Molecular Neurobiology
https://doi.org/10.1007/s12035-025-05182-z

RESEARCH

Pathway Analysis and Genetic Markers in Parkinson's Disease: Insights into Subtype-Specific Mechanisms

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Received: 12 February 2025 / Accepted: 24 June 2025

Abstract

Parkinson's disease (PD) is a complex disease influenced by both genetic and environmental factors. Despite advances in understanding PD genetics, subtype-specific mechanisms remain poorly characterized. This study aims to identify distinct genetic markers and pathways across PD subtypes, addressing this gap to enable targeted diagnostics and therapies. Genes associated with PD were collected from various databases and categorized into groups based on the PD type to assess the PD risk. Protein interaction analysis was conducted to identify functional clusters and key genes within each group. KEGG enrichment analysis revealed common genes and pathways among the different PD groups. This study conformed to the PRISMA 2020 guidelines for systematic data collection and analysis. Hub genes such as PRKN, SNCA, and LRRK2 have demonstrated considerable potential as biomarkers for genetic predisposition in PD, alongside the identification of additional complementary genes. Analysis of hub node variants highlighted specific genetic variations in these genes. We identified several microRNAs, including hsa-miR-335-5p, hsa-miR-19a-3p, and hsa-miR-106a-5p, as well as transcription factors that interact with crucial hub genes. This study refines subtype-specific mechanisms for established PD genes and identifies novel genetic markers and pathways associated with juvenile, young-onset, late-onset, familial, and sporadic Parkinson's disease, enhancing our understanding of their molecular mechanisms and potential for targeted diagnostics and therapies. Specifically, we highlight the roles of hub genes, such as PRKN, SNCA, and LRRK2, alongside significant microRNA interactions, which may serve as biomarkers for early detection and personalized treatment approaches.

Keywords Juvenile PD · Young-onset PD · Late-onset PD · Sporadic PD · Familial PD · Parkinson's disease · Biomarker

Introduction

Parkinson's disease (PD) is a genetically heterogeneous neurodegenerative disorder [1], can be classified into familial (fPD) and sporadic (sPD) forms, with genetic and environmental factors contributing to its pathogenesis [2, 3]. Overall, 10–15% of all PD cases are accounted for by the genetically inherited type [4], and the remaining cases are sPD. Over 90 risk loci have been identified through genome-wide association studies (GWAS) [5], with recent multi-ancestry analyses expanding this to 78 independent loci. Key genes such as SNCA, LRRK2, and PRKN dominate familial and early-onset subtypes, while polygenic risk scores and gene-environment interactions increasingly define sporadic and late-onset disease [4]. Genetic and environmental factors can influence the onset of human diseases, including PD, through complex interactions that may lead to genetic variants and epigenetic modifications [6]. PD, which begins after the age of 50 years, is called late-onset PD (LOPD) disease. jPD is defined explicitly for cases with onset before age 20 [7].

Genetic analyses have identified modules linked to PD, such as the SNCA module, which contains genes associated with an increased risk of PD [8]. Additionally, network-level changes induced by pathological alpha-synuclein affect neurotransmission and brain oscillatory dynamics, contributing

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Published online: 02 July 2025

to non-motor deficits in PD [9]. The non-specific lethal (NSL) complex, involved in chromatin modulation, regulates genes and pathways genetically associated with PD, underscoring the complex genetic factors influencing the disease[10].

Understanding the distribution of genes and regulatory networks related to PD is crucial. Studies have shown that genes associated with PD are clustered with non-specific lethal genes in co-expression modules, highlighting the interconnectedness of genetic pathways in the disease [10]. Furthermore, the expression and distribution of purinergic receptors in the basal ganglia play a role in PD pathology, with implications for innovative treatment strategies [11].

The discovery of genetic markers associated with Parkinson's disease onset types is crucial. It can help us better understand the disease and develop more targeted and effective treatments. This study aims to identify these potential markers and bring us one step closer to a cure.

Methods

The workflow in Fig. 1 shows how hub genes and variant association were discovered for PD groups, detailing the systematic approach that includes data collection, bioinformatics analysis, and statistical validation, ultimately leading to the identification of key genetic factors that play a critical role in the pathogenesis of PD.

Identification of Gene Associations and SNP Sites

We obtained all the PD gene association (PDGA) and PD variant association (PDVA) from the ten databases (including UniProt [12], ClinVar [13], GWAS Catalog [14], CTD [15], ORPHANET [16], CLINGEN [17], GENOMICS ENGLAND [18], CGI [19], PSYGENET [20], LHGDN [21], and dbSNP [22]. Also, PubMed, Embase, Web of Science, and Scopus were also systematically searched based on boolean query ("Parkinson Disease"[MeSH]) AND ("Genetic Markers" OR "Polymorphism" OR "Genotype" OR "Alleles" OR "Variant") NOT ("Review" OR "Animal"). PRISMA 2020 guidelines were followed (Supplementary Fig. S1). By April 05, 2025, about 113,500 reports for PDGA and PDVA were retrieved. Studies were included if they reported statistically significant associations in ≥ 2 independent cohorts. Subtypes were categorized as jPD for diagnoses at ≤ 20 years, YOPD for diagnoses between 21 and 50 years, LOPD for diagnoses > 50 years, fPD for cases with ≥ 2 affected first-degree relatives or confirmed monogenic mutations, and sPD for cases lacking family history or known mutations [7, 23]. Also, overlapping cases were assigned to both categories. After reviewing all the abstracts, each group's genetic and variant association studies were chosen. Next, we narrowed our focus to studies that reported a substantial correlation of gene(s) with each group from the pool of publications we retrieved. To minimize the occurrence of false-positive genes, the studies that reported insignificant or negative associations were deliberately excluded, despite the possibility that some genes in these studies may indeed be genuinely associated with PD groups. Subsequently, we carefully reviewed each selected publication's reports to ensure the conclusion aligned with its contents. In many studies, specific genes were discovered to function collaboratively and have considerable effects on PD groups, with each gene having a small or mild impact; these genes were also included in our list.

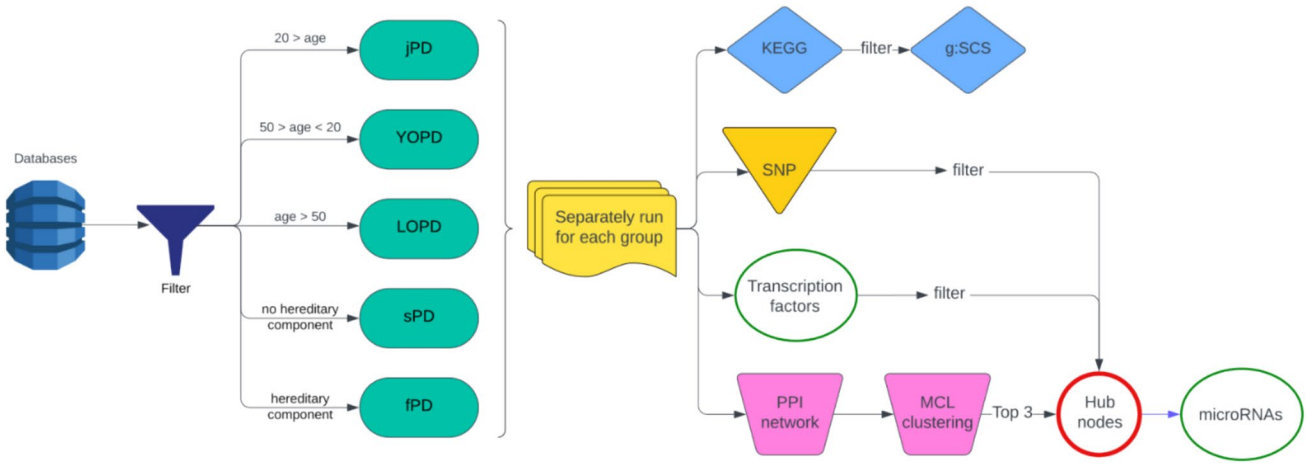

Fig. 1 Workflow for marker analyzing in Parkinson's disease. The methodological approach used to analyze genetic and clinical data about Parkinson's disease (PD)

GO and KEGG Pathway Enrichment Analysis

The g:Profiler [24] and Kyoto Encyclopedia of Genes and Genomes (KEGG) [25] databases were used to perform the functional analysis of genes and pathway enrichment using the g:SCS algorithm (set counts and sizes algorithm) for the most relevant ontology in each group. This methodological rigor enhances our findings' reliability and applicability in clinical settings.

PPI and Module Network Analysis

The STRING database [26] was used for each group to analyze the protein–protein interaction (PPI) network of expressed genes PPI network with a confidence score > 0.9 for significant results. The Cytoscape software [27] was used to visualize the PPI network. Then, the Markov cluster (MCL) [28] was used to analyze the PPIs' network modules with an inflation value set to 5 and an edge cutoff set based on a confidence score > 0.9. The top three clusters were prioritized based on modularity scores and biological coherence, ensuring representation of major functional modules while maintaining analytical tractability for further hub analysis. Though additional clusters may exist, this threshold captured > 80% of network connectivity across subtypes, consistent with prior studies [10]. Hubs were identified using cytoHubba [29] with maximal clique centrality and double-checked using CentiScaPe 2.2 in each cluster [30].

