

Oxidative stress factors in Parkinson's disease

<https://doi.org/10.4103/1673-5374.300980>

Date of submission: July 10, 2020

Date of decision: September 24, 2020

Date of acceptance: October 21, 2020

Date of web publication: December 12, 2020

Jolanta Dorszewska^{1,*}, Marta Kowalska¹, Michał Prendecki¹, Thomas Piekut¹, Joanna Kozłowska¹, Wojciech Kozubski²

Abstract

Parkinson's disease (PD) is the second most common cause of neurodegeneration. Over the last two decades, various hypotheses have been proposed to explain the etiology of PD. Among these is the oxidant-antioxidant theory, which asserts that local and systemic oxidative damage triggered by reactive oxygen species and other free radicals may promote dopaminergic neuron degeneration. Excessive reactive oxygen species formation, one of the underlying causes of pathology in the course of PD has been evidenced by various studies showing that oxidized macromolecules including lipids, proteins, and nucleic acids accumulate in brain tissues of PD patients. DNA oxidation may produce various lesions in the course of PD. Mutations incurred as a result of DNA oxidation may further enhance reactive oxygen species production in the brains of PD patients, exacerbating neuronal loss due to defects in the mitochondrial electron transport chain, antioxidant depletion, and exposure to toxic oxidized dopamine. The protein products of *SNCA*, *PRKN*, *PINK1*, *DJ1*, and *LRRK2* genes are associated with disrupted oxidoreductive homeostasis in PD. *SNCA* is the first gene linked with familial PD and is currently known to be affected by six mutations correlated with the disorder: A53T, A30P, E46K, G51D, H50Q and A53E. *PRKN* encodes Parkin, an E3 ubiquitin ligase which mediates the proteasome degradation of redundant and disordered proteins such as glycosylated α -synuclein. Over 100 mutations have been found among the 12 exons of *PRKN*. *PINK1*, a mitochondrial kinase highly expressed in the brain, may undergo loss of function mutations which constitute approximately 1–8% of early onset PD cases. More than 50 PD-promoting mutations have been found in *PINK1*. Mutations in *DJ-1*, a neuroprotective protein, are a rare cause of early onset PD and constitute only 1% of cases. Around 20 mutations have been found in *DJ1* among PD patients thus far. Mutations in the *LRRK2* gene are the most common known cause of familial autosomal dominant PD and sporadic PD. Treatment of PD patients, especially in the advanced stages of the disease, is very difficult. The first step in managing progressive PD is to optimize dopaminergic therapy by increasing the doses of dopamine agonists and L-dopa. The next step is the introduction of advanced therapies, such as deep brain stimulation. Genetic factors may influence the response to L-dopa and deep brain stimulation therapy and the regulation of oxidative stress. Consequently, research into minimally invasive surgical interventions, as well as therapies that target the underlying etiology of PD is warranted.

Key Words: genetic factors; molecular parameters; oxidative stress; Parkinson's disease; pharmacotherapy; surgical therapies

Introduction

Parkinson's disease (PD) is one of the most common central nervous system (CNS) degenerative diseases and affects almost 2% of the population over the age of 65 and 5% over the age of 85. Although PD was first described over 200 years ago, it still remains an incurable disease and its cause is not fully understood. Given that there are currently no specific diagnostic biomarkers, the diagnosis of PD is based on clinical criteria including the presence of motor disorders (tremor, rigidity, bradykinesia, and postural instability), other motor features (gait disturbance and abnormal posture), and nonmotor symptoms (dementia, depression and disordered sleep) (Braak et al., 2004; Tarakad et al., 2017). It is known that degenerative processes in PD begin years prior to the appearance of clinical symptoms. Currently, several

hypotheses exist to expound the mechanisms underlying the etiopathogenesis of PD (**Figure 1**).

One cause of PD might be the accumulation of pathological proteins in abnormal spatial conformations within specific CNS structures, leading to disorders of nerve cell metabolism and damage to macromolecular compounds (Deas et al., 2016; Draoui et al., 2020). According to another hypothesis, neuronal damage and ultimately death occur due to failure of the ubiquitin-proteasome system in removing pathological protein aggregates. Under physiological conditions, the ubiquitin-proteasome system is involved in recognizing and ubiquitinating abnormal proteins, thereby targeting them for proteasomal degradation. Energy is required for the process of protein removal, at the level of both ubiquitination and degradation. Intelligibly, diminished performance of the

¹Laboratory of Neurobiology, Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland; ²Chair and Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland

*Correspondence to: Jolanta Dorszewska, DSc, PhD, dorszewska.j@ump.edu.pl or jolanta.dorszewska@ump.edu.pl.
<https://orcid.org/0000-0002-8241-0403> (Jolanta Dorszewska)

Funding: This work was supported by the grant of NCBiR (European Union), No. POWR.03.01.00-00-T006/18-00.

How to cite this article: Dorszewska J, Kowalska M, Prendecki M, Piekut T, Kozłowska J, Kozubski W (2021) Oxidative stress factors in Parkinson's disease. *Neural Regen Res* 16(7):1383-1391.

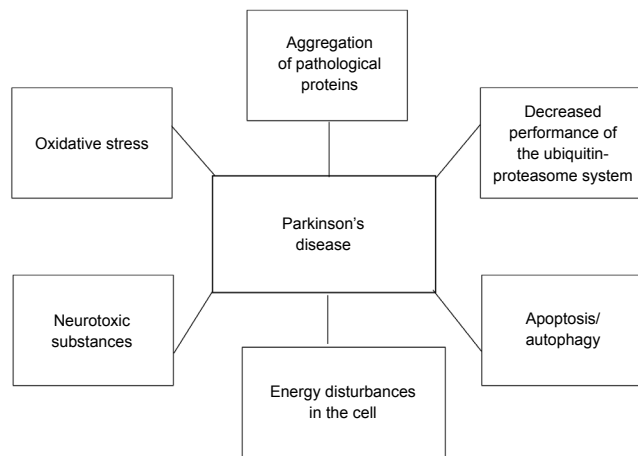


Figure 1 | Mechanisms of neurodegeneration in Parkinson's disease.

ubiquitin-proteasome system in degenerative diseases may stem from a decrease in energy in the form of ATP caused by defects in the mitochondrial electron transfer chain (Bragoszewski et al., 2017). Similarly, exposure to oxidative stress may lead to aberrant cellular bioenergetics and precipitate pathologic processes culminating in clinically-identifiable PD (Isobe et al., 2010; Andican et al., 2012; Subramanian et al., 2013; Puspita et al., 2017). Numerous reports also indicate a relationship between PD pathogenesis and the processes of apoptosis and/or autophagy (Banerjee et al., 2010; Lynch-Day et al., 2012).

The etiology of PD also has a genetic component. So far, many genes associated with familial PD (FPD) have been described and ascribed a 'PARK' designator. Mutations in *PRKN* (PARK2), *SNCA* (PARK1, 4), *PINK1* (PARK6), *DJ1* (PARK7), *LRRK2* (PARK8) may also be responsible for increasing one's susceptibility to sporadic PD (SPD) (Zhou et al., 2005; Clark et al., 2006; Hayashi et al., 2009; Kahle et al., 2009; Girotto et al., 2012; Kim et al., 2012; van der Merwe et al., 2015; Deas et al., 2016; Kalinderi et al., 2016). It has been shown that *PRKN*, *SNCA*, *PINK1*, *DJ1* and *LRRK2* genes are most likely involved in the generation of oxidative stress in PD, however, due to the frequency of genetic variants in individual populations, *PRKN* seems to have the highest diagnostic and therapeutic importance so far.

Moreover, oxidative stress may affect both α -synuclein (ASN) aggregation and disease progression, as well as the response to L-dopa pharmacotherapy and deep brain stimulation (DBS) therapy (Dorszewska et al., 2014). In this review, we reviewed the molecular factors involved in the generation of oxidative stress in PD and identified potential targets that may improve the diagnosis and treatment of this degenerative disease in the future.

Search Strategy and Selection Criteria

For this review, literature searches were performed on PubMed, Scopus and other public databases. The following keywords were used: ((Parkinson's disease) AND ((oxidative damage) OR (oxidative stress)) AND (((levodopa) OR (L-DOPA)) OR (therapy))). The articles included in this review were chosen base on relevance to the subject. Subsequent search was performed through articles' references. The last literature sweep was performed in June 2020.

Molecular Parameters and Oxidative Stress Generation

Oxidative stress is one of the main factors behind neurodegeneration in PD. Although increased generation

of reactive oxygen species (ROS) leads to oxidative stress, physiological levels of these molecules are a normal outcome of metabolic processes and play an important role in cellular defense (Puspita et al., 2017; Saito, 2017). ROS are produced via anterograde and retrograde electron motion along the mitochondrial electron transfer chain, metabolism of DA, and other redox reactions (Figure 1). In healthy dopaminergic neurons, levels of ROS are strictly controlled by various antioxidative mechanisms involving glutathione (GSH), superoxide dismutase (SOD) and DJ-1. These processes, however, tend to fail in patients with PD. Indeed, Bender et al. (2006) found a slightly higher number of mutations, specifically somatic deletions in mitochondrial DNA (mtDNA), in the substantia nigra of PD patients compared to age-matched controls corroborating the view that nigral neurons are disproportionately more affected by oxidative damage.

