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INTEGRATING GENOMICS AND PROTEOMICS TO IDENTIFY NOVEL TARGETS FOR PARKINSON'S DISEASE

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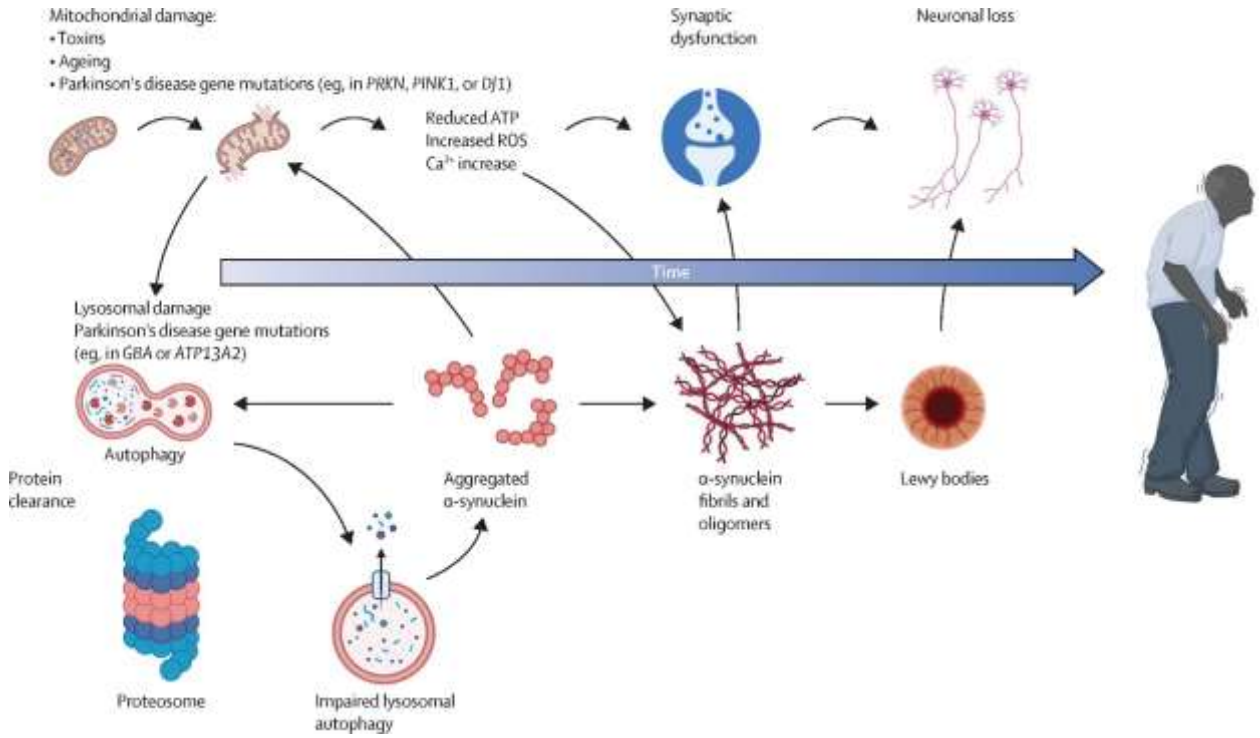
ABSTRACT:
Parkinson's disease (PD) is a chronic neurological disorder that primarily affects movement and progressively worsens over time. It occurs mainly due to the gradual loss of dopamine-producing neurons in the substantia nigra region of the brain. The reduction in dopamine disrupts normal motor control, leading to symptoms such as tremors, rigidity, and slowed movements. The development of PD is influenced by multiple factors, including genetic mutations, abnormal protein accumulation, mitochondrial dysfunction, oxidative stress, and defects in cellular clearance mechanisms. Several genes, including SNCA, LRRK2, PRKN, PINK1, DJ-1, VPS35, and GBA, are known to play key roles in disease progression. At the protein level, molecules such as alpha-synuclein, parkin, and tau contribute to neuronal damage and the formation of Lewy bodies. Integrating genomics and proteomics provides a deeper understanding of the molecular basis of Parkinson's disease. This combined approach supports the identification of novel biomarkers and helps in the development of targeted and personalized therapeutic strategies.

KEY WORDS: Parkinson's disease, Genomics, Proteomics, Dopaminergic neuron degeneration, α-Synuclein aggregation, Genetic mutations (SNCA, LRRK2, PRKN), Mitochondrial dysfunction, Oxidative stress, Biomarkers, Neurodegeneration.