Transcription Factor Network Construction of Modules

Indicated module transcription factors (TFs) were analyzed using the Top Rank integrated library in ChEA3 [31]. The top three putative TFs identified for each module with the lowest integrated scale rank were enumerated. Also, selected TFs were analyzed for any possible evidence of interaction. The scaled rank of < 0.05 was considered significant.

Nominate microRNAs

After finalizing and selecting the candidate genes, MIENTURNET [32] was used for hub genes to evaluate and select gene-related miRNAs. The *P*-value < 0.05 was considered significant.

Results

We identified 2077 genes and 990 variants associated with PD, with a breakdown of subtype-specific findings: jPD (67 genes, 37 variants), YOPD (51 genes, 32 variants), LOPD (247 genes, 76 variants), sPD (179 genes, 65 variants), and fPD (46 genes, 27 variants) which highlights the genetic diversity and potential for subtype-specific therapeutic strategies (Supplementary Table 1). This exceeds GWAS-derived loci due to the inclusion of candidate gene studies and replication in ≥ 2 independent cohorts.

Function and Pathway Annotation

All genes were uploaded to the g:Profiler online tool for KEGG pathway enrichment analysis. Table 1 presents the top ten pathways at each group. The expressed genes in YOPD and jPD were mainly enriched in Parkinson's disease, pathways of neurodegeneration—multiple diseases, and cocaine addiction. LOPD-associated genes were enriched in lipid metabolism (hsa, 05417), neuroinflammation (e.g., TNF/IL-17 signaling), and neurodegeneration pathways (Table 1). The expressed genes in sPD were mainly enriched in tuberculosis, inflammatory bowel disease (IBD), Parkinson's disease, Chagas disease, cocaine addiction, lipid and atherosclerosis, pathways of neurodegeneration—multiple diseases, fluid shear stress, atherosclerosis, and rheumatoid arthritis. The expressed genes in fPD were mainly enriched in pathways of neurodegeneration—multiple diseases, growth hormone synthesis, secretion and action, ErbB signaling pathway, T-cell receptor signaling pathway, Parkinson's disease, TNF signaling pathway, neurotrophin signaling pathway, prolactin signaling pathway, Yersinia infection, and colorectal cancer. Table 2 provides the gene ontology (GO) terms for biological process (GO:BP), molecular function (GO:MF), and cellular component (GO:CC) analyses, which include the expressed genes enriched in positive regulation.

Construction and Analysis of the PPI Network

We constructed a PPI network using the STRING database to explore the functional relations among all expressed genes. Cytoscape was utilized to assess and visualize different genes. The PPI network included 64 nodes and 95 edges for jPD, 51 nodes and 89 edges for YOPD, 233 nodes and 746 edges for LOPD, 164 nodes and 417 edges for sPD, and 46 nodes and 62 edges for fPD. Furthermore, the MCL plugin verified the functional clusters of each network that met the cutoff criteria, and cytoHubba (red nodes) and CentiScaPe detected the most significant module hub gene based on betweenness centrality, degree, and bridging.

Hub gene analysis across PD subtypes revealed distinct molecular networks (Figs. 2 and 3). In jPD, PRKN (Figs. 2A and 3A) reveals regulating mitophagy and ubiquitination pathways critical for neuronal survival. YOPD was characterized by SNCA (Figs. 2B and 3B), implicating α-synuclein aggregation as a key driver of early pathology. In contrast, fPD highlighted LRRK2 (Figs. 2C and 3C), with

Table 1 Gene classification in the functional modules based on KEGG with a false discovery rate of < 0.05 (top 10)

	Term ID	Term name	Count	*p*-value
jPD	hsa:05012	Parkinson disease	266	1.43E − 08
	hsa:05030	Cocaine addiction	49	0.000657513
	hsa:05022	Pathways of neurodegeneration—multiple diseases	474	0.00096473
YOPD	hsa:05012	Parkinson disease	266	3.01E − 08
	hsa:05022	Pathways of neurodegeneration—multiple diseases	474	0.000128781
	hsa:05030	Cocaine addiction	49	0.038243158
LOPD	hsa:05417	Lipid and atherosclerosis	214	7.64E − 08
	hsa:04933	AGE-RAGE signaling pathway in diabetic complications	100	6.31E − 07
	hsa:05022	Pathways of neurodegeneration—multiple diseases	474	2.57E − 06
	hsa:05144	Malaria	49	3.23E − 05
	hsa:05142	Chagas disease	101	5.00E − 05
	hsa:04668	TNF signaling pathway	113	1.69E − 04
	hsa:05030	Cocaine addiction	49	3.78E − 04
	hsa:05323	Rheumatoid arthritis	88	6.89E − 04
	hsa:05145	Toxoplasmosis	109	7.63E − 04
	hsa:04657	IL-17 signaling pathway	91	9.34E − 04
sPD	hsa:05152	Tuberculosis	175	1.15E − 07
	hsa:05321	Inflammatory bowel disease	62	7.38E − 07
	hsa:05012	Parkinson disease	266	7.58651E − 06
	hsa:05142	Chagas disease	101	8.7401E − 06
	hsa:05144	Malaria	49	2.26246E − 05
	hsa:05030	Cocaine addiction	49	2.26246E − 05
	hsa:05417	Lipid and atherosclerosis	214	8.89612E − 05
	hsa:05022	Pathways of neurodegeneration—multiple diseases	474	0.000100313
	hsa:05418	Fluid shear stress and atherosclerosis	138	0.000208787
	hsa:053s23	Rheumatoid arthritis	88	0.00023389
fPD	hsa:05022	Pathways of neurodegeneration—multiple diseases	474	1.90345E − 06
	hsa:04935	Growth hormone synthesis, secretion and action	120	0.000227166
	hsa:04012	ErbB signaling pathway	84	0.000708628
	hsa:04660	T cell receptor signaling pathway	103	0.001917558
	hsa:05012	Parkinson disease	266	0.002153468
	hsa:04668	TNF signaling pathway	113	0.00299982
	hsa:04722	Neurotrophin signaling pathway	118	0.003693473
	hsa:04917	Prolactin signaling pathway	70	0.007091669
	hsa:05135	Yersinia infection	136	0.007268465
	hsa:05210	Colorectal cancer	86	0.015792049

The "count" column indicates the number of associated genes for each term, while the "*P*-value" column reflects the statistical significance of the associations. The data highlight the relevance of gene-related pathways in the context of different groups, including jPD, YOPD, LOPD, sPD, and fPD

its kinase signaling activity suggesting a role in synaptic and cytoskeletal dysregulation. For LOPD, three functional modules were identified: (1) SNCA (Figs. 2D and 3D) dominated neurodegeneration pathways, (2) ALB (Figs. 2D' and 3D') linked to metabolic dysregulation, and (3) IL6 (Figs. 2D" and 3D") underscored chronic neuroinflammation. Meanwhile, sPD exhibited a tripartite architecture: (1) PRKN (Figs. 2E and 3E) in mitochondrial quality control, (2) inflammatory mediators (IL1A, TNF, IL10, and IL1B; Figs. 2E' and 3E') reflecting immune dysregulation, and (3) CYP1A1 (Figs. 2E" and 3E"), a xenobiotic metabolism gene, pointing to environmental interactions. These findings emphasize subtype-specific pathobiology, from mitophagy deficits in juvenile and young-onset forms to inflammatory-metabolic crosstalk in late-onset and sporadic PD.

The modules were filtered according to their groups to emphasize the most statistically significant genes related to the disease. Our analysis revealed that PINK1, SNCA, LRRK2, and PRKN are not only prevalent across all five disease groups but also exhibit distinct expression patterns and genetic variations that may contribute to subtype-specific pathophysiology (Fig. 4 and Supplementary Table 2).

