Parkinson's Disease: An update on Pathophysiology, Epidemiology, Diagnosis and Management. Part 2 : Etiology and Pathophysiology

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Abstract

Parkinson's disease is a common neurodegenerative disorder which involves the loss of nigral dopaminergic neurons in particular. The attributes of the cardinal motor are rigidity, bradykinesis, tremor in rest and postural instability. Nonmotor symptoms are normal in the course of the disease both early and late, and include autonomic, neuropsychiatric and cognitive disorders. Parkinson's disease has symptoms beyond the nigrostriatal system so it is not shocking that some motor characteristics (such as postural instability) and many non-motor characteristics have a restricted response to dopaminergic medications. The cause is uncertain but there is growing evidence that this could be due to a combination of ecological and hereditary factors. Treatment intends to control the patient's manifestations by renewing the dopaminergic framework with levodopa or dopamine agonists. Treatment during the early stage of Parkinson's disease has developed, and studies recommend that dopamine agonist monotherapy may forestall the response fluctuations that are associated with progression of the disease. However, L-dopa therapy remains the most effective treatment available. In the advanced stage, therapy focuses on improving the management of a variety of different health conditions. Successful control of motor activity variability (e.g. "wearing off," on-off variations, deterioration at night, early morning deterioration and dyskinesias) and psychological issues is frequently conceivable with explicit treatment approaches. Surgical treatment is a possibility for a well-defined patient category. The latest update of Parkinson's disease will be reviewed fully in eight review papers.

Key words: Parkinson, Etiology, pathophysiology, Genetic, Environment

Pathophysiology

Parkinson's disease is a neurodegenerative condition involving several neural pathways of the motor and the non-motor. It happens when all nerve cells in the brain area of the substantia nigra (i.e., "black substance") die or get damaged and degenerate (Aminoff, 2007). Such neurons usually produce dopamine, a chemical messenger responsible for transmitting signals between the substantia nigra in the basal ganglia and the next brain "relay station," the corpus striatum, to create smooth, deliberate muscle action. Loss of dopamine causes striatum nerve cells to fire out of control, leaving patients unable to normally guide or regulate their movements. Typically for many years after the start of neurodegeneration, the first signs of PD will not occur because there is plenty of dopamine left in storage to compensate for the diminishing supply. An individual will lose in any event half of the dopamine in their cerebrum before seeing that something isn't right with their body. In patients with PD, the substantia nigra can lose 60 per cent to 80 per cent or more of dopamine-producing cells. It is not clear what caused this cell death or disability (Hauser, 2006). (Figure 1)

There are no common, accepted criteria for Parkinson's disease neuropathological diagnosis, as the specificity and sensitivity of its characteristic findings have not been clearly defined. However, the following are the 2 main neuropathological findings in Parkinson's disease:

• Loss of substantia nigra pars compacta pigmented dopaminergic neurons
• The development of Lewy bodies and Lewy neurites (Figure 2).

The loss of dopamine neurons occurs most commonly in the lateral substantia nigra ventrals. Approximately 60-80 per cent of dopaminergic neurons are destroyed before the Parkinson disease motor symptoms appear.

Many people who at the time of their death were considered to be neurologically fine are found to have Lewy bodies (LB) on autopsy examination. Hypothesized to reflect the presymptomatic process of Parkinson's disease were these accidental Lewy bodies. With age the incidence of incidental Lewy bodies is growing. Note that Parkinson's disease is not unique to Lewy bodies, although they are present in some cases of atypical parkinsonism, Hallervorden-Spatz disease, and other disorders. These are nevertheless a hallmark result in Parkinson's disease pathology.

Parkinson's disease is depicted by two main pathological processes:

(a) premature preferential loss of dopamine neurons;
(b) accumulation of α-synuclein-composed Lewy bodies, which are misfolded and accumulate in various systems of Parkinson's disease patients; what cycle occurs first, is unclear.

LBs are intraneuronal, small, eosinophilic inclusions composed of more than 90 proteins with a hyaline core and a light peripheral halo; their main components are-Synuclein and ubiquitin (Spillantini et al, 1997). The ability of α-synuclein to misfold, become insoluble, and form b-sheet-rich amyloid aggregates that accumulate, form intracellular inclusions. The intermediates in this aggregation cycle are the toxic oligomeric and proto-fibrillary types that disrupt mitochondrial function (Hsu et al., 2000), lysosomal and proteasomal function (Snyder et al., 2003), damage biological membranes (Danzer et al, 2007) and cytoskeletons (Alim et al., 2004), alter synaptic function (Scott et al., 2010) and trigger neuronal degeration.