INTRODUCTION:
Parkinson's disease is a progressive disorder of the nervous system that mainly affects movement and is more common in older individuals. The condition develops slowly and worsens over time, affecting both motor and non-motor functions. A key feature of Parkinson's disease is the degeneration of neurons in the substantia nigra, a part of the brain responsible for producing dopamine. Dopamine plays an essential role in controlling smooth and coordinated muscle movements. When dopamine levels decline, communication between different parts of the brain becomes impaired, leading to movement-related symptoms[1].
Common symptoms include tremors, muscle stiffness, slow movements (bradykinesia), and problems with balance and posture. As the disease advances, patients may also experience difficulty in speaking, swallowing, and performing daily activities. Non-motor symptoms such as depression, sleep disturbances, and memory problems can also occur. Although the exact cause of Parkinson's disease is not fully understood, it is considered a multifactorial condition involving both genetic and environmental influences. Molecular changes such as protein misfolding, oxidative stress, and mitochondrial damage contribute significantly to disease progression. it is essential to understand these mechanisms for improving diagnosis and treatment[2].

PATHOPHYSIOLOGY:
Parkinson's disease is mainly caused by a decrease in dopamine levels in the brain. Dopamine is an important chemical that helps in controlling body movements. It is made in a region of the brain known as the substantia nigra. When the nerve cells in this area start to get damaged or die, the production of dopamine reduces. Because of this, the signals between different parts of the brain, especially the basal ganglia which controls movement, become disturbed. This leads to the movement problems seen in Parkinson's disease.
Another factor that plays a role is the accumulation of abnormal proteins in the brain. These proteins do not fold properly and start to collect inside the nerve cells. Over time, they create stress within the cells, known as oxidative stress, and also affect the mitochondria, which are responsible for energy production. This gradually damages the cells and eventually causes them to die. There is also a theory that Parkinson's disease may be related to the immune system. In this case, the body mistakenly attacks its own brain cells, thinking they are harmful. This immune response may contribute to the damage of neurons. Genetic factors can also be involved. Certain gene mutations can affect how brain cell's function. For example, changes in the SNCA gene can lead to the formation of an abnormal protein called alpha-synuclein. This protein tends to clump together and form structures known as Lewy bodies, which are commonly found in people with Parkinson's disease. Along with this, factors like oxidative stress and mitochondrial problems further contribute to the degeneration of neurons[3].



pathophysiology of Parkinson's disease

DRUGS USED IN THE TREATMENT OF PARKINSON'S DISEASE[4]:

Drugs affecting brain dopaminergic system

- Dopamine precursor- Levodopa
- Peripheral decarboxylase inhibitors– Carbidopa, Benserazide
- Dopaminergic agonists– Bromocriptine, Ropinirole, Pramipexole
- MAO-B inhibitors– Selegiline, Rasagiline
- COMT inhibitors- Entacapone, Tolcapone
- Glutamate (NMDA receptor) agonist (Dopamine facilitator)– Amantadine

Drugs affecting brain cholinergic system

- Central anticholinergics– Trihexyphenidyl, Procyclidine, Biperiden
- Antihistaminic – Orphenadrine, Promethazine

