# 1 Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis

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Doi: http://dx.doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch1

**Abstract:** Parkinson's disease (PD) is a common neurodegenerative disorder. While a number of non-motor manifestations arise, the typical clinical features involve a movement disorder consisting of bradykinesia, resting tremor, and rigidity, with postural instability occurring at a later stage. The cause of PD is not known, but a number of genetic risk factors have now been characterized, as well as several genes which cause rare familial forms of PD. Environmental influences such as smoking, caffeine consumption, and pesticide exposure have been postulated to alter the risk of PD development, although the role of these remains unclear. The movement disorder arises due to the loss of dopaminergic neurons of the substantia nigra pars compacta, with the pathological hallmark being intracellular aggregates of α-synuclein, in the form of Lewy bodies and Lewy neurites. Several processes have been implicated in PD, including mitochondrial dysfunction, defective protein clearance mechanisms, and neuroinflammation, but the way in which these factors interact remains incompletely understood.

In: *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Stoker TB, Greenland JC (Editors). Codon Publications, Brisbane, Australia. ISBN: 978-0-9944381-6-4; Doi: http://dx.doi.org/10.15586/codonpublications.parkinsonsdisease.2018

**Keywords:** α-synuclein; Lewy body; neurodegeneration; Parkinson's disease; pathogenesis

## 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) (1), 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 (2, 3). With an aging population, both the prevalence and incidence of PD are expected to increase by more than 30% by 2030 (4), which will result in both direct and indirect costs on both society and the economy as a whole.

PD is pathologically characterized by the loss of nigrostriatal dopaminergic innervation, although neurodegeneration is not limited to only the nigral dopaminergic neurons but also involves cells located in other regions of the neural network. Such a widespread pathology makes PD a very heterogeneous disorder, and a reliable diagnostic test is not yet available. 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.

Treatment predominantly focuses on symptomatic relief with drugs aiming to either restore the level of dopamine in the striatum or to act on striatal postsynaptic dopamine receptors. However, as dopamine is not the only neurotransmitter involved in PD, many other drugs are also being used to target specific symptoms, such as depression or dementia. Yet, further investigation on novel therapies to reduce the rate of neurodegeneration or even to replenish the loss of dopaminergic cells remains in the research setting, with some in the early stages of clinical trials. As our understanding of the pathogenesis of PD increases and more is learned about new therapeutic targets, the potential for the development of disease-modifying therapies is promising.

## CLINICAL FEATURES

The clinical features historically associated with PD are the triad of motor symptoms, namely, tremor, rigidity, and bradykinesia, with postural instability often appearing as the disease progresses. However, PD is also associated with many non-motor symptoms, and these often precede the motor symptoms by years or even decades.

The pre-motor or prodromal phase of PD may start as early as 12–14 years before diagnosis (5). There is now a great deal of evidence supporting the fact that the disease

may begin in the peripheral autonomic nervous system and/or the olfactory bulb, with the pathology then spreading through the central nervous system affecting the lower brainstem structures before involving the substantia nigra (6). This may thus explain the presence of hyposmia, constipation, and rapid eye movement sleep disorders in PD patients before motor symptoms begin. One study showed that patients with tremor, balance problems, depression, constipation, fatigue and urinary dysfunction at 5 years prior to diagnosis were more likely to develop PD than those without these symptoms (7). Additionally, individuals with constipation or tremor have a higher risk of developing PD over 10 years of follow-up (7).

There is increasing interest in this prodromal state of PD as it may be an ideal time point for therapeutic intervention. Many trials investigating potential therapies include patients with early PD, that is, those within 2 years of diagnosis, but even at this stage, significant dopaminergic neuron loss has already occurred (8)—therefore, it would be optimal for any future disease-modifying treatments to be initiated in the prodromal phase.

Clinical diagnosis of PD is based on the presence of bradykinesia in combination with a resting tremor or rigidity. Early symptoms generally present asymmetrically, with the absence of atypical symptoms (cerebellar signs, early severe autonomic dysfunction, vertical supranuclear palsies, or cortical sensory loss), which would be indicative of an alternative diagnosis (9). An asymmetric onset of symptoms and a good response to levodopa are supportive for a diagnosis of PD and are the two most important features to discriminate PD from other forms of Parkinsonism (9).

As the disease progresses, so does the severity of motor and non-motor symptoms. PD is a very heterogeneous disease and there have been attempts to subclassify the disease further. Although a consensus has yet to be met, one subclassification primarily based on clinical characteristics suggests two subtypes: a tremor dominant PD and a non-tremor dominant PD. A patient with tremor dominant PD predominantly lacks other motor symptoms and in general responds better to dopamine replacement therapy. On the other hand, a patient with a non-tremor dominant PD may have an akinetic-rigid syndrome and a postural instability disorder, as well as an increased incidence of non-motor features. The course of the disease and prognosis differs (10), and it has been postulated that the various subtypes have distinct pathogenesis and etiologies (11).