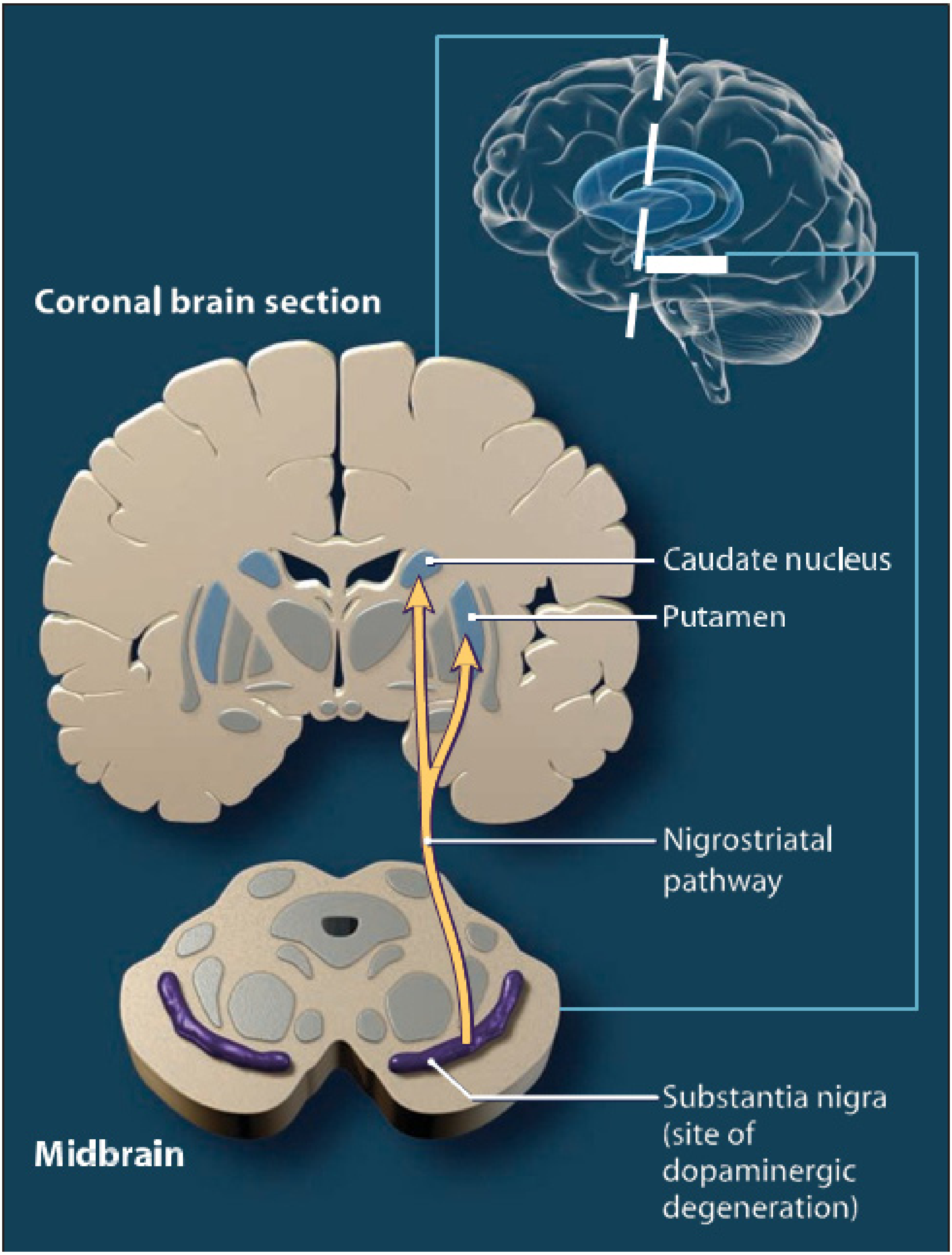
A sequential model of LB development and α-synuclein deposition, starting with the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus, eventually spreading to the brain stem and later to the mesocortex and allocortex and finally to the neocortex, was suggested (Braak et al., 2003) (Figure 1). α-Synuclein continues to propagate through the neurons in a prion-like fashion and this propagation mechanism is likely to underlie the development of previously reported pathological alterations (Brundin et al. 2016). In addition, some data indicate that α-synuclein aggregation can start and spread rostrally in the autonomic plexi of the gut (Klingelhoefer & Reichmann, 2015) and can be influenced by the gut microbiome (Sampson et al., 2016).

