



Molecular Genetics Of Parkinson's Disease: A Systematic Review

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms like bradykinesia, resting tremor, rigidity, and postural instability, caused by dopaminergic neuron loss in the substantia nigra. Its hallmark pathology is the accumulation of α -synuclein in Lewy bodies. While the exact causes are unclear, mitochondrial dysfunction, oxidative stress, impaired protein clearance, and neuroinflammation are key factors. Genetic mutations, such as those in PRKN, and environmental toxins are implicated, with over 200 genes linked to sporadic PD through genome-wide studies. This review explores genetic and molecular mechanisms of PD, recent research advancements, and how genetic insights can guide innovative therapies.

Keywords: Parkinson's disease, protein aggregation, alpha-Synuclein, genetic of parkinson's disease.

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease whose main symptoms are motor dysfunctions like bradykinesia, rigidity, tremor, and postural instability. These symptoms are caused by selective degeneration of dopaminergic neurons in the midbrain's substantia nigra. In addition to psychiatric symptoms like anxiety and depression, PD patients frequently experience comorbid non-motor symptoms like autonomic dysfunctions like constipation and orthostatic hypotension. As a result, PD is a systemic illness rather than a condition affecting just the central nervous system. It is obvious that aging is a risk factor for the development of Parkinson's disease (PD) because its prevalence rises with age. Since PD symptoms can be brought on by exposure to pesticides and other chemicals, environmental factors are also considered to be significant.^[1]

Developments in inheritable exploration styles have provided insight into the ways in which inheritable backgrounds influence the onset of Parkinson's disease. As a result, Parkinson's disease (PD) is a complicated inheritable condition that results from a confluence of environmental, genetic, and aging factors. Finding inheritable factors in Parkinson's disease can be done in two main ways. One is to look for the genes that cause rare Mendelian forms of Parkinson's disease. Finding threat variants through inheritable statistical analyses of sizable subject groups is the alternative. Although each approach has pros and cons, both are required to provide a more comprehensive picture of this complaint. More than 200 PD-related genes have been linked by inheritable studies. Molecular inheritable studies of Parkinson's disease have been complicated by indigenous differences, which are linked to variations in ethno-social factors. Next, we discuss the state and difficulties of molecular genetics research on Parkinson's disease.^[1]

1.1 Importance of Molecular Genetics in Understanding Parkinson's Disease

Molecular genetics has been pivotal in unravelling the complex pathophysiology of Parkinson's disease (PD), providing insights into its underlying mechanisms and paving the way for targeted therapeutic approaches. The discovery of mutations in key genes, such as SNCA, LRRK2, PARK2, PINK1, DJ-1, and GBA, has transformed PD research by identifying molecular pathways implicated in neurodegeneration. These findings emphasize the importance of mitochondrial function, protein homeostasis, and lysosomal integrity in maintaining neuronal health and highlight how their disruption contributes to disease progression.^[2]

For instance, mutations in the SNCA gene have elucidated the role of alpha-synuclein aggregation in Lewy body formation, a hallmark of PD pathology.^[3] Similarly, the identification of PINK1 and PARK2 mutations underscores the critical role of mitochondrial quality control and autophagy in neuronal survival, shedding light on why dopaminergic neurons are particularly vulnerable in PD.^[4] Furthermore, GBA mutations link lysosomal dysfunction with increased alpha-synuclein accumulation, highlighting the intersection between genetic and cellular mechanisms.^[5]

Molecular genetics has also provided valuable tools for distinguishing familial and sporadic PD forms, enabling the identification of genetic risk factors and biomarkers for earlier diagnosis.^[2]

1.2 Objectives of the Genetics of Parkinson's Disease

a) Identification of Genetic Risk Factors

One of the primary objectives is to identify the genetic mutations or polymorphisms that increase the risk of developing Parkinson's disease. Several genes have been linked to familial and sporadic forms of PD, including:

- **SNCA** (alpha-synuclein gene), mutations in which lead to familial PD and contribute to the formation of Lewy bodies, a hallmark of the disease.

- **LRRK2** (Leucine-rich repeat kinase 2), the most common genetic cause of PD, associated with both familial and sporadic cases.
- **PARK7, PINK1, and DJ-1**, which are involved in mitochondrial function and cellular protection from oxidative stress.
- **GBA** (glucocerebrosidase), a gene associated with an increased risk of PD when mutated, particularly in individuals with Gaucher disease.^[6]

b) Understanding Pathophysiological Mechanisms

The goal is to comprehend how genetic mutations contribute to the neurodegenerative processes underlying Parkinson's disease. This involves studying the molecular pathways affected by these mutations, such as:

- **Protein aggregation:** Many PD-related mutations lead to the misfolding and aggregation of proteins like alpha-synuclein. This protein aggregation disrupts cellular function and contributes to neurodegeneration.
- **Mitochondrial dysfunction:** Mutations in genes like PINK1 and DJ-1 are linked to impaired mitochondrial function, leading to oxidative stress and neuronal damage.
- **Autophagy and protein clearance:** Defective autophagy, a process by which cells remove damaged proteins and organelles, is a hallmark of PD. Several PD-related genes regulate autophagy, and studying their function could reveal therapeutic targets.
- **Neuroinflammation:** Genetic studies can shed light on how inflammation in the brain exacerbates neurodegeneration and how inflammatory pathways might be modulated to slow disease progression.^[6]

c) Exploring Genotype-Phenotype Correlations

Researchers aim to correlate specific genetic mutations with the clinical manifestations of Parkinson's disease. This includes investigating how different genetic backgrounds influence the age of onset, severity, and progression of the disease. For example, LRRK2 mutations may result in a different clinical presentation than mutations in the SNCA gene, despite both being linked to PD.^[6]

d) Characterizing Molecular Signaling Pathways

A critical objective is to dissect the molecular signaling pathways altered by genetic mutations. These pathways may involve:

- **Dopaminergic signaling:** Since PD primarily affects dopamine-producing neurons in the substantia nigra, understanding how genetic mutations affect dopaminergic transmission is crucial.
- **Cellular stress responses:** Investigating how genetic mutations influence the brain's ability to respond to oxidative stress, protein misfolding, and other cellular insults is essential for understanding disease mechanisms and identifying potential therapeutic strategies.
- **Gene-environment interactions:** Some genetic mutations may increase susceptibility to environmental factors (e.g., toxins, infections) that trigger or accelerate disease onset. Studying how genetics and the environment interact can offer insights into disease etiology.^[6]

e) **Developing Genetic Models and Therapeutic Strategies**

Creating animal models that accurately replicate the genetic mutations seen in human Parkinson's disease is key for testing potential treatments. The use of genetic engineering, such as CRISPR/Cas9 technology, allows for the creation of models with specific mutations that can help researchers explore how these mutations lead to disease and how they might be corrected or mitigated.