Aerobic respiration takes place in the inner mitochondrial membrane (IMM). The transfer of electrons between protein complexes with increasing reduction potentials allows for the concentration of protons in the intermembrane space, generating a potential difference that fuels ATP synthesis (Puspita et al., 2017). Although electrons are typically transferred sequentially from complex I to complex IV, mono-electron reduction of molecular oxygen, the final electron acceptor, occasionally occurs generating superoxide radical (O₂⁻). Electrons may escape from complex I (nicotinamide adenine dinucleotide, NADH) and complex III (cytochrome bc1) to generate ROS (Drose et al., 2008). Under physiological conditions, superoxide is converted into hydrogen peroxide by SOD2 and then detoxified by catalase (Subramanian et al., 2013). However, with insufficient antioxidants, superoxide and other reactive molecules oxidize mtDNA. mtDNA is not only very sensitive to oxidative damage because of its lack of histones and lower-fidelity DNA polymerase (Kowalska et al., 2020), but also encodes electron transfer chain genes, resulting in a degeneration-promoting positive feedback loop. Accumulation of these abnormalities leads to increased neuronal damage and loss resulting in faster progression of PD (Bender et al., 2006).

Apart from aerobic respiration and making certain reactive molecules less harmful, mitochondria play a pivotal role in maintaining proper protein function and structural integrity (Misgeld et al., 2017). These complex mechanisms engaging AAA proteases, ubiquitin-proteasome system, mitochondrial derived vesicles, and mitophagy, are collectively called mitochondrial quality control (MQC) (Amadoro et al., 2014; Misgeld et al., 2017; Figure 1). It has been shown that defects in function of Parkin and PINK1, whose interaction constitutes the first steps in the activation of MQC pathways, facilitate progressive mitochondrial dysfunction (Harper et al., 2018). Under physiological conditions, the TOM20 protein complex transfers PINK1 N-terminus from the OMM to the IMM, where it is cleaved and then proteasomally processed, preventing organelle from accumulation of PINK1 at the OMM, an induction of mitophagy signal. Mitochondrial complex disfunction, proteotoxicity, and membrane depolarization impair this process leading to PINK1 aggregation, homodimerization, and subsequent autophosphorylation promoting activation of C-terminus kinase domains localized at the OMM. This results in the binding of ubiquitin and Parkin, which is then phosphorylated by PINK1 at Ser65 leading to activation of its E3 ligase functionality (van der Merwe et al., 2015). Activated enzyme facilitates formation of ubiquitin chains that attract more Parkin molecules increasing detection of damaged mitochondria signal, targeting substrates for degradation and even inducing mitophagy (Kalinderi et al., 2016; Harper et al., 2018). Above information suggests that mutations in *PINK1* and *PRKN* genes should affect cell's ability to process dysfunctional organelles. Interestingly, mice with both of the genes knocked-out do not display

neurodegeneration, but loss of *PINK1* expression results in larger mitochondria with functional impairment (Palacino et al., 2004; Gautier et al., 2008). Moreover, results obtained during cell culture based experiments failed to confirm some of the aforementioned processes (van Laar et al., 2011; Rakovic et al., 2013). Elucidating diverse mechanisms of *PINK1*/*Parkin* interactions in MQC systems may bring us closer to understanding etiology of PD.

Initially, autophagy was thought to be a response to nutrient restriction that resulted in the degradation of specific organelles (**Figure 1**). Subsequent studies indicated that it is involved in a wide spectrum of physiological and pathological cellular processes such as development, cellular aging, cell death, and suppression of tumor growth. The organelles and proteins that are broken down in its course are building blocks in key biosynthesis pathways. In PD, autophagy should be a response to Lewy body (LB) accumulation and oxidative stress, however, in neurodegenerative diseases this mechanism does not function properly, depriving the cell of the only presently known means for the degradation of structures that cannot be proteasomally processed (Banerjee et al., 2010; Lynch-Day et al., 2012). Oxidation of the proteasome under conditions of elevated ROS significantly impairs its function and contributes to the aggregation of oxidized or otherwise damaged proteins in the cell (Shamoto-Nagai et al., 2003), highlighting the connection between mitochondrial impairment and LB pathology in PD-ravaged dopaminergic neurons (Braak et al., 2004).

Dopaminergic neurons tend to contain large amounts of ROS, derived from the enzymatic and nonenzymatic metabolism of DA (Saito, 2017). Consequently, they are more sensitive to various stress factors than other neurons (Lotharius et al., 2002; Saito, 2017).

DA may be catabolized by monoamine oxidase (MAO), a molecule bound to the OMM, in a process which generates H_2O_2 as a byproduct (Lotharius et al., 2002). In addition, DA oxidation may occur spontaneously in the presence of iron generating 6-hydroxydopamine (6-OHDA), which is subsequently transformed to a reactive electrophilic molecule, p-quinon in the presence of oxygen. DA can also be oxidized to DA-quinone (DAQ), a molecule whose toxic effects are derived from its reaction with cysteine sulfhydryl groups (Lavoie et al., 1999) (**Figure 1**). DAQ has been shown to affect the cell's ability to sequester ROS by reacting with Cys-106 of the neuroprotective protein DJ-1 (van Laar et al., 2009; Giroto et al., 2012). In nigral neurons not affected by PD, DJ-1 is mostly localized to the cytoplasm, however, when exposed to high levels of ROS, it is oxidized to the Cys-SO₂H form and translocated to the mitochondria and the nucleus (Kim et al., 2012). DJ-1 removes ROS with lower efficiency than other enzymes involved in oxidoreductive homeostasis (e.g. catalase), suggesting that it may act instead as an oxidative stress sensor by modulating signaling pathways and the expression of specific genes (Kahle et al., 2009). Zhou et al. (2005) demonstrated that increased levels of DJ-1 induce GSH synthesis, protecting DA neurons from the harmful effects of H_2O_2 and 6-OHDA. 6-OHDA, a substance typically elevated in animal models of PD accumulates in nigral neurons, leading to various types of mitochondrial dysfunction such as inhibition of respiratory chain function or a decrease in membrane potential. Further, it has been shown that elevated levels of ROS cause increased binding of DJ-1 to mitochondrial complex I, enhancing activity of NADH: ubiquinone oxidoreductase and ultimately, the entire respiratory chain (Hayashi et al., 2009).

The aforementioned high level of iron in DA neurons can also induce ROS generation in a different way. In recent years, there has been growing evidence of interaction between metal ions and ASN second to which decreased GSH levels, increased lipid peroxidation, resulting in membrane structural

damage, and elevated formation of H_2O_2 and hydroxyl radicals may occur (Deas et al., 2016). Other effects of these abnormalities include decreased ATP levels and nucleic acid damage. 8-Oxo-2'-deoxyguanosine (8-oxo2dG) is the main oxidation product of hydroxyl radicals and guanine residues in DNA (He et al., 2018). Its levels have been shown to be higher in cerebrospinal fluid, serum and urine of people with PD as compared to controls (Isobe et al., 2010). This deoxyguanosine derivative can base pair not only with cytosine as it should, but also with adenosine, leading to a possible mutation (Hirano, 2008). Interestingly, Dorszewska et al. (2011) showed that the levels of 8-oxo2dG and corresponding DNA alterations, may be caused by treatment with L-dopa depending on its duration.

L-dopa Therapy and Oxidative Stress Parameters in Parkinson's Disease

The most effective up-to-date treatment of PD symptoms is based on replenishing or mimicking DA in the dopaminergic system, to enhance dopaminergic transmission. Since DA does not cross blood-brain barrier (BBB), replenishing DA requires admission of its precursor, L-dopa (Kostrzewa et al., 2005). The use of L-dopa in the treatment of PD is considered a "gold standard" and L-dopa preparations have been successfully used as pharmacotherapy in PD since the 1960s (Fahn, 2015). Unfortunately, the L-dopa clinical outcome is weakened by motor and nonmotor side effects, including neurotoxic effects (Gesi et al., 2001), subsequent to long-term treatment (Thanvi et al., 2004). In recent years, more and more studies indicate that they may cause enhanced ROS generation. The mechanisms underlying the said side effects of L-dopa treatment likely include oxidative DA metabolism, an indirect outcome of which is the dysregulation of biothiol levels (e.g. homocysteine, Hcy) and induction of inflammatory, apoptotic, and autophagic processes (Dorszewska et al., 2011; Andican et al., 2012; Lynch-Day et al., 2012). Elevated Hcy levels following L-dopa treatment can result in vascular diseases, cognitive impairment, dementia, depression, neurodegeneration, amounting to a poor prognosis for PD patients (Kuhn et al., 1998). In addition, it has been shown that increased Hcy levels are accompanied by reduced levels of cysteine, and in turn reduced synthesis of GSH, changes that leave the cell more susceptible to oxidative stress. The key substance associated with increased production of Hcy and reduced level of GSH in PD might be the hydrogen sulfide as its serum level is decreased in this neurodegenerative process (Yin et al., 2017). Furthermore, the hydrogen sulfide has been shown to play a role in the regulation of GSH synthesis and Hcy turnover (Kimura et al., 2004).