There is a progressive degeneration of neurons over several years based on clinical research (Braak et al. 2003), with each affected site leading to a different symptomatology of Parkinson disease (Table 1). As motor symptoms are apparent, the substantia nigra on pathological inspection shows a 30–70 percent cell loss (Jankovic, 2005). PD's non-motor symptoms stem from the loss of neurons in areas of the brain outside the substantia nigra and include chemicals other than dopamine, particularly acetylcholine. Cognitive dysfunction, mood disturbances and impulse regulation disturbances are associated with dopamine deficiencies outside the basal ganglia, or in serotonergic and noradrenergic systems (Kim et al, 2015, Hemmerle e al., 2012). Autonomic dysfunction was associated with pathologies outside the brain including the spinal cord and the autonomic peripheral nervous system (Kieburtz & Wunderle 2013).

Etiology: Environmental and Genetic Factors

The precise cause of Parkinson's disease is unclear, although a combination of environmental factors superimposed on genetic predisposition or vulnerability is thought to result (Table 2). (Racette & Willis, 2013, Kieburtz & Wunderle, 2015, Covy & Giasson, 2011). There is growing proof that genetic and environmental insults that lead to Parkinson's disease commonly lead to abnormal forms of a normal protein, α–synuclein, that appears to contribute to cell death (Luk & Lee, 2014). Parkinson's onset can be graded as adolescent (age < 21 years), early onset (21–50 years), and late onset (generally > 60 years). The juvenile

Figure 1: Coronal section of the brain, showing nigrostriatal pathways and location of selective dopaminergic degeneration in patients with Parkinson's disease.



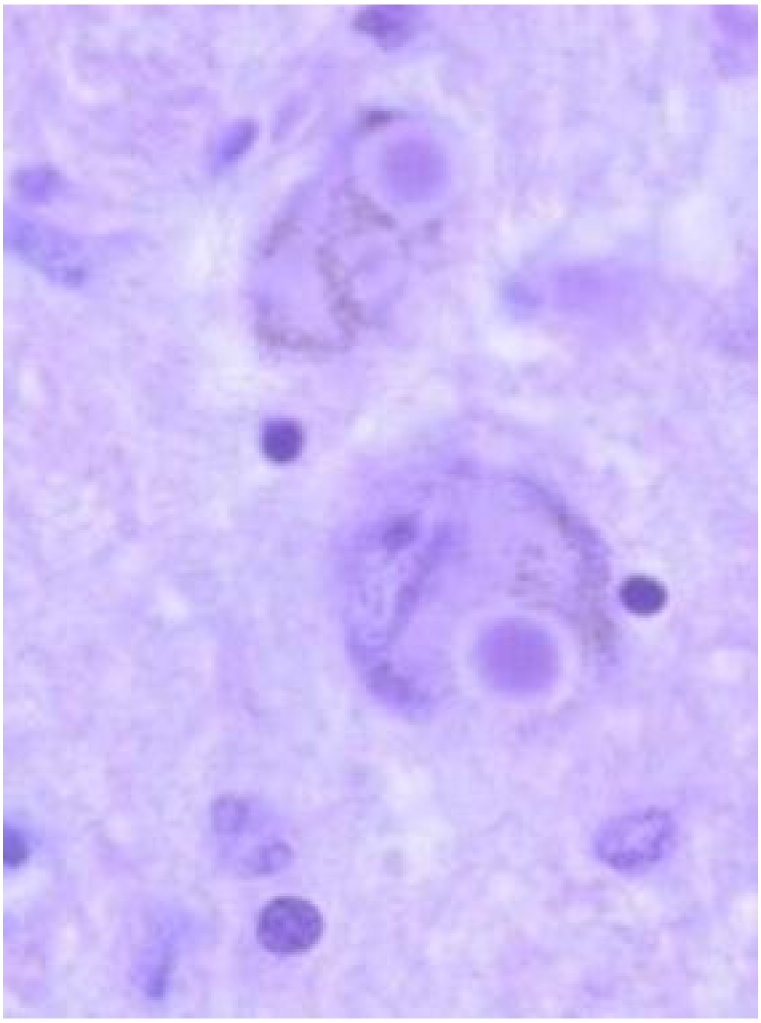


Figure 2: Lewy bodies are intracytoplasmic eosinophilic inclusions, often with halos, that are easily seen in pigmented neurons, as shown in this histologic slide. They contain polymerized alpha-synuclein; therefore, Parkinson disease is a synucleinopathy.

