genes were prioritized based on high association scores and biological relevance. Notably, SNCA, LRRK2, PRKN, GBA1, PINK1, and PARK7 exhibited the highest association score (Score_gda = 1.0), indicating strong and consistently reported links to Parkinson's disease (15, 16). Additional selected genes included VPS35, TH, DDC, SLC6A3, MAOB, MAPT,

ATP13A2, TNF, IL6, and others involved in dopaminergic regulation, mitochondrial function, protein homeostasis, and inflammatory signaling (15,16). The final curated 30-gene set provided a high-confidence and biologically relevant foundation for subsequent protein–protein interaction, network topology, pathway enrichment, transcriptomic validation, and drug–gene interaction analyses (15,16).

2. STRING Protein–Protein Interaction (PPI) Network Analysis

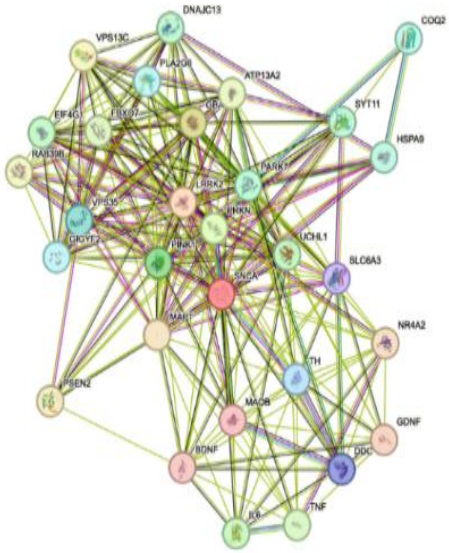

Figure 2: STRING protein–protein interaction network of 30 Parkinson's disease – associated genes

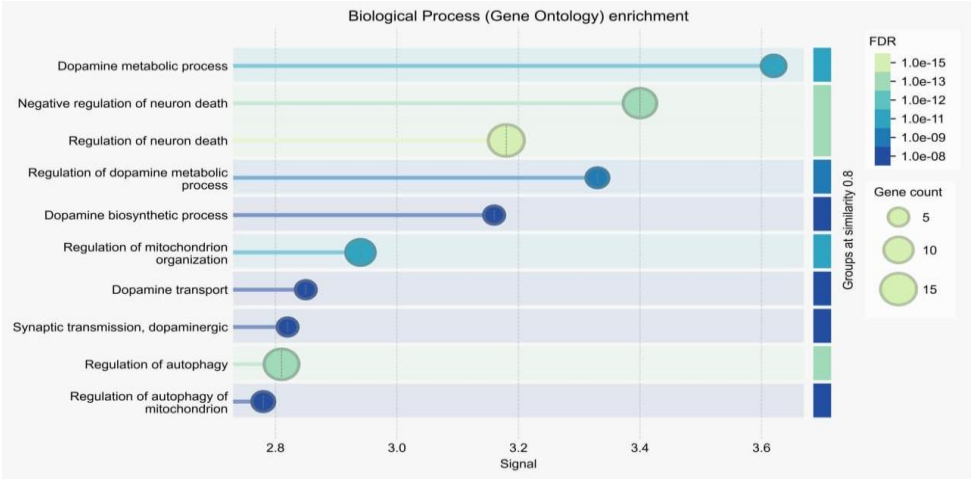

Figure 3: GO Biological Process enrichment of Parkinson's disease genes derived from the STRING network

STRING analysis of the 30 selected genes produced a significantly interconnected network with 30 nodes and 237 edges (26 expected), an average node degree of 15.8, clustering coefficient of 0.806, and a highly significant PPI enrichment ($p < 1.0 \times 10^{-16}$), indicating non-random functional connectivity (17,18).Major hub genes included SNCA, LRRK2, PINK1, PRKN, PARK7, MAPT, UCHL1, and TH (17,18).Gene Ontology (Biological Process) enrichment revealed significant overrepresentation of pathways related to dopaminergic signaling, mitochondrial

function, autophagy/mitophagy, oxidative stress, neuron death regulation, and inflammatory response, as summarized in the theme table (17,19).