Single Nucleotide Polymorphism (SNPs) Sites

Table 3 delineates each subtype's variant landscape associated with specific hub node genes. In the PRKN gene, most variants are missense changes, indicating a strong potential for functional impact on protein activity. Notable variants include rs1801474 (C/T, Ser/Asn) and rs1801582 (C/G, Val/Leu, Val/Ile). The SNCA gene also exhibits a high prevalence of intron variants, which may play a role in gene regulation, alongside significant missense variants like rs104893875 (C/T, Glu/Lys) and rs104893877 (C/T, Ala/

Table 2 Parkinson disease's gene ontology terms

	GO Terms								
	Biological	***P*-value**	**ID**	**Molecular**	***P*-value**	**ID**	**Cellular**	***P* − value**	**GO**
LOPD	Response to chemical	4.10E − 38	0042221	Signaling receptor binding	4.33E − 16	0005102	Extracellular region	1.10E − 18	0005576
		1.23E − 16	0042417		1.32E − 12	0042802		5.21E − 10	0044297
	Dopamine metabolic process	1.00E − 04	0007623	Identical protein binding	1.50E − 06	0035240	Cell body	6.42E − 06	0009986
		3.45E − 04	0070841		3.27E − 05	0004952	Cell surface	1.94E − 05	0045121
	Circadian rhythm	8.82E − 03	0016032	Dopamine binding	4.10E − 04	0046914	Membrane raft	2.73E − 05	0016234
	Inclusion body assembly	1.01E − 02	0014805	Dopamine neurotransmitter receptor activity	1.68E − 03	0016209	Inclusion body	8.12E − 05	0098691
		1.29E − 02	0051926		3.04E − 03	0008504	Dopaminergic synapse	1.04E − 03	0045178
	Viral process	1.34E − 02	0018130		6.36E − 03	0016491		1.28E − 02	0045177
	Smooth muscle adaption	1.57E − 02	0010875	Transition metal ion binding	8.17E − 03	0015378	Basal part of cell	3.27E − 02	0071682
		2.49E − 02	0070141		1.92E − 02	0001540	Apical part of cell	3.76E − 02	0043235
	Negative regulation calcium ion transport			Antioxidant activity			Endocytic vesicle lumen		
				Monoamine transmembrane transporter activity			Receptor complex		
	Heterocycle biosynthetic process								
	Positive regulation of cholesterol efflux			Oxidoreductase activity					
	Response to UV-A			Sodium:chloride symporter activity					
				Amyloid-beta binding					
YOPD	Dopamine transport	1.15E − 11	0015872	Cuprous ion binding	1.10E − 06	1903136	Neuron projection	6.86E − 09	0043005
		7.15E − 11	0042417		0.008	1990381	Mitochondrion	6.36E − 08	0005739
	Dopamine metabolic process	7.21E − 10	1902176	Ubiquitin-specific protease binding	0.017	1903135	Inclusion body	8.59E − 08	0016234
		1.10E − 09	0097479		0.029	0140662	Uniplex complex	5.44E − 05	1990246
	Negative regulation of oxidative stress-induced intrinsic apoptotic signaling pathway	2.06E − 09	0051402	Protease binding			Cell body	0.0001	0044297
		3.69E − 09	0007626	ATP-dependent protein folding chaperone			Multivesicular body, internal vesicle	0.018	0097487
		3.77E − 09	0010821						
		7.78E − 08	2,000,377						
		7.90E − 07	1,903,530						
		2.50E − 05	0007399						
	Synaptic vesicle localization								
	Neuron apoptotic process								
	Locomotory behavior								
	Regulation of mitochondrion organization								
	Regulation of reactive oxygen species metabolic process								
	Regulation of secretion by cell								
	Nervous system development								

Table 2 (continued)

	GO Terms								
	Biological	***P*-value**	**ID**	**Molecular**	***P*-value**	**ID**	**Cellular**	***P* – value**	**GO**
jPD	Cellular response to oxidative stress behavior Regulation of autophagy of mitochondrion Response to toxic substance Neuron apoptotic process Catecholamine biosynthetic process Dopamine transport Regulation of autophagy of mitochondrion in response to mitochondrial depolarization Synaptic signaling Homeostatic process	2.49E – 14 1.67E – 13 3.52E – 12 6.98E – 12 7.33E – 11 5.19E – 08 4.80E – 07 1.07E – 06 1.14E – 06 2.41E – 06	0034599 0007610 1903146 0009636 0051402 0042423 0015872 1904923 0099536 0042592	Enzyme binding Protein-folding chaperone binding Molecular function activator activity Copper ion binding Catalytic activity Ubiquitin conjugating enzyme activity Oxygen binding Signaling receptor binding Opioid peptide activity Protein-containing complex binding	3.58E – 12 1.89E – 07 0.0002 0.0006 0.0009 0.001 0.003 0.004 0.029 0.039	0019899 0051087 0140677 0005507 0003824 0061631 0019825 0005102 0001515 0044877	Axon Presynapse Cell body Synapse Mitochondrion Neuronal cell body Inclusion body Vesicle Dopaminergic synapse Mitochondrial outer membrane	1.02E – 13 5.80E – 10 6.81E – 10 4.46E – 08 8.79E – 08 2.73E – 07 1.56E – 05 4.77E – 05 0.001 0.009	0030424 0098793 0044297 0045202 0005739 0043025 0016234 0031982 0098691 0005741
sPD	Cellular catabolic process Response to oxygen-containing compound Dopamine metabolic process Peptidyl-serine phosphorylation Regulation of dopamine secretion Regulation of spontaneous synaptic transmission C-terminal protein lipidation Regulation of long-term synaptic potentiation Regulation of endothelial cell proliferation Intracellular distribution of mitochondria	1.06E – 27 1.04E – 26 3.73E – 17 2.88E – 06 1.87E – 05 8.45E – 05 0.0001 0.001 0.019 0.026	0044248 1901700 0042417 0018105 0014059 0150003 0006501 1900271 0001936 0048312	Signaling receptor binding Enzyme binding Catalytic activity Dopamine binding Protein serine kinase activity Dopamine neurotransmitter receptor activity Adenyl nucleotide binding Hydrolase activity, acting on glycosyl bonds Hsp90 protein binding Cuprous ion binding	2.87E – 07 7.82E – 06 8.67E – 06 0.0001 0.0009 0.003 0.005 0.010 0.020 0.021	0005102 0019899 0003824 0035240 0106310 0004952 0030554 0016798 0051879 1903136	Cell body Neuronal cell body Cytoplasm Mitochondrion Axon Neuron projection Presynapse Synapse Inclusion body Cell surface	5.24E – 14 1.53E – 12 3.36E – 11 3.23E – 10 3.14E – 09 1.08E – 07 3.43E – 07 4.52E – 07 0.0003 0.0258	0044297 0043025 0005737 0005739 0030424 0043005 0098793 0045202 0016234 0009986

Table 2 (continued)

	GO Terms								
	Biological	***P*-value**	**ID**	**Molecular**	***P*-value**	**ID**	**Cellular**	***P* – value**	**GO**
fPD	Positive regulation of cellular component organization	1.08E – 08 5.05E – 08 2.01E – 07	0051130 0007268 0032386	Cuprous ion binding Protein binding	0.0002 0.0004 0.0028	1903136 0005515 0004707	Synapse Mitochondrion Mitochondrion-derived vesicle	4.63E – 10 4.81E – 07 1.845E – 06	0045202 0005739 0099073
	Chemical synaptic transmission	1.20E – 06 3.28E – 05	0007626 0001933	MAP kinase activity	0.0068 0.0459	0106310 0140297	Inclusion body	2.113E – 06 3.733E – 06	0016234 0044297
	Regulation of intracellular transport	0.0011 0.0036 0.0123	2000377 0042416 0031398	Protein serine kinase activity DNA-binding transcription factor binding			Cell body Axon Vesicle	1.30E – 05 0.0007 0.0055	0030424 0031982 0005758
	Locomotory behavior	0.0154 0.0174	0040011 0042592				Mitochondrial intermembrane space Multivesicular body, internal vesicle	0.0138	0097487
	Negative regulation of protein phosphorylation								
	Regulation of reactive oxygen species metabolic process								
	Dopamine biosynthetic process								
	Positive regulation of protein ubiquitination								
	Locomotion								
	Homeostatic process								

The table presents a comprehensive overview of the GO terms into biological processes, molecular functions, and cellular components. The *P*-values provided reflect the strength of the association, with lower values indicating a more significant relationship

Thr). In the LRRK2 gene, diverse missense variants, such as rs34637584 (G/A, Gly/Ser), underscore the importance of kinase activity alterations in neuronal function. A significant number of variants in the PINK1 gene are nonsense variants that lead to the formation of a stop codon, resulting in truncated proteins, which have a severe impact on function. Moreover, there is a high rate of deletion variants, causing frameshift mutations to compromise other hubs. The IL1B and IL6 genes, while primarily associated with inflammatory responses, show upstream and intron variants that may influence gene expression and contribute to neuroinflammation, a known factor in PD progression. Lastly, the CYP1A1 gene presents missense and synonymous variants, with missense changes like rs1279844744 (A/G, Cys/Arg).

TF Networks' Construction of Modules

Transcription factors regulate gene expression and function by binding to specific DNA sequences. We utilized the ChEA3 to predict transcription factors within the modules. Table 4 reveals the top three predicted transcription factors that met scaled rank < 0.05 for each group.

In jPD, YOPD, and fPD clusters, MXI1 emerged as the most significant transcription factor governing the hub nodes, PRKN and SNCA. In LOPD, ESR2 plays a regulatory role for both SNCA and IL6, while ALB is regulated by the transcription factors FOXA3 and CREB3L3. In sPD, ESR2 regulates a broader set of genes, including PRKN, IL10, IL1A, TNF, and CYP1A1. Additionally, NFE2L2 regulates TNF, IL1A, ILB, and CYP1A1, whereas BATF3 specifically regulates TNF and IL10 (Table 4).