- **Gene therapy:** One objective is to explore the potential for gene therapies to correct mutations or boost the expression of protective genes.
- **Small molecules and RNA-based therapies:** Investigating how small molecules or RNA therapies (e.g., antisense oligonucleotides) can modulate gene expression or protein aggregation is another key area of focus.^[6]

f) **Identifying Potential Biomarkers**

Molecular genetics research also seeks to identify genetic biomarkers for early diagnosis, monitoring disease progression, and evaluating treatment responses. If specific genetic signatures could be linked to the onset or progression of PD, these could be used for earlier diagnosis or to track the effects of therapeutic interventions.^[6]

g) **Personalized Medicine Approaches**

Ultimately, one of the overarching goals of molecular genetics in PD is to move toward personalized medicine. By understanding an individual's genetic profile, clinicians may be able to tailor treatments based on the specific genetic causes and molecular mechanisms of that person's disease. This could lead to more effective and targeted interventions, minimizing side effects and improving quality of life for patients.^[6]

2. **EPIDEMIOLOGY AND CLINICAL FEATURES**

2.1 **Epidemiology**

Since the early 1800s, PD has gained widespread recognition, and doctors have given the disease its name when it is reported. PD, also referred to as "paralysis agitans," can occasionally be uncommon in young adults, especially those under 40. One million Americans are thought to have Parkinson's disease (PD), with about 60,000 new cases reported annually. Men are 1.5 times more likely than women to have Parkinson's disease (PD), which is estimated to affect 7–10 million people globally. A population-based analysis of Medicare beneficiaries revealed that the average frequency of PD in those 65 and older was 1.6%.^[7]

2.2 **Clinical Features**

Clinically, PD is defined by three motor symptoms that are comparable to bradykinesia, severity, and resting tremors. Postural insecurity, the fourth symptom, is non-specific and typically absent in early complaints, particularly in younger patients. Colourful non-motor symptoms, such as autonomic dysfunction, depression, and other mental changes like cognitive deficit, anxiety, psychosis, visions, insanity, sensitive symptoms, and disturbed sleep, frequently accompany motor abnormalities.^[8]

a) Motor Symptoms of Parkinson's Disease

➤ Bradykinesia (Slowness of Movement)

Bradykinesia is the most consistent and defining motor symptom of PD. Patients experience reduced speed and amplitude of movements, making daily tasks progressively difficult. It is often asymmetric in the early stages.^[3]

➤ Rigidity

Muscle stiffness or rigidity is another hallmark symptom. It can occur in any part of the body and is often accompanied by pain or discomfort, especially in the shoulders and neck. Rigidity is detectable during passive limb movement as resistance throughout the range of motion.^[5]

➤ Tremor at Rest

The characteristic resting tremor, often described as "pill-rolling," typically begins unilaterally and affects the hands more commonly than other regions. It is less prominent during voluntary movements and increases with stress.^[9]

➤ Postural Instability

Postural instability, a later-stage symptom, results in balance problems and a higher risk of falls. This is associated with decreased responsiveness to dopaminergic therapy and contributes significantly to disability.^[3]

b) Non-Motor Symptoms of Parkinson's Disease

➤ Neuropsychiatric Symptoms

- **Depression and Anxiety:** These are among the most common non-motor symptoms, affecting up to 50% of patients. Depression in PD is thought to result from neurochemical changes, including serotonin and dopamine dysregulation.^[9]

- **Cognitive Impairment:** Mild cognitive impairment (MCI) can appear early in the disease, progressing to dementia in advanced stages, particularly in patients with mutations in genes like GBA.^[3]

➤ Sleep Disorders

- **REM Sleep Behaviour Disorder (RBD):** Characterized by vivid dreams and acting out during sleep, RBD is a common prodromal feature of PD.

- **Insomnia and Excessive Daytime Sleepiness:** These result from disruptions in circadian rhythms and sleep regulation mechanisms.^[5]

➤ Sensory Symptoms

- **Anosmia (Loss of Smell):** Often predating motor symptoms, anosmia is linked to alpha-synuclein pathology in the olfactory bulb.
- **Pain and Dysesthesia:** Musculoskeletal pain and sensations of burning or tingling are frequently reported and may relate to rigidity or central pain processing abnormalities.^[3]

3. GENETIC BASIS OF PARKINSON’S DISEASE

Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by the progressive loss of dopamine-producing neurons in the substantia nigra. The genetic basis of PD is complex, involving both inherited mutations and sporadic cases. Several genes have been identified as playing a role in familial forms of Parkinson's (Table no. 1), including *SNCA* (which encodes α -synuclein), *LRRK2* (Leucine-rich repeat kinase 2), *PARK7* (DJ-1), and *PINK1* (PTEN-induced kinase 1), with mutations in these genes contributing to disease onset. In addition to these genetic factors, environmental influences and age-related changes also contribute to the risk of developing PD. Recent research continues to explore how genetic and environmental factors interact in the pathogenesis of PD, with a focus on understanding the molecular mechanisms involved.^[10]

	Gene (HGNC Approved Name)	Alternative Gene Names	Inheritance	Pathogenicity	PD Phenotype	Function
High penetrance	<i>SNCA</i>	<i>PARK1, PARK4, NCAP</i>	AD	Pathogenic	Early-onset	Uncertain (encodes α -synuclein)
	<i>VP535</i>	<i>PARK17, MEM3</i>	AD	Pathogenic	Typical	Retromer and endosomal trafficking
	<i>PINK1</i>	<i>PARK6</i>	AR	Pathogenic	Early-onset	Mitochondrial
	<i>PARK7</i>	<i>DJ-1</i>	AR	Pathogenic	Early-onset	
	<i>PRKN</i>	<i>PARK2, PARKIN</i>	AR	Pathogenic	Early-onset	
	<i>PLA2G6</i>	<i>PARK14, IPLA2</i>	AR	Pathogenic	Early-onset, atypical	Cell membrane
	<i>ATP13A2</i>	<i>PARK9</i>	AR	Pathogenic	Early-onset, atypical	Lysosomal
	<i>FBXO7</i>	<i>PARK15, FBX7</i>	AR	Pathogenic	Early-onset, atypical	Mitochondrial
	<i>POLG</i>	<i>POLG1, POLGA</i>	AD	Pathogenic	Early-onset, atypical	Mitochondrial DNA maintenance
	<i>DNAJC6</i>	<i>PARK19, DJC6</i>	AR	Likely pathogenic	Early-onset	Synaptic vesicle formation and trafficking
	<i>DNAJC13</i>	<i>PARK21, RME8</i>	AD	Conflicting reports	Typical	
	<i>TMEM230</i>	<i>C20ORF30</i>	AD	Conflicting reports	Typical	
	<i>SYNJ1</i>	<i>PARK20</i>	AR	Pathogenic	Early-onset, atypical	Mitochondrial
	<i>VPS13C</i>	<i>PARK23</i>	AR	Pathogenic	Early-onset	
	<i>CHCHD2</i>	-	AD	Pathogenic	Typical	Uncertain
	<i>DCTN1</i>	-	AD	Pathogenic	Atypical	Microtubule
Variable penetrance	<i>LRRK2</i>	<i>PARK8, DARDARIN</i>	AD	Pathogenic	Typical	Lysosomal, mitochondrial, microtubule
	<i>GBA</i>	<i>GBA1</i>	AD	Pathogenic	Typical	Lysosomal
Associated with PD but unlikely to be pathogenic	<i>HTRA2</i>	-	AD	Uncertain/likely benign	-	Mitochondrial
	<i>UCHL1</i>	<i>PARK5</i>	AD	Uncertain/likely benign	-	Ubiquitin-proteasome
	<i>GIGYF2</i>	<i>PARK11</i>	AD	Uncertain/likely benign	-	Uncertain
	<i>EIF4G1</i>	-	AD	Benign	-	mRNA translation
	<i>LRP10</i>	<i>LRP9</i>	AD ¹	Uncertain	-	Uncertain

Table No. 1: Summary of monogenic variants associated with Parkinson’s disease.