Integrated GO Analysis for Parkinson's disease (Biological Process vs Molecular Function)

Functional categories were derived from Gene Ontology (GO) enrichment analysis.

(Biological Process vs Molecular Function)

Table 1: Summary of major GO Biological Process and Molecular Function themes in Parkinson's diseases.

Themes	Represent Enriched Function and Processes
Dopaminergic Dysfunction	Dopamine metabolic and biosynthetic processes; regulation of dopamine metabolism; dopamine receptor and enzyme binding
Mitochondrial Dysfunction & Energy Metabolism	Mitochondrial Organization; ATP metabolic process; regulation of mitophagy; metal ion binding.
Neurodegeneration & Cell Death	Regulation of neuron death; apoptotic signalling; protease and enzyme binding
Protein Homeostasis & Ubiquitin System	Protein ubiquitination; Proteasomal degradation; ubiquitin ligase and protein binding.
Autophagy & Cellular Quality Control	Autophagy; mitophagy; cellular stress response; heat shock protein binding.
Oxidative Stress & Redox Balance	Response to oxidative stress; reactive oxygen species metabolism; metal ion binding.
Neuroinflammation	Microglial activation; inflammatory response; signalling receptor binding.

3. NetworkAnalyst – hub genes and modules

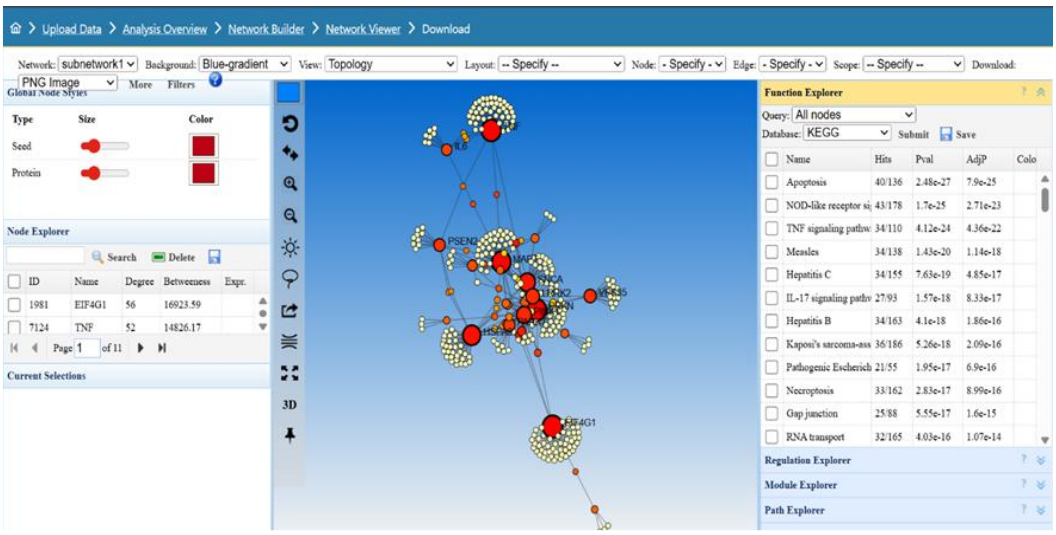

Figure 4: NetworkAnalyst protein- protein interaction network highlighting hub genes in Parkinsonism

NetworkAnalyst PPI analysis demonstrated significant network enrichment (PPI enrichment $p < 1.0 \times 10^{-16}$), confirming strong non-random connectivity among the differentially expressed Parkinson's disease genes (17, 18).

Degree centrality identified TNF, IL6, AKT1, TP53, MAPK1, APP, CASP3, and NFKB1 as major hub genes (>50 interactions), while betweenness centrality highlighted AKT1 and TP53 as key bridge nodes within the network (17, 18).

KEGG pathway enrichment revealed significant overrepresentation of Apoptosis ($P = 2.48 \times 10^{-27}$; FDR = 7.90×10^{-25}), TNF and NF-κB signaling, NOD-like receptor signaling, Mitophagy, and the Parkinson's disease pathway (17, 19).

