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# A Review on Parkinson's Disease: Progressive Neurodegenerative Disease Identification

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**ABSTRACT**

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as tremors, rigidity, bradykinesia, and postural instability and non-motor symptoms cognitive impairment, mental health disorders, dementia, sleep disorders, pain, sensory disturbances due to the loss of dopaminergic neurons in the substantia nigra (SN). This review aims to provide a comprehensive analysis of Parkinson's disease with a focus on various aspects including age-related prevalence, biochemical changes, immunological alterations, pathological hallmarks, and molecular level modifications. Through an integrative approach, this paper synthesizes current research to elucidate the multifaceted nature of PD, enhancing our understanding of its factors for developing effective diagnostic tools and therapeutic strategies.

## INTRODUCTION

Parkinson’s disease (PD) is a complex progressive neurodegenerative disease characterized by tremor, rigidity, and bradykinesia, with postural instability appearing in some patients as the disease progresses. It was first described by James Parkinson in 1817 and further characterized by Jean-Martin Charcot, and our knowledge of PD is continuing to expand.

PD is the second most common neurodegenerative disease after Alzheimer’s disease (AD) (Kalia LV, Lang AE,2015), with a prevalence of approximately 0.5–1% among those 65–69 years of age, rising to 1–3% among persons 80 years of age and older (Tanner CM, Goldman SM, 1996, Nussbaum RL, Ellis CE.2003). With an aging population, both the prevalence and incidence of PD are expected to increase by more than 30% by 2030 (Chen RC et al.,2001), which will result in both direct and indirect costs on both society and the economy.

Parkinson’s disease (PD) is the most prevalent neurodegenerative disease throughout the world (Kelly J, Moyeed R, Carroll C, Albani D, Li X.,2019), affecting approximately 1.04 million people in the US(Yang W et al.,2020) and 6.1 million worldwide(G. B. D. P. s. D.,2018). The symptoms can be divided into motor features, including bradykinesia, gait disturbance, tremor, rigidity, and speech deficits (Moustafa AA et al.,2016); and non-motor symptoms, such as depression, hyposmia, cognitive impairment, sleep disorders, and constipation (Schapira AHV, Chaudhuri KR, Jenner P.,2017). However, there exists a prodromal phase prior to the onset of PD where people may be asymptomatic or exhibit other symptoms that do not fall into the standard set of PD diagnostic markers (Mahlknecht P, Seppi K, Poewe W.,2015). Currently, several prodromal symptoms have been linked to a higher risk of developing PD in an otherwise healthy populations (Bloem BR, et.al.,2021). One of the highest PD risk symptoms is idiopathic rapid eye movement (REM) sleep behavior disorder (RBD), and it has been shown that 80% of the individuals with idiopathic RBD progress to develop PD (Mahlknecht *et al.*,2015).

PD cases can be classified into two major forms, monogenic and idiopathic. Five to 10% of all cases are monogenic, while the remaining majority are idiopathic (Schilder BM *et al.*,2022).

For the monogenic form, 13 loci and 9 genes have been shown to be involved in PD such as Synuclein Alpha (SNCA)/Parkinson Disease 1/4 (PARK1/4) that is associated with sporadic PD and early-onset cases, Leucine-Rich-Repeat Kinase 2 (LRRK2)/PARK8 that has been found in both autosomal dominant PD cases and sporadic cases, Parkin RBR E3 Ubiquitin Protein Ligase (PRKN)/PARK2 which causes early onset with slow progression, and PTEN-induced kinase 1 (PINK1)/PARK6 which is linked to the autosomal recessive form of PD (Lesage S & Brice A,2009).

In idiopathic PD, there are combination of known environmental factors and genetic elements that consist of many common variants of small efect size across the genome (Schilder BM *et al.*,2022). The pathological hallmarks of idiopathic PD include the death of dopaminergic neurons in the substantia nigra of the midbrain which mainly contribute to motor defcits, and the accumulation of α-synuclein in Lewy bodies and Lewy neurites (Borrageiro G *et.al.*,2018).