As the disease progresses, motor symptoms worsen over time, with the onset of further complications associated with long-term levodopa therapy. These include non-motor fluctuations, dyskinesias, and psychosis that are more difficult to manage. In an advanced disease stage, both motor and non-motor symptoms may become resistant to current medications. Postural instability and freezing of gait may lead to falls and fractures, while dementia and hallucinations can develop in some patients, which sometimes warrant care home placement.

Non-motor symptoms are common in early PD but also progress and become more challenging to manage. Early non-motor symptoms include impaired olfactory ability, autonomic dysfunction, pain, fatigue, sleep disorders, and cognitive and psychiatric disturbances. They have a significant impact on the patient's quality of life (12). Autonomic symptoms can be difficult to treat with orthostatic hypotension causing significant problems for patients. Urinary incontinence and constipation are common, and dementia occurs in 83% of patients with PD after 20 years of diagnosis (13). These non-motor symptoms contribute significantly to disability and poor quality of life and also strongly predict admission to care homes (14).

## ETIOLOGY

PD is a multifactorial disease, with both genetic and environmental factors playing a role. Age is the biggest risk factor for PD, with the median age of onset being 60 years of age (15). The incidence of the disease rises with age to 93.1 (per 100,000 person-years) in age groups between 70 and 79 years (16, 17). Additionally, there are cross-cultural variations, with higher prevalence reported in Europe, North America, and South America compared with African, Asian and Arabic countries (1).

### Cigarette smoking

Cigarette smoking has been extensively studied with respect to PD, with mostly consistent results. Most of the epidemiological reports are case-control studies showing a reduced risk of developing PD, with larger cohort studies also in agreement (18–20). A large meta-analysis including 44 case-control studies and 8 cohort studies from 20 countries showed an inverse correlation between smoking and PD, with a pooled relative risk of 0.39 for current smokers (21). Two other meta-analyses also reported an inverse correlation between smoking and PD, with a pooled odds ratio ranging from 0.23 to 0.70, indicating a protective mechanism against PD (22, 23). They also reported an inverse correlation between the number of pack years, the number of years smoking and the risk of PD, with the risk of developing PD being significantly reduced in heavy or long-term smokers compared with nonsmokers (23).

The reasons underlying this associated reduced risk are not fully understood. Activation of nicotinic acetylcholine receptors on dopaminergic neurons by nicotine or selective agonists has been shown to be neuroprotective in experimental models of PD (24, 25). Nevertheless, nicotine can also stimulate the release of dopamine, which is involved in the reward mechanisms; it is therefore difficult to confirm whether smoking prevents PD or whether PD helps prevent the habitual use of cigarettes. As a result of a reduction in dopamine in patients with PD, patients may be less prone to addictive behaviours, and thus less likely to smoke. This hypothesis is supported by the fact that patients with prodromal PD and PD were able to give up smoking much easier than controls, suggesting this association could be due to the decreased responsiveness to nicotine (26).

### Caffeine

Several studies have investigated the effect of caffeine on the development of PD and reported a reduced risk of developing PD among coffee drinkers. Caffeine is an adenosine $A_{2A}$ receptor antagonist, which is believed to be protective in PD (27) and has been shown to be neuroprotective in a mouse model of PD (28). It has been previously reported that there is a 25% risk reduction in developing PD among coffee drinkers (14). Two large prospective epidemiological studies (27, 29), as well as multiple retrospective studies (30), have also shown a reduced risk of developing PD with a relative risk ranging from 0.45 to 0.80 in coffee

drinkers versus non-coffee drinkers. A meta-analysis including eight case-control studies and five cohort studies also showed a significantly reduced risk of developing PD in coffee drinkers (RR 0.69) (21). Regular tea drinkers also have been reported to have a lower risk of developing PD (29).

As with smoking, the causative role of caffeine in preventing PD remains to be established. Furthermore, there were differences noted between studies with respect to gender. In two cohort studies (27, 29), there was a strong inverse correlation between coffee and the development of PD in men, whereas in women this association was weaker. Additionally, in post-menopausal women, the effect of caffeine depended on whether the females were taking hormone replacement therapy including estrogens. As estrogen competitively inhibits caffeine metabolism, interactions between estrogen and caffeine may explain in part why PD risk is dependent on hormone replacement therapy in post-menopausal women (31, 32).

## Pesticides, herbicides, and heavy metals

In 1983, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was first discovered to be associated with nigrostriatal degeneration when several people developed typical PD signs after injecting themselves with a drug contaminated with MPTP. MPTP is metabolized into the neurotoxin, MPP+ (1-methyl-4-phenylpyridinium), which is a mitochondrial complex-I inhibitor that selectively damages dopaminergic cells in the substantia nigra (32, 33). The identification of MPTP as a cause of nigral degeneration led to the idea that PD could be caused by an environmental toxin. Since then, several studies have shown an association between pesticides and PD, with one case-control study showing an increased association with professional pesticide exposure in men and late-onset PD (odds ratio [OR] 2.2) (34). Paraquat (a herbicide which is structurally very similar to MPP+) (35) and rotenone (a pesticide) are also selective complex-I inhibitors and induce dopaminergic depletion in animal models of PD (36). The relationship between exposure to these chemicals and the risk of developing PD has been investigated in other epidemiological studies (37). It has also led to the study of surrogate markers, including the association of farming, drinking well water, and living in rural areas with PD risk. Welding and heavy metal exposure (e.g., iron, copper, lead, aluminum, and zinc) have also been investigated, but the relationship between these and PD remains inconclusive.