Gene Ontology and Reactome analyses consistently showed enrichment of processes related to cell death regulation, mitochondrial organization, stress response, and immune/inflammatory signaling, including Toll-like receptor and cytokine-mediated pathways (17, 19, 20).

4. GeneMANIA – functional gene – gene network

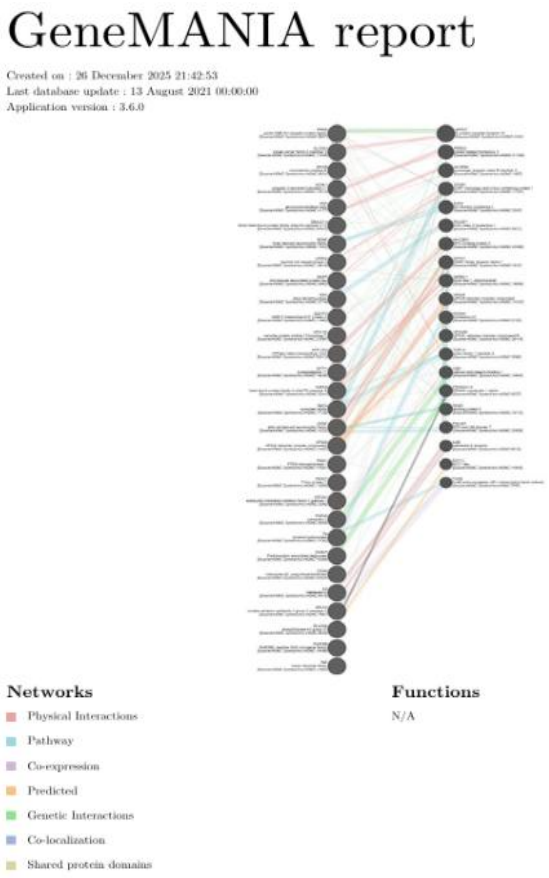

Figure 5: GeneMANIA function gene – gene interaction network for Parkinsonism – associated genes.

GeneMANIA analysis identified a highly interconnected network in Homo sapiens, dominated by physical (35.78%) and pathway (27.73%) interactions, followed by co-expression, predicted, and genetic links (14,22). Key genes (SNCA, LRRK2, PRKN, PINK1, MAPT, GBA, TNF, IL6) were embedded within shared networks connecting mitochondrial regulators (PINK1, PRKN, ATP13A2, COQ2), inflammatory mediators (TNF, IL6), and dopaminergic/synaptic genes (SLC6A3, DDC, TH, SNCA) (14, 22). These interactions support coordinated involvement of mitochondrial dysfunction, synaptic impairment, and neuroinflammatory signalling in Parkinsonism (14, 22).

5. KEGG pathway database

KEGG pathway enrichment identified two significantly enriched pathways: Parkinson's disease (hsa05012, $p = 1.2 \times 10^{-11}$) and Dopaminergic synapse (hsa04728, $p = 4.7 \times 10^{-10}$) (14, 22). Core genes including SNCA, LRRK2, PRKN, PINK1, GBA, MAPT, TNF, IL6, TH, DDC, and SLC6A3 were mapped within these pathways (14, 22).

Functional mapping showed PRKN involvement in the ubiquitin–proteasome system; PINK1, PRKN, LRRK2, and PARK7 in mitochondrial quality control and oxidative stress; SNCA in protein aggregation and synaptic vesicle regulation; TH and DDC in dopamine biosynthesis; and SLC6A3 in dopamine reuptake (14, 22).