Parkinson's disease is the second most common neurodegenerative disorder, predominantly affecting individuals over the age of 60 (Poewe *et al.*, 2017). It presents with motor symptoms such as tremor, rigidity, and bradykinesia, as well as non-motor symptoms including cognitive impairment and mood disorders (Jankovic, 2008). The etiology of PD involves a complex interplay of genetic, environmental, and age-related factors (Kalia and Lang, 2015).

**Materials and Methods**

**1. Age-Related Aspects of Parkinson's Disease**

**1.1 Epidemiology and Risk Factors**

The incidence of PD increases significantly with age. Approximately 1% of the population over 60 years is affected by PD, and this prevalence rises with advancing age (de Lau and Breteler, 2006). Aging is the most significant risk factor for PD, likely due to cumulative cellular and molecular damage over time (Collier et al., 2011).The overall annual incidence rate is around 0.012% for all age groups, while for patients over 50 years of age, the frequency is 0.044% (Van Den Eeden SK et al.,2003) In addition, the global prevalence is estimated at 0.3% for the overall population but increases dramatically to>3% for the population of>80 years of age (Poewe.W. et al., 2017).However, young onset PD, which refers to disease onset of less than 40 or 50 years of age, is of concern (Post B et al.,2020)Around 25% of PD patients experience onset at an age younger than 65 years old, with 5–10% younger than 50 years of age (Bloem Br *et al.*, 2021).

**1.2 Age-Related Pathophysiological Changes**

Age-related decline in mitochondrial function, increased oxidative stress, and reduced cellular repair mechanisms contribute to the vulnerability of dopaminergic neurons in older adults (Schapira and Jenner, 2011). The natural aging process leads to a reduction in dopamine production and neuron density in the substantia nigra, which may predispose individuals to PD (Vernon *et al.*, 2011).

**2.The Biochemical changes in Parkinson's Disease**

The biochemical changes associated with PD, focusing on alterations in neurotransmitter systems, mitochondrial dysfunction, oxidative stress, protein aggregation, and inflammation.

**2.1 Alterations in Neurotransmitter Systems**

The hallmark of PD is the degeneration of dopaminergic neurons, which leads to a significant reduction in dopamine levels in the striatum (Obeso *et al.*, 2017). This dopaminergic deficit is primarily responsible for the motor symptoms of PD, such as bradykinesia, rigidity, and tremors. Besides dopamine, other neurotransmitter systems, including serotonergic, noradrenergic, and cholinergic pathways, are also affected (Chaudhuri *et al.*,2006). These changes contribute to the non-motor symptoms of PD, such as depression, anxiety, and cognitive impairment.

### 2.2 Mitochondrial Dysfunction

Mitochondrial dysfunction is a critical factor in the pathogenesis of PD. Evidence suggests that mutations in genes such as PINK1, Parkin, and DJ-1, which are involved in mitochondrial quality control, lead to impaired mitochondrial function and increased neuronal vulnerability (Exner *et al.*, 2012). Additionally, defects in the electron transport chain, particularly complex I, have been observed in the substantia nigra of PD patients.

### 2.3 Oxidative Stress

Oxidative stress plays a pivotal role in the neurodegenerative process of PD. The substantia nigra is particularly susceptible to oxidative damage due to its high dopamine turnover, which generates reactive oxygen species (ROS) (Jenner, 2003). Reduced levels of antioxidants, such as glutathione, further exacerbate this oxidative stress .The accumulation of oxidative damage to proteins, lipids, and DNA contributes to neuronal death in PD.

### 2.4 Protein Aggregation

The accumulation of misfolded proteins, particularly alpha-synuclein, is a characteristic feature of PD. Alpha-synuclein aggregates to form Lewy bodies, which are intracellular inclusions found in the brains of PD patients (Spillantini et al., 1997). Mutations in the SNCA gene, which encodes alpha-synuclein, and impairments in protein degradation pathways, such as the ubiquitin-proteasome system and autophagy-lysosome pathway, are implicated in the abnormal accumulation of alpha-synuclein (Stefanis, 2012).

## 3. Immunological Changes in Parkinson's Disease

### 3.1 Neuroinflammation

Neuroinflammation is a hallmark of PD, characterized by the activation of microglia and astrocytes, which release pro-inflammatory cytokines. This inflammatory response contributes to neuronal damage and the progression of neurodegeneration (Hirsch and Hunot, 2009).