3.1 Overview of Genetic Contribution to Parkinson's Disease

Parkinson's disease (PD) has both genetic and environmental contributions to its development. While most cases are sporadic, 5-10% of cases are inherited, suggesting a strong genetic component. Multiple genes have been identified, particularly in familial forms of PD. Since the discovery of disease causing mutations in SNCA in a large Italian kindred and three unconnected Greek families in the late nineties, several genes have been linked to both autosomal dominant and recessive domestic PD. still, only SNCA, LRRK2, VPS35, PRKN, PINK1, GBA and DJ-1 have been convincingly associated with typical PD (Fig no.1).^[11]

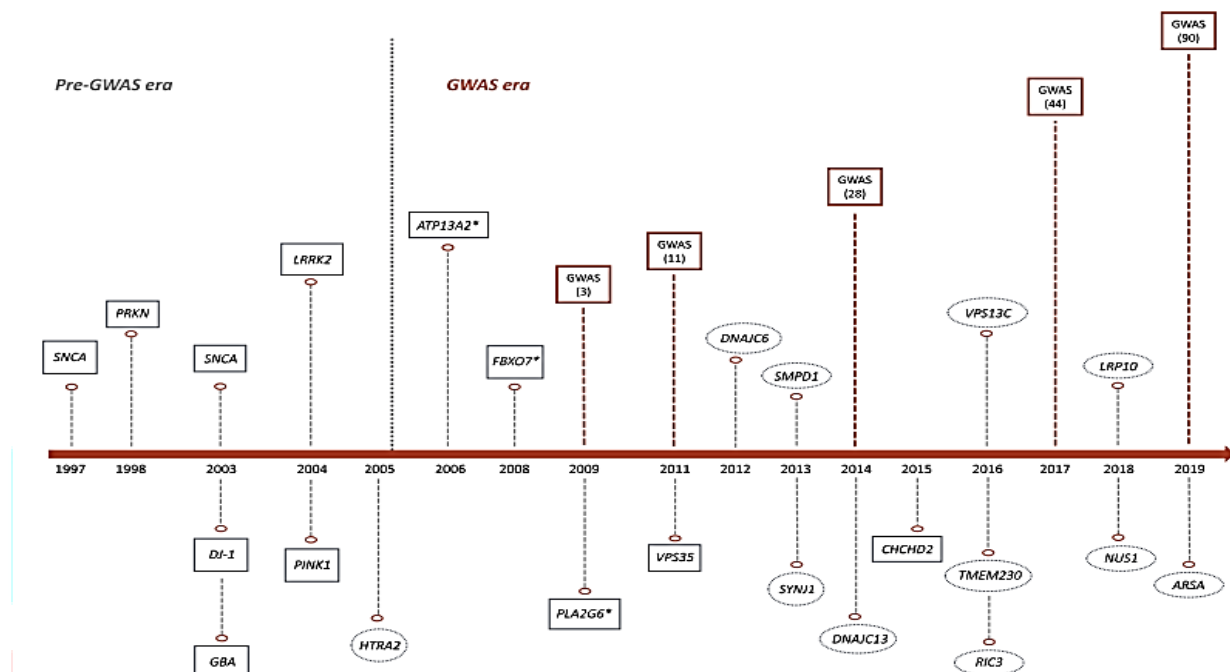


Figure No. 1: The genetics of Parkinson disease over time.

3.2 Role of Environmental – genetic Interaction

The role of environmental-genetic interactions in the development of Parkinson's Disease (PD) has become a critical area of research, as it helps explain why some individuals with genetic risk factors develop the disease, while others do not. These interactions involve the influence of environmental factors such as toxins, infections, and lifestyle choices, which can modify the expression of genetic susceptibility to PD.^[47]

- **Genetic Susceptibility and Environmental Exposures**

Genetic predisposition alone is often insufficient to trigger Parkinson's disease. Environmental factors can significantly influence whether an individual with certain genetic variants will go on to develop PD. This gene-environment interaction is particularly relevant in sporadic PD, where no single gene mutation accounts for the disease, but genetic risk factors may interact with external triggers to influence the onset and progression of the disease.^[47]

- **Genetic Predisposition and Environmental Toxins**

Studies have shown that exposure to environmental toxins like pesticides, herbicides, and heavy metals can increase the risk of developing PD in genetically predisposed individuals. For example, mutations in the LRRK2 or GBA genes have been shown to increase susceptibility to the toxic effects of these substances, especially when combined with environmental exposures. Gene-environment interactions may accelerate neurodegeneration or trigger pathological changes like the accumulation of alpha-synuclein in dopaminergic neurons, a hallmark of PD.^[12]

- **Pesticide Exposure and Genetic Risk in PD**

Pesticide exposure has been shown to interact with genetic susceptibility, especially in individuals carrying certain genetic variants, such as those in the LRRK2 gene, a common mutation associated with familial PD. People with LRRK2 mutations who are exposed to pesticides have a higher likelihood of developing PD compared to those who are not exposed.^[13]

- **Alpha-Synuclein and Environmental Stressors**

Alpha-synuclein is a key protein involved in the pathology of PD, and mutations in the SNCA gene (which codes for alpha-synuclein) can lead to PD in some families. Environmental stressors, such as toxins or infections, may exacerbate the accumulation and aggregation of alpha-synuclein, increasing the risk of PD in individuals with these mutations.

This gene-environment interaction might explain why some individuals with SNCA mutations develop PD early, while others with similar mutations may remain asymptomatic throughout their life.^[14]

4. KEY GENES IMPLICATED IN PARKINSON'S DISEASE

Parkinson's disease (PD) is influenced by a combination of genetic mutations and variations. While the majority of cases are sporadic, several genes have been identified that contribute to familial forms of PD, as well as increase susceptibility in sporadic cases. These genes are involved in various cellular processes, including protein degradation, mitochondrial function, and neuroinflammation.^[2]

4.1 Autosomal dominant genes

The first type of familial PD caused by a point mutation in the α -synuclein gene (SNCA) was discovered in 1997. Four fresh point mutations, as well as gene duplication or triplication, have now been linked to autosomal dominant PD. still, these mutations are fairly rare. The most frequent autosomal dominant monogenic PD is caused by mutations in the gene garbling leucine-rich reprise kinase 2 (LRRK2). Six LRRK2 mutations have been verified as pathogenic, the most common of which is p.G2019S, estimated to account for 1% of sporadic and 4% of familial PD worldwide.^[15]

- **SNCA (Alpha-Synuclein)**

SNCA is the first gene discovered to be associated with PD, particularly in familial cases. Mutations in SNCA lead to the overproduction or misfolding of alpha-synuclein, a protein that aggregates into Lewy bodies, a pathological hallmark of PD. The role of alpha-synuclein in PD pathogenesis has led to extensive research into protein aggregation and neurodegeneration.^[2]

- **LRRK2 (Leucine-Rich Repeat Kinase 2)**

Mutations in LRRK2 are the most common cause of familial PD, especially in certain populations like Ashkenazi Jews and North African Arabs. LRRK2 is involved in various cellular functions, including autophagy, vesicle trafficking, and neuroinflammation. Mutations in this gene lead to dysfunctional kinase activity, contributing to neurodegeneration through disrupted protein processing and cellular stress responses.^[5]

