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# Genetic causes of Parkinson's disease

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**ABSTRACT** • Parkinson's disease is one of the most common neurodegenerative disorders. The disease presents with resting tremor, rigidity, bradykinesia, and a stooping posture. The pathognomonic significance of the disease is the development of neuronal Lewy bodies, which results in the accumulation of alpha-synuclein, leading to degeneration of dopaminergic neurons in the substantia nigra. Parkinson's disease is correlated with risk factors including aging, family history, and exposure to environmental chemicals. The cause of these sporadic cases remains unclear. Recent genetic studies show that there are several forms of Parkinson's disease, and some of the genetic components increase the risk of developing the disease. It is crucial to know the genetic factors as well as how the dysfunction occurs and affects the cellular pathways in Parkinson's disease. Therefore, we focused the pathogenesis and genetics of the disease, the latter of which is thought to play an important part in Parkinson's disease.

## INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disease after Alzheimer's disease, and its prevalence is expected to increase in the coming years (1). It was first defined as "shaking palsy" by James Parkinson in 1817 (2). In the modern era, Jean-Martin Charcot identified and named the disease as "Parkinson's" (3).

One of the first symptoms in early PD is a reduced sense of smell. Other clinical symptoms include resting tremor, muscular rigidity, bradykinesia, and postural instability (4). Hypophonia, drooling of saliva (from reduced swallowing), and impairment of postural reflexes may develop in the late stages. Lewy bodies, in addition to ubiquitin, contain the filamentous forms of the synaptic protein alpha-synuclein (5). Accumulation of ubiquitin is responsible for defects in trafficking and disposal pathways in cells, although ubiquitin monomers or polyubiquitin chains are necessary for the proper intracellular trafficking and disposal of many proteins (6).

Almost 100 years ago, Gowers and Leroux reported that 15% of their PD patients had an affected family member, and the importance of genetic factors in PD etiology has been debated ever since. The majority of other studies have stated evidence

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in genetic relations by comparing the familial aggregation in first- and/or second-degree relatives of PD patients with that observed in the general population (7). The risk of PD was between 3 and 14 times higher in first-degree relatives of an affected individual than in members of unaffected families (8). Between 5% and 10% of cases in the past 20 years have been attributed to familial genetic mutations (9). Although PD is usually a sporadic disease, there are single gene mutations that have been discovered to have a role in PD, such as alpha-synuclein (SNCA), ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PARK2), leucine-rich repeat kinase 2 gene (LRRK 2), PTEN-induced putative kinase 1 (PINK 1), and DJ-1, and more genetic mutations related to PD continue to be sought (Table 1).

Recent reports focused on environmental and metabolic factors of the disease. However, increases in prevalence were correlated with the increase in life expectancy, and the improvement of genetic studies points out the importance of genetics in the pathology of PD. Therefore, this review focuses on the genetic factors of PD.

## Pathogenesis of PD

The pathogenesis of PD depends on many genetic mechanisms. Dysfunction of some biological pathways leads to progressive loss of nerves in the striatum and death of neurons in the midbrain. It is known that there are some connections between neuronal loss and damage to related cellular pathways. Some of the components of implicated mechanisms are endosomal trafficking, lysosomal autophagy, and energy metabolism or mitophagy.

## Synaptic Transmission

Alpha-synuclein is a protein that takes part in synaptic release and is found in presynaptic terminals of neurons (10). Its monomeric forms are thought to activate exo- and endocytosis of the synaptic vesicle by assisting endophilin-A1- linked mem-

**Table 1** Genes related to Parkinson's disease and their cellular functions.

| Gene | Chromosome | Protein | Inheritance | Potent Physiologic Functions of Protein | References |
|---|---|---|---|---|---|
| Park2 | 6q25–q27 | Parkin | AR | Ubiquitin ligase, regulator of mitophagy | 7, 31, 49 |
| Dj-1 | 1p36.23 | DJ-1 | AR | Redox-dependent molecular chaperone in mitochondria | 7, 49–51 |
| Pink1 | 1p36.12 | PINK1 | AR | Kinase, phosphorylates parkin, and ubiquitin to regulate mitophagy | 49,51 |
| Lrrk2 | 12q12 | LRRK2 | AD | Kinase, GTPase | 49, 52 |
| Snca | 4q21–q23 | α-Synuclein | AD | Potential SNARE-complex assembly chaperone | 51, 53 |
| Vps35 | 16q11.2 | VPS35 | AD | Retromer subunit | 19 |
| Synj1 | 21q22.11 | Synaptojanin-1 | AR | Phosphoinositide phosphatase | 54 |
| Eif4g1 | 3q27.1 | EIF4G1 | AD | Translation initiation factor involved in mitochondrial activity | 55 |
| Atp13a2 | 1p36.13 | ATPase 13A2 | AR | ATPase cation transporter | 25 |
| Rab39b | Xq28 | RAB39B | X | Rab GTPase | 56 |
| Uch-l1 | 4p14 | UCH-L1 | AD | Synaptic vesicle recycling | 57 |
| Gba | 1q21 | GBA | AR | Glucocerebrosidase | 58 |
| Mapt | 17q21 | MAPT | Multifactorial | Provides instructions for making tau protein | 59 |

AD: Autosomal dominant. AR: Autosomal recessive.

brane curvature (11). Alpha synuclein is a good demonstrative example of how point mutations of each monomer's amino terminals cause the same functional deficits (12). Previous studies revealed that when alpha-synuclein is expressed in high amounts, the conformation of alpha-synuclein is critical in interactions with mitochondria and vesiculotubular or endosomal structure in presynaptic terminals (13,14).