Table 1: Braak staging of Lewy body deposition[10]

Stage	Sites affected by Lewy bodies	Major symptoms
I	Dorsal motor nucleus of the vagus nerve & olfactory tract	Constipation, anosmia
[illegible]	Locus coeruleus and subcoeruleus complex	Sleep and mood dysfunction
[illegible]	Substantia nigra	Motor symptoms of Parkinson
IV–VI	Cortical involvement	Dementia, psychosis

type is uncommon, is frequently hereditary (in as many as 50 percent of cases), is most commonly associated with a mutation of the parkin gene and has an atypical appearance. (Ferguson and others, 2016). For Parkinson's disease patients, 10 percent -16 percent have a first- or second-degree relative affected; first-degree relatives may have twice the chance for Parkinson's disease compared to the general population. The occurrence of a healthy family history is not significantly significant for early- and late-onset Parkinson's disease (Ferguson et al, 2016).

While the cause of Parkinson's disease is still unclear, it is generally accepted that most idiopathic disease cases are triggered by environmental and genetic factors interacting.

Oxidation Hypothesis

While PD pathogenesis is unclear, one mechanism of substantia nigra toxicity that may play a role is the production of cellular damage from oxyradicals (Alam, 1997). Dopamine creates free radicals from auto-oxidation and the metabolism of monoamine oxidase (MAO). Typically, there are many anti-oxidant mechanisms inside and outside the neurons to minimize any damage that may be evoked by an attack by free radicals, but such defense in PD can be overcome or impaired. Often known as the etiological mechanism of PD (LeWitt, 2000) are excitotoxicity, programmed initiation of cell death, and chronic infection.

The oxidation hypothesis indicates that free radical damage resulting from the oxidative metabolism of dopamine plays a role in Parkinson's disease development or progression. MAO's oxidant metabolism of dopamine contributes to hydrogen peroxide formation. Normally, glutathione cleans hydrogen peroxide easily, but if hydrogen peroxide is not sufficiently cleansed, it can lead to the formation of highly reactive hydroxyl radicals that can react with lipid membrane lipids to cause lipid peroxidation and cell harm. The levels of reduced glutathione in Parkinson's disease are decreased, indicating a lack of protection against free radical development. In substantia nigra, iron is increased and can serve as a source of donor electrons, thereby facilitating the creation of free radicals.
Parkinson's disease is associated with increased dopamine production, decreased protective mechanisms (glutathione), increased iron (a molecule of pro-oxidation), and increased lipid peroxidation proof. This hypothesis raises concern that increased dopamine turnover due to administration of levodopa could increase oxidative damage and accelerate dopamine neuron loss. There's no convincing evidence, though, that levodopa accelerates the progression of disease.

Environmental Factors

Several scientists have proposed that PD happens when either an external toxin or an internal toxin selectively kills dopaminergic neurons (Leegwater & Waters 2008). Environmental risk factors generally associated with the development of Parkinson's disease include pesticide use, rural living, well water use, herbicide exposure and close proximity to industrial plants or quarries (Wirdefeldt, 2011). An environmental risk factor, such as pesticide exposure or food supply toxin, is an example of an external trigger which could cause PD. The hypothesis is based on the fact that such chemicals, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and neuroleptic medications, cause parkinsonic symptoms in humans. Nevertheless, no study has yet provided definitive proof that the cause of the disease is a toxin.

Many individuals were identified who developed tetrahydropyridine (MPTP) parkinsonism after self-injection of 1-methyl-4-phenyl-1,2,3,6-. These patients developed bradykinesia, stiffness and tremor which progressed over several weeks and improved with replacement therapy with dopamine. MPTP crosses the blood-brain barrier and is oxidized by monoamine oxidase (MAO)-B to 1- methyl-4-phenylpyridinium (MPP+). (Ballard et al., 1985). MPP+ accumulates in mitochondria and interferes with the function of complex I of the respiratory chain. A chemical resemblance between MPTP and certain herbicides and pesticides indicated that an MPTP-like environmental toxin may be a cause of Parkinson's disease but no particular agent has been confirmed. Nonetheless, the function of mitochondrial complex I in Parkinson's disease is decreased, indicating a common pathway with parkinsonism induced by MPTP.