The ChEA3 application also identifies putative transcription factors based on their co-expression similarity. In the YOPD TF network, MXI1 represents a significant co-expression and co-occurrence effect on FOXO4 (Fig. 5A). In the LOPD TF network, FOXA3 and CREB3L3 reveal mutual co-expression and co-occurrence but not in a significant manner (Fig. 5B). In the fPD TF network presented, the TF co-expression network SOX2 represents the co-occurrence effect on SOX6, while both represent the co-expression effect on MXI1 (Fig. 5C).

Nominate microRNAs

After identifying ten proteins LRRK2, SNCA, PRKN, IL6, IL1A, IL1B, CYP1A1, TNF, IL10, and ALB, we isolated and selected the most relevant microRNAs (Fig. 6). Accordingly, hsa-miR-335-5p, hsa-miR-19a-3p, and hsa-miR-106a-5p

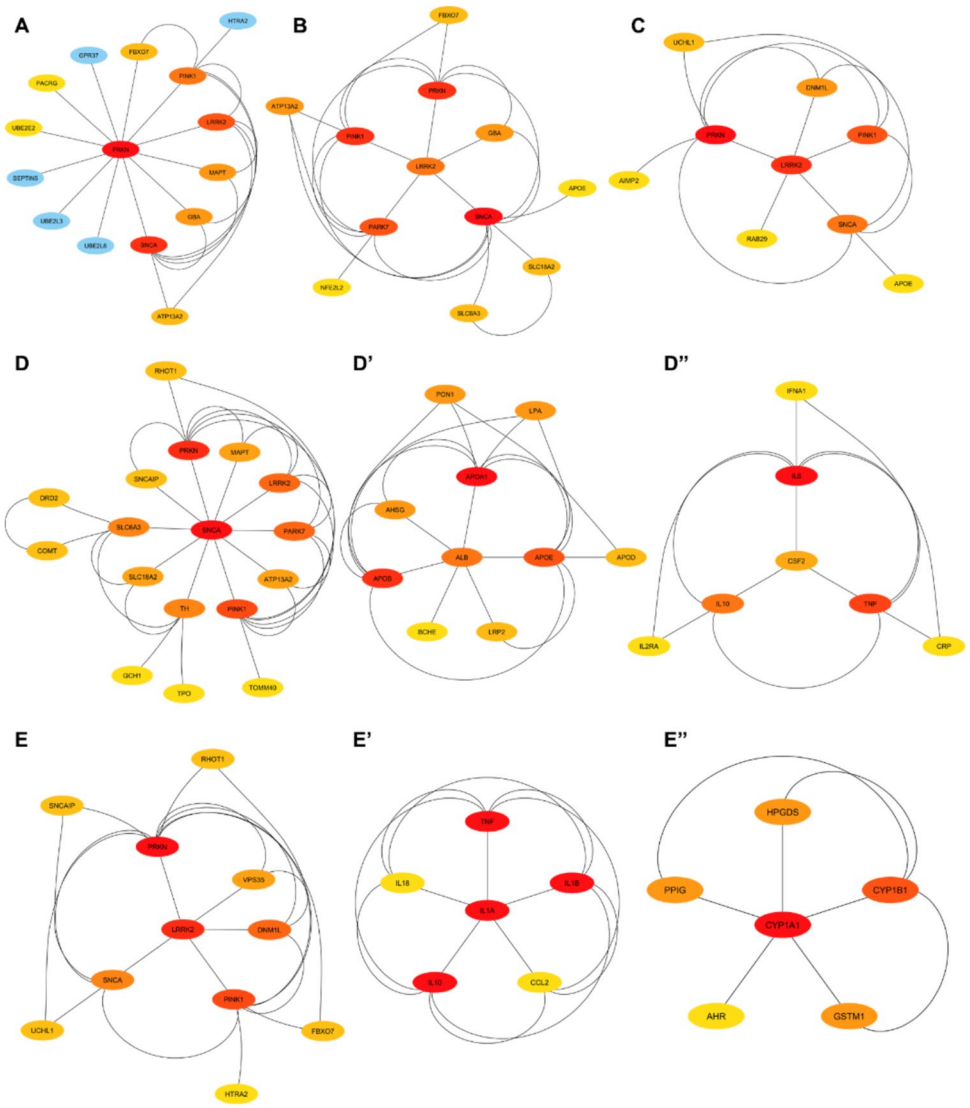

Fig. 2 MCL modules and candidate hub genes are visualized using the Cytoscape cytoHubba plugin. This figure illustrates the results of the MCL clustering analysis applied to PPI networks across different subtypes of PD. Each sub-panel represents distinct clusters identified for various onset categories, highlighting candidate hub proteins based on their clique centrality. **A** Juvenile, **B** young-onset, **C** familial, **D** late-onset module top first, **D'** module top second, **D"** module top third, **E** sporadic module top first, **E'** module top second, and **E"** module top third. The edges reflect interactions between proteins

were more significant than other miRNAs. As revealed in Fig. 6, hsa-miR-335-5p interacted with four targets PRKN, IL6, IL1A, and LRRK2, hsa-miR-19a-3p interacted with TNF, PRKN, and IL10, and hsa-miR-106a-5p interacted with IL10, IL1B, and IL6. A detailed table of these microRNAs and transcription factors with their target genes is included in Supplementary Table 3 to emphasize their potential regulatory roles in PD.

Discussion

This study provides insights into the genetic architecture of PD, revealing distinct genetic markers and pathways associated with different PD subtypes. Recent multi-ancestry GWAS identified 78 independent PD risk loci, reinforcing the role of genes like SNCA and LRRK2 [33]. Our findings highlight the potential role of cytokines and other genes that may have been previously underappreciated in PD as the second most common neurodegenerative disorder [34, 35]. Although progress has been made in identifying genetic factors associated with PD risk, most of the common variants driving the disease have yet to be identified, and even for well-characterized loci, the identity of the functional effector variant remains unknown.

jPD/YOPD modules implicate mitochondrial dysfunction (e.g., PRKN/PINK1-driven mitophagy), aligns with mechanisms in Huntington's disease and ALS, whereas LOPD's lipid-inflammatory axis (e.g., AGE-RAGE) reflects aging-related metabolic decline, suggesting distinct therapeutic targets for jPD and YOPD versus LOPD. However, the LOPD and fPD types are significantly related to neurodegenerative pathways, while the sPD is related to anti- and inflammatory pathways (Table 1). Various studies have implicated lipids in different aspects of PD pathology, from cytotoxic interactions with disease-causing genes to