4.2 Autosomal recessive genes

Autosomal recessive forms of PD generally present with an earlier onset than classical PD. Three of the Demosne-designated genes causing autosomal recessive PD have been linked to mitochondrial homeostasis (PRKN, PINK1, and DJ-1). Specifically, the proteins PINK1 and parkin (encoded by the PRKN gene) are both involved in the same mitochondrial quality control pathway, with PINK1 recruiting parkin to dysfunctional mitochondria and therefore initiating mitophagy. Mutations in PRKN are the most common cause of autosomal recessive domestic PD, being in over 50 of all early-onset cases. Eventually, several of the autosomal recessive genes have been linked to atypical parkinsonism with variable features, including ATP13A2 (PARK9), PLA2G6 (PARK14), FBX07 (PARK17), and SYNJ1 (PARK20).^[15]

- **PARK2 (Parkin)**

PARK2, which encodes the protein parkin, is associated with early-onset, autosomal recessive PD. Parkin plays a crucial role in the ubiquitin-proteasome system, which is responsible for tagging defective proteins for degradation. Mutations in PARK2 impair this system, leading to the accumulation of damaged proteins and mitochondrial dysfunction, contributing to neuronal death.^[3]

- **PINK1 (PTEN Induced Kinase 1)**

Similar to PARK2, PINK1 is involved in the maintenance of mitochondrial function. Mutations in PINK1 impair the ability of cells to clear damaged mitochondria, leading to cellular energy deficits and increased oxidative stress. This is thought to contribute to dopaminergic cell death in the substantia nigra, a key area affected in PD.^[2]

- **DJ-1 (PARK7)**

The DJ-1 gene encodes a protein involved in protecting cells from oxidative stress. Mutations in DJ-1 lead to a loss of function of this protective mechanism, resulting in increased vulnerability of dopaminergic

neurons to oxidative damage. This is thought to contribute to the early-onset form of PD, although DJ-1 mutations are relatively rare compared to other genetic mutations.^[5]

4.3 Risk-Modifying Genes

These genes increase susceptibility to PD but typically exhibit incomplete penetrance or modest effects on disease risk.^[16]

- **GBA (Glucocerebrosidase)**

Mutations in the GBA gene, which encodes the enzyme glucocerebrosidase, are the most common genetic risk factor for PD. While mutations in GBA are also linked to Gaucher disease, a lysosomal storage disorder, they are associated with an increased risk of developing PD, often with an earlier onset and more rapid disease progression. The connection between GBA mutations and PD is thought to involve lysosomal dysfunction and impaired protein degradation, contributing to neurodegeneration.^[3]

Mutations in GBA, a lysosomal enzyme gene, increase the risk of PD by 5–10 times. Common mutations, such as N370S and L444P, lead to lysosomal dysfunction, alpha-synuclein accumulation, and neuronal death.^[17]

- **VPS35 (Vacuolar Protein Sorting 35)**

The D620N mutation in VPS35 impairs endosomal trafficking and protein sorting, leading to neuronal dysfunction. It is associated with autosomal dominant PD and late-onset disease.^[18]

- **MAPT (Microtubule-Associated Protein Tau)**

MAPT encodes the tau protein, which is primarily involved in stabilizing microtubules. Mutations in MAPT are linked to tauopathies, including certain forms of Parkinsonism. While MAPT mutations are more commonly associated with tau-related diseases like progressive supranuclear palsy, they have also been implicated in PD, particularly in those with overlapping clinical features.^[9]

5. PATHOGENESIS OF PARKINSON'S DISEASE

A number of mechanisms have been intertwined in PD pathogenesis, with α -synuclein aggregation central to the development of the complaint. Multiple other processes are allowed to be involved, with several studies suggesting that abnormal protein concurrence, mitochondrial dysfunction, and neuroinflammation play a part in the onset and progression of PD. still, the relationship between these pathways remains unclear.^[15]

5.1 Alpha-synuclein Misfolding and Aggregation

Native α -synuclein in the brain is substantially unfolded without a defined tertiary structure, although in waterless results it can be present in stable tetramers that repel aggregation. Upon commerce with negatively charged lipids, similar as the phospholipids that make up cell membranes, α -synuclein crowds into α -spiral structures through its N-terminal.^[15]

In PD, α -synuclein adopts a β -distance-rich amyloid- suchlike structure that's prone to total. Indeed, misfolded α -synuclein is set up within LBs as 5–10 nm long fibres (Fig. 2). The conformational changes that cause aberrant α -synuclein aggregation have been attributed to a number of mechanisms, such as C-terminal truncation, ubiquitination, and serine 129 phosphorylation.^[15]

Hence, different species of α -synuclein are set up in the PD brain, including unfolded monomers, answerable oligomers, protofibrils, and high molecular weight undoable fibrils. Recent studies in rodents indicated that the most neurotoxic α -synuclein species is the early oligomeric form, rather than the mature undoable fibrils. The increased toxin of these oligomers, as opposed to the fibrillary α -synuclein, was validated in cell-grounded assays.^[15]

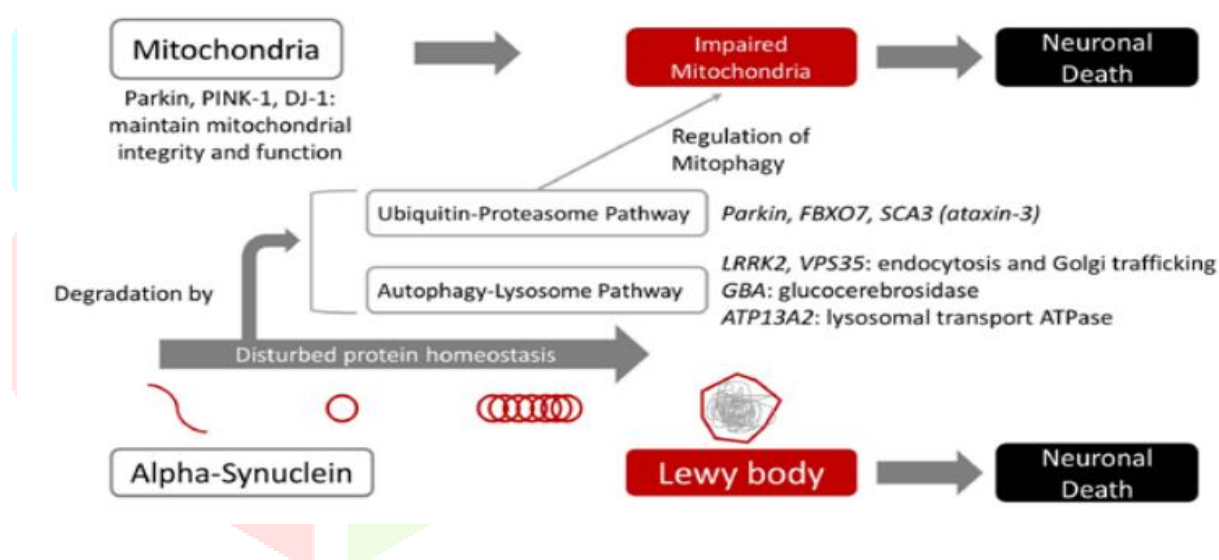


Figure No. 2: Molecular mechanism of PD based on genetic findings.^[19]