A meta-analysis of 89 studies, including 6 prospective and 83 case-control studies, found that exposure to pesticides could increase the risk of PD by as much as 80 per cent. (Anderson, 2013, Pezzoli & Cereda , 2103). Particularly toxic is exposure to weed killer paraquat or fungicide maneuvering or mancozeb, increasing the risk of PD by about 2 times. Some of the agents researched in the United States and Europe are no longer used; however, others are still used in developing parts of the world (Anderson, 2013, Pezzoli & Cereda , 2103).

In case-control studies, PD was associated with exposure to any type of pesticide, herbicide, insecticide, and solvent, with risks ranging from 33% to 80%. (Anderson, 2013, Pezzoli & Cereda , 2103). Increased PD risk was also associated with proxy conditions of exposure to organic pollutants such as agriculture, well-water drinking, and rural life. Additionally, the risk appeared to increase with the exposure length. (Anderson, 2013, Pezzoli & Cereda, 2103).

As well as a meta-analysis of prospective research, the National Institutes of Health-AARP Diet and Health Survey found that higher consumption of caffeine was correlated with lower risk for Parkinson's disease in both men and women. A similar association for smoking and risk of Parkinson's disease has been found.[Liu et al, 2012). The biological mechanisms underlying the inverse relationship between the risk of caffeine or smoking and Parkinson's disease are not well elucidated.

Genetic Factors

Parkinson's disease is usually intermittent, and the disorder has no family history. A variety of genetic variants of the disease have been identified recently, and studies into these unusual inherited types may help to explain this condition's pathophysiology. Eight genetic loci have been identified for monogenic manifestations of Parkinson's disease, or dopa-responsive parkinsonism (Table 3). (Gasser, 2001, Valente and others, 2002, Van Duijin et al., 2001).

In the pedigrees of autosomal dominant Parkinson's disease, in several Greek and Italian families and in a German family, 2 missense mutations in the α-synuclein gene (PARK1) have been identified. Although the 2 mutations tend to be a rare cause of the disease, α-synuclein has gained a great deal of attention because it is one of the Lewy bodies' main constituents. A large range of mutations in the parkin gene (PARK2) were observed in pedigrees of autosomal recessive early onset parkinsonism in around 50 per cent of families in which at least one of the affected siblings exhibited symptoms at or before age 45. A broad twin study revealed that genetic factors play a major role in pathogenesis of Parkinson's early onset disease but not Parkinson's late-onset disease (diagnosed after age 50) (Tanner et al., 1999).

LRRK2 is the first gene often mutated to late-onset autosomal-dominant PD (Di Fonzo et al., 2006). Many distinct mutations have been associated with genetic causes. Recently, nine mutations involving a novel gene, leucine-rich repeat kinase 2 (LRRK2), were identified as the cause of autosomal-dominant PD in parentages, and some of them were previously related to the PARK8 locus on chromosome 12. LRRK2 mutations are hereditary and sporadic PD fairly normal genetic causes.

Those mutations were also found in different populations. LRRK2-associated PD's clinical and pathological characteristics are distinct from those of idiopathic PD; however, there is significant clinical and pathological variation even among parents (Whaley et al., 2006).

Recently, mutations in the LRRK2 gene encoding have been linked to autosomal-dominant parkinsonism, clinically indistinguishable from normal, idiopathic, late-onset PD. Thus the LRRK2 protein has emerged as a potential therapeutic treatment option. LRRK2 is large and complex, with numerous enzymatic and protein interaction domains, each targeting pathogenic mutations in fam ilies with Parkinson disease.

A genome-wide search for idiopathic Parkinson's disease (DeStefano et al., 2001) found no clear evidence for association. Another late-onset Parkinson's disease genomic test (onset 40–90 years) however indicated several genetic influences (Scott et al., 2001). A recent heritage research in Iceland indicated a major genetic link to the development of Parkinson's late-onset disease (onset after 50 years) in the population, and a locus of susceptibility to Parkinson's disease in Icelandic patients was identified (Sveinbjornsdottir et al., 2000, Hicks et al., 2002).