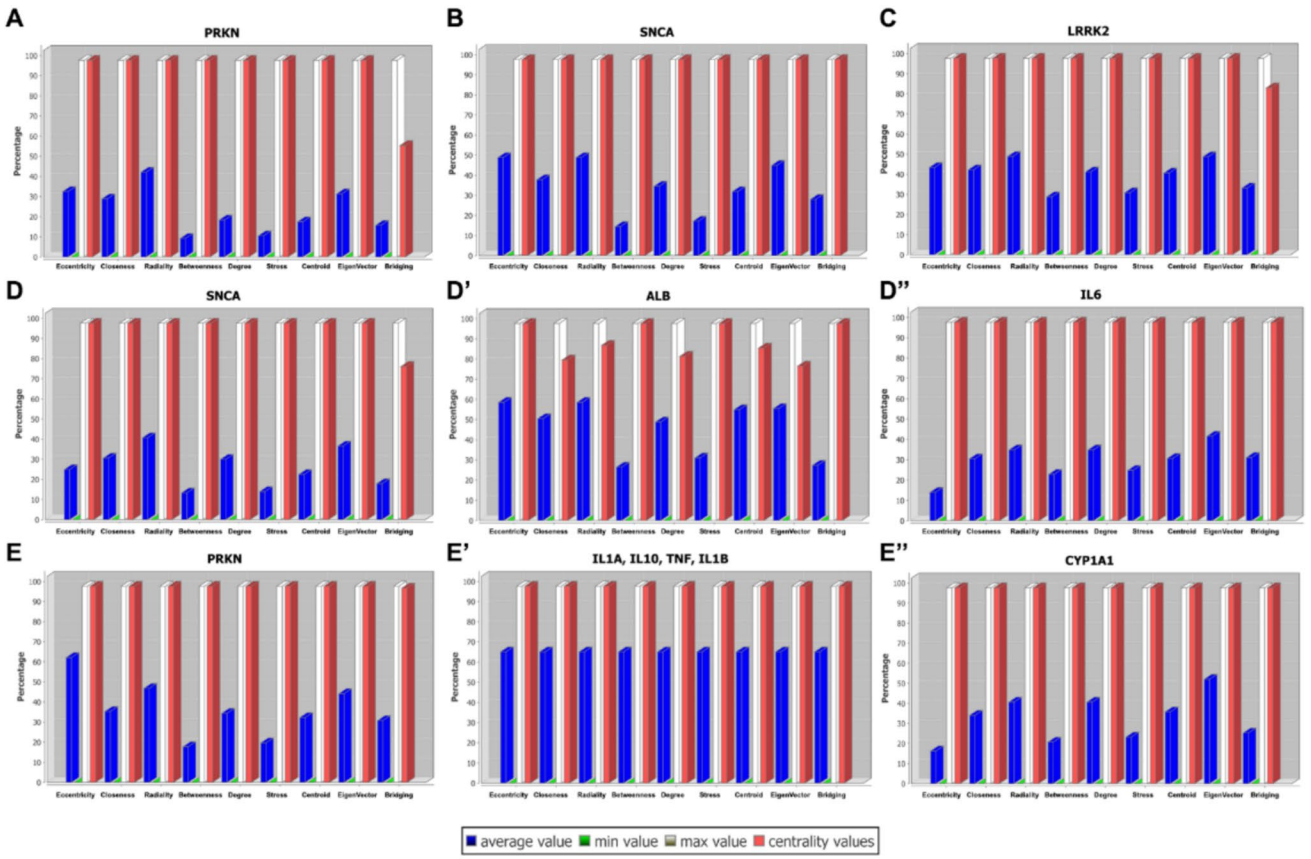

Fig. 3 Network analysis of the most crucial hub genes. This figure illustrates the network analysis of critical hub genes employing the Centiscape plug-in, emphasizing bridging, degree, and betweenness centrality across various PD subtypes, highlighting their roles in connecting the regulatory network. **A** The top hub gene within the jPD module, **B** YOPD module, **C** fPD module, **D** LOPD module top first, **D'** LOPD module top second, **D"** LOPD module top third, **E** sPD module top first, **E'** sPD module top second, and **E"** sPD module top third

alterations in lipid pathways [36, 37]. Research has shown disturbances in sphingolipid metabolism, highlighting the potential involvement of lipids in PD [38–40]. LOPD has been linked to various genetic factors, such as mutations in TWNK [41], PLA2G6 [42], and GBA [43]. The interaction between advanced glycation end products (AGEs) and the receptor for AGEs (RAGE) triggers the activation of various downstream pathways such as NF-κB, ERK1/2, p38, JNK, and PI3K, leading to neuronal cell death, neurodegeneration, and neuroinflammation [44].

In neurodegenerative diseases (Table 1), the Nrf2-ARE pathway, indicative of oxidative stress, has been associated with neuronal cell death, highlighting its role in the pathogenesis of chronic neurodegenerative diseases [23]. The distinction between YOPD and LOPD Parkinson's is supported by genetic and clinical differences, with genetic factors playing a more significant role in YOPD and jPD cases. The link between tuberculosis, IBD, and sPD may stem from the immune response triggered by tuberculosis infection or the inflammatory response to IBD and contribute to developing neurodegenerative diseases like PD [45, 46]. The TNF/IL17 neuroinflammatory signaling in LOPD overlaps with mechanisms in multiple sclerosis, while sPD's immune dysregulation (e.g., IL10/TNF) parallels Crohn's disease; the LOPD's lipid metabolism links mirror Alzheimer's disease (e.g., APOE), implicating shared inflammatory-metabolic axes in neurodegeneration. Familial PD's neurodegeneration pathways (e.g., ErbB signaling) are conserved in ALS and glioblastoma, highlighting broader regulatory disruptions. The role of the remaining enriched pathways in PD types still requires further exploration.

Further, we constructed the PPI network using all genes for functional interactions in five types. The three most significant functional modules were filtered (Fig. 2). We found that the hub gene for jPD was PRKN (Figs. 2A and 3A), which encodes the Parkin protein [47]. Biallelic pathogenic variants in PRKN are frequently found in cases of jPD. Variants in PRKN (Table 3), known to play a critical role in mitochondrial function and cellular stress response, are directly linked to jPD and YOPD forms of PD, suggesting

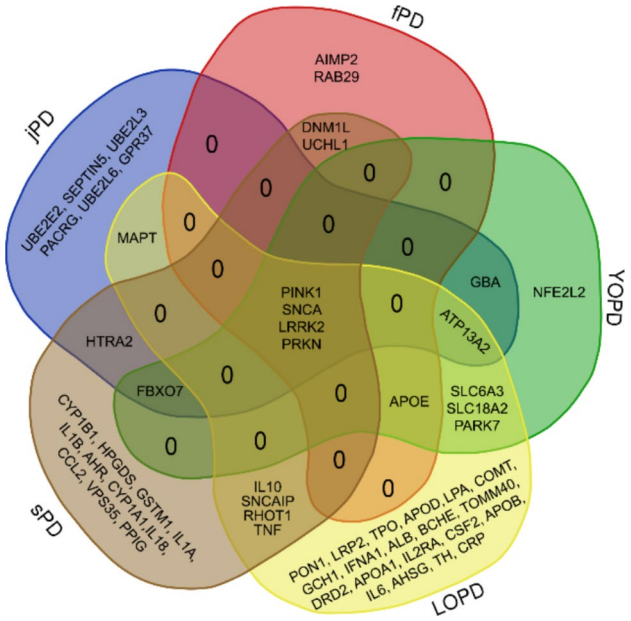

Fig. 4 Venn diagram. The diagram illustrates the genetic factors associated with different subtypes of PD, including jPD, YOPD, sPD, and LOPD. Each colored region corresponds to a specific PD subtype, with overlaps indicating shared genetic risk factors

that alterations in amino acid sequences may disrupt normal protein function, contributing to disease pathology. The frequency of these missense variants highlights their relevance in the genetic predisposition to PD [48].

The SNCA gene was identified as a hub gene in YOPD, as seen in Figs. 2B and 3B. Mutations and copy number variations in the SNCA gene have been identified as causes of YOPD and fPD [49, 50]. Additionally, SNCA triplications have been associated with aggressive and young-onset Parkinsonism [49]. The emphasis on SNCA indicates that pathophysiological mechanisms may differ in younger patients compared to those with later-onset forms of the disease. The gene dosage of SNCA has been linked to the severity of clinical trajectories in PD, with triplications leading to young onset, rapid disease progression, and prominent dementia [51]. Furthermore, SNCA has been consistently highlighted as a risk-associated region for PD in genome-wide association studies [52]. Variants within SNCA highlight that the combination of intron and missense variants suggests a multifaceted approach to understanding the gene's contribution to disease mechanisms.

LRRK2 (Figs. 2C and 3C) in fPD performs the role of a hub gene, reinforcing its established role in autosomal dominant forms of the disease. LRRK2 G2019S [53] and other mutations are a common cause of fPD and are associated with an increased risk for sPD [54, 55]. This mutation has been shown to trigger neurotoxic protein aggregation and is associated with various pathological features [53]. Additionally, LRRK2 mutations have been linked to alterations in endolysosomal trafficking, compromising the subcellular distribution of lysosomes [56, 57], which can also impact microglial actin dynamics and suppress lysosome degradative activity in macrophages and microglia [58]. The fPD cases driven by LRRK2 mutations are prime candidates for emerging kinase inhibitors (e.g., DNL201) [59].

The identified hub genes in the LOPD modules were SNCA in the first module (Figs. 2D and 3D), ALB in the second (Figs. 2D' and 3D'), and IL6 in the third (Figs. 2D" and 3D"). Studies revealed that the gene dosage effect of SNCA on disease progression underscores its importance in PD [60]. SNCA duplications are associated with a more typical LOPD phenotype [51]. Moreover, the relationship between specific SNCA gene polymorphisms and the risk of late-onset idiopathic PD development underscores the genetic complexity of the disease [61]. In addition to SNCA, the IL6 gene has also been implicated in PD. Genetic variations in IL6 have been suggested to influence the onset and progression of neuroinflammatory disorders, including PD [62]. Studies have emphasized the significance of genes such as PRKN/PINK1 mutations in Parkinsonism, highlighting IL6 as a potential progression marker in PD [63]. There is limited direct evidence linking ALB with PD; however, a recent study reveals that the mortality of PD patients is related to a higher level of C-reactive protein–albumin ratio [64]. SNCA-centric YOPD/LOPD cohorts might respond to therapies reducing α-synuclein aggregation, such as monoclonal antibodies in clinical trials (e.g., prasinezumab) [65].

