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# Parkinson Disease Epidemiology, Pathology, Genetics and Pathophysiology

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## INTRODUCTION

Parkinson disease (PD) is a complex progressive neurodegenerative disease described by James Parkinson in his 1817 publication, "Essay on the Shaking Palsy"(1). In that essay Dr. Parkinson optimistically declared that "there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped." More than 200 years later we have yet to definitively achieve neuroprotective therapy for PD. However, there has been great progress in recent decades in understanding the molecular basis for neurodegeneration in PD, hopefully bringing us steadily getting closer to achieving truly disease-modifying therapies for PD.

Pathologically, PD is defined by loss of dopaminergic neurons in the substantia nigra pars compacta (SN) located in the midbrain and associated with Lewy bodies, which are cytoplasmic inclusions that include insoluble alpha-synuclein aggregates. However, PD is characterized by more widespread pathology in other brain regions and involves non-dopaminergic neurons as well. The clinical diagnosis of PD is based primarily on motor features, such as a slowly progressive asymmetric resting tremor, cogwheel rigidity and bradykinesia, although non-motor features, which include anosmia, constipation, depression

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and REM sleep behavior disorder, can develop years before motor deficits. During later stages of the disease, additional non-motor features, such as autonomic dysfunction, pain and cognitive decline, can appear(2).

## NEUROPATHOLOGY

The neuropathological hallmarks of PD are the degeneration of dopaminergic neurons in the SN and intraneuronal protein aggregates called Lewy bodies and Lewy neurites(3). It was long considered that 50–70% of SN dopaminergic neurons have died by the time that clinical motor symptoms become evident(4). However, more recent work suggests that the loss of dopaminergic terminals in the basal ganglia, as opposed to loss of the neurons in the SN, is crucial for onset of motor symptoms (6).

## EPIDEMIOLOGY

### Distribution of disease

In estimates based on health care utilization, PD incidence ranges from 5/100,000 to over 35/100,000 new cases yearly(5). Incidence increases 5 to 10 fold from the sixth to the ninth decades of life. PD prevalence also increases with age. In a meta-analysis of four North American populations, prevalence increased from less than 1 percent of men and women aged 45–54 years to 4 percent of men and 2 percent of women aged 85 or older(6). Mortality is not increased, compared to non-affected individuals, in the first decade after PD is diagnosed, but increases thereafter (7). As the global population ages, PD prevalence is expected to increase dramatically, doubling in the next two decades(8). Accompanying this increase, the societal and economic burden of PD will escalate, unless more effective treatments, cures or means of prevention are identified(9).

### Determinants of disease

Most PD cases likely have a multifactorial etiology, resulting from the combined effects of environmental and genetic factors. Exposure to toxicant chemicals and head injury may increase the risk of PD, while certain lifestyle factors may lower risk. Genetic susceptibility factors may modify the effects of environmental exposures. Although identifiable mutations in certain genes cause PD in around 5–10% of cases, these mutations are absent in most people with PD. Moreover, the most common PD-associated genetic mutations have incomplete penetrance, indicating that other environmental or genetic factors are involved. A study comparing concordance rates in monozygotic and dizygotic twins estimated the heritability of PD to be only 30%, suggesting that the majority of PD risk is related to environmental and behavioral factors(10).

### Toxicant chemical exposure

In studies spanning many decades in numerous populations worldwide, pesticide exposure, farm work or rural residence have been associated with an increased PD risk(11). Occupational exposure as well as “passive” exposure due to residence near to pesticide treated fields is associated with a greater risk of PD. Pesticides associated with PD, including paraquat, rotenone, 2,4-D and several dithiocarbamates and organochlorines, cause