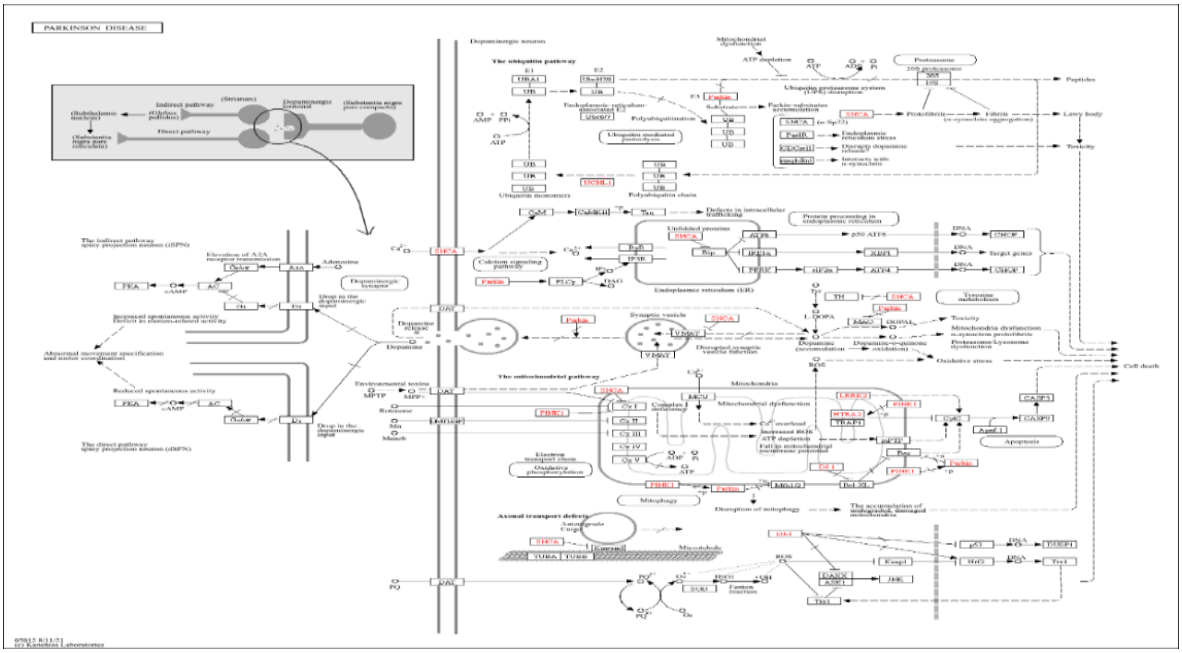

Figure 6: KEGG Parkinson's disease pathway highlighiting mapped genes

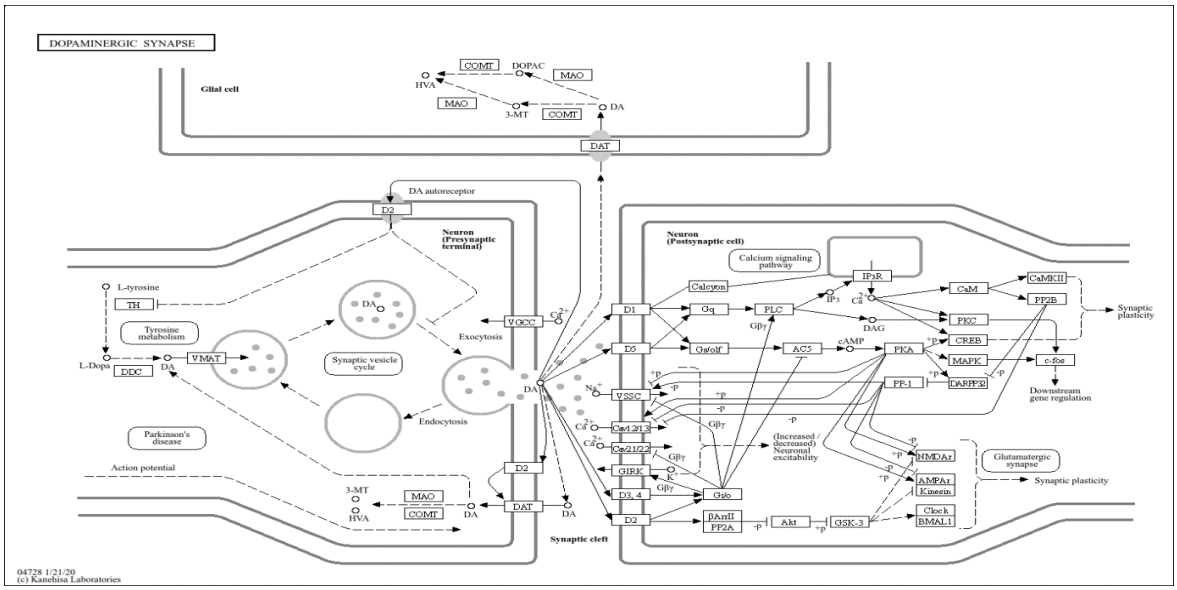

Figure 7: KEGG dopaminergic synapse pathway with *Parkinsonism-related genes*

6. Reactome pathway analysis

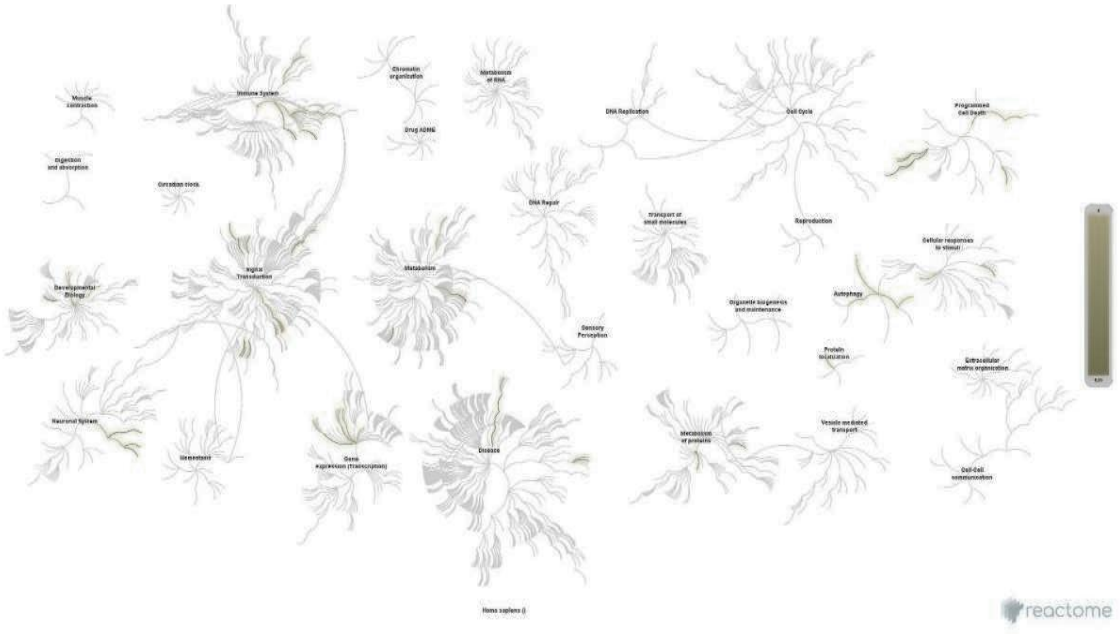

Figure 8: Reactome pathway overview showing enriched biological systems for Parkinsonism – associated genes

Reactome pathway enrichment analysis showed significant overrepresentation of immune-related signalling pathways in the Parkinsonism-associated gene set. The most enriched pathway was Cytokine Signalling in the Immune System (R-HSA-1280215), with 12 mapped genes ($p = 6.37 \times 10^{-4}$; FDR = 0.017), confirming statistical significance (14, 22).

Additional enrichment included Interferon signalling, Interleukin signalling, and the JAK–STAT cascade, indicating activation of inflammatory and immune-response mechanisms. Key genes such as TNF, IL6, and NFKB1 were directly mapped to these pathways, supporting cytokine-driven neuroinflammation as a dominant process in Parkinsonism (14, 22).

7. Differential gene expression (GEO2R and DESseq2, GSE120746)

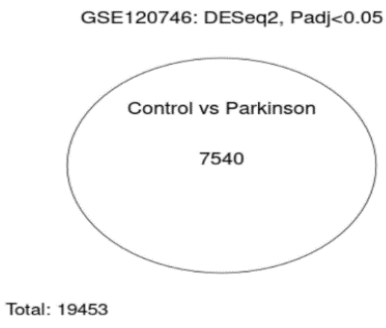

Figure 9: Differential gene expression profile of GSE120746 analysed using DESeq2

Differential expression analysis of GSE120746 using GEO2R and DESeq2 (Padj < 0.05) identified 7,540 significantly differentially expressed genes (DEGs) out of 19,453 (~39%), indicating widespread transcriptomic alterations in Parkinson's disease (33, 34).