In sPD the first module includes the PRKN (Figs. 2E and 3E), again establishing its central role across various forms of PD. The second module includes the IL1A, IL1B, IL10, and TNF (Figs. 2E' and 3E'), implying that anti- and inflammatory cytokines significantly contribute to the sporadic form of the disease, highlighting the interaction between genetic variants and environmental factors. The third module includes the CYP1A1 (Figs. 2E" and 3E") as hub genes indicate the potential influence of environmental toxins and metabolic processes on the risk for developing sporadic PD, suggesting a pathway through which exposure may modify disease outcomes. Studies have shown that biallelic variants in PRKN have been identified in a notable percentage of sPD cases, highlighting the importance of this gene in the pathogenesis of the disease [66]. While PRKN mutations are a common cause of PD, heterozygous carriers of PRKN mutations do not necessarily have an increased risk of developing PD [67]. Therefore, genetic and environmental factors may influence the impact of PRKN mutations on sPD risk, including IL1A, IL1B, IL10, and TNF [68], which received comparable scores for the hub role in the second module (Fig. 3E') in our study. Studies have revealed elevated levels of proinflammatory cytokines, like TNF-α and

Table 3 Hub nodes SNPs association in Parkinson's disease

Gene	Variant	Consequence	Alleles	Codon	Referenced PMIDs
PRKN	rs1801474	Missense variant	C/T	Ser/Asn	31512170, 19909784, 12584415, 10511432, 12165399
	rs1801582	Missense variant	C/G, T	Val/Leu, Val/Ile	31512170, 14639672, 22361577
	rs1438259227	Missense variant	T/A	Asp/Val	24313877, 18704525
	rs1801334	Missense variant	C/T	Asp/Asn	12165399, 19909784
	rs34424986	Missense variant	G/A, T	Arg/Trp, Arg/Arg	16019250, 29353703
	rs1258359845	Synonymous variant	T/C	Lys/Lys	12165399
	rs1330260959	Missense variant	A/C, T	Ile/Met, Ile/Ile	25029497
	rs147757966	Missense variant	C/A, G, T	Arg/Leu, Arg/Pro, Arg/Gln	26631732
	rs182893847	Missense variant	T/C, G	Met/Val, Met/Leu	29223129
	rs199657839	Missense variant	G/A	Arg/Cys	16793319
	rs368134308	Missense variant	C/A, G, T	Arg/Leu, Arg/Pro, Arg/His	16793319
	rs377591051	Missense variant	C/T	Glu/Lys	31178336
	rs56092260	Missense variant	G/A	Arg/Trp	10965160
	rs571092914	Missense variant	C/A, T	Ala/Ser, Ala/Thr	25865804
	rs62637702	3 prime UTR variant	T/C	–	23275044
	rs72480422	Missense variant	C/A, T	Asp/Tyr, Asp/Asn	18514563
	rs754604402	Missense variant	C/T	Ser/Asn	30404819
	rs766948045	Missense variant	G/A	His/Tyr	29353703
	rs778798543	Missense variant	T/C	Tyr/Cys	16793319
	rs9347683	5 prime UTR variant	A/C, G, T	–	21176923, 18387843
IL6	rs1800795	Intron variant	C/G	–	22155094
IL1B	rs1143623	Upstream gene variant	C/G	–	30813952
	rs16944	Upstream gene variant	A/G	–	27640071
CYP1A1	rs1279844744	Missense variant	A/G	Cys/Arg	25648260
	rs1368310331	Synonymous variant	T/C	Val/Val	25648260
	rs777119337	Missense variant	C/T	Arg/Lys	25648260
SNCA	rs356219	Intron variant	G/A	–	31244647, 31234232, 31325583, 31041581
	rs356220	Intron variant	T/A, C, G	–	31863812
	rs356182	Intron variant	G/A, C	–	28892059, 28078311, 26738859, 30598082
	rs181489	Intron variant	T/A, C	–	22438815, 21738487, 25656566
	rs356221	Intron variant	A/T	–	21738487, 23182315, 22438815
	rs168552	Intron variant	C/T, A, G	–	23071545
	rs356169	Intron variant	G/T	–	1977,175
	rs356181	Intron variant	G/A, C	–	36092799, 33804213, 30618224, 30336481
	rs2736990	Intron variant	G/A, T	–	30410434, 28844730, 24511991, 24005725, 25,129,240
	rs356203	Intron variant	C/T	–	30957308, 21738487, 22438815

Table 3 (continued)

Gene	Variant	Consequence	Alleles	Codon	Referenced PMIDs
	rs356165	3 prime UTR variant	G/A	–	24418406, 25370538, 25623333
	rs3822086	Intron variant	C/T	–	26203864, 26208350, 31325583
	rs7684318	Intron variant	T/C	–	22425546, 20513365, 21738487
	rs2737029	Intron variant	T/C	–	30410434, 21738487, 22438815
	rs894278	Intron variant	T/G	–	22438815, 23853107, 30778284
	rs356168	Intron variant	G/A	–	28979294, 21738487, 20711177
	rs356204	Intron variant	T/C	–	18606870, 22438815
	rs3775439	Intron variant	G/A	–	21738487, 22912757, 22438815
	rs3857059	Intron variant	A/G, T	–	21738487, 22438815, 27332068
	rs10516845	Intron variant	A/G, T	–	21738487
	rs2197120	Intron variant	A/G	–	21738487, 22438815
	rs2298728	Intron variant	G/A, T	–	21738487
	rs356188	Intron variant	T/C	–	22438815
	rs356200	Intron variant	T/C	–	21738487
	rs3775423	Intron variant	C/T	–	21738487
	rs3796661	Intron variant	C/T	–	22438815
	rs3857053	3 prime UTR variant	C/T	–	21738487
	rs8180209	Intron variant	A/G	–	28011712
	rs104893875	Missense variant	C/T	Glu/Lys	31136022, 30989398, 31405930, 31242217, 31048377, 31111370, 31178336
	rs104893877	Missense variant	C/T	Ala/Thr	31417337, 31092553, 31709672, 31552910, 31816026
	rs201106962	Missense variant	A/C	His/Gln	28373279 29398121, 30777422
	rs431905511	Missense variant	C/T	Gly/Asp	27613114, 30777422, 31643109
	rs542171324	Missense variant	G/A, C	Ala/Val, Ala/Gly	29771508, 28666710
	rs10014396	Intron variant	T/C	–	22912757
	rs17016074	3 prime UTR variant	G/A	–	19540308
	rs356186	Intron variant	A/G	–	25656566
	rs3775442	Intron variant	C/T	–	21812969
	rs3775444	Intron variant	C/T	–	26208350
	rs777296100	3 prime UTR variant	-/TAA, TAAAA	–	28431219
	rs11931074	Intron variant	G/A, C, T	–	30120622, 30424941, 31243602, 31758346
	rs2572323	Intron variant	A/G	–	21738487
	rs356174	Intron variant	G/T	–	21738487
	rs356180	Intron variant	A/G	–	21738487
	rs1372520	Intron variant	T/C	–	21738487
	rs104893878	Missense variant	C/G	Ala/Pro	29191831, 29718367, 29503608, 29524599, 31426448

Table 3 (continued)

Gene	Variant	Consequence	Alleles	Codon	Referenced PMIDs
	rs1330229174	Missense variant	T/C	Lys/Glu	28911198, 31048377
	rs2301135	5 prime UTR variant	G/C	–	23182315
	rs2619363	Intron variant	G/C, T	–	17872362
	rs2583988	Non-coding transcript exon variant	C/A, T	–	22438815, 17872362, 19890971
	rs1372519	5 prime UTR variant	A/G	–	21738487
	rs2301134	Intron variant	A/G	–	23182315
	rs2619364	Non-coding transcript exon variant	A/C, G	–	17872362
	rs3756063	Intron variant	G/C	–	27423554
LRRK2	rs66737902	3 prime UTR variant	T/C	–	24758914
	rs34637584	Missense variant	G/A	Gly/Ser	31813996, 31292011, 31373835, 31605779
	rs1491942	Intron variant	C/G	–	22438815, 22451204, 22438815, 24842889
	rs28903073	Intron variant	G/A	–	27182965, 21738487
	rs33939927	Missense variant	C/A, G, T	Arg/Ser, Arg/Gly, Arg/Cys	29177506, 30592623, 31495079
	rs33949390	Missense variant	G/A, C, T	Arg/His, Arg/Pro, Arg, Leu	31487119, 31041581, 29567424
	rs7133914	Missense variant	G/A, T	Arg/His, Arg/Leu	31487119, 29593234, 29241968
	rs34995376	Missense variant	G/A	Arg/His	27423549, 24591621, 23726462
	rs34410987	Missense variant	C/T	Pro/Leu	22575234, 21406209
	rs7308720	Missense variant	C/A, G	Asn/Lys, Asn/Lys	31487119, 29593234, 29241968
	rs11564148	Missense variant	T/A	Ser/Thr	28395805, 27734136, 26346174
	rs17466213	Missense variant	A/G	Ile/Val	31029016, 29480226, 21796139
	rs34594498	Missense variant	C/T	Ala/Val	22575234, 22807999, 26234753
	rs35870237	Missense variant	T/C	Ile/Thr	24695735, 17395370, 16939701
	rs74163686	Missense variant	A/C	Asn/His	30592623, 29519959, 22154298
	rs35173587	Missense variant	G/A, T	Arg/Lys, Arg/Met	19006185, 17078063, 20177695
	rs35507033	Missense variant	G/A, C	Arg/Gln, Arg/Pro	17149721, 25174650, 17216639
	rs35801418	Missense variant	A/C, G	Tyr/Ser, Tyr/Cys	20,301,387, 18,591,067, 15,541,309, 15,541,308, 16,003,110, 21,885,347
	rs11176013	Synonymous variant	A/G	Lys/Lys	23115130, 27734136
	rs34015634	Missense variant	T/C	Ile/Thr	27628070, 29127874
	rs35658131	Missense variant	A/G	Tyr/Cys	21885347, 22166457
	rs10878307	Missense variant	A/G	Ile/Val	31790336
	rs111341148	Missense variant	G/A	Arg/Gln	19343804
	rs111501952	Missense variant	G/A, C	Val/Ile, Val/Leu	23124679
	rs112998035	Synonymous variant	C/T	Arg/Arg	18353371
	rs200660418	Missense variant	C/A, G, T	Pro/Thr, Pro/Ala, Pro/Ser	22023810