experimental parkinsonism in laboratory studies, supporting the possibility that these associations reflect causal effects(11, 12). Genetically determined impairment in toxicant handling can amplify the effect of pesticide exposure on PD risk, an example of gene-environment interaction. Conversely, behaviors such as good hygiene practices or eating a healthy diet may protect against the adverse effects of pesticide exposure(13, 14). Chlorinated solvents (trichloroethylene, perchloroethylene, carbon tetrachloride), used in dry cleaning, degreasing, as an anesthetic and viscose rayon manufacturing and polychlorinated biphenyls, formerly used as coolants and lubricants, have also been associated with increased PD risk in humans and cause parkinsonism-associated toxicity in animal models(12, 15). While some of these pesticides and toxicant chemicals are no longer in use, they are environmentally persistent, and remain common contaminants of soil and water. Others, such as trichloroethylene, have continuing applications and can be found in nearly one third of US drinking water supplies, as well as in air, soil, food and human breast milk. (16) Working as a welder also has been associated with greater risk of PD, possibly as the result of manganese in welding fumes(17, 18). Manganese exposure also can cause PD-like pathology in mice (19). However, data on the association of welding with PD are mixed(20). Exposure to other metals such as iron, and lead, has been suggested to increase risk of PD, based on experimental *in vitro* and *in vivo* studies, but human evidence remains inconclusive. Ambient total suspended particles (TSP) from traffic has also been associated with an increased risk of PD(21), possibly due to metal exposure or to induction of inflammatory processes, but these findings have been inconsistent.

## Head injury

Mild to moderate head injury occurring decades before PD onset is associated with higher risk of PD in most but not all studies(12, 22). Risk increases with the number of head injuries, and genetic susceptibility factors such as certain variants in or near the gene encoding alpha-synuclein may increase risk 2 – 5 fold.

## Lifestyle Factors

A number of life-style factors have been associated with reduced risk of developing PD. The most consistent association is a reduced risk of PD in cigarette smokers and, in a few studies, other tobacco users(23, 24). Longer duration and greater frequency of tobacco use confer lower risk and there is some evidence of genetic modification. Nicotine has been suggested to play a central role in this association, although a recently completed clinical study failed to detect a disease modifying effect of the nicotine patch in PD patients. Coffee drinking and caffeine use are also associated with a lower risk of PD(25, 26), particularly in men. The effect is greatest in men with the highest levels of coffee use, and may be further modified by genetic factors. Similarly, reports have shown reduced risk of PD in heavy tea drinkers in some, but not all populations studied. Conversely, higher dietary intake of dairy products has been associated with a higher risk of PD, possibly due to the concentration of toxicants in milk(27). Other dietary associations generally support a reduced risk of PD in those eating “healthy” diets higher in fruits, vegetables and grains(28). Physical activity has been associated with a lower risk of PD, especially in men and particularly at higher intensities of physical activity, although even modest levels reduce risk(29) (Fig. 1). The

combined effects of these lifestyle factors appear to be additive, suggesting an approach to disease prevention(30).

## GENETICS AND PATHOPHYSIOLOGY

Specific genetic factors that play a major role in PD risk can be identified in a subset of PD patients (Fig. 2). Polymeropoulos et al identified a mutation in the alpha-synuclein gene, SNCA, in association with rare families with autosomal dominant PD in 1997(31). Families with these high-penetrant mutations are quite rare, but this seminal discovery led to the recognition that alpha-synuclein comprises a major component of Lewy bodies even in sporadic PD patients. The later discovery of autosomal dominant PD families with alpha-synuclein gene duplications or triplications added to other data indicating that high levels of alpha-synuclein contribute to the pathogenesis of PD(32).

Mutations in the PARKIN(33) and PINK1(34) genes are causes of early-onset autosomal recessive PD. Both PARKIN and PINK1 have been linked to a cellular pathway involving the preferential degradation in lysosomes of dysfunctional mitochondria through macro-autophagy, a process termed “mitophagy”. Loss of function of these genes leads to impaired mitophagy, resulting in the accumulation of dysfunctional mitochondria. PARKIN also indirectly regulates levels of an important transcriptional regulator, PGC-1alpha, which coordinately regulates the expression of genes required for mitochondrial biogenesis as well as multiple antioxidant defenses(35). PGC-1alpha levels also are low in sporadic PD(36), suggesting that these data are relevant beyond rare genetic forms of PD. These genetic links to both mitochondrial degradation and to mitochondrial biogenesis implicate dysfunction of mitochondrial turnover in PD.