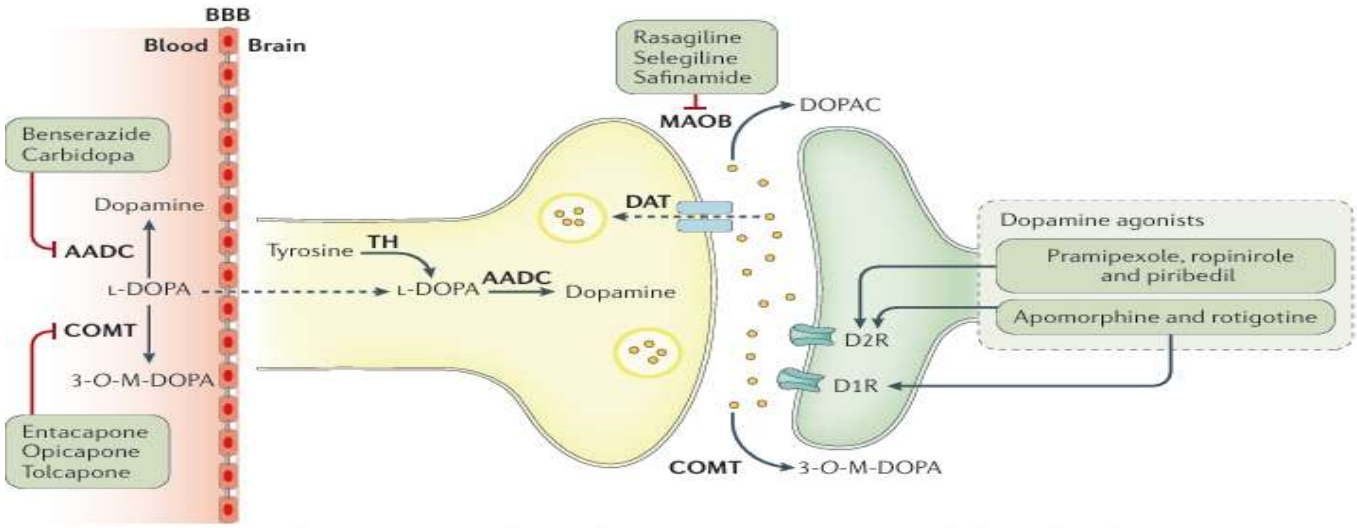


Figure 7 | **Dopaminergic drug targets in Parkinson disease.** Presynaptic targets include L-DOPA substitution combined with peripherally active inhibitors of aromatic amino acid decarboxylase (AADC) or catechol-*O*-methyltransferase (COMT). Monoamine oxidase type B (MAOB) inhibitors enhance the synaptic availability of dopamine (both endogenous and exogenous), whereas dopamine agonists act postsynaptically. Dashed arrow from blood to brain designates blood–brain barrier (BBB) transport of L-DOPA. Dashed arrow through the dopamine transporter (DAT) denotes reuptake of dopamine from the synaptic cleft. 3-*O*-M-DOPA, 3-*O*-methyl-DOPA; D1R, dopamine D1 receptor; DOPAC, 3,4-dioxy-phenylacetic acid; TH, tyrosine hydroxylase.

drugs affecting brain dopaminergic system[5]

CENTRAL ANTICHOLINERGICS:

- Cholinergic antagonists compete with Ach for binding to post-synaptic receptors.

- These drugs show competitive antagonism. The binding of the antagonist to the receptor prevents the binding of the agonist to that same receptor.
- These drugs block the muscarinic receptors in the brain to reduce excessive cholinergic signalling. It helps to rebalance the relationship between dopamine and acetylcholine.
- They also inhibit the reuptake of dopamine in they striatum and controls the motor functions.[6]

ANTIHISTAMINICS

- **Neuroprotection via histamine receptor antagonism:** Antihistamines block histamine from binding to histamine receptors.
- **H1 receptor antagonism:** By blocking H1 receptors, the antihistamines can safeguard against histamine-induced dopaminergic neuron death.
- **Reducing oxidative stress:** The mechanism can involve downregulating oxidative stress, a process contributing to neurodegeneration in PD.
- **Decreasing inflammation:** Antihistamines can help by decreasing inflammatory mediators that contribute to dopaminergic neurotoxicity and cell death.[7]

POTENTIAL DRUG TARGETS FOR TREATMENT OF PARKINSON'S DISEASE

1.COMT (Catechol O methyl transferase): The COMT enzyme is involved in breaking down neurotransmitters like dopamine and is encoded by the COMT gene. COMT metabolizes L-DOPA (levodopa) into an inactive metabolite called 3-O-methyldopa (3-OMD). This process is a major pathway for L-DOPA degradation, particularly in the peripheral tissues (liver, kidneys, gastrointestinal tract)[8].

2.AADC (Aromatic amino acid decarboxylase):is an enzyme that catalyses the synthesis of key neurotransmitters like dopamine and serotonin by removing a carboxyl group from their precursor amino acids. It converts the drug levodopa to dopamine in periphery. To enhance the therapeutic effect of levodopa for conditions like Parkinson's disease, peripheral decarboxylase inhibitors (PDIs), such as carbidopa or benserazide, are used to block this peripheral conversion, allowing more levodopa to reach the brain[9].

3.MAO-B (Mono amine oxidase): It an enzyme that oxidizes neurotransmitters like dopamine and is involved in the metabolism of monoamines. It is a target for drugs, particularly for treating neurological disorders like Parkinson's disease, and its activity can increase with age. MAO-B converts dopamine into DOPAC (3,4-dihydroxyphenylacetic acid).[10]

INTRODUCTION TO GENOMICS:

Genomics is the study of an organism's entire set of DNAS, or its genome, which includes all of its genes and how they interact with each other and the environment. This multidisciplinary field uses techniques like DNA sequencing and bioinformatics to analyse the structure, function, and evolution of genomes, providing a more comprehensive view than classical genetics, which focuses on individual genes.