Table 3 (continued)

Gene	Variant	Consequence	Alleles	Codon	Referenced PMIDs
	rs747338046	Missense variant	G/C	Gly/Ala	17078063
	rs75148313	Missense variant	G/A	Ser/Asn	17523199
	rs78365431	Missense variant	G/T	Gln/His	21632271
	rs1491923	Intron variant	A/G	–	19915575
	rs34778348	Missense variant	G/A	Gly/Arg	31487119, 31041581, 30133089, 31824408
	rs76904798	Intron variant	C/T	–	28892059, 26738859, 25064009
	rs2046932	Intron variant	G/A	–	24842889
	rs11564273	Intron variant	T/G	–	22438815
	rs117762348	Non-coding transcript exon variant	A/G	–	23967090
	rs10878226	Non-coding transcript exon variant	G/A, C	–	23115130
PINK1	rs768091663	Missense	G > C	Ala/Pro	23303188, 23459931, 15349860, 16009891, 23063710, 33845304
	rs1480758482	Frameshift	deletion	Tyr	15087508, 15349870, 32713623
	rs775479526	Frameshift	deletion	Tyr	24677602, 15349870, 17960343, 18785233
	rs2154533643	Nonsense	G > A	Trp/Ter	15087508, 15349870
	rs2053233432	Splice donor	G > A	–	17576681, 9536098, 20356854, 27574110
	rs2053228483	Splice acceptor	G > A	–	16199547, 15087508, 15349870
	rs755000580	Frameshift	deletion	Cys	24677602, 15087508, 15349870
	rs1005937012	Nonsense	C > T	Gln/Ter	15087508, 15349870
	rs756783990	Nonsense	C > A	Tyr/Ter	16482571, 20558144, 21996382
	rs1557561340	Frameshift	deletion	Ala	28492532, 15087508, 15349870
	rs34208370	Nonsense	C > T	Arg/Ter	15349870, 17960343, 18785233, 20547144, 29255601, 25741868
	rs756677845	Frameshift	deletion	Arg	24033266
	rs45539432	Nonsense	C > T	Gln/Ter	16769864, 18685134, 28502045, 15087508, 15349870
	rs74315360	Missense	C > A	Ala/Asp	16966503
	rs74315359	Missense	C > T	Thr/Met	18541801, 18785233, 26274610, 22238344, 23303188, 23459931, 29255601
	rs750664040	In-frame insertion	CAACAA, CAACAACAA	Gln/duplicate	15970950
	rs730880302	Frameshift	duplicate	Asp	15349871
	rs28940285	Missense	T > C	Leu/Pro	15349870, 17055324, 22956510, 15824318, 17579517, 18359116, 23303188
	rs74315357	Nonsense	C > T	Arg/Ter	15349870

Table 3 (continued)

Gene	Variant	Consequence	Alleles	Codon	Referenced PMIDs
	rs74315356	Nonsense	G > A	Trp/Ter	15087508, 16207731, 18524835
	rs28940284	Missense	C > A	His/Gln	15349870
	rs74315355	Missense	G > A	Gly/Asp	18003639, 16207731, 15087508

Table 4 Transcription factor analysis of PD modules (scaled rank < 0.05)

Modules	TFs	Integrated scaled rank	Overlapping genes
jPD	MXI1	6.14×10^{-04}	PINK1, LRRK2, MAPT, FBXO7, SNCA
	FIZ1	6.22×10^{-04}	ATP13A2, MAPT, UBE2L3
	SOX10	7.12×10^{-04}	GPR37, MAPT, SNCA
YOPD	MXI1	6.14×10^{-04}	PINK1, LRRK2, FBXO7, SNCA
	SNAPC5	6.22×10^{-04}	PRKN, PINK1, PARK7
	FOXO4	7.12×10^{-04}	PINK1, APOE, SNCA, NFE2L2
LOPD	FOXA3	6.14×10^{-04}	AHSG, PON1, ALB, APOA1, APOB
	CREB3L3	6.22×10^{-04}	CRP, GCH1, AHSG, PON1, ALB, APOA1, APOB, LPA
	ESR2	7.12×10^{-04}	PRKN, IL10, IL6, MAPT, TNF, SNCA
sPD	NFE2L2	6.14×10^{-04}	IL1A, UCHL1, IL1B, CYP1B1, AHR, TNF
	BATF3	6.22×10^{-04}	IL10, CCL2, TNF
	ESR2	7.12×10^{-04}	PRKN, IL10, IL1A, UCHL1, IL1B, CYP1A1, CCL2, CYP1B1, AHR, TNF, SNCA
fPD	MXI1	6.14×10^{-04}	PINK1, LRRK2, SNCA
	SOX6	6.22×10^{-04}	PRKN, AIMP2, PINK1
	SOX2	7.12×10^{-04}	UCHL1, APOE, SNCA

The analysis identifies MXI1 in jPD, YOPD, fPD, and ESR2 in LOPD and sPD as the most significant TFs since more hub genes are covered

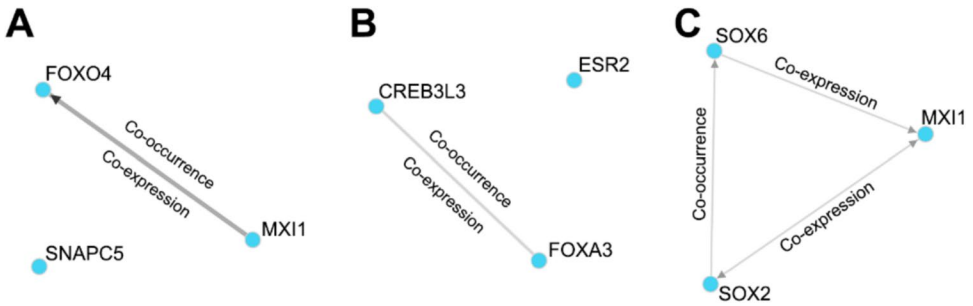

Fig. 5 TFs co-expression and co-occurrence scatter plot. This plot presents the critical transcription factors and their effects on one another within the context of Parkinson's disease. **A** Depiction of a network of MXI1 on FOXO4, highlighting direct interactions and the strength of their co-occurrence and expression through varying line thickness in YOPD. **B** The relationships among FOXA3 and CREB3L3, showcasing how these transcription factors influence each other in LOPD. **C** The interaction network of MIX1, SOX2, and SOX6 is presented, emphasizing co-occurrence and co-expression, with dual labeling on the connecting line to reflect the complexity of their interactions fPD

IL-1β, affecting the expression of P450s in patients with PD. P450s are involved in neurotransmitter, neurotoxic metabolite processing, neuroprotective hormone biosynthesis and catabolism, contributing to neurodegenerative disease progression [69]. Specific polymorphisms in genes encoding CYP1A1 increase PD risk [69]. The interplay between genetic predisposition and environmental factors in sPD highlights the need for further research into how lifestyle and exposure may influence disease onset and progression. For example, CYP1A1's role in sPD aligns with epidemiological links between pesticide exposure and PD risk, warranting studies on gene-environment interactions.