These genetic data are complemented by many other lines of data implicating mitochondrial dysfunction in the pathogenesis of PD. For example, exposure to a toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), causes a rapid onset parkinsonian phenotype and death of dopaminergic neurons in the SN, likely due to inhibition of mitochondrial complex I activity. Chronic exposure of rodents to rotenone, also a potent mitochondrial complex I inhibitor, also causes preferential degeneration of dopaminergic neurons(37), and exposure to pesticides (including rotenone) is a risk factor for PD(38).

Mutations in the DJ-1 gene also cause autosomal recessive early-onset PD(39). DJ-1 has antioxidant effects through multiple mechanisms, including regulation of NRF2, a transcription factor the upregulates multiple antioxidant defenses, and by stimulating glutathione synthesis(40).

Mutations in the *LRRK2* gene are associated with autosomal dominant PD with incomplete penetrance (about 25% for the G2019S mutation, but much higher for the R144G mutation), and are present in about 1 to 2 percent of all PD patients and 5% in familial PD, but higher in some populations such as patients of Ashkenazi Jewish ancestry and in North African Berbers(41). Prior studies suggest that mutations in LRRK2 lead to increased kinase activity(42), and that LRRK2 kinase inhibitors may be protective(43), although the possibility of a role for loss of LRRK2 function has been raised(44).

Another common genetic factor contributing to PD risk relates to mutations in the GBA gene associated with autosomal recessive Gaucher's disease(45). Carriers of a GBA mutation have an approximately 4-fold increased risk of PD, although the risk varies with different GBA mutations. Some studies suggest an increased risk of dementia in GBA mutation associated PD(46). PD-linked GBA mutations cause a loss of activity of the lysosomal enzyme glucocerebrosidase (GCase), and agents that upregulate GCase activity and an agent targeting "substrate reduction" have shown promise in animal models and are now moving forward in clinical trials(47).

Neuroinflammation previously was often viewed only as a response to ongoing neurodegeneration. More recent studies suggest that neuroinflammation might be a significant and essential upstream contributor to alpha-synuclein aggregation and to the neurodegenerative process(48), and epidemiological studies have provided evidence of associations between diseases with peripheral inflammation (e.g. type 2 diabetes and inflammatory bowel disease) and elevated PD risk(49, 50). Genetic studies also have linked HLA gene variants with the risk of late-onset PD(51).

PD genetics are complex. Common variants may contribute to PD risk, and can interact with other genetic factors and with environmental factors. The most recent large genome wide association study (GWAS) identified 70 loci that affect PD risk(52). Several of these loci are close to genes involved in the lysosomal-autophagy system and in immunity, which are both functions expected to play important roles in the handling of misfolded alpha-synuclein. Acquired (somatic) mitochondrial DNA mutations are increased in SN neurons in early PD and also may play a role(53). Epigenetic factors also may contribute to PD pathogenesis(54).

Given the strong genetic and experimental data linking alpha-synuclein toxicity to PD, many potential neuroprotective strategies have focused on mechanisms for clearing away alpha-synuclein aggregates(55, 56). Clinical studies currently are underway using infusion of monoclonal antibodies to target oligomeric alpha-synuclein, or using an active vaccine strategy. Other strategies use more indirect approaches, such as ongoing studies of nilotinib, a c-abl inhibitor, that may reduce inflammation and promote clearance of alpha-synuclein(57). Additional strategies that specifically target genetically defined subpopulations, such as LRRK2 kinase inhibitors or GCase activators, are moving forward in clinical trials. Although currently genetic testing has a limited role clinically, already it is an important research tool, and one can envision a not-too-distant future when genetic testing will be routine for all PD patients to guide the selection of targeted therapies.