GENOMICS IN PARKINSON'S DISEASE:

Genomics in Parkinson's disease reveals that the disorder results from a complex interplay of multiple genetic and environmental factors. Several genes have been linked to Parkinson's, such as SNCA, LRRK2, PRKN, PINK1, DJ-1, and GBA. Mutations in these genes affect vital cellular processes including protein folding, mitochondrial function, lysosomal degradation, and dopamine regulation. Some genes follow autosomal dominant inheritance, meaning a single mutation can increase risk, while others are recessive and require mutations in both gene copies. Genome-wide studies have identified common and rare genetic variants that contribute to Parkinson's risk in different ways. Understanding these genetic factors helps explain disease onset, progression, and individual differences in symptoms. It also guides research toward personalized treatment options targeting specific molecular pathways disrupted by these genes. Genomic insights continue to improve diagnostic accuracy and advance therapeutic development for Parkinson's disease.

Genes Linked to Parkinson's disease:

1. SNCA (PARK1/4):

SNCA codes for alpha-synuclein protein, found in presynaptic terminals of dopaminergic neurons. It helps regulate synapse function and vesicle trafficking for smooth nerve signalling. Mutations cause abnormal protein clumping into Lewy bodies, disrupting neuron communication. This leads to early-onset PD with symptoms like sleep issues around age 50. The protein's three domains misfold into toxic fibrils when mutated. Alpha-synuclein normally maintains synaptic plasticity but aggregates under stress.

Pathogenesis: involves fibrillogenesis and enhanced clumping from glucocerebroside buildup. It inhibits lysosomal enzymes, worsening neuron death.

2. LRRK2 (PARK8):

LRRK2 encodes a large protein kinase called dardarin, active in neurons and glial cells. It supports neurite growth, autophagy, and immune regulation via GTPase and kinase activities. Mutations like G2019S alter protein interactions and kinase function. This causes late-onset dominant PD, common in certain populations.

Pathogenesis: stems from disrupted trafficking and heightened kinase activity, leading to neuron loss. The protein's multidomain structure fails, promoting inflammation.

3. PRKN/Parkin (PARK2):

PRKN codes for E3 ubiquitin ligase protein in mitochondria. It tags damaged proteins for degradation via proteasome or autophagy. Mutations cause early-onset recessive PD with hyper-reflexia. Without functional Parkin, receptors like Pael-R accumulate, killing neurons.

Pathogenesis: involves failed mitophagy and protein buildup in synaptic vesicles

4. PINK1 (PARK6):

PINK1 encodes a mitochondrial serine/threonine kinase on the membrane. It recruits Parkin for mitophagy, clearing faulty mitochondria. Mutations lead to recessive PD with dystonia.

Pathogenesis: features deformed mitochondria and oxidative stress from poor quality control.

5. DJ-1 (PARK7):
DJ-1 codes for a 189-amino-acid protein forming dimers in nerve cells. It protects against oxidative stress and regulates mitochondria. Mutations cause rare recessive PD with tremors.
Pathogenesis: includes heightened reactive oxygen species and altered mitochondrial shape.
6. VPS35 (PARK17):
VPS35 codes for Vacuolar protein sorting 35, a key part of the retromer complex in lysosomal vesicles. These complex handles transport of membrane-bound compartments from the plasma membrane to Golgi bodies inside cells. It ensures proteins move correctly between cell parts for healthy neuron function. In brain cells, VPS35 supports recycling of key receptors needed for signalling. Mutations disrupt this traffic, causing buildup of waste in neurons. The gene links to autosomal dominant PD with tremors, bradykinesia, limb rigidity, and gait defects.
Pathogenesis: involves failed retromer function, leading to protein mishandling and dopaminergic neuron death in the substantia nigra.
7. GBA (GBA1):
GBA codes for beta-glucocerebrosidase, a lysosomal enzyme active in the endoplasmic reticulum. This enzyme breaks down glycolipids, keeping lysosomes clear of fatty waste. Healthy GBA prevents toxic buildup in neurons by regulating lysosomal activity. Mutations produce faulty enzyme, mimicking Gaucher disease traits. It worsens PD progression, seen in 8-14% of cases at autopsy. Symptoms include hallucinations and cognitive decline. Variants like E326K, T369M, N370S, D409H, and L444P are noted.
Pathogenesis: features non-functional enzyme causing glucocerebroside accumulation, which boosts alpha-synuclein clumping and neuron loss.
8. CHCHD2:
CHCHD2 codes for coiled-coil-helix-coiled-coil-helix domain containing protein 2, a mitochondrial protein in cortical neurons. It boosts mitochondrial oxygen use for energy production. The protein supports cell survival by maintaining mitochondrial function. Mutations trigger apoptosis and reactive oxygen species overproduction. This recessive form causes bradykinesia, rigidity, hypo mimic face, and dilated pupils. Variants are G66V and P80L.
Pathogenesis: involves mitochondrial dysfunction, oxidative stress, and neuron death resembling PD features.
These genes contribute to PD through mechanisms like protein aggregation, mitochondrial dysfunction, and lysosomal impairment.[11]