## Genetics

Although PD is generally an idiopathic disorder, there is a minority of cases (10–15%) that report a family history, and about 5% have Mendelian inheritance (38). Furthermore, an individual's risk of PD is partially the product of as-yet poorly defined polygenic risk factors. The genes that have been found to potentially cause PD are assigned a "PARK" name in the order they were identified. To date, 23 PARK genes have been linked to PD. Mutations in the PARK genes demonstrate either autosomal dominant (e.g., *SCNA, LRRK2,* and *VPS32*) or autosomal recessive inheritance (e.g., *PRKN, PINK1,* and *DJ-1*) and are summarized in Table 1. The involvement of some of these genes has not been conclusively confirmed

(PARK5, PARK11, PARK13, PARK18, PARK21, and PARK23), while others are considered risk factors (PARK3, PARK10, PARK12, PARK16, and PARK22) (39).

The numerically most important genetic risk factors predisposing to PD are mutations in *GBA1*, a gene encoding β-glucocerebrosidase—a lysosomal enzyme responsible for the hydrolysis of glucocerebrosides (see Chapter 3) (40). *GBA1* mutations are known to cause Gaucher disease, which is the most common lysosomal storage disorder (41). Other genetic risk factors include the major histocompatibility complex, class II (HLA-DQB1) (42) and the gene encoding the protein tau, *MAPT* (43), among others.

### Autosomal dominant PD

The first type of familial PD caused by a point mutation in the α-synuclein gene (*SNCA*) was discovered in 1997 (44). Four additional point mutations, as well as gene duplication or triplication, have now been linked to autosomal dominant PD (45–50). 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 (51), the most common of which is p.G2019S, estimated to account for 1% of sporadic and 4% of familial PD worldwide (51). More recent genetic studies have led to the discovery of additional mutations in other genes responsible for autosomal dominant PD, including *VPS35* (Table 1).

### 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 (52). Mutations in *PRKN* are the most common cause of autosomal recessive familial PD, occurring in up to 50% of all early-onset cases (39). Finally, several of the autosomal recessive genes have been linked to atypical parkinsonism with variable features (Table 1), including *ATP13A2* (PARK9), *PLA2G6* (PARK14), *FBX07* (PARK17), and *SYNJ1* (PARK20) (53–56).

## NEUROPATHOLOGY OF PARKINSON'S DISEASE

Macroscopically, the brain in idiopathic PD is often unremarkable with mild atrophy of the frontal cortex and ventricular dilation in some cases. The main distinctive morphological change in the PD brain is observed in transverse sections of the brainstem, where almost all cases present with loss of the darkly pigmented area in the substantia nigra pars compacta (SNpc) and locus coeruleus. This pigmentation loss directly correlates with the death of dopaminergic (DA) neuromelanin-containing neurons in the SNpc and noradrenergic neurons in the locus coeruleus (71). Cell death in the SNpc is mostly restricted to a specific

## TABLE 1 PARK-designated genes involved in familial Parkinson's disease

| PARK | Gene | OMIM reference | Inheritance | Description | Clinical features |
|---|---|---|---|---|---|
| PARK1 PARK4 | *SNCA* (44,45,57) | 168601 | AD | α-synuclein | Ranging from classical PD to early-onset cases with dementia, autonomic dysfunction, and rapid progression |
| PARK2 | *PRKN* (58) | 600116 | AR | parkin RBR E3 ubiquitin protein ligase | Early-onset PD, slow progression, often features of dystonia |
| PARK5 | *UCHL1* (59) | 613643 | AD | ubiquitin C-terminal hydrolase L1 | Classical PD—only one family, findings not since replicated |
| PARK6 | *PINK1* (60) | 605909 | AR | PTEN-induced putative kinase 1 | Early-onset PD, slow progression |
| PARK7 | *DJ-1* (61) | 606324 | AR | Parkinsonism-associated deglycase | Early-onset PD, slow progression |
| PARK8 | *LRRK2* (62) | 607060 | AD | Leucine-rich repeat kinase 2 | Classical PD with less frequent dementia and slower progression |
| PARK9 | *ATP13A2* (53) | 606693 | AR | Cation-transporting ATPase 13A2 | Early-onset (adolescence), atypical parkinsonism with dementia, spasticity and supranuclear palsy (Kufor–Rakeb syndrome) (63) |
| PARK11 | *GIGYF2* (64) | 607688 | AD | GRB10 interacting GYF protein 2 | Classical PD |
| PARK13 | *HTRA2* (65) | 610297 | AR | HtrA serine peptidase 2 | Classical PD |
| PARK14 | *PLA2G6* (54) | 612593 | AR | Calcium-independent phospholipase A2 enzyme | Early onset with atypical features (dystonia parkinsonism) |
| PARK15 | *FBX07* (55) | 260300 | AR | F-box protein 7 | Early onset with atypical features (pallido-pyramidal syndrome) |
| PARK17 | *VPS35* (66) | 614203 | AD | Vacuolar protein sorting-associated protein 35 | Classical PD |
| PARK18 | *EIF4G1* (67) | 614251 | AD | Eukaryotic translation initiation factor 4 gamma 1 | Classical PD |
| PARK19 | *DNAJC6* (56) | 615528 | AR | HSP40 Auxilin | Early-onset PD, slow progression |
| PARK20 | *SYNJ1* (68) | 615530 | AR | Synaptojanin 1 | Parkinsonism with dystonia and cognitive decline |
| PARK21 | *DNAJC13* (69) | 616361 | AD | Receptor-mediated endocytosis 8 (RME-8) | Classical PD |
| PARK23 | *VPS13C* (70) | 616840 | AR | Vacuolar protein sorting-associated protein 13C | Early-onset PD, rapid progression |