## ALPHA-SYNUCLEIN AGGREGATION AND SPREAD OF PATHOLOGY

### Alpha-synuclein aggregation

The presence of Lewy pathology is pathognomonic for sporadic PD, although some rare inherited genetic forms of PD that exhibit loss of SN dopaminergic neurons do not display these protein aggregates(58). Alpha-synuclein is normally enriched in synapses where it is thought to participate in synaptic vesicle function(59). Alpha-synuclein is also present in non-neuronal cells, e.g. liver, muscle, lymphocytes and red blood cells(59), and its normal functional roles are not fully elucidated. In a series of seminal studies, Heiko Braak and

colleagues proposed that there are six stages of Lewy pathology in PD(60). They suggested that in the first stages the Lewy pathology is limited to the dorsal motor nucleus of the vagal nerve, located on the medulla oblongata and the origin of the nerve fibers innervating the gut and other visceral organs, and the olfactory bulb and closely associated olfactory nucleus. They also suggested that the pathology subsequently spreads in a stereotypic fashion along neural pathways throughout the brain, not reaching the SN until the third neuropathological stage, and eventually involving the cerebral hemispheres in the terminal sixth stage (60). The Braak staging model is based on post-mortem observations, and it has not been possible to obtain definitive proof that pathology spreads in accordance with the Braak stages(61). Indeed, some subsequent reports indicate that the anatomical pattern of Lewy pathology in some people clinically diagnosed with PD is not consistent with the Braak staging(62). Still, this model has gained significant traction over the past two decades, and it has been proposed that the earliest stages of Lewy pathology (before the SN is engaged) are coupled to the symptoms and signs of pre-motor PD (discussed above)(63). Notably, alpha-synuclein aggregates have been reported in the gut of neurologically normal people(64) and around 10% of people who die without a diagnosis of PD still display alpha-synuclein aggregates in the brain (so-called Incidental Lewy Body Disease) and show mild levels of SN dopaminergic neuronal loss(65). These observations suggest that these people had elevated risk of developing PD or a related synucleinopathy if they had lived longer.

## A prion-like role for alpha-synuclein assemblies?

Different alpha-synuclein assemblies have been shown to be secreted by neurons, via a process that is elevated if the lysosomal-autophagy system is inhibited, and then be taken up by neighboring neurons where they are capable of seeding monomeric alpha-synuclein into Lewy-like aggregates(66). The realization that misfolded alpha-synuclein exhibit such prion-like properties has increased the spotlight on the Braak staging system. Because these pathogenic alpha-synuclein assemblies can be transported intra-axonally to interconnected nuclei, prion-like behavior of alpha-synuclein assemblies might explain how Lewy pathology propagates from one brain region to another(66) and could be consistent with the spread of alpha-synuclein pathology proposed by Braak and colleagues.

An important question is what might be the initial trigger of alpha-synuclein aggregation. One model proposes that numerous factors are involved, including some of the environmental risk factors we discussed earlier, i.e. pesticides and environmental pollutants, as well as common pathogens (e.g. viruses, bacteria and fungi) that all can gain access to alpha-synuclein containing cells initially in the olfactory system and gut(67). For the most part, these aggregates are handled by normal cellular proteostatic mechanisms and do not lead to spreading Lewy pathology. In the simultaneous presence of facilitating factors, e.g. aging, genetic predisposition and peripheral inflammation, the model proposes that alpha-synuclein aggregates can bypass normal clearance and cause synucleinopathy in the brain(67). Although a role for alpha-synuclein is well-established in PD, it is worth noting that it remains controversial whether or not the aggregates themselves are pathogenic(68) (see Table 1).

## Summary

PD is a complex disorder, with both environmental and genetic factors converging on a common set of pathways including mitochondrial dysfunction, oxidative stress, protein aggregation, impaired autophagy and neuroinflammation. Reducing the burden of PD can be approached with a two-pronged strategy: the implementation of interventions to reduce modifiable factors such as behavioral or environmental risk factors and the development of drugs targeting the mechanisms of genes or environmental exposures associated with PD. PD incidence is increased in persons with prodromal symptoms such as impaired olfaction, sleep disorders and constipation(71). Targeting people in this prodromal stage of disease may be an effective strategy for reducing the burden of PD in future decades. Clinical testing of interventions aimed at identifying disease-modifying therapies thus far has yielded mainly negative results, perhaps in part because the pathophysiological factors contributing to PD differ between patients. The lack of clinically proven success at slowing disease progression highlights the need for more research to better understand the molecular pathophysiology of subtypes of PD.