5.2 Mitochondrial Dysfunction

The pathophysiology of both familial and idiopathic Parkinson's disease is thought to be significantly influenced by mitochondrial dysfunction. An essential part of the electron transport chain, the mitochondrial complex-I, was found to be lacking in the SPPC of PD brains in early postmortem investigations. These findings offered one of the earliest clear connections between Parkinson's disease and mitochondrial dysfunction. In comparison to healthy subjects, PD patients' skeletal muscle and platelets also showed Complex-I deficiency. The finding that MPTP abuse resulted in long-lasting Parkinsonian symptoms, with postmortem examination showing dopaminergic cell loss, provided more proof. Subsequent research revealed that oxidized MPTP is absorbed by DA neurons and causes complex-I inhibition. In animals, and possibly in humans, other toxins and pesticides that disrupt mitochondrial complex-I activity, such as

paraquat and rotenone, also result in DA cell loss and a Parkinsonian phenotype. Energy depletion in DA cells may be primarily caused by defects in the mitochondrial complex-I.^[15]

Another major indication pointing to the part of mitochondria in PD pathogenesis is that numerous of the known genes that beget familial PD play a part in mitochondrial homeostasis. One illustration is the involvement of PINK1 and parkin (PARK2 and PARK6, independently), both of which are vital factors of the pathway that regulates the junking of dysfunctional mitochondria, a process called mitophagy. Loss-of-function mutations in either gene lead to disabled mitochondrial quality control and beget autosomal recessive PD.^[15]

Eventually, α -synuclein by itself is known to intrude with mitochondrial function. For case, α -synuclein can interact with the mitochondrial membrane and accumulate inside the organelles. This leads to the damage of complex-I exertion, eventually performing in mitochondrial dysfunction and increased oxidative stress.^[15]

5.3 Dysfunctional Protein Clearance Systems

There are two central protein concurrence systems within cells responsible for the junking of dysfunctional proteins the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway. The UPS is primarily responsible for breaking down abnormal proteins, and it does so by “trailing” them with ubiquitin and transporting them to the proteasome for declination. The autophagy-lysosome pathway is divided into three ingredients macro-autophagy, micro-autophagy and chaperone-intermediated autophagy (CMA).^[15]

- **Ubiquitin-proteasome System**

Proteasomal abnormalities are a participated point among numerous proteinopathies that's neurodegenerative conditions characterized by abnormal protein accumulation. substantiation of similar abnormalities in PD was first handed by posthumous studies in the SNPC, where the catalytic exertion of the UPS was set up mainly reduced compared to healthy smarts. The same findings were latterly reported in supplemental blood mononuclear cells of PD but not in healthy individualities. piecemeal from diminished exertion, a lower expression of different proteasomal factors has also been linked in the SNPC of PD smarts.^[15]

Specifically, the 20S proteasome α - subunit and other motes involved in the normal function of the UPS, like PA700 and PA28 (proteasome activators), are reduced. fresh substantiation is handed from inheritable studies and the discovery that two of the Demesne genes linked to monogenic PD render proteins involved in UPS function, parkin (PARK2; E3 ubiquitin ligase) and UCH- L1 (PARK5; Ubiquitin C-terminal hydrolase). Following on from findings in mortal PD, altered proteasome exertion was observed in different complaint models. Marmosets fitted with the poison MPTP had lowered enzyme exertion in the UPS, in addition to dropped situations of the 26S subunit factors. In an alternate set of trials, the same group showed that pharmacological inhibition of the proteasome in wild-type rats leads to dopaminergic cell death.^[15]

Also, Bedford and associates using transgenic mice with proteasomal blights (knockout for 26S proteasome nonsupervisory subunit 4) showed dopaminergic cell degeneration and observed LB-suchlike eliminations in the brain, which still demanded the thick core of classical mortal LBs, and it's unclear whether they contained added up α -synuclein. Nevertheless, all these studies show that dysfunction of protein development can affect in neuronal cell death, therefore furnishing an implicit pathogenic medium for PD. [15]

• Autophagy-lysosome System

Analogous to findings in the UPS system, multitudinous lysosomal and autophagy- related factors are conking or differentially expressed in PD. In nigral neurons of PD smart, the situations of the autophagosome marker LC3-II were increased, suggesting an accumulation of autophagic vacuoles. In discrepancy, vital proteins of lysosomal membranes (LAMP1 and LAMP2A), and several molecular chaperones from the heat- shock protein family (similar as hsc70 and hsp35) were set up to be dropped at posthumous examination. likewise, of particular note is the discovery of a point mutation in the gene of the lysosomal protein ATP13A2 (PARK9), leading to an autosomal sheepish atypical Parkinsonian pattern, appertained to as Kufor – Rakeb pattern. Point mutations in two further Demesne genes vitiate the function of either parkin (PARK2) or PINK1 (PARK6), both of which are involved in the autophagic development of mitochondria. [15]

The notion that the lysosome-autophagy system plays a significant role in the development of Parkinson's disease is further supported by the discovery that GBA1 mutations, which impair its function, are a potent heritable risk factor for the disease. These studies advance support to the thesis that malfunction in the autophagy-lysosome pathway may be contributing to the pathogenesis of PD. [15]

5.4 Neuroinflammation

Postmortem brain studies have described microglial and complement activation, T-lymphocyte infiltration, and increased attention of pro-inflammatory cytokines in the SNpc and striatum of PD cases compared to healthy individualities. Likewise, positron emigration tomography (PET) neuroimaging with the (11 C)-PK11195 radioligand has demonstrated increased microglial activation beforehand on in PD in the brainstem, rudimentary ganglia, and frontotemporal cortices, with added involvement of the parietal and occipital cortices in cases with PD madness, compared to healthy subjects. [15]

While originally allowed to be a secondary miracle, there's now substantiation that seditious responses can by themselves contribute to complaint pathogenesis. It has been demonstrated in early studies with rodent models of PD (6- hydroxydopamine and MPTP) that inhibition of microglial activation with minocycline pre- and post-neurotoxic personality led to a significant attenuation of DA cell death in the SNpc, suggesting that microglia-convicted seditious processes may be contributing to the degeneration of these cells. There's also a plethora of substantiation suggesting that α -synuclein can directly spark microglial activation and initiate seditious processes. For case, in primary societies, α -synuclein mediates a cure-dependent activation of microglia. [15]

Inheritable suggestions suggesting that vulnerable activation might contribute etiologically in PD come from the identification of a strong association between the human leucocyte antigen (HLA) class II region (a crucial patch of the vulnerable system) and the threat of developing PD-a finding that was latterly verified in genome-wide association studies. Also, expansive epidemiological studies suggest a dropped PD threat with regular use of the nonsteroidal anti-inflammatory medicine ibuprofen.^[15]

Eventually, recent data showed that in PD cases at opinion a more pro-inflammatory vulnerable marker profile in the serum is associated with a briskly motor symptom progression and further disabled cognitive function. Anyhow of whether neuroinflammatory responses are a direct detector of neuro-degeneration in PD or are actuated as a response to neuronal damage, it's now getting clear that the engagement of the vulnerable system can initiate a vicious cycle, thereby aggravating neuronal dysfunction.^[15]

5.5 Oxidative Stress

Increased production of extremely reactive free radicals, decreased scavenging of these reactive species, increased production of oxidatively damaged proteins, lipids, and DNA, and decreased removal of oxidized products that may be harmful to cells are the causes of oxidative stress. Signs of oxidative stress are abundant in the substantial nigra of patients of PD. These include reactive oxygen species (ROS) such as hydrogen peroxide, hydroxyl, superoxide and peroxy radicals. Nitric oxide and other reactive nitrogen species (RNS) are examples of oxidants. These potent oxidants alter the structure of proteins, lipids, and DNA, resulting in cellular damage.^[8]