INTRODUCTION TO PROTEOMICS:
Proteomics is the large- scale study of proteins, particularly their structure, function, expression, and relations within a natural system. It complements genomics and is pivotal for understanding cellular processes, complaint mechanisms, and medicine discovery. Proteomics is the methodical analysis of the entire set of proteins(proteome) expressed by a cell, towel, or organism under specific conditions. Proteomics provides direct perceptivity into cellular functions because proteins carry out utmost of the gene functions in cells.
Proteomics can be used to study the expression of proteins. also, proteomics can reveal how proteins are modified, similar as by post-translational variations. Proteomics can also give information on the movement of proteins between different subcellular chambers, as well as their involvement in metabolic pathways and relations with other proteins. Proteomics can also be used to identify implicit medicine targets and develop more effective curatives by studying the protein- protein relations in diseased cells[12].

PROTEOMICS IN PARKINSON'S DISEASE:
Importance of Proteomics in Parkinson's Disease:

- Reveals dysregulated proteins and pathways linked to PD pathogenesis.
- Identifies biomarkers for early detection and disease progression.
- Helps understand protein aggregation (e.g., α-synuclein misfolding).
- Supports drug target discovery and therapeutic development.

Several proteins are involved in Parkinson's disease. If any mutations or changes in gene sequences occur, they code for abnormal proteins and results in degeneration of neurons which leads to Parkinson's disease[13].
The list of Proteins involved in Parkinson's disease are:
1. α-Synuclein (SNCA): It is involved in synaptic vesicle regulation and neuronal function.
• Tends to misfold and aggregate in the brain.
• Forms Lewy bodies which is the hallmark of Parkinson's disease.
Pathogenesis:
• Mutation in SNCA gene leads to familial Parkinson's disease.
• Accumulation of α-synuclein disrupts cellular functions, especially in dopaminergic neurons[14].
2. Leucine-rich repeat kinase 2 (LRRK2): LRRK2 is a kinase that plays a key role in neuronal signalling and vesicle trafficking. It is also involved in Autophagy & Lysosomal Function.
Pathogenesis: Mutations in LRRK2 lead to abnormal kinase activity, which causes neurodegeneration by promoting α synuclein aggregation and impairing autophagy[15].
3. Parkin (PRKN):
• An E3 ubiquitin ligase involved in the ubiquitin-proteasome system (UPS).
• Responsible for removing damaged or misfolded proteins.
Pathogenesis:
• Mutations in the PRKN gene lead to early-onset Parkinson's disease.
• Dysfunction causes accumulation of toxic proteins, resulting in neuronal damage[16].
4. PTEN (Phosphate and TENsin homolog)-induced kinase 1 (PINK1): Regulates mitochondrial quality control.
Promotes degradation of damaged mitochondria through autophagy (mitophagy).
Pathogenesis: Mutations in PINK1 gene cause autosomal recessive Parkinson's disease.
PINK1 dysfunction impairs mitochondrial function, leading to neuronal death[17]
5. DJ-1 (PARK7): DJ-1 is an antioxidant protein that protects neurons from oxidative stress.

Pathogenesis: Loss-of-function, mutations in DJ-1 reduce the neuronal defence against oxidative stress, leading to mitochondrial dysfunction and increased apoptosis[18].

6. Glucocerebrosidase (GBA): GBA is a lysosomal enzyme that is responsible for glycolipid metabolism.

Pathogenesis: Mutations in GBA gene decrease enzyme activity, resulting in α-synuclein accumulation and lysosomal dysfunction, which drive neurodegeneration[19]

7. Tau (MAPT): TAU protein is a microtubule-associated protein that stabilizes neuronal microtubules.

Pathogenesis: In Parkinson's disease, hyper phosphorylated TAU forms neurofibrillary tangles that disrupt cytoskeletal stability, contributing to neuronal death[20].

8. Ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1): UCHL1 is a neuron-specific deubiquitinase enzyme that maintains protein homeostasis by recycling ubiquitin and regulating the ubiquitin-proteasome system.