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**Key points**

- Parkinson disease (PD) is a complex age-related neurodegenerative disease associated with dopamine deficiency and both motor and nonmotor deficits.
- Many environmental and genetic factors influence PD risk, with different factors predominating in different patients.
- These factors converge on specific pathways, including mitochondrial dysfunction, oxidative stress, protein aggregation, impaired autophagy and neuroinflammation.
- Ultimately, treatment of PD may focus on targeted therapies for pathophysiologically defined subtypes of PD patients.

## SYNOPSIS

Parkinson's disease (PD) is a complex age-related neurodegenerative disease associated with dopamine deficiency and both motor and nonmotor deficits. Many environmental and genetic factors influence PD risk, with different factors predominating in different patients. These factors converge on specific pathways, including mitochondrial dysfunction, oxidative stress, protein aggregation, impaired autophagy and neuroinflammation. Ultimately, treatment of PD may focus on targeted therapies for pathophysiologically defined subtypes of PD patients.

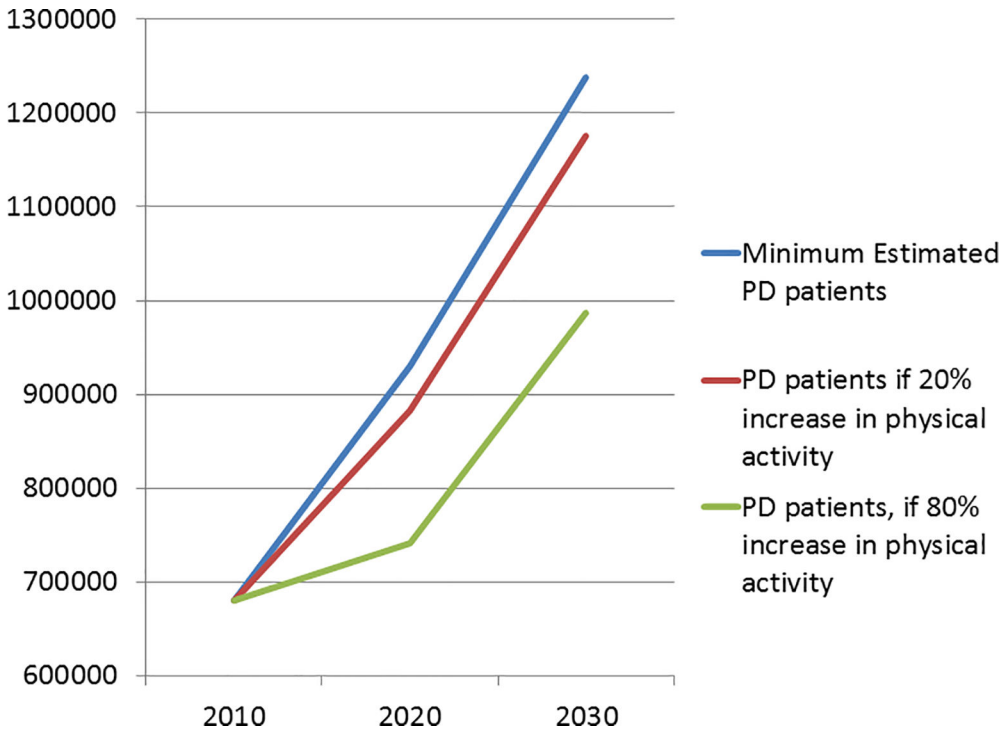


**FIGURE 1:**

Estimated number of people with PD in the U.S. (blue line) & the projected reduction in PD if physical activity in adults increases by 20% (red line) or 80% (green line). Estimates based on Marras et al, 2018(6).