OMIM: Online Mendelian Inheritance in Man database, AD: autosomal dominant, AR: autosomal recessive. PARK3 PARK10, PARK12, PARK16, and PARK22 are considered risk factors or the genes have not been identified yet and are not included in this table.

group of neuromelanin-containing dopaminergic neurons, namely the A9 neurons, while other neuronal and glial cell types are largely spared (Figure 1).

Quantitative morphometric studies in postmortem PD brains have calculated approximately 30% loss of DA neurons in the SNpc by motor symptom onset, adjusting for age (8, 72–75). After the motor symptoms appear, nigral DA neuron loss increases up to 60% or higher and strongly correlates with the severity of motor features and disease duration (8, 76, 77). The result of this remarkable cell loss is the denervation of the nigrostriatal pathway, leading to diminished dopamine levels in the striatum. The reduction of dopaminergic signaling is considered responsible for the appearance of the cardinal motor symptoms in PD. Recent work has shown that nerve cell death in the SNpc is preceded by the loss of axon terminals projecting to the striatum (77). Mechanistically, the early neuron and axon terminal loss observed in PD suggests a substantial preclinical stage that predates the onset of symptoms by several years.

Apart from the SNpc, widespread cell loss can be found in several subcortical nuclei, including the locus coereleus, the nucleus basalis of Meynert, the dorsal

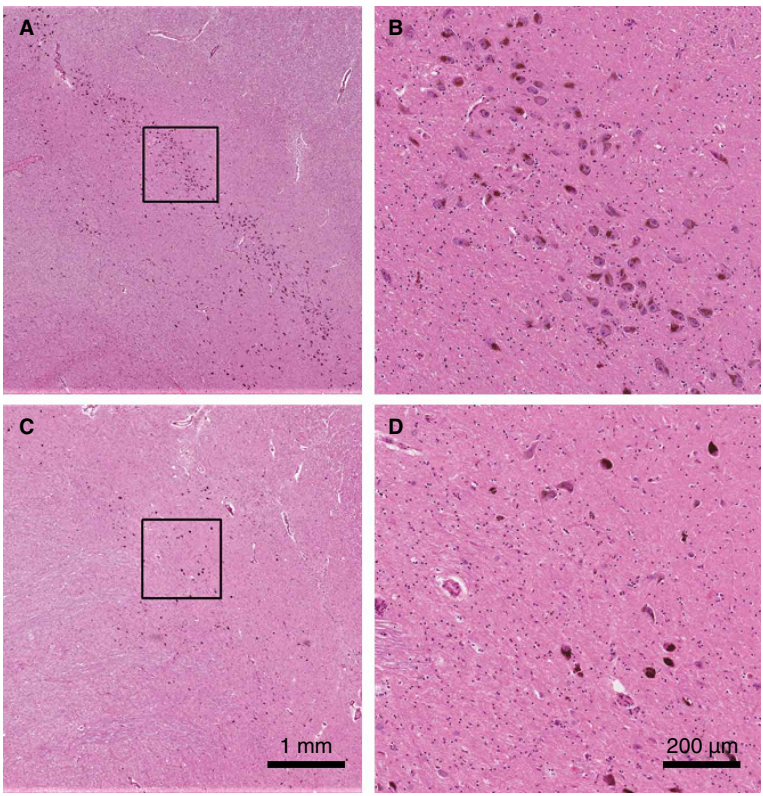


**Figure 1 Coronal section at the level of the substantia nigra pars compacta (SNpc) in a control (A and B) and a PD brain (C and D) stained by hematoxylin and eosin.** In both sections, the dark brown cells are the neuromelanin-containing dopaminergic (DA) neurons. Dopaminergic cell loss is evident in the SNpc of the PD brain. The squared areas in A and C are magnified in B and D, respectively, to show a closer view of the darkly pigmented DA neurons.

motor nucleus of the vagus nerve, the pedunculopontine nucleus, the raphe nuclei, and also the hypothalamus and the olfactory bulb (76). Multiple non-dopaminergic neurotransmitter systems are affected, such as the cholinergic, adenosinergic, glutamatergic, GABAergic, noradrenergic, serotonergic, and histaminergic (78). Degeneration in those systems is thought to account for some of the non-motor symptoms of PD that do not respond well to dopamine replacement therapies (79). However, the precise pathological mechanisms underlying the non-motor symptoms in PD are still relatively unclear.