### 3.2 Peripheral Immune System

Recent studies suggest that peripheral immune alterations also play a role in PD. Increased levels of systemic inflammation, changes in T-cell populations, and the presence of autoantibodies against neuronal antigens have been observed in PD patients (Kannarkat *et al.*, 2013).

### 3.3 Immune-Targeted Therapies

The involvement of the immune system in PD has led to the exploration of immune-modulating therapies. Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and monoclonal antibodies targeting specific cytokines or inflammatory pathways are being investigated for their potential to slow disease progression (Tansey and Goldberg, 2010).

### 3.4 Immunoglobulin Profiles

Studies have shown that patients with Parkinson's disease exhibit altered levels of various immunoglobulin classes, including IgG, IgA, and IgM. These changes may reflect an underlying dysregulation of the immune system in PD (Schwab *et al.*, 2013). For instance, elevated levels of IgG and IgA have been observed in the cerebrospinal fluid (CSF) of PD patients, suggesting an ongoing immune response within the central nervous system (CNS) (Qin *et al.*, 2016).

#### 3.4.a IgG and Its Subclasses

IgG is the most abundant immunoglobulin in the blood and plays a critical role in neutralizing pathogens and mediating antibody-dependent cellular cytotoxicity. Within the IgG class, there are four subclasses: IgG1, IgG2, IgG3, and IgG4. Research indicates

that PD patients may have altered IgG subclass distributions, with some studies reporting increased levels of IgG1 and IgG3 (Papachroni *et al.*, 2019). These changes could be linked to the autoimmune components of PD, as these IgG subclasses are involved in inflammatory responses.

**3.4.b IgA and Mucosal Immunity**

IgA is the primary immunoglobulin found in mucosal areas, such as the gut, respiratory tract, and urogenital tract, and plays a pivotal role in mucosal immunity. Elevated IgA levels in PD patients' serum and CSF might indicate a systemic immune activation, possibly related to gut dysbiosis, which has been implicated in PD pathogenesis (Mulak and Bonaz, 2015). The gut-brain axis is a significant area of interest, as the aggregation of alpha-synuclein, a hallmark of PD, might initiate in the gut and travel to the brain via the vagus nerve (Fitzgerald *et al.*, 2019).

**3.4.c IgM and Early Immune Response**

IgM is the first antibody produced in response to an infection and is crucial for initial immune defense.Altered IgM levels in PD patients have been documented, though findings are somewhat inconsistent. Some studies report increased IgM levels, which could indicate an ongoing inflammatory process or a response to persistent infections or autoantigens (He *et al.*, 2016). However, other research has found reduced IgM levels, which might reflect immune exhaustion or a compromised immune system in advanced PD (Katsarou *et al.*, 2013).

**3.5 Autoimmunity and Immunoglobulins in PD**

There is growing evidence to suggest that autoimmunity plays a role in PD. The presence of autoantibodies against neuronal antigens, including alpha-synuclein, supports this hypothesis (Yanamandra *et al.*, 2011). These autoantibodies are predominantly of the IgG class, particularly IgG1 and IgG3, which are known to participate in inflammatory immune responses. Their elevated levels in PD may contribute to neuroinflammation and neuronal damage, exacerbating disease progression (Papachroni *et al.*, 2019).

**4. Pathological Changes in Parkinson's Disease**

The pathological hallmarks of PD are the degeneration of dopamine-producing neurons in the ventral midbrain substantia nigra (SN) and associated widespread intraneuronal α-synuclein aggregation in Lewy bodies (Braak et al. 2003; Maiti et al. 2017). As the disease progresses, the loss of SN dopaminergic neurons results in the typical motor symptoms, such as bradykinesia, rigidity, impaired postural balance, and a characteristic resting tremor. PD patients develop dementia as the disease progresses (Goetz CG,2011; Moustafa *et al.*, 2016). In addition, prodromal symptoms have been reported by PD patients years before the onset of disease. Some of these signs include constipation, insomnia, mood disorders, depression and anxiety (Mahlknecht *et al.*, 2015). Currently, diagnosis is based on clinical symptoms with the criteria for a diagnosis requiring the presence of two of the following clinical features: resting tremor, bradykinesia, rigidity and/or postural instability. Clinical criteria, however, can only lead to a diagnosis of probable PD, while a definitive diagnosis requires histopathological assessment, with the identification of α-synuclein-containing Lewy bodies (LBs) or Lewy neurites.