Immune-related genes (TNF, IL6, IFIT1, STAT1, and JAK2) were significantly upregulated, whereas neuronal and mitochondrial genes (SNCA, MAP2, SYN1, NDUFS1, COX7C) were downregulated. These findings align with enrichment of cytokine signalling, dopaminergic dysfunction, and mitochondrial impairment (14, 22).

8. DGIdb. Drug–Gene Interactions

Figure 10: Overview of drug-gene interactions for Parkinsonism-associated gene for DGidb

Drug–gene interaction analysis using DGIdb on the 7,540 DEGs identified strong translational relevance for key hubs. TNF (93 interactions) and IL6 (49) showed the highest interaction counts, followed by PLA2G6 (44), MAPT (40), SNCA (35), and GBA1 (35). Additional interactions were observed for LRRK2, PARK2, DDC, and UCHL1, whereas mitophagy-related genes (PINK1, ATP13A2, PARK7, VPS35) showed limited or no documented interactions (36, 37).

Most interactions were classified as inhibitors, including MAOB inhibitors (selegiline, rasagiline), levodopa (TH-related), carbidopa (DDC inhibitor), TNF inhibitors (infliximab, etanercept), IL6 inhibitor (tocilizumab), LRRK2 kinase inhibitors, and ambroxol (GBA1-targeting) (36, 37).

Discussion

The integrated bioinformatics analysis revealed interconnected molecular mechanisms involved in Parkinson's disease (PD). DisGeNET confirmed the presence of well-established PD genes such as SNCA, LRRK2, PRKN, PINK1, GBA1, and PARK7, supporting the reliability of the selected dataset (1, 5, 6).

Protein–protein interaction analysis showed highly significant non-random connectivity (PPI enrichment $p < 1.0 \times 10^{-16}$) and identified major hub genes including SNCA, LRRK2, PINK1, PRKN, MAPT, UCHL1, and TH. These genes were mainly associated with dopaminergic dysfunction, mitochondrial damage, protein misfolding, oxidative stress, autophagy defects, and neuroinflammation (14, 22, 36). Network topology further highlighted TNF and IL6, along with AKT1 and TP53, as key regulators linking inflammation with apoptosis and cell survival (36, 37). GeneMANIA also supported strong physical and pathway-based interactions among immune, mitochondrial, and synaptic genes (28, 29).

KEGG analysis confirmed enrichment in Parkinson's disease, dopaminergic synapse (30, 31), while Reactome highlighted cytokine signalling and JAK–STAT pathways, indicating active neuroinflammation (32, 33). Differential expression analysis showed widespread gene dysregulation (~39%), with immune genes upregulated and neuronal/mitochondrial genes downregulated, consistent with pathway findings (34, 35).

DGIdb results suggested strong druggability of immune and dopaminergic genes, whereas mitophagy-related genes showed limited therapeutic targeting (36, 37).

Overall, the findings support a unified model of PD involving dopaminergic loss, mitochondrial dysfunction, impaired protein clearance, oxidative stress, and chronic neuroinflammation.

Conclusion

This study applied an integrated bioinformatics workflow combining gene mining, differential expression analysis, protein–protein interaction networks, topology analysis, functional association, pathway enrichment, and drug–gene interaction analysis to investigate the molecular basis of Parkinsonism (1,13). The findings indicate that Parkinsonism is driven by interconnected mechanisms including mitochondrial dysfunction, protein aggregation, impaired dopamine metabolism, and neuroinflammation (3, 4,6,9).

Key hub genes such as SNCA, LRRK2, PRKN, PINK1, and TNF occupied central positions within disease networks, while transcriptomic analysis confirmed upregulation of inflammatory and aggregation-related genes and downregulation of neuronal and dopamine-associated genes (10,11).

Overall, the results support Parkinsonism as a complex network-driven disorder and identify biologically significant hub genes and pathways that may serve as potential biomarkers and therapeutic targets (12,13). Further experimental and clinical validation is required to translate these findings into disease-modifying strategies (1,13).

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