## Lewy body pathology

Microscopically, the pathological hallmark of PD is the presence of abnormal cytoplasmic deposits within neuronal cell bodies which are immunoreactive for the protein α-synuclein. These pathological protein aggregates are called Lewy bodies (LBs) and are often accompanied by dystrophic neurites (Lewy neurites), which are mostly axonal (80) (Figure 2A–2C).

LBs are intracytoplasmic inclusions consisting of a granular and fibrillar core with a surrounding halo (Figure 2A and 2B). The size of an LB can vary from 5 to 30 μm in diameter, and more than one LB can be found inside a single neuron (81). Two LB types have been described in the literature: classical brainstem

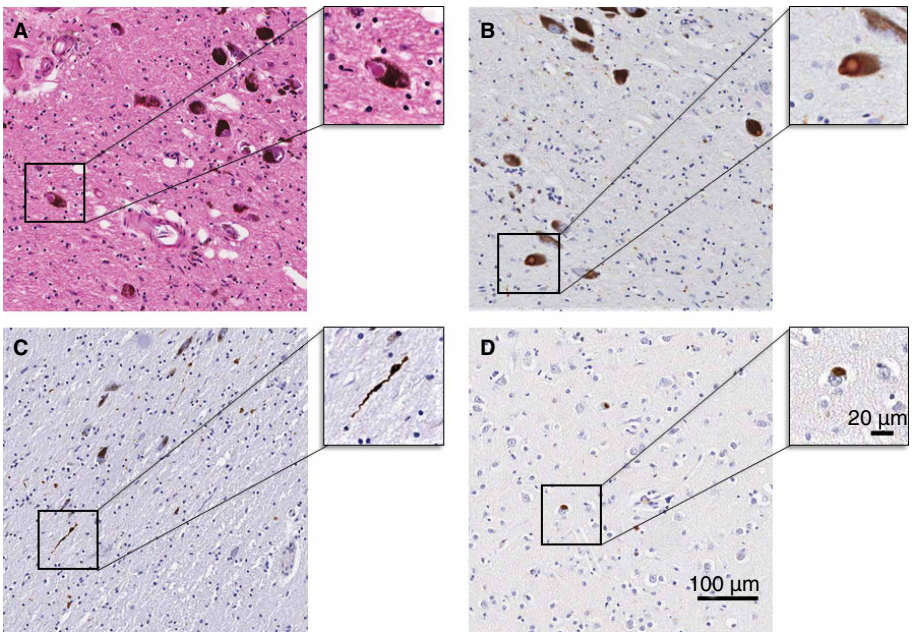


**Figure 2 Examples of Lewy-pathology in the SNpc (A–C) and the prefrontal cortex (D) in coronal sections of a PD brain.** (A) Typical brainstem Lewy body inside a neuromelanin-containing DA neuron in routine hematoxylin and eosin histological staining. Lewy neurites are not visible in this type of histological preparation. (B) Typical brainstem Lewy body with the characteristic halo, visualized by α-synuclein immunohistochemistry, a much more sensitive method that can also reveal dystrophic Lewy neurites as seen in (C). (D) Cortical Lewy body, less well defined and without a halo.

and cortical LBs (Figure 2B and 2D). Morphologically, the main difference is that cortical LBs have less distinct outlines, are usually smaller, and lack the halo. In the SN, structures that resemble cortical LBs are sometimes called "pale bodies" and are considered LB precursors.

The primary structural component of LBs is filamentous α-synuclein (80), a protein ubiquitously expressed in the brain. In PD and other synucleinopathies, it acquires an amyloid-like filamentous structure and becomes abnormally phosphorylated and aggregated. The halo of an LB is primarily made up of α-synuclein (82). Apart from α-synuclein, the molecular components of an LB include a number of proteins, such as ubiquitin, tau, parkin, heat shock proteins (HSPs), oxidized/nitrated proteins, cytoskeletal proteins (such as neurofilaments, MAPs, and tubulin), proteasomal and lysosomal elements, and others (83).