Subsequently, it has been shown that side-synthesis of dihydroxyphenylacetic acid (DOPAC) and H_2O_2 during the metabolism of DA in the stratum of PD patients by monoamine oxidase (MAO) may be another mechanism underlying elevated ROS formation in DA neurons (Gesi et al., 2001). This data is confirmed by *in vitro* studies showing that incubation with L-dopa may increase intracellular ROS and lead to cell death. This effect was attenuated by inhibition of MAO by pargyline in studied RN46A-B14 serotonergic cell line, which were shown to be able to produce dopamine after incubation with L-dopa (Stansley and Yamamoto, 2013). This property was reduced by co-incubation with the AADC inhibitor, NSD-1015, what further reduced ROS production and improved cell viability (Stansley et al., 2013). These data suggest that substantial doses of L-dopa may be toxic not only to dopaminergic neurons, but may also affect serotonergic cells, leading to psychiatric symptoms of PD, like depression or anxiety (Eskow Jaunarajs et al., 2011).

Moreover, in PD, the brain deposition of heavy metals ions, such as iron ions (Fe^{2+}), may lead to non-enzymatic Fenton reaction that produces ROS, like $OH\cdot$ and may stimulate ASN

Review

aggregation (**Figure 1**) (Weinreb et al., 2013). Fenton reaction produces ROS, like OH \cdot (Weinreb et al., 2013). Subsequently, cortical neurons growing in the presence of L-dopa showed significant buildup of intracellular Fe $^{2+}$, followed by reduced cell viability. This effect was partially reduced for cells co-incubated with L-dopa in astrocyte conditioned medium, suggesting the significant role of molecular environment to L-dopa toxicity (Du et al., 2009). This observation is in line with the study by Billings et al. (2019) who investigated the effect of L-dopa in transgenic hA53T mice, expressing mutated ASN with or without presence of excessive Fe $^{2+}$. The authors demonstrated that *in vivo* L-dopa may act as a mild Fe $^{2+}$ chelator, comparable to Clioquinol. In the brains of wild-type mice treated with multiple doses of L-dopa, Billings et al. (2019) found no evidence of increased oxidative stress. What is more, L-dopa improved motor functions in mice with overload of Fe $^{2+}$. This protective effect was attenuated in hA53T transgenic murine model of PD in the presence of Fe $^{2+}$, suggesting that L-dopa effects may depend on Fe $^{2+}$ brain content and genetic mutations that affect PD proteins, such as ASN.

While Fe $^{2+}$ ions are catalyst of DA and L-dopa oxidation, these processes can occur spontaneously in the brain, as DA and L-dopa may undergo auto-oxidation, thus generating H $_2$ O $_2$ and the more stable DA-quinone (Sulzer et al., 1999; Pattison et al., 2002). There are reports showing that DA-quinone further disturbs DA turnover, e.g. by halting the functions of TH enzyme and DA transporter (DAT), followed by mitochondrial damage resulting in ATP deficiency (Berman et al., 1999; Kuhn et al., 1999; Khan et al., 2001).

The toxic DA-quinone is further metabolized to aminochrome, a metabolite that was shown to induce formation of ASN aggregates (Muñoz et al., 2012). In the healthy brain, there are numerous mechanisms protecting against aminochrome toxicity. First, as DA oxidation is mostly dependent on pH and Fe $^{2+}$ content, thus DA present in neuronal cytoplasm is quickly absorbed by synaptic vesicles by abovementioned VMAT2. Second, DA-quinone, aminochrome, and other oxidation product, 5,6-indolequinone undergo quick polymerization to neuromelanin that stains dopaminergic neurons black, and renders the toxins inert. Third, toxic aminochrome is reduced in enzymatic reaction catalyzed by DT-diaphorase. The excessive aminochrome is conjugated with GSH by glutathione S-transferase M2-2 (GSTM2) (Segura-Aguilar et al., 2014). On the other hand, it has been hypothesized that GSH-aminochrome conjugate, a building block of neuromelanin may be able to accumulate heavy metal ions such as pro-oxidative Fe $^{2+}$ (Zucca et al., 2017). It seems that, neuromelanin, a DA autooxidation endpoint metabolite may also exert neuroprotective and antioxidative effect by eliminating free Fe $^{2+}$. Subsequently, the neuromelanin damage in the course of PD may cause premature ageing due to accumulation of ASN and excessive ROS, followed by neuroinflammation and reduction of neurogenesis (Nekrasov et al., 2018). Thus it is suggested that disturbances in protective mechanisms and accumulation of L-dopa and DA oxidation products may play a role in the development of PD (Herrera et al., 2017).

Genetic Variants and Oxidative Stress in Parkinson's Disease

SNCA

SNCA encodes ASN, a protein involved in synaptic vesicle trafficking, regulation of DA biosynthesis, neuronal differentiation, chaperone activity, antioxidative processes, and suppression of apoptosis. The accumulation of ASN in nerve cells of the substantia nigra, pons, and medulla leading to cell death is a hallmark of PD (Emamzadeh, 2016). Moreover, ASN may interact with other proteins e.g. Parkin and disrupt their function. Mutations in SNCA contribute

to ASN aggregation and oxidative stress (**Table 1**) and the declined capacity to scavenge ROS can further exacerbate ASN aggregation (Scudamore et al., 2018). Both point mutation and duplication or triplication of SNCA lead to the aggregation of ASN, however, triplications are responsible for the more severe phenotype typified by early onset PD and dementia (Fuchs et al., 2007). Ko et al. (2000) demonstrated that overexpression of mutant SNCA increases the sensitivity of transfected human cells to oxidative injury. Moreover, oxidation of ASN decreases its capacity for forming either α - or β -type secondary structures integral to the construction of fibrils.

PRKN and PINK1

PRKN encodes Parkin, an E3 ubiquitin ligase, which mediates the proteasome-dependent degradation of redundant and disordered proteins, e.g. glycosylated ASN. It is necessary for the survival of DA neurons as it protects against ASN toxicity and oxidative stress (Feany et al., 2003). PRKN mutations impair the ability of protein to bind ASN and result in the aggregation of the latter (Shimura et al., 2001) in addition to slower mutant protein turnover and increased levels of oxidative stress markers such as protein carbonyls, lipid peroxides, and nitrated proteins (Hyun et al., 2002). Loss of function mutations in PRKN causes recessively inherited PD and contributes to nearly half of the cases of familial early onset PD (EOPD) and one fifth of sporadic EOPD cases. The clinical symptoms of PD patients bearing PRKN mutations resemble idiopathic PD, with good response to L-dopa, slower disease progression and more symmetric onset (Lücking et al., 2000). Furthermore, patients with PRKN mutations more commonly suffer from depression without an impact on executive function as compared to individuals with EOPD caused by other factors (Song et al., 2020). PRKN mutations can also be identified in late onset PD (LOPD) (**Table 1**).

PINK1 encodes the phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1), which as a mitochondrial kinase is highly expressed in the brain, heart, and muscles (Barodia et al., 2017). PINK1 loss of function mutations can cause recessive EOPD and stand for approximately 1–8% of EOPD cases (Kawajiri et al., 2011). The overexpression of PINK1 has neuroprotective properties, and it protects against oxidative stress-induced cell death by inhibiting the release of cytochrome c from mitochondria what depends on phosphorylation of a mitochondrial chaperone TRAP1 by PINK1 (Pridgeon et al., 2007). PINK1 sometimes is called a guard of mitochondrial quality control and its deficiency was linked to changes in mitochondrial morphology associated with loss of mitochondrial enzyme activity, especially complex I. The knockdown of PINK1 results in decreased mtDNA synthesis followed by decreased ATP production and it induces mitochondrial fragmentation and autophagy what promote oxidative stress (Dagda et al., 2009; Dias et al., 2013).

PINK1 together with Parkin is involved in the removal of impaired mitochondria by autophagy. The accumulation of PINK1 on the surface of dysfunctional mitochondria signals Parkin to commence degradation of the damaged organelle (Narendra et al., 2008). PINK1 or Parkin deficiency inhibits autophagy of dysfunctional mitochondria, which can lead to increased ROS and subsequent nigral cell loss. Further, impaired DA release and synaptic plasticity and defects in mitochondrial respiration and ATP-generation were found in pink1 knockout mice. Moreover, reduced fission and increased aggregation of mitochondria follow from conditions of increased oxidative stress (Gispert et al., 2009).