Dopamine metabolism, the mitochondrial electron transport chain, iron metabolism, and inflammation all produce oxidants, or ROS. Free radicals are produced by the enzymatic metabolism or auto-oxidation of dopamine. Dopamine metabolism by MAO-A leads to production of dihydroxy phenylacetic acid (DOPAC) and H₂O₂ with the consumption of O₂ and H₂O₂. Intracellular auto-oxidation of dopamine generates dopamine-quinone and H₂O₂. Dopamine-quinone has been demonstrated to suppress glutamate and dopamine transporter function in synaptosomes, inhibit tyrosine hydroxylase in cell-free systems, and promote H⁺ leakage from mitochondria, which results in the uncoupling of respiration to ATP synthesis. It also engages in a nucleophilic reaction with sulfhydryl groups of proteins, causing structural modification and decreased glutathione levels. H₂O₂ produced can be converted to hydroxyl radical by Fenton reaction in presence of ferrous ion. In the presence of ferrous ion, the superoxide anion and H₂O₂ two weakly reactive free radical species can combine in the Haber-Weiss reaction to produce the more reactive OH radical.^[8]

Complex I is inhibited by reactive oxygen species, which also cause mitochondrial dysfunction. The iron intermediated catalysis of hydroxyl radical generation could be a crucial medium in pathogenesis intermediated by oxidative stress. Elevation of iron situations are detected in the SNpc in cases of PD. The iron situations are increased by 35 in PD cases compared to age matched control. One important cellular antioxidant that combats oxidative stress is glutathione (GSH).^[8]

6. SPORADIC PARKINSON'S DISEASE AND GENETIC RISK FACTORS

Sporadic Parkinson's disease (PD), accounting for 90–95% of cases, arises from a complex interplay between genetic susceptibility and environmental influences. While it lacks a clear hereditary pattern, advances in genetics have identified several risk factors that contribute to the likelihood of developing sporadic PD.

6.1 Common Genetic Variants Identified Through GWAS in Parkinson's Disease

Genome-wide association studies (GWAS) have identified numerous genetic variants associated with Parkinson's disease (PD). These common variants, while individually conferring modest risk, collectively provide significant insights into the pathogenesis of both sporadic and familial PD. GWAS findings have highlighted genes involved in key biological processes such as protein aggregation, mitochondrial function, and neuroinflammation.

- **SNCA (Alpha-Synuclein)**

Variants in SNCA, the gene encoding alpha-synuclein, were among the first identified by GWAS as risk factors for sporadic PD. Polymorphisms in the promoter region of SNCA influence gene expression levels, with increased alpha-synuclein production promoting protein aggregation and Lewy body formation, hallmark features of PD.^[3]

- **LRRK2 (Leucine-Rich Repeat Kinase 2)**

GWAS have identified common risk variants in LRRK2, including G2385R and R1628P, which are prevalent in Asian populations. These variants affect kinase activity and vesicle trafficking, contributing to neuronal dysfunction. Although rare LRRK2 mutations cause familial PD, common variants increase susceptibility to sporadic cases.^[20]

- **GBA (Glucocerebrosidase)**

Polymorphisms in GBA, a gene linked to lysosomal function, significantly elevate PD risk. GWAS findings confirm that even heterozygous carriers of GBA variants, such as N370S and L444P, are at an increased risk of sporadic PD. These variants impair the clearance of misfolded proteins, including alpha-synuclein, highlighting the role of lysosomal dysfunction in PD pathogenesis.^[9]

- **MAPT (Microtubule-Associated Protein Tau)**

Variants in the MAPT gene region are strongly associated with PD, particularly in European populations. These variants are thought to influence tau protein expression, which can disrupt cytoskeletal stability and neuronal transport. While MAPT is more commonly linked to tauopathies, its role in PD underscores the shared mechanisms among neurodegenerative diseases.^[2]

- **GAK (Cyclin G-Associated Kinase) and BST1 (Bone Marrow Stromal Antigen 1)**

GWAS have identified risk variants in GAK and BST1, which are involved in vesicle-mediated transport and immune system regulation, respectively. These findings highlight the contribution of cellular trafficking and neuroinflammation to PD pathology.^[20]

- **PARK16 Locus**

The PARK16 locus, which includes genes like NUCKS1, has been identified in GWAS as a protective factor in some populations. Variants in this region are associated with reduced PD risk, emphasizing the importance of understanding both risk and protective mechanisms in genetic research.^[3]

6.2 Polygenic Risk Scores and Their Predictive Value in Parkinson's Disease

Polygenic risk scores (PRS) are emerging tools for assessing the cumulative effect of multiple genetic variants on the risk of developing Parkinson's disease (PD). By aggregating the impact of numerous common single-nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS), PRS provide a quantitative measure of genetic predisposition.

➤ Concept and Calculation of PRS

PRS are calculated by summing the risk alleles weighted by their effect sizes, derived from GWAS. Each SNP contributes a small risk individually, but their combined effect offers significant insight into genetic susceptibility. In PD, PRS incorporates loci associated with key genes, such as SNCA, LRRK2, GBA, and MAPT, among others.^[20]

➤ Predictive Value of PRS in PD

- **Risk Stratification:** PRS enables stratification of individuals into low-, medium-, and high-risk categories based on their genetic predisposition. Studies show that individuals in the highest decile of PRS have a substantially increased risk of developing PD compared to those in the lowest decile.^[21]

- **Early Identification:** PRS can identify individuals at higher risk before the onset of symptoms, potentially guiding early interventions, such as lifestyle changes or participation in clinical trials targeting prodromal PD stages.^[22]

- **Complementing Environmental Risk Factors:** Combining PRS with environmental risk factors, such as pesticide exposure or smoking history, enhances predictive accuracy by accounting for gene-environment interactions.^[23]

6.3 Epigenetic Modification

Epigenetics is the study of molecular processes that impact the regulation of gene expression without altering the beginning DNA sequence. In recent times, epigenetics has also been intertwined in other neurodegenerative diseases, similar as Alzheimer's complaint, and there's adding substantiation that epigenetics may play an important part in Parkinson's. Importantly, epigenetic studies in Parkinson's smarts may not only unravel new mechanisms underpinning complaint development and progression but also uncover new medicine targets and so advance new remedial approaches. The development of new PD treatments would be particularly poignant as there are presently no treatments that can cure or modify the complaint. The many treatments that do live, including levodopa (LDOPA), dopamine agonists and monoamine oxidase-B impediments, are characteristic and only palliate symptoms temporarily. also, these treatments come mainly less effective after only many times and generally lead to problematic side goods similar as dyskinesia. thus, new complaint- modifying curatives that can decelerate, help or indeed rear PD progression are urgently needed. crucial epigenetic mechanisms include DNA methylation, DNA hydroxymethylation, histone variations and conduct intermediated by non-coding RNAs similar as microRNAs (miRNAs).^[24]