## Braak staging

The main staging system of PD pathology was introduced in 2003 by Braak and colleagues. This was based on the semiquantitative assessment of LB distribution, at postmortem, in a large autopsy series. This work revealed that LB pathology spreads rostrocaudally throughout the brain, in a chronologically predictable sequence (84). At Braak stages 1 and 2, LB lesions are mainly observed in the dorsal motor nucleus (IX/X), the reticular formation, and the anterior olfactory nucleus. At these stages, patients are considered asymptomatic or presymptomatic, although they may present with some early non-motor features, mainly autonomic (e.g., constipation), olfactory, and sleep-related dysfunctions (85, 86). As the disease progresses (Stage 3), the SNpc becomes involved, with LB pathology and neuronal loss being observed in melanized neurons. At this stage, the pathology also extends to the locus coeruleus and the amygdala, subsequently reaching the temporal limbic cortex (transentorhinal region) at Stage 4. During stages 3 and 4, the typical clinical motor features begin to manifest. Finally, during stages 5 and 6, the key feature is the involvement of the entire neocortex and high-order areas, including the prefrontal cortex and primary sensory and motor areas (84, 87). Clinically, this is thought to translate to severe PD with significant gait problems and dementia. The Braak hypothesis was later revised to propose that α-synuclein-associated pathology may in fact be initiated in nasal and intestinal mucosal sites, specifically in the olfactory bulb and the enteric cell plexuses ("dual-hit hypothesis") (88).

Since its introduction in 2003, the Braak staging system has been a subject of controversy. Subsequent studies have shown that a proportion of PD brains do not appear to match this pattern (89, 90), while attempts to correlate Braak staging with clinical dysfunction were also unsuccessful (91). Another criticism of the Braak system is that it is based not on neuronal loss but on the distribution of Lewy-related pathology (92).

## α-synuclein and Lewy body distribution outside the brain

Phosphorylated α-synuclein histopathology has also been observed outside the brain. Specifically, it is found in the spinal cord and cervical and thoracic sympathetic ganglia (93). Furthermore, α-synuclein deposition is observed in

several peripheral organs, including the retina, the uterus, the bladder, the skin, parts of the cardiovascular system (predominantly in the aorta and heart ventricles), and the gastrointestinal system, particularly in the submandibular gland, stomach, and the bowels (94, 95). This points to a significant involvement of the peripheral nervous system in PD and raises the question of whether α-synuclein pathology originates in the brain or in the periphery. An epidemiological study from Denmark has revealed that a full truncal vagotomy is associated with a reduced risk of subsequent PD (96), leading to recent interest in the possible role of the gut–brain axis in the pathogenesis of PD (97).

## Interaction of α-synuclein with other proteins

Protein misfolding within particular brain areas is a shared feature among many neurodegenerative diseases, such as AD and PD. Therefore, an umbrella term often used for these disorders is "proteinopathy." The type of protein and the characteristic distribution of the pathology is the significant attribute that defines each proteinopathy. Nevertheless, it is now becoming increasingly clear that there is often overlap between the different diseases and an interaction between the pathogenic, misfolded forms of proteins (98). One factor contributing to this phenomenon might be aging, and it is well established that abnormal protein accumulation can occur with age in the absence of neurodegenerative disease (99). Accumulating evidence now shows that within the context of PD there is a clear cross talk between different aggregated forms of proteins with distinct molecular pathways.

One such protein is tau, encoded by the *MAPT* gene. In pathological situations, tau can become abnormally hyperphosphorylated forming intracytoplasmic inclusions, called neurofibrillary tau tangles (NFTs). These aggregates are characteristic of AD, together with amyloid-β plaques. However, abnormal tau protein has been linked to PD as well. Specifically, postmortem studies have revealed a significant increase of tau hyperphosphorylation at Ser262 and Ser396/404 in the striatum of patients with PD and PD dementia (100). Animal studies have further added to this by showing that increased α-synuclein expression can trigger tau hyperphosphorylation both *in vitro* and *in vivo* (101, 102). Furthermore, genome-wide association studies found a strong link between *MAPT* and the risk of PD (43), and subsequent longitudinal work showed that the H1/H1 haplotype of *MAPT* is a strong predictor of early development of PD dementia (103).

Amyloid-β has also been reported to act together with α-synuclein. Cortical deposition of α-synuclein has been associated with amyloid-β plaque formation in a subgroup of PD patients (104). Furthermore, both NFTs and amyloid-β senile plaques are widespread at postmortem in some, though not all, PD patients who develop cognitive dysfunction and dementia (105–108). Current literature seems to suggest that the manifestation of dementia in PD may be due to the convergence of both PD and AD pathology in the cortex, and that a combination of these pathologies is a better correlate of PD dementia (107).

## PATHOGENESIS OF PARKINSON'S DISEASE

A number of mechanisms have been implicated in PD pathogenesis, with α -synuclein aggregation central to the development of the disease. Multiple other processes are thought to be involved, with several studies suggesting that abnormal protein clearance, mitochondrial dysfunction, and neuroinflammation play a role in the onset and progression of PD. However, the relationship between these pathways remains unclear.