Melanoma

Speculation has been rife over a relationship between PD and melanoma for years. It was originally theorized that the medication levodopa contributed to an increased risk of skin cancer but this was not supported by research. However, subsequent trials in patients with PD have since found an increased risk of melanoma. One specific 2017 study found that Parkinson's patients had around a 4-fold increased risk of pre-existing melanoma(Dalvin et al., 2017). Another study found the risk to be 7-fold (Constantinescu et al., 2014).

Mechanisms of disease and genetics

The reason for PD degeneration of the nerve cells has not been established. Genetics can be a tiny part of this. Studies of toxic PD models and genes involved in hereditary manifestations of PD suggest two main pathogenetic mechanisms: (1) protein misfolding and aggregation, and (2) mitochondrial dysfunction contributing to oxidative stress (Leegwater, 2008).

SNCA, the gene encoding for α-synuclein, was the first gene linked to PD, and A53 T was the first pathogenic SNCA mutation found (Polymeropoulos et al., 1997). This mutation, like other pathogenic mutations, gives α-synuclein a greater tendency to misfold and accumulate than the wild-type mutation; other pathogenic SNCA mutations affect the amount of synuclein (either through duplications or triplications, either altering its expression or its clearance), and alter its post-transcriptional modifications, and/or its interaction with other cellular organelles and transport systems. In addition, existing evidence has highlighted the function of α-synuclein in triggering immunological response, and it has been shown that activated microglial cells directly engulf α-synuclein in an effort to clear it up (Rocha et al., 2018). Interestingly, upregulation of α-synuclein expression has also been observed in idiopathic PD patients (Chiba-Falek et al.,).

Several genes found in familial PD (α-synuclein, parkin, and ubiquitin carboxy-terminal hydroxylase L1) encode for proteins involved in the ubiquitin – proteosome system, which is responsible for normal protein degradation and clearance within eukaryotic cells. Mutations in these genes appear to be related to mishandling and protein aggregation, which in turn results in cell death (Leegwater-Kim, 2008).

Another essential disease mechanism is dysfunction of the mitochondrial function (Schapira et al., 1989). In family types of PD specific genes control mitochondrial functions. PINK1 (Valente et al., 2004) and Parkin (Kitada et al., 1998) interact in a quality control pathway for mitochondria: PINK1 is a serine/threonine kinase that 'tags' damaged mitochondria and activates the mitophagy pathway by recruiting Parkin, an E3 ubiquitin ligase. DJ-1 (Bonifati et al., 2003) plays a key role in controlling calcium flux in the mitochondrion, shielding the cell from oxidative stress

Table 3: Summary of genes associated with Parkinson disease (PD)

Gene	Locus name	Protein name	Chromosome	Inheritance	Clinics	Frequency in PD	Protein function
SNCA	PARK1/4	a-synuclein	4q21–23	AD	EOPD	<1%	Synaptic
PRKN	PARK2	Parkin	6q25–27	AR	EOPD, slow progression, + dystonia	1%–5% (up to 44% in EOPD)	Ubiquitin-ligase
UCHL1	PARK5	UCHL-1	4p14	AD	EOPD, LOPD	<1%	Uncertain
PINK1	PARK6	PTEN-induced putative kinase I	1p35–37	AR	EOPD, slow progression	2%–5%	Mitochondrial kinase
DJ-1	PARK7	Protein DJ-1	1p36	AR	EOPD, slow progression	1%	Cellular sensor of oxidative stress
LRRK2	PARK8	Leucine-rich repeat serine/ threonine-protein kinase 2	12p11–q13	AD	LOPD, slow progression	1%–5% (up to 40% in North African Berber Arab patients)	Multiple functional domain dependent
ATP13A2	PARK9	ATPase type 13A2	1p36	AR	Atypical parkinsonism, Kufor Rakeb syndrome	<1%	Lysosomal protein
PLA2G6	PARK14	A2 phospholipase	22q13	AR	EOPD, dystonia-parkinsonism	<1%	Unknown
FOXB7	PARK15	F-box protein 7	22q12–13	AR	EOPD, atypical parkinsonism	<1%	Unknown
VPS35	PARK17	Vacuolar protein sorting-associated protein 35	16q11	AD or risk	LOPD	<1%	Unknown
GBA					Glucocerebrosidase	1q21	Risk factor
Earlier onset +	dementia	5%–25% (10%–30% in Ashkenazi Jewish patients)	Lysosomal protein				

AD, autosomal dominant; AR, autosomal recessive; EOPD, early onset PD; LOPD, late onset PD.

induced by the dopaminergic neuron and dopamine toxic city's pace-making operation. Within the SNpc of PD brains there are records of mitochondrial DNA abnormalities, probably somatic, (Bender et al., 2006).