PINK1 can also interact with DJ-1. Overexpression of these proteins synergistically protects cells against MPTP-induced cell death, an effect that was abolished in the presence of PINK1 or DJ1 mutations (Tang et al., 2006). It is proposed

Table 1 | Genetic variants of *SNCA*, *PRKN*, *PINK1*, *DJ-1*, *LRRK2* and the development of Parkinson's disease (PD)

Gene	Genetic variants	Clinical symptom	Response to L-dopa therapy	Molecular mechanism of mutations	References
<i>SNCA</i>	A53T Italian origin	- Early onset PD, mean age 46.5 years - Fast disease progression averaged 9.7 years from onset to death - Typical course of PD - Most patients developed dementia	- Good - Numerous dyskinesia	- Tau phosphorylation-dependent postsynaptic dysfunction by decreased AMPA to NMDA receptor current ratio - ASN aggregation	Teravskis et al. (2018)
	A30P German origin	- Early age at onset - Milder course of PD	- Good	- Loss of viability protection against oxidative stress - ASN aggregation	Krüger et al. (1998)
	E46K Spanish origin	- Motor disorders - Dementia - Visual hallucinations - Neuropsychological disorders	- From moderate to good	- Increased ability of ASN to bind to phospholipids and filament assembly - ASN aggregation	Zarranz et al. (2004)
	G51D British origin	- Early onset PD	- Good	- α -Synucleinopathy - Promotion of cellular toxicity under oxidative stress conditions - Decreased rate of ASN aggregation	Kiely et al. (2013); Fares et al. (2014); Rutherford et al. (2014)
	H50Q British and Canadian origin	- Late onset PD	- Good	- Promotion of cellular toxicity under oxidative stress conditions	Appel-Cresswell et al. (2013); Rutherford et al. (2014)
	A53E Finish origin	- Early onset PD - atypical MSA and PD	- Good	- Promotion of cellular toxicity under oxidative stress conditions - Reduced ASN aggregation propensity	Pasanen et al. (2014); Rutherford et al. (2015)
<i>PRKN</i>	- Over 100 mutations - Point missense and nonsense mutations - Large chromosomal deletions and duplications - Mutation in promoter region	- Missense mutations in functional domains of protein correlate with earlier disease onset - Single heterozygous mutation correlate with later and more asymmetrical onset and more frequent L-dopa-induced fluctuations and dystonia - Polymorphisms with exposure to environmental risk factors of PD decrease the age of onset	- Good - Slower disease progression - More symmetric onset	- Loss of ability to bind ASN by Parkin - increased level of oxidative stress markers - Abnormal morphology of mitochondria, abnormal mitophagy - Reduced complex I activity	Hyun et al. (2002); Barodia et al. (2017); et al. (2018)
<i>PINK1</i>	- More than 50 mutations - Point missense and nonsense mutations - Genomic rearrangements - Whole gene deletions	- Early age of onset - Slower disease progression - Homozygous mutations lead to lower age at onset	- Good - Frequent L-dopa-induced dyskinesia	- Declined mitochondrial quality control - Abnormal morphology of mitochondria, abnormal mitophagy - Oxidative stress-induced cell death - Increased mitochondrial ROS and reduced GSH after cytotoxicity	Pridgeon et al. (2007); Dagda et al. (2009); Kawajiri et al. (2011); Barodia et al. (2017); Sison et al. (2018)
<i>DJ1</i>	- About 20 mutation - Missense point mutations - Deletions	- Phenotype similar to patients with <i>PRKN</i> or <i>PINK1</i> mutation	- Good - Early onset of dystonic features followed later by psychiatric symptoms	- Impaired antioxidant, antiapoptotic and anti-inflammatory function - Increased oxidative stress	Schiesling et al. (2008); Repici et al. (2019)
<i>LRRK2</i>	- More than 30 mutations	- Less non-motor symptoms - Clinical features similar to patients with sporadic LOPD - Point mutations sometimes are associated with dementia and autonomic system disorders	- Good	- ASN accumulation - Defects in mitochondrial network integrity, increased mtDNA damage - Increased ROS and oxidative stress	Kestenbaum et al. (2017); Sison et al. (2018)

that DJ-1 acts either downstream to PINK1 or parallel to the PINK1/Parkin pathway (Thomas et al., 2011), however, the exact mechanism of the interaction between PINK1 and DJ-1 is still unknown.

DJ1

DJ-1 is another neuroprotective protein which regulates numerous processes e.g. anti-oxidative, anti-apoptotic and anti-inflammatory pathways. Mutations in *DJ1* gene are a rare cause of EOPD and constitute only 1% of cases. DJ-1 protects substantia nigra DA neurons from oxidative stress. Waragai et al. (2006) found elevated levels of DJ-1 in the cerebrospinal fluid of sporadic PD patients, especially in the early stages of the disease (I–II HY scale), and suggested that the protein plays a protective role against oxidative stress during PD onset. Interestingly, rapid relocalization of DJ-1 to mitochondria has been shown to occur under oxidative stress conditions (Junn et al., 2009) and may be implicated in inhibiting autophagy (Thomas et al., 2011). Cytologic analyses of fibroblasts or lymphoblasts isolated from PD patients with

mutations in *DJ1* gene showed mitochondrial fragmentation, impaired bioenergetics, and increased sensitivity to ROS and toxins (Yan et al., 2013). Kim et al. (2005) found that *dj1* knockout mice had increased levels of mitochondrial oxidative stress and were more sensitive to MPTP toxicity as compared to wild-type animals. Interestingly, however, the *dj1* knockout animals did not exhibit any significant motor impairment.

LRRK2

Leucine-rich repeat kinase-2 (LRRK2), also called dardarin, is responsible for numerous processes, including cytoskeletal dynamics, vesicular trafficking, calcium signaling, and mitochondrial function (Weindel et al., 2020). LRRK2 controls mitochondrial network dynamics and mitophagy through interactions with the mitochondrial fusion proteins and mitochondrial outer membrane proteins (Wang et al., 2012; Hsieh et al., 2016). LRRK2 located within the cytoplasm is necessary for phosphorylation of protein, e.g. ASN and tau (Zimprich et al., 2004). Moreover, overexpression of LRRK2 or synergism with ASN may intensify destructive processes

during PD (Schapira, 2006).

Mutations in the *LRRK2* gene are the most commonly known cause of familial autosomal dominant PD and sporadic PD. For the first time they have been described in the Basque population. Most of the *LRRK2* mutations are localized in catalytic core domains of the protein, especially Roc-GTPase and kinase domains, and alter the enzyme activity. The results of *LRRK2* mutations are abnormalities in mitochondrial fusion and fission dynamics, mitophagy, mitochondrial DNA (mtDNA) damage (Mancini et al., 2020). They contribute to elevated ROS production, inhibition of peroxidase activity, and in consequence to increased oxidative stress (Angeles et al., 2014). The most common mutation in the *LRRK2* gene, G2019S, is present with a frequency of 10–18% in the Ashkenazi Jewish population, and with 3–13% in the European population (Lesage et al., 2005; Ozelius et al., 2006; Clark et al., 2006). The penetrance of the G2019S mutation has an age-dependent effect and varies from 28% at the age of 59 years, 51% at the age of 69 years, and 74% at the age of 79 years (Healy et al., 2008).

Other Treatments in Parkinson's Disease and Oxidative Stress

In progressive PD, optimization of dopaminergic therapy is recommended in the first place (increasing the doses of dopamine agonists and L-dopa), and then advanced therapy, including DBS, subcutaneous apomorphine, and enteral L-dopa. DBS is the leading surgical intervention for PD (Lozano et al., 2017). Still, studies have suggested that DBS is over-indicated, highlighting the need for careful assessment of patient eligibility (Bronstein et al., 2011).

Following its clinical implementation, DBS quickly became the standard of care for medication-refractory motor disorders, and principally PD (Lozano et al., 2019), however, it was not until 2006 that a randomized-pairs trial evidenced that subthalamic nucleus (STN) DBS combined with medical treatment was superior to medical treatment alone in alleviating L-dopa-related motor dysfunction (Desuchl et al., 2013). A randomized controlled trial published a few years later demonstrated that DBS was superior to medication alone when stratified by patient age (Weaver et al., 2009). Nonetheless, both trials reported more serious adverse health risks associated with DBS as compared to medication alone. Current literature indicates that the STN, GPI, and the ventral intermediate thalamic nucleus (VIM), are the only foci routinely targeted using DBS in clinical practice (Deuschl et al., 2013), however, stimulation of the pedunclopontine nucleus has been shown to improve gait disturbances, and stimulation of the nucleus basalis has been investigated for the treatment of dementia (Gratwicke et al., 2018). Whether an ideal target for DBS in the treatment of PD exists remains contested. A 2010 study failed to observe any significant changes between patients having undergone pallidal or subthalamic DBS 24 months post-operatively, as measured using the Unified Parkinson's Disease Rating Scale 3 (UPDRS3; the segment dedicated to assessing rigidity, tremor, bradykinesia, and postural instability). Further, STN DBS allowed for L-dopa dose reduction, but it was correlated with worsened visuomotor processing and depression. Nonetheless, the STN is the most common target for DBS (Deuschl et al., 2013; Lozano et al., 2019) and researchers have sought to identify optimal regions for neurostimulation within it. This task, however, has been burdened by the STN's shape and anatomic position, in addition to limitations in visualization. Still, the dorsolateral STN, zona in certa and Forel-H2 field, or boundaries contacting both of these regions have been purported to yield maximally efficacious results. Recently, a high angular resolution diffusion imaging analysis evidenced that DBS applied to the central superolateral STN best ameliorated PD tremor and

neurostimulation within the posteromedial superolateral STN was most effective for treating rigidity and bradykinesia (Akram et al., 2017).