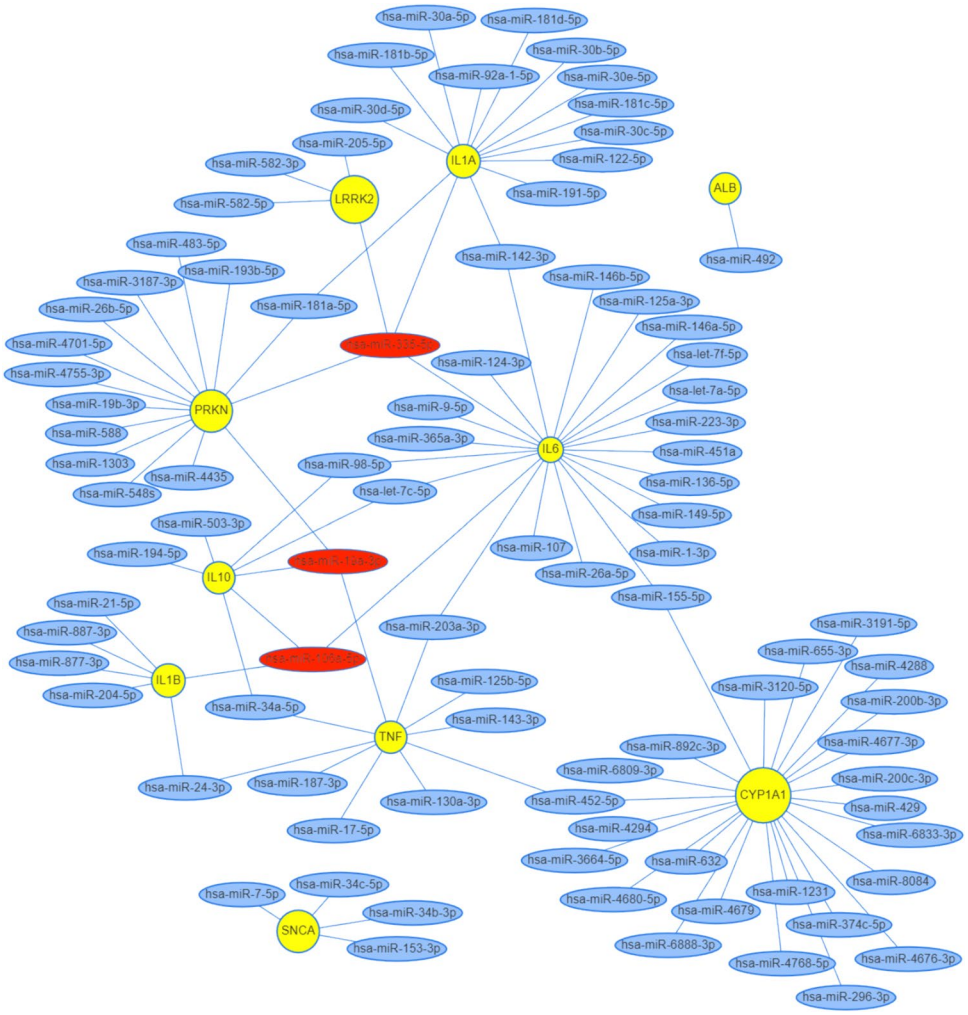

Fig. 6 The communication network between hub genes and miRNAs. This figure illustrates the communication network between selected hub genes and their associated miRNAs, mapped using the MIENTURNET tool. The yellow nodes represent the selected hub genes, highlighting their significance within the network. The blue elliptical nodes denote the related miRNAs interacting with the hub genes, indicating potential regulatory relationships. Notably, key miRNAs, such as hsa-miR-335-5p, hsa-miR-19a-3p, and hsa-miR-106a-5p, are highlighted in red due to their greater significance in regulating hub gene interactions

While MXI1's role in PD has not been extensively studied, its involvement in regulating proliferation mechanisms and cellular response to hypoxia suggests a potential impact on disease pathways [70, 71]. In our study of TFs' functional enrichment, MXI1 has emerged as a critical regulator in jPD, YOPD, and fPD, significantly influencing the hub nodes PRKN and SNCA, which highlights its potential role in modulating pathways linked to neurodegeneration (Table 4). In LOPD, ESR2 assumes a vital regulatory function, particularly in modulating SNCA and IL6, suggesting its involvement in inflammatory processes. In sPD, ESR2 expands its regulatory influence to a broader spectrum of genes, including PRKN, IL10, IL1A, TNF, and CYP1A1, underscoring its multifaceted role in neuroprotection and inflammation. ESR2's role in PD is exciting due to the neuroprotective, inflammation modulation, and regulatory effects of estrogen and the observation that estrogen levels and receptor activity might influence neurodegenerative processes [72, 73]. This result supports our prediction regarding the pivotal role of candidate transcription factors in the mechanisms underlying this study (Table 4). The co-expression and co-occurrence of FOXO4, SOX2, and SOX6 with MXI1 highlight a significant interaction among these transcription factors that may regulate gene expression and influence cellular mechanisms (Fig. 5). This interconnectedness suggests a complex regulatory network where FOXO4, SOX2, and SOX6 collaboratively impact MXI1 transcription, potentially affecting various biological processes such as cell differentiation, stress response, and neurodegeneration [74–76].

As shown in Fig. 6, hsa-miR-335-5p has been associated with regulating hub genes and inflammatory responses. It can be modulated by shear stress and NF-κB signaling factors, highlighting the intricate regulatory mechanisms involved [77–79]. Additionally, studies have suggested a link between hsa-miR-30e-5p and PD, suggesting a broader role of miRNAs, including hsa-miR-335-5p, in neurodegenerative conditions [80]. Recent research has highlighted the downregulation of hsa-miR-144-3p in YOPD, suggesting a potential role for microRNAs in the disease's progression [81]. Additionally, another research highlighted that hsa-miR-133b and hsa-miR-1-3p were downregulated in postmenopausal osteoporosis, indicating a connection between

miRNA dysregulation and bone health, which could be relevant in PD where bone health issues are prevalent [82]. Research on miRNAs like hsa-miR-106a-5p has shown their potential role in various diseases, which has been implicated in regulating inflammatory responses [83] and promoting angiogenesis [84]. The miR-335-5p (targeting PRKN/IL6) could serve as a plasma biomarker for early PD detection, while repurposing TNF-α inhibitors (e.g., etanercept) IL-6 receptor antagonists may benefit sPD patients with elevated neuroinflammation [85].

There are a few limitations to consider in this study; first, clinical overlap between subtypes (e.g., YOPD vs. jPD or fPD vs. LOPD) may confound genetic associations, as age-at-onset thresholds are not universally standardized, potentially introducing heterogeneity. Second, the exclusion of studies reporting non-significant or negative associations risks publication bias, skewing results toward well-established loci and overlooking genes (e.g., PRKN, SNCA) with rare or dependent variants. While this approach enhances focus on replicated findings, future meta-analyses integrating negative results are needed to refine subtype-specific genetic architectures. Third, reliance on common variants overlooks rare alleles and structural variations (e.g., PRKN exon rearrangements), which are critical in YOPD or fPD cases. Finally, while miRNA-TF networks (e.g., miR-335-5p regulation of PRKN/IL6 and ESR2) were computationally predicted, functional validation through in vitro or in vivo models is pending, which necessitates future experimental studies to confirm these interactions.

This study's findings on the distinct genetic markers and pathways associated with each Parkinson's disease subtype provide a foundation for developing targeted diagnostic tools and therapeutic strategies, highlighting the importance of personalized medicine in managing this complex disorder. Hub genes such as LRRK2, predominantly associated with fPD, may serve as definitive biomarkers, indicating a potential genetic predisposition in younger patients. The SNCA gene exhibits critical involvement in both YOPD and LOPD; specific mutations within this gene can suggest a diagnosis of YOPD, while its association with inflammatory markers like IL6 is informative for LOPD presentations. PRKN is particularly relevant for cases of jPD; prioritizing its sequencing in early-onset cases could streamline genetic counseling, enabling families to anticipate disease progression and participate in surveillance programs for pre-symptomatic interventions. In contrast, inflammatory and anti-inflammatory cytokines such as IL1A, TNF, IL10, and IL1B, along with CYP1A1, are more commonly implicated in sPD. These hub node genes collectively contribute to developing a comprehensive diagnostic toolkit, enabling precise identification of PD subtypes, which may ultimately enhance patient outcomes and deepen our understanding of the disease's etiology. Plasma miR-335-5p, regulating PRKN/IL6, emerges as a non-invasive biomarker candidate for early PD detection, warranting validation in longitudinal cohorts. Future studies should focus on validating these genetic markers in larger, diverse cohorts and exploring their functional implications in PD pathology. Additionally, investigating the role of identified microRNAs in disease progression could provide new avenues for therapeutic intervention.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12035-025-05182-z.

Author Contribution D Z: Conceptualization, Methodology, Supervision and Validation. D Z and S TH: Data curation, Formal analysis, Visualization, Investigation, Writing-Original draft preparation.

Funding None.

Data Availability The PDGA and PDVA data during the current study obtained from UniProt (http://www.ebi.ac.uk/uniprot), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar), GWAS Catalog (https://www.ebi.ac.uk/gwas), CTD (http://ctdbase.org), ORPHANET (https://www.orpha.net/consor/cgi-bin/index.php), CLINGEN (https://www.clinicalgenome.org), GENOMICS ENGLAND (https://panelapp.genomicsengland.co.uk), CGI (https://www.cancergenomeinterpreter.org/home), PSYGENET (http://psygenet.org), LHGDN (https://www.dbs.ifi.lmu.de/~bundschu/LHGDN.html), and dbSNP (https://www.ncbi.nlm.nih.gov/snp). However, the raw data is available as jPD, YOPD, LOPD, sPD, and fPD (Supplementary Table 1) for further analysis and validation. The enrichment of GO terms, TFs, and miRNAs during the study was analyzed using g:Profiler (https://biit.cs.ut.ee/gprofiler/gost), ChEA3 (https://maayanlab.cloud/chea3), and MIENTURNET (http://userver.bio.uniroma1.it/apps/mienturnet), respectively.

Declarations

Ethics Approval and Consent to Participate None.

Conflict of interest The authors declare no competing interests.

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