Pathogenesis: Mutations or post-translational modifications impair its function, leading to defective proteostasis, increased α-synuclein accumulation and Lewy-body formation[21]

9. VPS35 (Vacuolar protein sorting 35): Vacuolar protein sorting is a component of the retromer complex involved in endosomal/lysosomal protein sorting, autophagy, mitochondrial quality control.

Pathogenesis: Mutations in VPS35 cause autosomal-dominant PD by disrupting retromer function (sort and transport membrane proteins), leading to accumulation of dysfunctional mitochondria, α-synuclein aggregation and dopaminergic neuron death[22].

10. Synphilin-1 (SNCAIP): Synphilin-1 is a synaptic protein that interacts with α-synuclein and parkin. It promotes protein aggregation and is involved in synaptic function and the ubiquitin-proteasome system.

Pathogenesis: Synphilin-1 is found in Lewy bodies; its co-aggregates with α-synuclein and can promote formation of inclusions. Its interaction with parkin and impaired degradation may lead to accumulation of toxic aggregates and contribute to dopaminergic neuron loss[23].

Investigational molecules targeting on alpha- synuclein:

MOLECULES	CURRENT STATUS
1.MINZASOLMIN	Present in phase 2 clinical trials
2.NILOTINIB	Present in phase 2 clinical trials
3.VADOBATINIB/K0706	Present in phase 2 clinical trials
4.Anle138b [Emrusolmin]	Present in phase 1 clinical trials
5.UCB0599[UCB7853]	Present in phase 2 clinical trials

Investigational molecules targeting on [lrrk2]:

MOLECULES	CLINICAL STATUS
1.DNL201	Completed phase 1 trials.
2.DNL151(also known as BIIB122 or Denali/Biogen drug)	It is being testing in clinical trials[24].

Investigational molecules targeting on pten ((pink1):

MOLECULES	CURRENT STATUS
1.bpV (Phen) (Potassium bisperoxo(1,10-phenanthroline) xovanadate)	Used as a research molecule in preclinical studies (in vitro and in vivo animal models). It is not an FDA-approved drug for human clinical use.
2.bpV (HOpic)	Used as a research molecule in preclinical studies. Not an FDA-approved drug for human clinical use[25].

Investigational molecules targeting on dj-1 (park 7):

MOLECULES	CURRENT STATUS
1.Phenylbutyrate (PB)	Present in phase 1 clinical trials
2.UCP0045037 (DJ-1-binding compound)	Present in preclinical trials[26]

Investigational molecules targeting on glucocerebrosidase (GCase):

MOLECULES	CURRENT STATUS
1. Ambroxol	Present in Phase II clinical trials[28]
2.Venglustat (GZ/SAR402671)	Present in phase II clinical trials[27]

investigational molecules targeting on tau (mapt) protein:

MOLECULES	CURRENT STATUS
1.Metformin	Present in Phase II clinical trials
2.Nilotinib	Present in Phase II clinical trials[29]

LITERATURE REVIEW:

Shen et al. (2020), in their study titled "Identification of Parkinson's Disease-Related Pathways and Potential Risk Factors," conducted a gene expression analysis of peripheral blood mononuclear cells (PBMCs) from Parkinson's disease (PD) patients and healthy controls to identify dysregulated pathways and potential risk factors associated with the disease. Using robust multi-array average (RMA) normalization and the Limma package, they identified 333 differentially expressed genes (DEGs), including 293 upregulated and 40 downregulated genes in PD samples. Pathway analysis using Pathifier revealed significant alterations in

biological processes such as inflammation, intercellular communication, and cytoskeletal remodeling. Additionally, protein–protein interaction network analysis via STRING identified ten hub genes, which were used to develop a support vector machine (SVM) model achieving a validation accuracy of 75%. The study emphasized the role of neuroinflammatory and platelet-related mechanisms in PD pathogenesis, suggesting that dysregulation of genes such as ITGB5, ITGB3, and ITGA2B may contribute to α-synuclein toxicity and progressive neurodegeneration, thereby highlighting the importance of immune and platelet-associated pathways in Parkinson's disease progression.[30]