Although the pathogenesis of PD is not yet fully understood, striatal dopamine deficiency due to the degeneration of dopaminergic neurons of the substantia nigra pars compacta has been recognized as a PD hallmark.( Poewe W *et al.*,2017; Kalia LV *et al.*, 2016)The substantia nigra(SN)appears depigmented macroscopically due to the death of neuromelanin containing dopaminergic neurons, and there are two distinct microscopic features for the pathological diagnosis of PD: intracellular α-synuclein aggregations and dopaminergic cell degeneration.( Farrer MJ,2006; Mor DE *et al.*, 2018). α-Synuclein can exist as a small soluble monomer which can form oligomers or larger protein aggregates, that are components of Lewy bodies and Lewy neurites in dopaminergic neurons. (Mor DE *et al.*,2018; Kaila *et.al.*,2013).Due to the dopaminergic neuronal dysfunction and cell death, there is insufficient dopamine in the striatum, which affects the initiation of movement, ( *Kalia et al.*,*2015*;Farrer MJ,2006) that in turn accounts for the movement symptoms displayed by patients. Therefore, replacing striatal dopamine through medications such as l-dopa is an effective symptomatic treatment, (Poewe *et.al.*,2017, Farrer MJ,2006)but all existing symptomatic therapies for PD (including l-dopa) do not target the underlying molecular mechanisms of the disease, and have little to no impact on disease progression.

### 4.1 α-Synuclein Aggregation

The presence of Lewy bodies and Lewy neurites, primarily composed of aggregated α-synuclein, is the pathological hallmark of PD. These protein inclusions are found in various brain regions and are associated with neuronal dysfunction and death (Spillantini *et al.,* 1997). The α-synuclein aggregation has recently been demonstrated to begin in the enteric nervous system and propagates to the brain via the vagus nerve (Kim *et al.,* 2019).

### 4.2 Dopaminergic Neuron Degeneration

The selective loss of dopaminergic neurons in the substantia nigra pars compacta is central to PD pathology. This degeneration leads to a significant reduction in striatal dopamine levels, which underlies the motor symptoms of the disease (Gibb and Lees,1991). An electron microscopic observation of PD brain samples suggested apoptotic, necrotic, and autophagic cell death of nigral dopaminergic neurons (Anglade *et al.*,1997). The presence of an autophagosomal marker, the microtubule-associated protein 1A/1B-light chain 3 (LC3), in the Lewy bodies of the PD patients supports the active role of autophagy in this disease (*Tanji et al.*, 2013).

### 4.3 Other Neuropathological Features

PD pathology extends beyond the substantia nigra, affecting other brain regions such as the locus coeruleus, dorsal motor nucleus of the vagus, and olfactory bulb. This widespread neurodegeneration contributes to the diverse range of motor and non-motor symptoms observed in PD patients (Braak *et al.,* 2004).

## 5. Molecular Level Changes in Parkinson's Disease

### 5.1 Genetic Factors

Genetic mutations play a crucial role in familial and sporadic PD.

**5.1.a Autosomal dominant PD**:

The first type of familial PD caused by a point mutation in the α-synuclein gene (SNCA) was discovered in 1997 (Polymeropoulos MH et al.,1997). Four additional point mutations, as well as gene duplication or triplication, have now been linked to autosomal dominant PD (Singleton AB, *et al.,* 2003;Zarranz JJ *et al.,* 2004;Chartier-Harlin M C *et al.*,2004;Krüger R *et al.*,1998,Appel-Cresswell S *et al.*,2013;Lesage S *et al.*,2013). However, these mutations are relatively rare. The most frequent autosomal dominant monogenic PD is caused by mutations in the gene encoding leucine-rich repeat kinase 2 (LRRK2). Six LRRK2 mutations have been confirmed as pathogenic (Healy DG *et al.*,2008), the most common of which is p.G2019S, estimated to account for 1% of sporadic and 4% of familial PD worldwide (Healy DG *et al.,* 2008). More recent genetic studies have led to the discovery of additional mutations in other genes responsible for autosomal dominant PD, including VPS35.