➤ DNA Methylation

DNA methylation is the most well studied epigenetic revision and consists of the addition of a methyl group to the 5- carbon position of a cytosine in a CpG dinucleotide (cytosine in the 5' - to-3' direction, followed by guanine). This process is catalyzed by DNA methyltransferases (DNMTs), which are involved in either de novo (DNMT3a and 3b) or conservation (DNMT1) methylation. CpG spots (CpGs) are generally concentrated in CpG islets, which are generally located in gene promoters. Methylation of CpG islets within promoters has generally been associated with transcriptional silencing, either through blocking recap factor list or recruiting methyl-CpG list proteins that themselves intervene transcriptional suppression. Still, this isn't always the case; for illustration, gene body DNA methylation has been associated with an raised position of gene expression and the regulation of indispensable splicing.^[24]

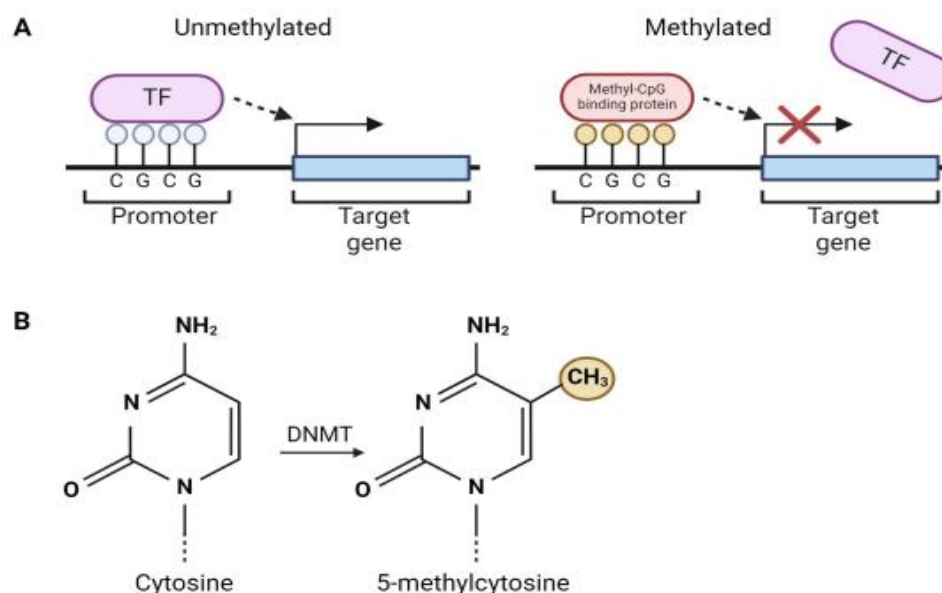


Figure No. 3: DNA methylation overview.

(A) Schematic of an unmethylated (left) and methylated (right) CpG islet in a gene promoter and target gene. When unmethylated, recap factors can generally bind, allowing the gene to be expressed. When methylated, recap factor list is generally averted, and a methyl- CpG list protein is signed. The gene may become silent as a result of either of these occurrences. (B) Cytosine and 5-methylcytosine structural formulas. DNA methylation is catalyzed by DNMT enzymes (Fig. 3).^[24]

➤ Histone Modifications

The alternate type of epigenetic modification that will be considered as histone modification. These are post-translational variations to the N-terminal tails of histone octamers and include methylation, acetylation, phosphorylation, ubiquitination, SUMOylation and ADP-ribosylation. These marks generally regulate chromatin structure and so alter the availability of DNA to the transcriptional ministry, with largely compacted chromatin(heterochromatin) associated with transcriptional suppression and open chromatin(euchromatin) associated with transcriptional activation. Whether a given revision is cathartic or active generally depends on the exact residue that's pronounced, although acetylation (which is the most well studied type of histone revision in PD) is typically associated with transcriptional activation.^[24]

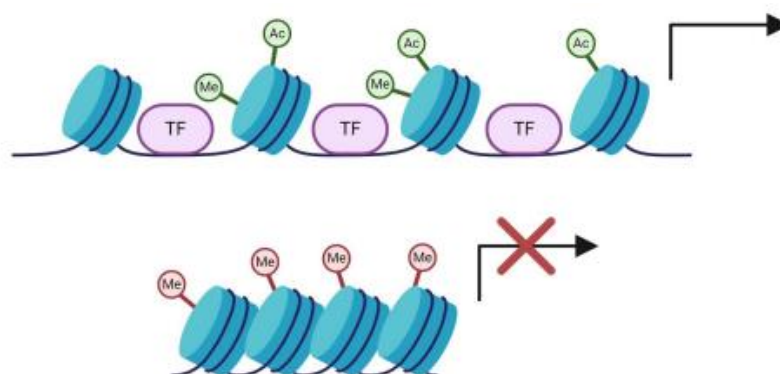


Figure No. 4: Histone modifications overview.

The top picture depicts an open chromatin region where the histone octamers contain active acetylation and active methylation marks, resulting in transcription factor binding and gene expression. The bottom picture depicts a compacted chromatin region where the histone octamers contain repressive methylation marks (Fig. 4). This prevents transcription factors from binding, resulting in gene silencing.^[24]

7. ANIMAL AND CELLULAR MODELS IN PARKINSON'S DISEASE GENETICS

Research into the genetic basis of Parkinson's disease (PD) relies heavily on animal and cellular models to replicate the pathological and molecular mechanisms underlying the disease. These models are instrumental in understanding disease pathways, testing therapeutic strategies, and validating the roles of specific genes implicated in PD.^[25]

7.1 Rodent Models of PD

a) **Transgenic Models:** Mouse models engineered to express human PD-associated genes, such as **SNCA**, **LRRK2**, **PARK2**, and **GBA**, have been widely used to study PD. For example:

- **SNCA Transgenic Mice:** Mice overexpressing mutant or wild-type **SNCA** mimic alpha-synuclein aggregation seen in PD. These models help explore the role of alpha-synuclein in dopaminergic neuronal loss and motor symptoms.^[26]
- **LRRK2 Models:** Mice carrying the **G2019S** mutation in **LRRK2** exhibit age-dependent motor deficits and dopaminergic degeneration, reflecting late-onset PD.^[27]

b) **Knockout Models:** Knockout models, such as **PARK2** or **PINK1** null mice, are used to study autosomal recessive PD. These mice exhibit mitochondrial dysfunction and increased sensitivity to oxidative stress, replicating cellular defects seen in early-onset PD.^[28]

7.2 Non-Human Primate Models

Non-human primates (NHPs) are valuable for studying PD due to their similarity to humans in brain structure and function. Genetic manipulation in NHPs, including **SNCA** overexpression or **LRRK2** mutations, enables the study of PD-related pathology and motor deficits in a physiologically relevant system. These models are particularly useful for evaluating advanced therapeutic strategies like gene therapy.^[29]

7.3 Cellular Models of PD

➤ Induce Pluripotent Stem Cells (iPSCs)

Patient-derived iPSCs carrying PD-associated mutations, such as **SNCA**, **LRRK2**, or **GBA**, are differentiated into dopaminergic neurons for in vitro studies. These models allow researchers to study

disease mechanisms in a human cellular context, including alpha-synuclein aggregation, mitochondrial dysfunction, and lysosomal defects.^[30]

➤ **CRISPR-Cas9 Edited Cell Lines**

Gene-editing technologies like CRISPR-Cas9 are used to introduce specific PD-associated mutations into neuronal or glial cell lines. These models facilitate the investigation of how individual genetic variants contribute to PD pathogenesis, particularly for high-risk genes like GBA or MAPT.^[31]