Li et al. (2021), in their study titled "Characterizing the Expression Patterns of Parkinson's Disease Associated Genes," analyzed 107 genes associated with Parkinson's disease (PD) to investigate their expression patterns and relationship to disease onset. Utilizing data from the GTEx database, the authors found that these genes were highly expressed in key brain regions implicated in PD. Single-cell transcriptomic analysis further revealed that PD-associated genes exhibited higher expression in excitatory neurons compared to inhibitory neurons. Developmental analysis using BrainSpan data and weighted gene co-expression network analysis (WGCNA) identified distinct fetal-active and adult-active gene modules. Notably, adult-active gene modules were associated with early-onset PD, whereas fetal-active gene modules were linked to late-onset PD. These findings demonstrate that variations in gene expression across different tissues, neuronal subtypes, and developmental stages contribute to the heterogeneity of Parkinson's disease onset, providing insights into why the disease manifests earlier in some individuals and later in others.[31]

Teng et al. (2025), in their study titled "Exploring and Validating Key Genetic Biomarkers for Diagnosis of Parkinson's Disease," identified and validated crucial genetic biomarkers for Parkinson's disease (PD) using an integrative bioinformatics and experimental approach. The authors analyzed four GEO datasets derived from both brain and blood tissues to identify common differentially expressed genes (DEGs). Advanced machine learning techniques, including LASSO regression and support vector machine (SVM) analysis, were employed to screen and identify hub genes. Functional enrichment analyses further revealed the biological pathways associated with these genes. To validate their findings, blood samples from 60 PD patients and 60 healthy controls were analyzed using RT-qPCR, and receiver operating characteristic (ROC) curve analysis demonstrated strong diagnostic potential. Additionally, human brain cell models treated with MPP^+ were used to confirm gene function. Ultimately, three genes—GPX2, CR1, and ZNF556—were identified as key biomarkers, highlighting their potential utility in the early and accurate diagnosis of Parkinson's disease.[32]

Chen et al. (2015), in their study titled "Combining Human Disease Genetics and Mouse Model Phenotypes towards Drug Repositioning for Parkinson's Disease," developed an integrative approach to identify repurposable drugs for Parkinson's disease (PD) by combining human genetic data with mouse model phenotypes. The study analyzed 15 PD-associated genes and 358 mouse phenotypes, which were systematically categorized into 24 phenotype groups. Phenotype vectors were constructed for 1,197 FDA-approved drugs and compared with a PD-specific phenotype vector using semantic similarity measures to rank drugs based on their potential relevance. Notably, several known PD drugs ranked highly, supporting the validity of the approach, while novel candidate drugs demonstrated improved predictive accuracy. Further validation using GEO gene expression data involved comparing PD samples with healthy and drug-treated tissues to identify significant differentially expressed genes (DEGs) ($p < 0.05$). The analysis also assessed opposite regulation patterns, revealing that top-ranked drugs, such as Quetiapine, could reverse PD-associated gene expression signatures. Overall, the study concluded that cross-species integration of human genetics, mouse phenotypes, and drug–target biology is an effective strategy for prioritizing repurposable drugs for Parkinson's disease.[33]

Rahman and Liu (2023), in their study titled "A Genome-Wide Association Study Coupled with Machine Learning Approaches to Identify Influential Demographic and Genomic Factors Underlying Parkinson's Disease," employed an integrative framework combining genome-wide association study (GWAS) data with machine learning techniques to investigate the key demographic and genetic determinants of Parkinson's disease (PD). The study analyzed clinical, demographic, and genomic datasets to identify significant single nucleotide polymorphisms (SNPs) associated with PD. Multiple machine learning models, including artificial neural networks (ANN), random forest (RF), support vector machines (SVM), and logistic regression (LR), were utilized to prioritize important risk factors and highlight top predictive SNPs. Furthermore, gene set enrichment analysis (GSEA) was conducted to uncover the biological pathways involved in PD pathogenesis. The findings provide comprehensive insights into both the major risk factors and the underlying biological mechanisms of Parkinson's disease, contributing to a better understanding of disease development and progression.[34]

Kim et al. (2020), in their study titled "Large Scale Pathway Specific Polygenic Risk and Transcriptomic Community Network Analysis Identifies Novel Functional Pathways in Parkinson's Disease," employed an integrative approach combining large-scale polygenic risk scoring and transcriptomic network analysis to uncover genes and biological pathways associated with Parkinson's disease (PD). The study analyzed 2,199 biological pathways using polygenic risk score (PRS) and rare variant burden testing, alongside RNA sequencing-based network analysis and cell-type-specific mapping. This comprehensive strategy revealed significantly enriched transcriptional pathways implicated in PD. Additionally, Mendelian randomization analysis was used to identify causal relationships between gene expression and disease risk. The findings not only confirmed several previously known PD-associated genes but also identified 17 novel genes that may serve as potential therapeutic targets. Overall, the network-based analysis provided valuable insights into key biological processes underlying Parkinson's disease and expanded the understanding of its molecular mechanisms. [35]