Although multiple genes have been shown causative for PD , two important PD causative genes identified so far are SNCA and LRRK2. SNCA encodes a-synuclein, a major component of pathological hallmark of Lewy bodies in PD,(Spillantini M.G *et al.*,1997) while mutations in LRRK2 are the most common indicators of inherited PD.( Ross OA, et al.,2006, Giasson B.I., Covy J.P., Bonini N.M *et.al.*,2006)Over time, more PD causative genes with autosomal dominant inherence were identified , but none has overtaken the importance of SNCA or LRRK2 from pathological or genetic perspective.

**5.1.b Autosomal recessive PD**

Autosomal recessive forms of PD typically present with an earlier onset than classical PD. Three of the PARK-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 thus initiating mitophagy (Pickrell AM and Youle RJ.2015). Mutations in PRKN are the most common cause of autosomal recessive familial PD, occurring in up to 50% of all early-onset cases (Schulte

C and Gasser T. 2011 Jun). Finally, 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)(Ramirez A *et.al.*, 2006; Paisan-Ruiz C *et.al.*,2009;Di Fonzo A *et.al.*,2009;Olgiati S *et.al.*,2016).

PD causative genes with AR inherence often occur in PD patients with early onset. Among them, the most common mutations are in PRKN (previously known as PARK2), followed by PINK1, Polymeropoulos (MH *et al.*,1997) and DJ-1,(Singleton AB *et al.*, 2003) accounting for about 18%, 15% and 0.2% of early onset PD respectively.(ZarranzJJ *et.al.*,2004,Chartier-HarlinM-C,et.al.,2004,KrügerR,et.al.,1998, Appel-Cresswell S, et.al., 2013)Deletions and mutations in PRKN gene are associated with degeneration of pigmented neurons in the substantia nigra, similar to that seen in PD, but without Lewy bodies on brain autopsy.(Lesage S *et.al.*,2013;HealyDG *et.al.*,2008) However, the compound heterozygous PRKN or PINK1 mutations had dopaminergic neuron loss in substantia nigra and the presence of Lewy bodies. (Lesage S *et al.*, 2013; Healy DG *et al.*, 2008)

**5.1.c Genes associated with PD Susceptibility.**

Since 2009, genome wide association studies (GWAS) have opened a new era to identify PD susceptibility genes via comparison between PD and controls. The first European PD GWAS analysis identified two genetic risk loci with 1713 PD cases and 3978 controls and replicated with 3361 cases and 4573 controls.(Kitada T, Asakawa S. *et.al.*,1998) The risk loci identified were SNCA and MAPT, containing risk SNPs rs2736990 and rs393152, respectively.(Kitada T *et.al.*,1998) This study also replicated PARK16 and the SNPs rs823128 as one of the SNPs previously identified in a Japanese cohort.(Kitada T *et.al.*,1998)

In 2017, Chang et al's GWAS identified 12 risk loci, one of them being the novel locus: rs9468199.(Zimprich A *et.al.*,2004) On the other hand, the GWAS analysis included six East Asian regions, including mainland China, Hong Kong, Taiwan, Singapore, Malaysia, and Korea, also confirming SNCA and LRRK2 as the most significant risk loci, as well as MCCC1, and 14 other loci reported in European studies.(Williams DR *et.al.*,2005)

This finding suggested mutations in SNCA and LRRK2 significantly change corresponding protein functions causing PD, while their non-coding genetic variants lead to subtle changes in protein functions, conferring risk to develop PD.

The 2019 meta-analysis Nalls et al performed included 17 recent GWAS datasets in European populations, involving over 37,000 cases, over 18,000 PD family cases and 1.4 million controls. (Strauss KM *et.al.*,2005) However, GWAS studies of PD with Asian populations are still at a relatively early stage, with a limited number of studies. Future studies are needed to explore the genetic risk factors of PD in different ethnic groups and obtain a better understanding of any common or population-specific genetic variants amongst different ancestries.