DBS is contraindicated for atypical parkinsonism and affords those patients who are generally responsive to L-dopa, however, nonetheless experience medication-related side effects (e.g. off-periods and dyskinesia) an optimal response (Bronstein et al., 2011). Multiple predictors of DBS outcome exist. Anatomic variations both due to and independent of PD-related regional brain atrophy can influence targeting accuracy and the efficacy of stimulation (Younce et al., 2019). Specifically, mesencephalic surface area (Bonneville et al., 2005), paracentral region thickness (Muthuraman et al., 2017), and PD-related atrophy of the hippocampus (Aybeck et al., 2009) and sensorimotor cortex (Hwang et al., 2013) affect the response to DBS. In a recent MRI analysis, smaller thalamic volumes and larger ventricular volumes were correlated with poorer DBS outcomes, as measured using the UPDRS3 (Younce et al., 2019). Genetic factors also influence response to DBS (Artusi et al., 2019; de Oliveria et al., 2019; Kuusimäki et al., 2019). While carriers of the common p.G2019S mutation in leucine-rich repeat kinase 2 (*LRRK2*) and *PINK1* mutations were generally found to experience positive outcomes following DBS, those with the rarer p.R1441G *LRRK2* mutation do not face such a good prognosis. Moreover, improvements in motor function of patients carrying *SNCA*, *GBA*, and *LRRK2* p.T2031S mutations appear to co-occur with worsened nonmotor symptoms of PD following DBS (Kuusimäki et al., 2019). Interestingly, dysregulation of calcium homeostasis and ensuing oxidative stress underlies many of the mutations for which a correlation with DBS outcome exists. *LRRK2* has been shown to upregulate the expression of the mitochondrial calcium uniporter (MCU) and the mitochondrial calcium uptake 1 (MICU1) protein, without altering expression of the mitochondrial $\text{Na}^+/\text{Ca}^{2+}/\text{Li}^+$ NCLX antiporter (Verma et al., 2017). These changes promote mitochondrial calcium overload, which has been implicated in PD pathophysiology (Kowalska et al., 2020). Further, the decreased sequestration of synaptic vesicles (Piccoli et al., 2014) and increased activation of presynaptic voltage-gated calcium channels (Bedford et al., 2016) seen with certain pathologic *LRRK2* variants explain the heightened cortical glutamatergic signaling that occurs due to these mutations (Verma et al., 2017). Enhanced excitatory transmission in the cortex might in turn disturb corticostriatal dynamics (e.g. overactivate the indirect pathway). DBS has been shown to induce calcium-dependent astrocytic release of glutamate (Tawfik et al., 2010). In contrast to *LRRK2*, *PINK1*, a mitochondrial kinase, does regulate NCLX, however, its deficiency in PD also ultimately promotes mitochondrial calcium overload and ROS generation (Ghandi et al., 2009). Lastly, Schöndorf et al. (2014) demonstrated that induced pluripotent stem cell-derived neurons from PD patients bearing mutations in the β -glucocerebrosidase (*GBA1*) gene featured aberrant calcium homeostasis and lysosomal functioning.

Technological improvements including increasingly efficient implantable programmable generators (IPGs), MRI compatible hardware (alleviating the need for stereotactic ventriculography), and more recently, directional leads, have allowed DBS to maintain its ascendancy among treatments for advanced PD (Lozano et al., 2019). Moreover, there is ongoing research into developing and implementing closed-loop stimulation systems, wherein feedback between the stimulating electrode and another which detects biomarkers (e.g. action or local field potentials, electrocorticograms, and electroencephalograms) allows for continually adjustable modifications to pulse amplitude, frequency, and duty cycle (the ratio of pulse width to signal period). In this manner, the need for a physician to routinely perform adjustments to the neurostimulation regimen according to a largely trial-and-error

approach would be nullified. Nonetheless, closed-loop systems are considerably more energy-demanding, necessitating the use of larger batteries or wireless means of energy transfer (Ghasemi et al., 2018). Further, notwithstanding the foreseeable transition to adaptive systems in the coming years, DBS is an invasive procedure, and as such carries a risk of infection and hemorrhage (Lozano et al., 2019). Seminally, Grossman et al. (2017) showed that the interference of two electric fields oscillating at minimally offset frequencies, each individually too high to stimulate neurons due to their intrinsic low-pass filter, can be used to target subcortical structures from areas outside of the brain. However, although the potential for non-invasive, temporal interference DBS has been demonstrated in mice, the technology has not yet been applied clinically. Lastly, while PD and other motor disorders typically feature complex aberrations to neural circuits, DBS is limited in its ability to modulate a single anatomic target.

Conclusion

Generating oxidative stress in PD may occur in various mechanisms, is associated with the failure of complex I of the respiratory chain and the presence of certain genetic variants of the PARK. At the same time, the level of oxidative stress may be responsible for both the effectiveness of antiparkinsonian pharmacotherapy and DBS therapy. It seems that finding genetic and environmental factors associated with the generation of oxidative stress may be of importance in the future for improving the diagnostic processes and prognostic disorders of the extrapyramidal system and may contribute to the introduction of more effective pharmacologic and non-pharmacologic treatments.

Author contributions: *Review concept and review design: JD; literature retrieval and manuscript writing: JD, MK, MP, TP, JK; critically revising the manuscript for important intellectual content: WK. All authors provided final approval of this manuscript for publication.*

Conflicts of interest: *The authors declare that there are no conflicts of interest associated with this manuscript.*

Financial support: *This work was supported by the grant of NCBIR (European Union), No. POWR.03.01.00-00-T006/18-00.*

Copyright license agreement: *The Copyright License Agreement has been signed by all authors before publication.*

Plagiarism check: *Checked twice by iThenticate.*

Peer review: *Externally peer reviewed.*

Open access statement: *This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.*

References

Akram H, Sotiropoulos S, Jbabdi S, Georgiev D, Mahlkecht P, Hyam J, Foltyniec T, Limousin P, De Vita E, Jahanshadi M, Hariz M, Ashburner J, Behrens T, Zrinzo L (2017) Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. *Neuroimage* 158:332-345.

Amadoro G, Corsetti V, Florenzano F, Atlante A, Bobba A, Nicolini V, Nori SL, Calissano P (2014) Morphological and bioenergetic demands underlying the mitophagy in post-mitotic neurons: the pink-parkin pathway. *Front Aging Neurosci* 6:18.

Andican G, Konukoglu D, Bozulolcay M, Bayülkem K, Firtina S, Burcak G (2012) Plasma oxidative and inflammatory markers in patients with idiopathic Parkinson's disease. *Acta Neurol Belg* 112:155-159.

Angeles DC, Ho P, Chua LL, Wang C, Yap YW, Ng C, Zhou ZD, Lim KL, Wszolek ZK, Wang HY, Tan EK (2014) Thiol peroxidases ameliorate LRRK2 mutant-induced mitochondrial and dopaminergic neuronal degeneration in *Drosophila*. *Hum Mol Genet* 23:3157-3165.

Appel-Cresswell S, Vilarino-Guell C, Encarnacion M, Sherman H, Yu J, Shah B, Weir D, Thompson C, Szu-Tu C, Trinh J, Aasly JO, Rajput A, Rajput AH, Jon Stoessl A, Farrer MJ (2013) Alpha-synuclein p.H50Q, a novel pathogenic mutation for Parkinson's disease. *Mov Disord* 28:811-813.

Artusi CA, Dwivedi AK, Romagnolo A, Pal G, Kauffman M, Mata I, Patel D, Vizcarra JA, Duker A, Marsili L, Cheeran B, Woo D, Contarino MF, Verhagen L, Lopiano L, Espay AJ, Fasano A, Merola A (2019) Association of subthalamic deep brain stimulation with motor, functional, and pharmacologic outcomes in patients with monogenic Parkinson disease: a systematic review and meta-analysis. *JAMA Netw Open* 2:e187800.

Aybek S, Lazeyras F, Gronchi-Perrin A, Burkhard PR, Villemure JG, Vingerhoets FJ (2009) Hippocampal atrophy predicts conversion to dementia after STN-DBS in Parkinson's disease. *Parkinsonism Relat Disord* 15:521-524.

Banerjee R, Beal MF, Thomas B (2010) Autophagy in neurodegenerative disorders: Pathogenic roles and therapeutic implications. *Trends Neurosci* 33:541-549.

Barodia SK, Creed RB, Goldberg MS (2017) Parkin and PINK1 functions in oxidative stress and neurodegeneration. *Brain Res Bull* 133:51-59.

Bedford C, Sears C, Perez-Carrion M, Piccoli G, Condliffe SB (2016) LRRK2 regulates voltage-gated calcium channel function. *Front Mol Neurosci* 9:35.

Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK, Perry RH, Jaros E, Hershenson JS, Betts J, Klopstock T, Taylor RW, Turnbull DM (2006) High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat Genet* 38:515-517.

Berman SB, Hastings TG (1999) Dopamine oxidation alters mitochondrial respiration and induces permeability transition in brain mitochondria: implications for Parkinson's disease. *J Neurochem* 73:1127-1137.