Kia and Ruth (2018), in their study titled "Stratification of Candidate Genes for Parkinson's Disease Using Weighted Protein–Protein Interaction Network Analysis," applied a weighted protein–protein interaction (PPI) network approach to systematically prioritize candidate genes associated with Parkinson's disease (PD). The authors curated Mendelian PD-associated seed genes and integrated them with high-quality human PPI data, carefully filtering out non-specific and predicted interactions to enhance reliability. Multi-layered interaction networks were then constructed to explore disease-relevant biological processes. The analysis identified key PD-associated pathways, including mitochondrial-mediated cell death, immune response, and autophagy. To ensure robustness, the findings were validated through 100,000 random simulations. This network-based strategy not only reinforced the involvement of known PD genes but also uncovered 17 novel candidate genes, providing deeper insights into the molecular mechanisms underlying Parkinson's disease.[36]

Factor and Hill-Burns (2014), in their study titled "Identification of Novel Parkinson's Disease Locus via Stratified Genome-Wide Association Study," conducted a stratified genome-wide association study (GWAS) to investigate genetic factors underlying Parkinson's disease (PD) by analyzing familial and sporadic cases separately. Through comprehensive genome-wide single nucleotide polymorphism (SNP) analysis, followed by replication and post-GWAS validation, the authors identified a novel risk locus on chromosome 1p21 associated with sporadic PD. Additionally, the study demonstrated that previously known PD-associated genes exhibit differential roles in familial versus sporadic forms of the disease. These findings enhance the understanding of the genetic architecture and underlying mechanisms of Parkinson's disease, highlighting the importance of stratified approaches in uncovering disease-specific genetic variations. [37]

Peng et al. (2019), in their study titled "Predicting Parkinson's Disease Genes Based on Node2vec and Autoencoder," proposed a computational framework for identifying genes associated with Parkinson's disease (PD) using network-based and machine learning approaches. The authors constructed gene networks from protein–protein interaction data and applied node2vec to generate numerical feature representations through biased random walks. To enhance model efficiency, the high-dimensional features were reduced using an autoencoder, and a support vector machine (SVM) classifier was trained to distinguish PD-related genes from non-related genes. Model performance was assessed using 10-fold cross-validation, demonstrating that the N2A-SVM model achieved superior prediction accuracy compared to traditional methods. This approach successfully identified several novel candidate PD genes, many of which were supported by existing literature, underscoring the effectiveness of combining network embedding and dimensionality reduction techniques for Parkinson's disease gene prediction.[38]

Quan et al. (2021), in their study titled "Integrated Network Analysis Identifying Potential Novel Drug Candidates and Targets for Parkinson's disease," employed a comprehensive network pharmacology and transcriptomic strategy to uncover potential drug candidates and therapeutic targets for Parkinson's disease (PD). The study collected 970 PD-related genes from multiple databases and performed enrichment analyses to identify key biological processes and pathways involved in disease pathogenesis. Protein–protein interaction (PPI) networks were constructed to investigate gene interactions, while drug–target information from Drug Bank was integrated. Network proximity analysis ranked drugs based on the closeness of their targets to PD-associated genes, and integrated gene set enrichment analysis (IGSEA) evaluated the capacity of these drugs to reverse PD-related gene expression patterns. Differential expression analysis further identified drug-target genes altered in PD patients compared to controls. The study concluded that this integrated approach revealed several promising repurposable drugs and novel target genes with potential therapeutic value, supporting multi-target treatment strategies and providing a solid foundation for future experimental and clinical research in Parkinson's disease.[39]

CONCLUSION:

In conclusion, integrating genomics and proteomics offers a powerful approach to understanding Parkinson's disease (PD) as a multifactorial disorder driven by genetic mutations, protein misfolding, mitochondrial dysfunction, oxidative stress, and impaired cellular degradation. Genomic studies have highlighted key PD-associated genes such as SNCA, LRRK2, PRKN, PINK1, DJ-1, VPS35, and GBA, while proteomic analyses have identified dysregulated proteins including α-synuclein, parkin, tau, and UCH-L1 contributing to neurodegeneration. Combined multi-omics analyses facilitate the discovery of novel biomarkers for early diagnosis, elucidate molecular mechanisms of disease progression, and support the development of targeted, personalized, and disease-modifying therapies. This integrative strategy, enhanced by bioinformatics and machine learning, represents a promising avenue for advancing PD research and clinical management.

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