➤ **Organoids**

Brain organoids, derived from iPSCs, replicate three-dimensional brain structures and provide insights into PD-related neurodevelopmental and degenerative processes. These models help in studying the interactions between neurons and glial cells, particularly in the presence of genetic mutations like those in SNCA or LRRK2.^[32]

7.4 Limitations and Challenges

- **Incomplete Recapitulation of Human PD:** No model fully replicates the complexity of sporadic PD or the full spectrum of its pathology.^[33]
- **Species Differences:** Animal models, particularly rodents, have limitations in mirroring human-specific PD features, such as alpha-synuclein aggregation.^[34]
- **Ethical and Practical Constraints:** NHP models, while physiologically relevant, are limited by ethical concerns and high costs.^[35]

8. THERAPEUTIC IMPLICATIONS OF PARKINSON'S DISEASE

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies. Understanding the genetic underpinnings of PD has significantly advanced therapeutic development, enabling precision medicine approaches. Genetic discoveries provide insight into disease mechanisms, identify novel drug targets, and facilitate the design of personalized treatment strategies. Advances in genetics have significantly enhanced our understanding of its pathogenesis. Genetic findings have spurred targeted treatments, such as LRRK2 inhibitors and gene therapies.^[2]

8.1 Targeting Genetic Pathways

➤ **LRRK2 Inhibitors**

Mutations in the **LRRK2** gene, particularly **G2019S**, are common in familial and sporadic PD. These mutations result in hyperactive kinase activity.

- **Therapeutic Approach:** Small-molecule inhibitors, such as DNL151 and DNL201, aim to reduce kinase activity, improving neuronal survival and reducing neuroinflammation. These inhibitors are currently undergoing clinical trials.^[36]

➤ **GBA-Related Therapies**

Variants in **GBA**, linked to lysosomal dysfunction, are associated with increased alpha-synuclein aggregation.

- **Therapeutic Approach:** Chaperone therapies (e.g., ambroxol) aim to enhance GBA enzyme function, restoring lysosomal activity and reducing toxic protein accumulation.^[37]

8.2 Alpha-Synuclein Targeting

➤ **Immunotherapy**

Overexpression or mutation in **SNCA**, the gene encoding alpha-synuclein, is a key factor in PD pathogenesis.

- **Therapeutic Approach:** Antibody-based therapies, such as prasinezumab, target extracellular alpha-synuclein to prevent its aggregation and propagation. These therapies aim to slow disease progression and are in advanced clinical trials.^[38]

➤ **RNA-Based Therapies**

RNA interference (RNAi) or antisense oligonucleotides (ASOs) targeting **SNCA** mRNA aim to reduce alpha-synuclein production. These approaches are promising for reducing toxic protein accumulation in early-stage PD.^[39]

8.3 Gene Therapy

Gene therapy offers a direct approach to address the underlying genetic defects in PD.

- **AAV-Mediated Gene Delivery:** Techniques using adeno-associated viruses (AAV) deliver therapeutic genes, such as **GDNF** or **PINK1**, to enhance neuroprotection and improve mitochondrial function.^[40]
- **CRISPR-Cas9:** This gene-editing tool holds promise for correcting pathogenic mutations, though its application in PD remains largely preclinical.^[41]

8.4 Personalised medicine

The conception of personalised medicine is subject to interpretation. The American Medical Association defines this 'as each person's unique clinical, inheritable and environmental information' while others consider personalised drug purely from an inheritable or pharmacogenetic 'perfection' remedy viewpoint.

The conception of personalised drug is particularly applicable for PD, a condition with multiple pathology and neurotransmitter- linked syndrome.^[42]

Advances in Parkinson's disease (PD) genetics are driving personalized medicine approaches and improving genetic counselling practices. By tailoring treatment based on individual genetic profiles, clinicians can enhance therapeutic efficacy, predict disease risk, and offer precise guidance to patients and families.^[21]

9. FUTURE DIRECTIONS IN PARKINSON'S DISEASE GENETICS

The rapidly advancing field of Parkinson's disease (PD) genetics is paving the way for more effective treatments, improved risk assessment, and deeper understanding of disease mechanisms. Several key areas of focus hold promise for future breakthroughs in PD research and clinical applications.^[43]

9.1 Expanding the Genetic Landscape

➤ Identifying Novel Risk Genes and Variants

- Advances in whole-genome sequencing (WGS) and long-read sequencing are expected to uncover additional rare variants and structural genomic changes contributing to PD.
- Current genome-wide association studies (GWAS) identify risk loci but do not always pinpoint causal variants, which future integrative multi-omics approaches may resolve.^[21]

➤ Focus on Understudied Populations

- The majority of PD genetic studies have been conducted in European populations. Efforts to include diverse ethnic groups will help identify population-specific variants and enhance global understanding of PD genetics.^[44]

9.2 Integration of Multi-Omics Approaches

➤ Transcriptomics and Epigenomics

- Combining genetic data with transcriptomic (RNA-sequencing) and epigenomic (DNA methylation, histone modifications) studies will clarify how genetic variants influence gene expression and PD pathogenesis.
- Single-cell multi-omics will offer insights into cell type-specific mechanisms in brain regions affected by PD.^[45]

➤ Proteomics and Metabolomics

- Proteomic profiling may help link genetic variants, such as those in SNCA and LRRK2, to specific protein dysfunctions.
- Metabolomic studies could uncover biomarkers and metabolic pathways impacted by genetic mutations, offering targets for therapeutic intervention.^[46]

9.3 Precision Medicine and Genetic Testing

➤ Polygenic Risk Scores (PRS)

- PRS, which aggregate multiple genetic variants to estimate PD risk, are expected to become more refined, enabling earlier detection and preventive interventions.
- Machine learning models trained on genetic and clinical data will enhance PRS accuracy and predictive value.^[20]

9.4 Enhancing Animal and Cellular Models

➤ Advanced Cellular Models

- Development of more physiologically accurate models, such as brain organoids incorporating patient-derived neurons, will enhance the study of PD-related genetic mutations in a human-like context.
- CRISPR-Cas9 gene-editing technology will enable precise modeling of disease-relevant mutations in cellular and animal systems.^[31]

➤ Artificial Intelligence in Model Development

- AI-driven simulations of genetic pathways and protein interactions could predict the effects of mutations, streamlining the development of therapeutic targets and enhancing the reproducibility of preclinical studies.^[32]

9.5 Studying Gene-Environment Interactions

➤ Integrative Epidemiology

- Genetic studies will increasingly incorporate environmental and lifestyle data to understand the interplay between genetic susceptibility and external factors, such as toxins, diet, and physical activity.
- Epigenetic modifications induced by environmental exposures may provide insights into sporadic PD mechanisms and novel intervention strategies.^[47]

➤ Longitudinal Cohort Studies

- Large-scale longitudinal studies, such as the Parkinson's Progression Markers Initiative (PPMI), are expected to elucidate how genetic predisposition interacts with environmental exposures over time.^[48]

CONCLUSION

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of α -synuclein-containing Lewy bodies. While some cases are linked to genetic mutations, most arise from a combination of genetic and environmental factors. Key mechanisms implicated in PD include mitochondrial dysfunction, impaired protein clearance, and oxidative

stress. Current treatments, such as levodopa, are symptomatic and do not address the underlying causes. Advances in molecular genetics and pathophysiology research offer hope for developing disease-modifying therapies that could prevent or halt disease progression, improving patient outcomes.

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