Billings JL, Gordon SL, Rawling T, Doble PA, Bush AI, Adlard PA, Finkelstein DJ, Hare DJ (2019) L-3,4-Dihydroxyphenylalanine (L-DOPA) modulates brain iron, dopaminergic neurodegeneration and motor dysfunction in iron overload and mutant alpha-synuclein mouse models of Parkinson's disease. *J Neurochem* 150:88-106.

Bonneville F, Welter ML, Elie C, du Montcel ST, Hasboun D, Meneul C, Houeto JL, Bonnet AM, Mesnage V, Pidoux B, Navarro S, Cornu P, Agid Y, Dormont D (2005) Parkinson disease, brain volumes, and subthalamic nucleus stimulation. *Neurology* 64:1598-1604.

Braak H, Ghebremedhin E, Rub U, Braatzke H, Del Tredici K (2004) Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* 318:121-134.

Bragoszewski P, Turek M, Chacinska A (2017) Control of mitochondrial biogenesis and function by the ubiquitin-proteasome system. *Open Biol* 7:170007.

Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkman J, Stefani A, Horak FB, Okun MS, Foote KD, Krack P, Pahwa R, Henderson JM, Hariz MI, Bakay RA, Reza A, Marks WJ Jr, Moro E, Vitek JL, Weaver FM, Gross RE, DeLong MR (2011) Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol* 68:165.

Clark LN, Wang Y, Karlins E, Saito L, Mejia-Santana H, Harris J, Louis ED, Cote LJ, Andrews H, Fahn S, Waters C, Ford B, Frucht S, Ottman R, Marder K (2006) Frequency of LRRK2 mutations in early- and late-onset Parkinson disease. *Neurology* 67:1786-1791.

Dagda RK, Cherra SJ 3rd, Kulich SM, Tandon A, Park D, Chu CT (2009) Loss of PINK1 function promotes mitophagy through effects on oxidative stress and mitochondrial fission. *J Biol Chem* 284:13843-13855.

de Oliveira LM, Barbosa ER, Aquino CC, Munhoz RP, Fasano A, Cury RG (2019) Deep brain stimulation in patients with mutations in Parkinson's disease-related genes: A systematic review. *Mov Disord Clin Pract* 6:359-368.

Deas E, Cremades N, Angelova PR, Ludtmann MHR, Yao Z, Chen S, Horrocks MH, Banushi B, Little D, Devine MJ, Gissen P, Klenerman D, Dobson CM, Wood NW, Gandhi S, Abramov AY (2016) Alpha-synuclein oligomers interact with metal ions to induce oxidative stress and neuronal death in Parkinson's disease. *Antioxid Redox Signal* 24:376-391.

Deuschl G, Schüpbach M, Knudsen K, Pinsker M, Cornu P, Rau J, Agid Y, Schade-Brittinger C (2013) Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: Concept and standards of the EARLYSTIM-study. *Parkinsonism Relat Disord* 19:56-61.

Dias V, Junn E, Mouradian MM (2013) The role of oxidative stress in Parkinson's disease. *J Parkinsons Dis* 3:461-491.

Dorszewska J, Kozubski W (2011) Oxidative DNA damage and the level of biothiols, and L-dopa therapy in Parkinson's disease. In: *Etiology and Pathophysiology of Parkinson's Disease* (Rana AQ, ed), pp349-372.

Dorszewska J, Prendecki M, Lianeri M, Kozubski W (2014) Molecular effects of L-dopa therapy in Parkinson's disease. *Curr Genomics* 15:11-17.

Draoui A, El Hiba O, Airrane A, El Khiaat A, Gamrani H (2020) Parkinson's disease: From bench to bedside. *Rev Neurol* pii: S0035-3787(19)30913-0.

Drose S, Brandt U (2008) The mechanism of mitochondrial superoxide production by the cytochrome bc1 complex. *J Biol Chem* 283:21649-21654.

Du F, Qian ZM, Zhu L, Wu XM, Yung WH, Tsim TY, Ke Y (2009) L-DOPA neurotoxicity is mediated by up-regulation of DMT1-IRE expression. *PLoS One* 4:e4593.

Emamzadeh FN (2016) Alpha-synuclein structure, functions, and interactions. *J Res Med Sci* 21:29.

Eskow Jaunarajs KL, Angoa-Perez M, Kuhn DM, Bishop C (2011) Potential mechanisms underlying anxiety and depression in parkinson's disease: consequences of L-DOPA treatment. *Neurosci Biobehav Rev* 35:556-564.