The body of evidence links PD to dysfunction in the cell clearance pathways, and PD has been correlated with multiple genes linked to autophagy (Gan-Or et al., 2015). Mutant LRRK2 (Funayama et al., 2002) interferes with autophagy, and alpha-synuclein degradation has been reported to slow, leading to its accumulation (Yue & Yang, 2013). ATP132A mutations establish lysosomal dysfunction (Dehay et al., 2012) and induce parkinsonism (Kufor Rakeb syndrome), whereas its expression is upregulated in idiopathic PD surviving dopaminergic neurons, indicating its neuroprotective effect (Ramirez et al., 2006).

GBA1 mutations, which encode for glucocere-brosidase (GCase), a lysosomal enzyme that metabolizes glucosylceramide and whose defects cause Gaucher disease, constitute the most important genetic risk factor currently identified for PD. GBA1 mutations are highly prevalent in PD patients with an odds ratio of 5.43; GBA1 mutations occur between 5% and 25% of PD patients. GBA's contribution to PD pathogenesis is complex, and PD pathogenesis includes interactions with different pathways: a reciprocal relationship with α -synuclein accumulation, endoplasmic reticulum stress, and mitochondrial dysfunction. GBA-related PD is clinically distinct from sporadic PD, while patients normally experience earlier onset, quicker decline (depending on the mutation) and increased risk of cognitive dysfunction (Balestrino et al., 2018).

Nine rare LRP10 variants have recently been associated with LBs (DLB) in family PD, PD dementia and dementia (Quadri, et al., 2018). LRP10 is a protein that shuts between the trans-Golgi network, plasma membrane and endosomes. Certain proteins involved in this network, including VPS35 and GGA1, were previously linked to PD. More study is required to explain the pathogenetic role of PD and other neurodegenerative disorders with LB pathology alterations in these pathways (Williams, 2017).

Several causative genes have been identified, usually eliciting young-onset parkinsonism. However, identified genetic and familial forms of PD are rare. Mutations in the gene for the protein α-synuclein, located on chromosome 4, result in autosomal-dominant parkinsonism. The function of this protein is not known. The most commonly occurring genetic defect affects the gene for the protein called parkin on chromosome 6 (Kawahara, et al., 2008). Mutations in this gene result in autosomal-recessive parkinsonism, which is slowly progressive with onset before the age of 40.

A relatively new theory looks at the role of genetic factors in PD growth. Around 15% to 20% of patients with PD have a close relative who has had parkinsonian symptoms such as tremor (Nelson et al., 2005, Jankovic et al., 2008).

Several causative genes have been identified, causing typical parkinsonism in the young. However, genetic and family types known for PD are rare. Mutations in the α-synuclein protein gene, located on chromosome 4, result in parkinsonism which is autosomal dominant. The protein's function is not understood. The most common genetic mutation involves the protein gene called parkin on chromosome 6 (22). Mutations in this gene result in autosomal-recessive parkinsonism, which is gradually progressive, starting before the age of 40 years.

Mutations in the parkin gene are the most common cause of parkinsonism in the family, and a growing number of studies indicate that stress factors associated with sporadic PD encourage accumulation of parkin in the insoluble fraction. Accumulation and mutations of parkin and α-synuclein in these genes were associated with familial PD. Accumulation of α-synuclein may contribute to the pathogenesis of PD and other Lewy body diseases by promoting alterations in solubility of parkin and tubulin, which may in effect compromise neural function by damaging the cytoskeleton of the neurons. Such results provide new insights into the possible existence of pathogenic α-synuclein and parkin interactions in PD (Kawahara et al., 2008).

Why SNpc dopaminergic neurons are especially vulnerable to neurodegeneration remains obscure; the autonomous pace-making function of SNpc dopaminergic neurons and calcium homeostasis has been suggested to play a significant role (Cali et al., 2011). As of late, there has been growing interest in the role of the microbiome in pathogenesis of PD and other neurodegenerative diseases. Pathogenetic pathways include dopamine synthesis and metabolism modifications, immune system dysregulation and inflammation, and improvements in enteral mucosal permeability (Spielman et al., 2018).

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