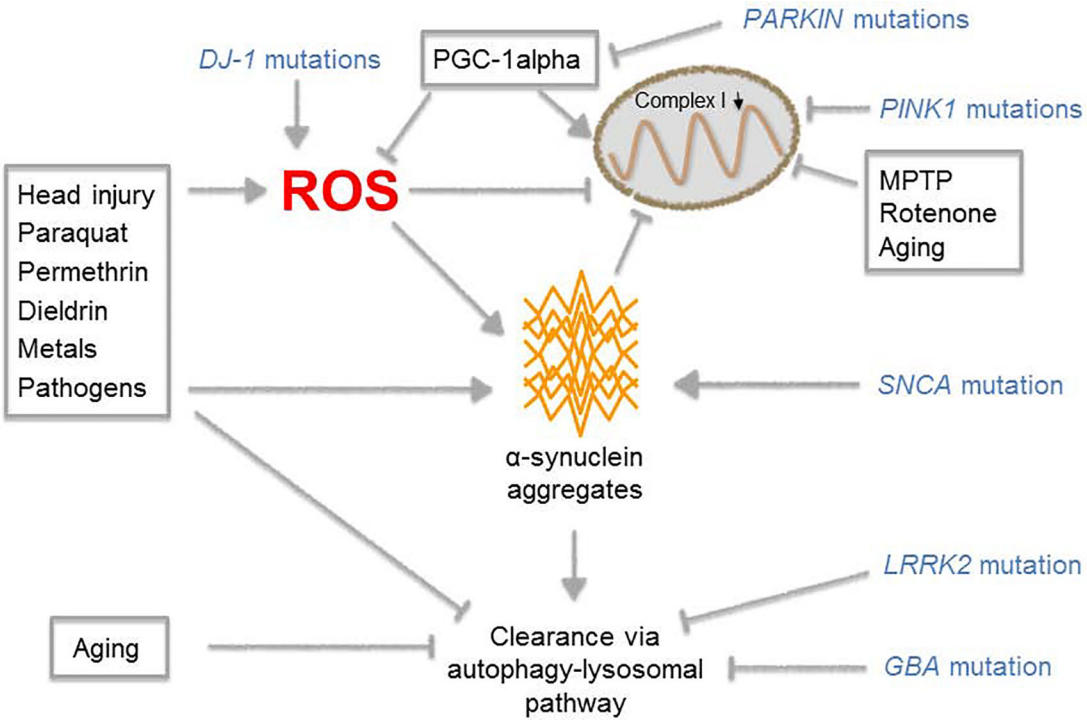


**FIGURE 2:**

Environmental and genetic factors influence PD pathogenesis by impacting similar pathways, including mitochondrial function, oxidative stress, alpha-synuclein aggregation, and clearance pathways for abnormal proteins.

**TABLE 1:**

**KEY GENETIC FACTORS ASSOCIATED WITH PD** (partial list; see Schulte and Gasser 2011(69), and Lin and Farrer, 2014(70) for a more comprehensive reviews)

| GENE | Gene product | Inheritance | mutation types | penetrance | Age of onset | Frequency | notes |
|---|---|---|---|---|---|---|---|
| ***SNCA*** | alpha-synuclein | AD | point mutations; duplications; triplications | high | late (earlier onset with triplications) | Very rare | earlier onset for triplications compared to duplications |
| ***PRKN*** | Parkin | AR | multiple, including point mutations; deletions, duplication,… (loss of function) | high | early, often teens or 20s | Rare, 3 to 7% with onset 30 – 45; up to 50% with onset <25 | role in protein degradation; mitophagy |
| ***PINK1*** | PINK1 | AR | | high | early | Rare (2 to 4% of early-onset cases) | role in mitophagy |
| ***LRRK2*** | Leucine rich repeat kinase 2 | AD | G2019S; many other point mutations | moderate (~25%) | late | ~1 to 2% of all PD cases; higher in Ashkenazi Jews, North African Berbers, and Basques | Mutations cause increased kinase activity |
| ***DJ-1*** | DJ-1 | AR | point mutations | high | early | Rare (1% of early-onset cases) | protects against oxidative stress |
| ***GBA*** | Glucocerebrosidase | mixed | point mutations (loss of function) | low (~4-fold increased risk) | late | 5 – 10% of all PD patients; higher in Ashkenazi Jews | Lysosomal enzyme |