Review

- Fahn S (2015) The medical treatment of Parkinson disease from James Parkinson to George Cotzias. *Mov Disord* 30:4-18.
- Fares MB, Ait-Bouziad N, Dikly I, Mbefo MK, Jovičić A, Kiely A, Holton JL, Lee SJ, Gitler AD, Eliezer D, Lashuel HA (2014) The novel Parkinson's disease linked mutation G51D attenuates in vitro aggregation and membrane binding of α -synuclein, and enhances its secretion and nuclear localization in cells. *Hum Mol Genet* 23:4491-4509.
- Feany MB, Pallanck LJ (2003) Parkin: a multipurpose neuroprotective agent? *Neuron* 38:13-16.
- Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schule B, Langston JW, Middleton FA, Ross OA, Hulihan M, Gasser T, Farrer MJ (2007) Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. *Neurology* 68:916-922.
- Gandhi S, Wood-Kaczmar A, Yao Z, Plun-Favreau H, Deas E, Klupsch K, Downward J, Latchman DS, Tabrizi SJ, Wood NW, DuChen MR, Abramov AY (2009) PINK1-associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. *Mol Cell* 33:627-638.
- Gautier CA, Kitada T, Shen J (2008) Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. *Proc Natl Acad Sci U S A* 105:11364-11369.
- Gesi M, Santinami A, Ruffoli R, Conti G, Fornai F (2001) Novel aspects of dopamine oxidative metabolism (confounding outcomes take place of certainties). *Pharmacol Toxicol* 89:217-224.
- Ghasemi P, Sahraee T, Mohammadi A (2018) Closed- and open-loop deep brain stimulation: methods, challenges, current and future aspects. *J Biomed Phys Eng* 8:209-216.
- Giroto S, Sturlese M, Bellanda M, Tessari I, Cappellini R, Bisaglia M, Bubacco L, Mammi S (2012) Dopamine-derived quinones affect the structure of the redox sensor DJ-1 through modifications at Cys-106 and Cys-53. *J Biol Chem* 287:18738-18749.
- Gispert S, Ricciardi F, Kurz A, Azizov M, Hoepken HH, Becker D, Voos W, Leuner K, Müller WE, Kudin AP, Kunz WS, Zimmermann A, Roeper J, Wenzel D, Jendrach M, García-Areñcibia M, Fernández-Ruiz J, Huber L, Rohrer H, Barrera M, Reichert AS, Rüb U, Chen A, Nussbaum RL, Auburger G (2009) Parkinson phenotype in aged PINK1-deficient mice is accompanied by progressive mitochondrial dysfunction in absence of neurodegeneration. *PLoS One* 4:e5777.
- Gratwicke J, Zrinzo L, Kahan J, Peters A, Beigi M, Akram H, Hyam J, Oswal A, Day B, Mancini L, Thornton J., Yousry T, Limousin P, Hariz M, Jahanshahi M, Foltynie T (2018) Bilateral deep brain stimulation of the nucleus basalis of Meynert for Parkinson disease dementia: a randomized clinical trial. *JAMA Neurol* 75:169-178.
- Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk HJ, Cassara AM, Neufeld E, Kuster N, Tsai LH, Pascual-Leone A, Boyden ES (2017) Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* 169:1029-1041.e16.
- Harper JW, Ordureau A, Heo JM (2018) Building and decoding ubiquitin chains for mitophagy. *Nat Rev Mol Cell Biol* 19:93-108.
- Hayashi T, Ishimori C, Takahashi-Niki K, Taira T, Kim Y, Maita H, Maita C, Ariga H, Iguchi-Ariga SMM (2009) DJ-1 binds to mitochondrial complex I and maintains its activity. *Biochem Biophys Res Commun* 390:667-672.
- He R, Yan X, Guo J, Xu Q, Tang B, Sun Q (2018) Recent advances in biomarkers for Parkinson's disease. *Front Aging Neurosci* 10:305.
- Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, Brice A, Aasly J, Zabetian CP, Goldwurm S, Ferreira JJ, Tolosa E, Kay DM, Klein C, Williams DR, Marras C, Lang AE, Wszolek ZK, Berciano J, Schapira AH, Lynch T, Bhatia KP, Gasser T, Lees AJ, Wood NW (2008) International LRRK2 Consortium. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol* 7:583-590.
- Herrera A, Muñoz P, Steinbusch HWM, Segura-Aguilar H (2017) Are dopamine oxidation metabolites involved in the loss of dopaminergic neurons in the nigrostriatal system in Parkinson's disease? *ACS Chem Neurosci* 8:2766-2777.
- Hirano T (2008) Repair system of 7,8-dihydro-8-oxoguanine as a defense line against carcinogenesis. *J Radiat Res* 49:329-340.
- Hsieh CH, Shaltouki A, Gonzalez AE, Bettencourt da Cruz A, Burbulla LF, St Lawrence E, Schüle B, Krainc D, Palmer TD, Wang X (2016) Functional impairment in mito degradation and mitophagy is a shared feature in familial and sporadic Parkinson's disease. *Cell Stem Cell* 19:709-724.
- Hwang K, Beyer M, Green A, Chung C, Thompson P, Janvin C, Larsen J, Aarsland D, Apostolova L (2013) Mapping cortical atrophy in Parkinson's disease patients with dementia. *J Parkinsons Dis*. 2013;3:69-76.
- Hyun DH, Lee M, Hattori N, Kubo S, Mizuno Y, Halliwell B, Jenner P (2002) Effect of wild-type or mutant parkin on oxidative damage, nitric oxide, antioxidant defenses, and the proteasome. *J Biol Chem* 277:28572-28577.
- Isobe C, Abe T, Terayama Y (2010) Levels of reduced and oxidized coenzyme Q-10 and 8-hydroxy-2'-deoxyguanosine in the cerebrospinal fluid of patients with living Parkinson's disease demonstrate that mitochondrial oxidative damage and/or oxidative DNA damage contributes to the neurodegenerative process. *Int J Mol Sci* 11:159-163.
- Junn E, Jang WH, Zhao X, Jeong BS, Mouradian MM (2009) Mitochondrial localization of DJ-1 leads to enhanced neuroprotection. *J Neurosci Res* 87:123-129.
- Kahle PJ, Waak J, Gasser T (2009) DJ-1 and prevention of oxidative stress in Parkinson's disease and other age-related disorders. *Free Radic Biol Med* 47:1354-1361.
- Kalinderi K, Bostantjopoulou S, Fidani L (2016) The genetic background of Parkinson's disease: current progress and future prospects. *Acta Neurol Scand* 134:314-326.
- Kawajiri S, Saiki S, Sato S, Hattori N (2011) Genetic mutations and functions of PINK1. *Trends Pharmacol Sci* 32:573-580.
- Kestenbaum M, Alcalay RN (2017) Clinical features of LRRK2 carriers with Parkinson's disease. *Adv Neurobiol* 14:31-48.
- Khan FH, Saha M, Chakrabarti S (2001) Dopamine induced protein damage in mitochondrial-synaptosomal fraction of rat brain. *Brain Res* 895:245-249.
- Kiely AP, Asi YT, Kara E, Limousin P, Ling H, Lewis P, Proukakis C, Quinn N, Lees AJ, Hardy J, Revesz T, Houlden H, Holton JL (2013) α -Synucleinopathy associated with G51D SNCA mutation: a link between Parkinson's disease and multiple system atrophy? *Acta Neuropathol* 125:753-769.
- Kim RH, Smith PD, Aleyasin H, Hayley S, Mount MP, Pownall S, Wakeham A, You-Ten AJ, Kalia SK, Horne P, Westaway D, Lozano AM, Anisman H, Park DS, Mak TW (2005) Hypersensitivity of DJ-1-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and oxidative stress. *Proc Natl Acad Sci U S A* 102:5215-5220.
- Kim SJ, Park YJ, Hwang IY, Youdim MB, Park KS, Oh YJ (2012) Nuclear translocation of DJ-1 during oxidative stress-induced neuronal cell death. *Free Radic Biol Med* 53:936-950.
- Kimura Y, Kimura H (2004) Hydrogen sulfide protects neurons from oxidative stress. *FASEB J* 18:1165-1167.
- Ko L, Mehta ND, Farrer M, Easson C, Hussey J, Yen S, Hardy J, Yen SH (2000) Sensitization of neuronal cells to oxidative stress with mutated human alpha-synuclein. *J Neurochem* 75:2546-2554.
- Kostrzewa RM, Nowak P, Kostrzewa JP, Kostrzewa RA, Brus R (2005) Peculiarities of L-DOPA treatment of Parkinson's disease. *Amino Acids* 28:157-164.
- Kowalska M, Piekut T, Predecki M, Sodel A, Kozubski W, Dorszewska J (2020) Mitochondrial and nuclear DNA oxidative damage in physiological and pathological aging. *DNA Cell Biol* 39:1410-1420.
- Krüger R., Kuhn W, Müller T, Voitalla D, Graeber M, Kösel S, Przuntek H, Epplen JT, Schöls L, Riessi O (1998) Ala30P mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat Genet* 18:106-108.
- Kuhn DM, Arthur Jr RE, Thomas DM, Elferink LA (1999) Tyrosine hydroxylase is inactivated by catechol-quinones and converted to a redox-cycling quinoprotein: possible relevance to Parkinson's disease. *J Neurochem* 73:1309-1317.
- Kuhn W, Roebroek R, Blom H, van Oppenraaij D, Przuntek H, Kretschmer A, Büttner T, Voitalla D, Müller T (1998) Elevated plasma levels of homocysteine in Parkinson's disease. *Eur Neurol* 40:225-227.
- Kuusimäki T, Korpela J, Pekkonen E, Martikainen M, Antonini A, Kaasinen V (2019) Deep brain stimulation for monogenic Parkinson's disease: a systematic review. *J Neurol* 267:883-897.
- Lavoie MJ, Hastings TG (1999) Dopamine quinone formation and protein modification associated with the striatal neurotoxicity of methamphetamine: evidence against a role for extracellular dopamine. *J Neurosci* 19:1484-1491.
- Lesage S, Ibanez P, Lohmann E, Pollak P, Tison F, Tazir M, Leutenegger AL, Guimaraes J, Bonnet AM, Agid Y, Dürr A, Brice A; French Parkinson's Disease Genetics Study Group (2005) G2019S LRRK2 mutation in French and North African families with Parkinson's disease. *Ann Neurol* 58:784-787.
- Lotharius J, Brundin P (2002) Pathogenesis of Parkinson's disease: dopamine, vesicles and alpha synuclein. *Nat Rev Neurosci* 3:932-942.
- Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, Matthews K, McIntyre CC, Schlaepfer TE, Schulder M, Temel Y, Volkman J, Krauss JK (2019) Deep brain stimulation: current challenges and future directions. *Nat Rev Neurol* 15:148-160.
- Lozano C, Tam J, Lozano A (2017) The changing landscape of surgery for Parkinson's Disease. *Mov Disord* 33:36-47.
- Lücking CB, Dürr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denèfle P, Wood NW, Agid Y, Brice A; French Parkinson's Disease Genetics Study Group, European Consortium on Genetic Susceptibility in Parkinson's Disease (2000) Association between early-onset Parkinson's disease and mutations in the Parkin gene. *N Engl J Med* 342:1560-1567.
- Lynch-Day MA, Mao K, Wang K, Zhao M, Klionsky DJ (2012) The role of autophagy in Parkinson's disease. *Cold Spring Harb Perspect Med* 2:a009357.
- Mancini A, Mazzocchetti P, Sciacaluga M, Megaro G, Bellingacci L, Beccano-Kelly DA, Di Filippo M, Tozzi A, Calabresi P (2020) From synaptic dysfunction to neuroprotective strategies in genetic Parkinson's disease: lessons from LRRK2. *Front Cell Neurosci* 14:158.
- Misgeld T, Schwarz TL (2017) Mitostasis in neurons: maintaining mitochondria in an extended cellular architecture. *Neuron* 96:651-666.