Key genes implicated include SNCA (encoding α-synuclein), LRRK2, PARK2 (parkin), and PINK1. These genetic factors influence disease onset, progression, and response to therapies (Klein and Westenberger, 2012).

**5.2 Mitochondrial Dysfunction**

The first demonstration that mitochondria play a role in PD pathogenesis was after an individual consumed drug contaminated with the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Studies show MPTP undergoes oxidation by MAO-B, forming 1-methyl-4-phenylpyridinium (MPP+), which enters DA neurons in SN via DA reuptake system. Subsequently, MPP+ inhibits mitochondrial ETC Complex I enzyme and NADH ubiquinone oxidoreductase leading to electron leakage and ROS production.

PD-related genes, PINK1, PARK2 (Parkin), DJ-1, and LRRKS encode proteins that regulate mitochondria and ROS homeostasis. PINK1 is rapidly degraded in healthy mitochondria while in those exhibiting misfolded proteins, high oxidative stress, or reduced membrane potential, PINK1 degradation is impeded, leading to PINK1 accumulation in the outer mitochondrial membrane. PINK1 recruits Parkin and induces E3 ubiquitin ligase activity. Parkin modifies mitochondrial membrane protein by adding ubiquitin chains, thus signaling for autophagy. Such autophagy, called mitophagy, results in mitochondria engulfment and degradation (Ganguly G *et.al.*,2017) During oxidative stress, DJ-1 translocates to the outer membrane and prevents MPP+ induced cell death, although the mechanism is unclear. The homozygous mutation of DJ-1 increased mitochondrial oxidative stress, accumulation of α-synuclein, and DA oxidation (Bur bulla L.F *et.al.*,2017).

Mitochondrial dysfunction is a critical feature of PD, leading to impaired ATP production, increased oxidative stress, and neuronal death. Mutations in genes like PARK2 and PINK1 disrupt mitochondrial quality control and dynamics, exacerbating neurodegeneration (Exner *et al.*,2012).

**5.3 Oxidative Stress and Reactive oxygen species**

Oxidative stress occurs due to the imbalance between production of ROS and the availability of antioxidants or radical scavengers (Forrester *et al.*, 2018;Ng *et al.*, 2013;Pizzino *et al.*, 2017) Oxidative stress is an important factor in cell death in response to a variety of pathophysiological conditions. Different pathways generate ROS in the brain during routine cellular processes; however, sometimes either overproduction or defective clearance leads to the accumulation of these free radicals (Dias *et al.*,2013). Mitochondria are significant contributors to ROS production (Cui *et al.*,2012), but oxidative stress is also reported to result from defective lipid peroxidation (Niki.2008), DNA damage (Narciso *et al.*,2016), formation of insoluble Parkin aggregates, decreased E3 ligase activity (LaVoie *et al.*,2007), and possibly α-synuclein aggregation (Scudamore and Ciossek.2018). Dopamine metabolism also results in ROS production, probably contributing to SN dopaminergic neuron vulnerability to oxidative damage (Jenner.2003).

Elevated oxidative stress and the accumulation of reactive oxygen species (ROS) contribute to the degeneration of dopaminergic neurons. The high metabolic activity and dopamine metabolism in these neurons make them particularly susceptible to oxidative damage (Dias, Junn and Mouradian.2013).

**5.4 Proteostasis and Autophagy**

Disruptions in proteostasis and impaired autophagy-lysosomal pathways lead to the accumulation of misfolded proteins, such as α-synuclein, in PD. Enhancing autophagy to clear these protein aggregates is a potential therapeutic strategy under investigation (Menzies, Fleming and Rubinsztein, 2015).

**6. Conclusion**

Parkinson's disease is a complex disorder with multifactorial etiology involving age-related, biochemical, immunological, pathological, and molecular changes. Aging remains the most significant risk factor, while biochemical symptoms reflect the extensive neurodegeneration characteristic of PD. Immunological alterations and pathological features such as α-synuclein aggregation provide insights into disease mechanisms, and molecular changes highlight potential therapeutic targets. Future research should continue to integrate these aspects to develop comprehensive treatment strategies for PD.

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