### α-synuclein misfolding and aggregation

Native α-synuclein in the brain is mostly unfolded without a defined tertiary structure (109), although in aqueous solutions it can be present in stable tetramers that resist aggregation (110). Upon interaction with negatively charged lipids, such as the phospholipids that make up cell membranes, α-synuclein folds into α-helical structures through its N-terminal (111). In PD, α-synuclein adopts a β-sheet-rich amyloid-like structure that is prone to aggregate. Indeed, misfolded α-synuclein is found within LBs as 5–10 nm long filaments. Several mechanisms have been proposed for the conformational changes that lead to abnormal α-synuclein aggregation, including serine 129 phosphorylation, ubiquitination, and C-terminal truncation (112, 113). Hence, different species of α-synuclein are found in the PD brain, including unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils (114).

Recent studies in rodents indicated that the most neurotoxic α-synuclein species is the early oligomeric form, rather than the mature insoluble fibrils (115, 116). The increased toxicity of these oligomers, as opposed to the fibrillary α-synuclein, was validated in cell-based assays (115). The oligomeric species of α-synuclein are capable of "seeding" and accelerating abnormal protein aggregation and Danzer et al. (2011) proposed that this might be the mechanism underlying the spread of α-synuclein pathology in the brain (117).

### Mitochondrial dysfunction

Mitochondrial dysfunction is considered a key element in the pathogenesis of both idiopathic and familial PD (118). Early postmortem studies in the SNpc of PD brains reported a deficiency of the mitochondrial complex-I, which is a vital component of the electron transport chain. These data provided one of the first direct links between mitochondrial dysfunction and PD (119). Complex-I deficiency was also found in skeletal muscle and platelets of PD patients compared to healthy subjects (120, 121). Further evidence arose by the discovery that abuse of the substance MPTP caused permanent Parkinsonian symptoms (34), with postmortem examination revealing dopaminergic cell loss (122). Follow-up studies showed that MPTP when oxidized is taken up by DA neurons and leads to complex-I inhibition (123). Other toxins and pesticides that impair mitochondrial complex-I activity, like rotenone and paraquat, also cause a Parkinsonian phenotype and DA cell loss in animals, and potentially in humans (124). Defects in the mitochondrial complex-I may be crucial in driving DA cell death due to energy depletion (118).

Another major clue pointing to the role of mitochondria in PD pathogenesis is that many of the known genes that cause familial PD play a role in

mitochondrial homeostasis. One example is the involvement of PINK1 and parkin (PARK2 and PARK6, respectively), both of which are vital components of the pathway that regulates the removal of dysfunctional mitochondria, a process called mitophagy (52). Loss-of-function mutations in either gene lead to impaired mitochondrial quality control and cause autosomal recessive PD (58, 125).

Finally, α-synuclein by itself is known to interfere with mitochondrial function. For instance, α-synuclein can interact with the mitochondrial membrane and accumulate inside the organelles. This leads to the damage of complex-I activity, ultimately resulting in mitochondrial dysfunction and increased oxidative stress (126, 127). A more recent study reported an interaction between oligomeric (but not monomeric or fibrillar) α-synuclein and the mitochondrial receptor TOM20 (128). This interaction resulted in impairment of the mitochondrial protein import machinery, reduced respiration, and led to excessive production of reactive oxygen species (ROS).

## Dysfunctional protein clearance systems

There are two central protein clearance systems within cells responsible for the removal 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 "tagging" them with ubiquitin and transporting them to the proteasome for degradation. The autophagy-lysosome pathway is divided into three constituents: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Briefly, in macroautophagy, intracellular components, including cytosolic proteins, are engulfed by the autophagosome, which then fuses with the lysosome, leading to the breakdown of its contents. On the other hand, in microautophagy, the lysosome alone engulfs and destroys cytoplasmic components. CMA is a more selective process, whereby molecular chaperones target specific proteins and transport them to the lysosome for degradation (129). Monomeric α-synuclein is generally cleared by both the UPS and the autophagy-lysosome pathway (130), and damage in either of their machineries is implicated in the pathogenesis of PD by contributing to the accumulation of defective proteins, in particular soluble misfolded α-synuclein (131, 132).

## Ubiquitin-proteasome system

Proteasomal abnormalities are a shared feature among many proteinopathies, that is, neurodegenerative diseases characterized by abnormal protein accumulation (133). Evidence of such abnormalities in PD was first provided by postmortem studies in the SNpc, where the catalytic activity of the UPS was found substantially reduced compared to healthy brains (134). The same findings were later reported in peripheral blood mononuclear cells of PD but not in healthy individuals (135). Apart from diminished activity, a lower expression of different proteasomal components has also been identified in the SNpc of PD brains. Specifically, the 20S proteasome α-subunit (136) and other molecules involved in the normal function of the UPS, like PA700 and PA28 (proteasome activators), are reduced (137). Additional evidence is provided from genetic studies and the discovery that two of the PARK genes linked to monogenic PD encode proteins

involved in UPS function, namely, parkin (PARK2; E3 ubiquitin ligase) (58, 138) and UCH-L1 (PARK5; Ubiquitin C-terminal hydrolase) (59).