- Muñoz P, Huenchuguala S, Paris I, Segura-Aguilar J (2012) Dopamine oxidation and autophagy. *Parkinsons Dis* 2012:920953.
- Muthuraman M, Deuschl G, Koirala N, Riedel C, Volkmann J, Groppa S (2017) Effects of DBS in Parkinsonian patients depend on the structural integrity of frontal cortex. *Sci Rep* 7:43571.
- Narendra D, Tanaka A, Suen DF, Youle RJ (2008) Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J Cell Biol* 183:795-803.
- Nekrasov PV, Vorobyov VV (2018) Dopaminergic mediation in the brain aging and neurodegenerative diseases: a role of senescent cells. *Neural Regen Res* 13:649-650.
- Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, Hunt AL, Klein C, Henick B, Hailpern SM, Lipton RB, Soto-Valencia J, Risch N, Bressman SB (2006) LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med* 354:424-425.
- Palacios JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, Klose J, Shen J (2004) Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J Biol Chem* 279:18614-18622.
- Pasanen P, Myllykangas L, Siitonen M, Raunio A, Kaakkola S, Lyytinen J, Tienari PJ, Pöyhönen M, Paetau A (2014) Novel α -synuclein mutation A53E associated with atypical multiple system atrophy and Parkinson's disease-type pathology. *Neurobiol Aging* 35:2180.e1-5.
- Pattison DI, Dean RT, Davies MJ (2002) Oxidation of DNA, proteins and lipids by DOPA, protein-bound DOPA, and related catechol(amine)s. *Toxicology* 177:23-37.
- Piccoli G, Onofri F, Cirnaru M, Kaiser C, Jagtap P, Kastenmuller A, Pischedda F, Marte A, von Zweydford F, Vogt A, Giesert F, Pan L, Antonucci F, Kiel C, Zhang M, Weinkauff S, Sattler M, Sala C, Matteoli M, Ueffing M, Gloeckner CJ (2014) Leucine-rich repeat kinase 2 binds to neuronal vesicles through protein interactions mediated by its c-terminal WD40 domain. *Mol Cell Biol* 34:2147-2161.
- Pridgeon JW, Olzmann JA, Chin LS, Li L (2007) PINK1 Protects against oxidative stress by phosphorylating mitochondrial chaperone TRAP1. *PLoS Biol* 5:e172.
- Puspita L, Chung SY, Shim JW (2017) Oxidative stress and cellular pathologies in Parkinson's disease. *Mol Brain* 10:53.
- Rakovic A, Shurkewitsch K, Seibler P, Grünewald A, Zanon A, Hagenah J, Krainc D, Klein C (2013) Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1)-dependent ubiquitination of endogenous Parkin attenuates mitophagy: study in human primary fibroblasts and induced pluripotent stem cell-derived neurons. *J Biol Chem* 288:2223-2237.
- Repici M, Giorgini F (2019) DJ-1 in Parkinson's disease: clinical insights and therapeutic perspectives. *J Clin Med* 8:1377.
- Rutherford NJ, Moore BD, Golde TE, Giasson BI (2014) Divergent effects of the H50Q and G51D SNCA mutations on the aggregation of α -synuclein. *J Neurochem* 131:859-867.
- Rutherford NJ, Giasson BI (2015) The A53E α -synuclein pathological mutation demonstrates reduced aggregation propensity in vitro and in cell culture. *Neurosci Lett* 597:43-48.
- Saito Y (2017) DJ-1 as a biomarker of Parkinson's disease. *Adv Exp Med Biol* 1037:149-171.
- Schapira AH (2006) The importance of LRRK2 mutations in Parkinson disease. *Arch Neurol* 63:1225-1228.
- Schiesling C, Kieper N, Seidel K, Krüger R (2008) Familial Parkinson's disease – genetics, clinical phenotype and neuropathology in relation to the common sporadic form of the disease. *Neuropathol Appl Neurobiol* 34:255-271.
- Schöndorf D, Aureli M, McAllister F, Hindley C, Mayer F, Schmid B, Sardi S, Valsecchi M, Hoffmann S, Schwarz L, Hedrich I, Berg D, Shihabuddin LS, Hu J, Pruszkak J, Gygi SP, Sonnino S, Gasser T, Deleidi M (2014) iPSC-derived neurons from GBA1-associated Parkinson's disease patients show autophagic defects and impaired calcium homeostasis. *Nat Commun* 5:4028.
- Scudamore O, Ciossek T (2018) Increased oxidative stress exacerbates α -synuclein aggregation in vivo. *J Neuropathol Exp Neurol* 77:443-453.
- Segura-Aguilar J, Paris I, Muñoz P, Ferrari E, Zecca L, Zucca FA (2014) Protective and toxic roles of dopamine in Parkinson's disease. *J Neurochem* 129:898-915.
- Shamoto-Nagai M, Maruyama W, Kato Y, Isobe KI, Tanaka M, Naoi M, Osawa T (2003) An inhibitor of mitochondrial complex I, rotenone, inactivates proteasome by oxidative modification and induces aggregation of oxidized proteins in SH-SY5Y cells. *J Neurosci Res* 74:589-597.
- Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, Mizuno Y, Kosik KS, Selkoe DJ (2001) Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. *Science* 293:263-269.
- Sison SL, Vermilyea SC, Emborg ME, Ebert AD (2018) Using patient-derived induced pluripotent stem cells to identify Parkinson's disease-relevant phenotypes. *Curr Neurol Neurosci Rep* 18:84.
- Song J, Shen B, Yang YJ, Liu FT, Zhao J, Tang YL, Chen C, Ding ZT, An Y, Wu JJ, Sun YM, Wang J (2020) Non-motor symptoms in Parkinson's disease patients with Parkin mutations: more depression and less executive dysfunction. *J Mol Neurosci* 70:246-253.
- Stansley BJ, Yamamoto BK (2013) L-Dopa-induced dopamine synthesis and oxidative stress in serotonergic cells. *Neuropharmacology* 67:243-251.
- Subramaniam SR, Chesselet MF (2013) Mitochondrial dysfunction and oxidative stress in Parkinson's disease. *Prog Neurobiol* 106-107:17-32.
- Sulzer D, Zecca L (1999) Intraneuronal dopamine-quinone synthesis: a review. *Neurotox Res* 1:181-195.
- Tang B, Xiong H, Sun P, Zhang Y, Wang D, Hu Z, Zhu Z, Ma H, Pan Q, Xia JH, Xia K, Zhang Z (2006) Association of PINK1 and DJ-1 confers digenic inheritance of early-onset Parkinson's disease. *Hum Mol Genet* 15:1816-1825.
- Tarakad A, Jankovic J (2017) Diagnosis and management of Parkinson's disease. *Semin Neurol* 37:118-126.
- Tawfik V, Chang S, Hitti F, Roberts D, Leiter J, Jovanovic S, Lee K (2010) Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. *Neurosurgery* 67:367-375.
- Teravskis PJ, Covelo A, Miller EC, Singh B, Martell-Martinez HA, Benneyworth MA, Gallardo C, Oxnard BR, Araque A, Lee MK, Liao D (2018) A53T Mutant alpha-synuclein induces tau-dependent postsynaptic impairment independently of neurodegenerative changes. *J Neurosci* 38:9754-9767.
- Thanvi BR, Lo TCN (2004) Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad Med J* 80:452-458.
- Thomas KJ, McCoy MK, Blackinton J, Beilina A, van der Brug M, Sandebring A, Miller D, Maric D, Cedazo-Minguez A, Cookson MR (2011) DJ-1 Acts in parallel to the PINK1/parkin pathway to control mitochondrial function and autophagy. *Hum Mol Genet* 20:40-50.
- van der Merwe C, Jalali SD, Christoffels A, Loos B, Bardien S (2015) Evidence for a common biological pathway linking three Parkinson's disease-causing genes: parkin, PINK1 and DJ-1. *Eur J Neurosci* 41:1113-1125.
- van Laar VS, Arnold B, Cassady SJ, Chu CT, Burton EA, Berman SB (2011) Bioenergetics of neurons inhibit the translocation response of Parkin following rapid mitochondrial depolarization. *Hum Mol Genet* 20:927-940.
- van Laar VS, Mishizen AJ, Cascio M, Hastings TG (2009) Proteomic identification of dopamine-conjugated proteins from isolated rat brain mitochondria and SH-SY5Y cells. *Neurobiol Dis* 34:487-500.
- Verma M, Callio J, Otero P, Sekler I, Wills Z, Chu C (2017) Mitochondrial calcium dysregulation contributes to dendrite degeneration mediated by PD/LBD-associated LRRK2 mutants. *J Neurosci* 37:11151-11165.
- Wang X, Yan MH, Fujioka H, Liu J, Wilson-Delfosse A, Chen SG, Perry G, Casadesu G, Zhu X (2012) LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. *Hum Mol Genet* 21:1931-1944.
- Waragai M, Wei J, Fujita M, Nakai M, Ho GJ, Masliah E, Akatsu H, Yamada T, Hashimoto M (2006) Increased level of DJ-1 in the cerebrospinal fluids of sporadic Parkinson's disease. *Biochem Biophys Res Commun* 345:967-972.
- Weaver F, Follett K, Stern M, Hur K, Harris C, Marks Jr W, Rothlind J, Sagher O, Reda D, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein J, Stoner G, Heemskerck J, Huang GD; CSP 468 Study Group (2009) Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 301:63-73.
- Weindel CG, Bell SL, Vail KJ, West KO, Patrick KL, Watson RO (2020) LRRK2 maintains mitochondrial homeostasis and regulates innate immune responses to Mycobacterium tuberculosis. *Elife* 9:e51071.
- Weinreb O, Mandel S, Youdim MBH, Amit T (2013) Targeting dysregulation of brain iron homeostasis in Parkinson's disease by iron chelators. *Free Radic Biol Med* 62:52-64.
- Yan MH, Wang X, Zhu X (2013) Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic Biol Med* 62:90-101.
- Yin WL, Yin WG, Huang BS, Wu LX (2017) Neuroprotective effects of lentivirus-mediated cystathionine-beta-synthase overexpression against 6 OHDA-induced parkinson's disease rats. *Neurosci Lett* 657:45-52.
- Younce J, Campbell M, Perlmutter J, Norris S (2019) Thalamic and ventricular volumes predict motor response to deep brain stimulation for Parkinson's disease. *Parkinsonism Relat Disord* 61:64-69.
- Zarranz JJ, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atarés B, Llorens V, Gomez Tortosa E, del Ser T, Muñoz DG, de Yebenes JG (2004) The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann Neurol* 55:164-173.
- Zhou W, Freed CR (2005) DJ-1 up-regulates glutathione synthesis during oxidative stress and inhibits A53T alpha-synuclein toxicity. *J Biol Chem* 280:43150-43158.
- Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Müller-Miyhok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T (2004) Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* 44:601-607.
- Zucca FA, Segura-Aguilar J, Ferrari E, Muñoz P, Paris I, Sulzer D, Sarna T, Casella C, Zecca L (2017) Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. *Prog Neurobiol* 155:96-119.

C-Editors: Zhao M, Song LP; T-Editor: Jia Y