Following on from findings in human PD, altered proteasome activity was observed in different disease models. Marmosets injected with the toxin MPTP had diminished enzyme activity in the UPS, in addition to decreased levels of the 26S subunit components (139). In a second set of experiments, the same group showed that pharmacological inhibition of the proteasome in wild-type rats leads to dopaminergic cell death (140). Similarly, Bedford and colleagues using transgenic mice with proteasomal defects (knockout for 26S proteasome regulatory subunit 4) showed dopaminergic cell degeneration and observed LB-like inclusions in the brain, which however lacked the dense core of classical human LBs, and it is unclear whether they contained aggregated α-synuclein (141). Nevertheless, all these studies show that dysfunction of protein turnover can result in neuronal cell death, thus providing a potential pathogenic mechanism for PD.

## Autophagy- lysosome system

Similar to findings in the UPS system, numerous lysosomal and autophagy-related components are malfunctioning or differentially expressed in PD. In nigral neurons of PD brains, the levels of the autophagosome marker LC3-II were increased, suggesting an accumulation of autophagic vacuoles (142, 143). In contrast, vital proteins of lysosomal membranes (LAMP1 and LAMP2A), and several molecular chaperones from the heat-shock protein family (such as hsc70 and hsp35) were found to be decreased at postmortem examination (144, 145). Furthermore, of particular note is the discovery of a point mutation in the gene of the lysosomal protein ATP13A2 (PARK9), leading to an autosomal recessive atypical Parkinsonian syndrome, referred to as Kufor–Rakeb syndrome (63). Point mutations in two more PARK genes impair the function of either parkin (PARK2) (58) or PINK1 (PARK6) (60), both of which are involved in the autophagic turnover of mitochondria (52). Additionally, the emergence of *GBA1* mutations, which result in dysfunction of the lysosome-autophagy system, as a strong genetic risk factor for PD adds weight to the idea that this system is important in the development of PD (see Chapter 3). These studies lend support to the hypothesis that malfunction in the autophagy-lysosome pathway may be contributing to the pathogenesis of PD.

## Neuroinflammation

Postmortem brain studies have described microglial and complement activation, T-lymphocyte infiltration, and increased concentration of pro-inflammatory cytokines in the SNpc and striatum of PD patients compared to healthy individuals (146–149). Furthermore, positron emission tomography (PET) neuroimaging with the [$^{11}$C]-PK11195 radioligand has demonstrated increased microglial activation early on in PD in the brainstem, basal ganglia, and frontotemporal cortices, with added involvement of the parietal and occipital cortices in patients with PD dementia, compared to healthy subjects (150, 151).

While initially thought to be a secondary phenomenon, there is now evidence that inflammatory responses can by themselves contribute to disease 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 insult led to a significant attenuation of DA cell death in the SNpc, suggesting that microglia-induced inflammatory processes may be contributing to the degeneration of these cells (152, 153). There is also a plethora of evidence suggesting that α-synuclein can directly trigger microglial activation and initiate inflammatory processes. For instance, in primary cultures, α-synuclein mediates a dose-dependent activation of microglia (154).

Genetic clues suggesting that immune activation might contribute etiologically in PD come from the identification of a strong association between the human leucocyte antigen (HLA) class II region (a key molecule of the immune system) and the risk of developing PD (155)—a finding that was later confirmed in genome-wide association studies (42). Additionally, extensive epidemiological studies suggest a decreased PD risk with regular use of the nonsteroidal anti-inflammatory drug ibuprofen (156). Finally, recent data showed that in PD patients at diagnosis a more 'pro-inflammatory' immune marker profile in the serum is associated with a faster motor symptom progression and more impaired cognitive function (157).

Regardless of whether neuroinflammatory responses are a direct trigger of neurodegeneration in PD or are activated as a response to neuronal damage, it is now becoming clear that the engagement of the immune system can initiate a vicious cycle, thereby exacerbating neuronal dysfunction. Hence, manipulation of the immune system remains a promising topic for disease-modifying therapies.

## CONCLUSION

PD is a complex neurodegenerative condition, for which the etiology and pathogenic mechanisms remain incompletely understood. While a small proportion of PD patients have a monogenic cause for their disease, the majority of cases probably are not associated with a specific genetic abnormality. Instead, it is likely that the risk of PD is in part, determined by a combination of polygenic susceptibility factors. Environmental influences may also contribute to PD risk, although the relationship between the development of the disease and factors such as smoking, caffeine, and pesticide exposure continues to be poorly understood. Pathologically, the movement disorder occurs due to loss of dopaminergic neurons in the SNpc, with a number of other brain regions also being involved. The histopathological hallmark of PD are LBs, which predominantly contain aggregated α-synuclein, but it is not clear how these may result in neurodegeneration. Understanding these pathogenic processes can allow for the identification of novel therapeutic targets, and, hopefully, the development of disease-modifying treatments in the future.

**Conflict of interest:** The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

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**Acknowledgment:** The authors acknowledge the financial support from the following organizations: The Rosetrees Trust and the Onassis Foundation.

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