LRRK2 levels have a role in regulation of glutamate transmission and cellular plasticity, which depends on dopamine and synaptic signal transduction in the striatum (10). LRRK2 levels and mutant-specific phenotypes have previously been observed in neuritic growth and neurogenesis in some living organsims. In Drosophila, it is reported that LRRK2 kinase regulates phosphorylation, and pathogenic mutations interfere with synaptic endocytosis (15). It is also stated to be important through its interaction with GTPases, which are a dynamin superfamily that mediates membrane division in clathrin-dependent endocytosis and mitochondrial conjunction (16). In *Caenorhabditis*, impaired LRRK-1 (single homolog of mammalian LRRK1 and LRRK2) causes improper presynaptic protein sorting and axonal trafficking (17). LRRK2 also has critical roles in innate immunity and in non-neuronal cells, including kidney cells (18).

### Endosomal Trafficking

Endosomal trafficking has a complicated and dynamic mechanism. Vesicles and cargo are recycled and transmitted for degradation by lysosomal autophagy. Late-onset Lewy body parkinsonism has lately been reported to have a correlation with mutations in vacuolar protein sorting 35 (VPS35) and RME-8, which is implicated in interference with endosomal trafficking (19). Neurons' tendency to recycle membrane receptors can be overcome through the clathrin-independent retromer complex, a tubular three-part complex of vacuolar protein sorting 26 (VPS26), vacuolar protein sorting 29 (VPS29), and VPS35 that relies on sorting nexins to direct specific cargo to its destination, such as neurotransmitter receptors. FAM21 is a subunit of the Wiscott-Aldrich syndrome protein (WASH) complex around which VPS35 subunits gather to provide actin remodeling (20). To influence WASH and cargo trafficking, RME-8 binds, sorting nexins and FAM21.

### Lysosomal Autophagy

Lysosomal deficits are one of the most important components of the pathogenesis of PD in terms of the lysosome's critical function in preserving protein and organelle integrity. Alpha-synuclein degradation deficits in proteosomal and lysosomal systems lead to aggregation in the form of Lewy body inclusions, which are a pathological hallmark of PD. It is still unknown whether aggregation of intracellular proteins, which is observed in late-onset neurodegenerative diseases, is a cause or result of impairment in these pathways (21). In some ceroid lipofuscinoses diseases, such as Gaucher's and Niemann-Pick type C, there are also intracellular protein aggregates such as alpha-synuclein or tau inclusions.

When Glucocerebroside loses its activity, whether intracellular glucosylceradation and subsequent accumulation of alpha-synuclein obstructs the traffic from the endoplasmic reticulum and Golgi to lysosomes or whether it comes directly from impaired lysosomal function is not known (22). According to previous studies in genetically engineered mice, Glucocerebroside mutations aggravate alpha-synuclein accumulation, in a time dependent manner, leading animals to develop Lewy-like pathology in the brain in association with motor and cognitive symptoms. On the contrary, loss of Glucocerebroside activity results in neuronal ubiquitinopathy and formation of axonal spheroids, a phenotype that is also seen in other lysosomal storage disorders as a result of excess alpha-synuclein density (23).

Mutations in lysosomal proteins directly lead to some forms of typical parkinsonism at an early age, such as X-linked Parkinsonism, which begins to be seen at the age of 14–50. This pathology has a correlation with post-mortem tau inclusions and comes from splicing or protein isoform defects in ATP6AP2 (24). Recessively inherited pathogenic mutations in ATP12A2 also cause lysosomal proteolysis and lead to a syndrome named Kufor-Rakeb (25). According to previous studies, patients and mice develop ceroid lipofuscin neuronal pathology and accompanying upregulation of alpha-synuclein in the mouse hippocampus (26). Many genes are thought to be associated with degeneration in neurons and iron accumulation in brain, such as ATP13A2, PLA2G6, PANK2, FA2H, WDR45, FTL, CP, and DCAF17 (9).

### Mitochondrial Metabolism

It is clearly known that PD and mitochondrial dysfunction have a close relation, which is observed most often in drug users. One of the factors in PD prior to mitochondrial dysfunction is toxic MTPM, which is a non-competitive complex inhibitor of the electron transport chain. It occurs when MPTP becomes oxidized after being transported into dopamine by transporters which are specific to dopamine (27). However, evidence from direct sequencing studies of the normal brain has proven equivocally that deficits of the mitochondrial complex can be noted in idiopathic PD (28). Mitochondrial mutations in our genes lead to several neuromuscular disorders (29). Even though most of them do not have an association with PD, similar movement disorders can be caused by some mutations in a mitochondrial proofreading enzyme named polymerase gamma (POLG) whether they are accompanied with chronic progressive ophthalmoplegia or not. Previous studies have shown that deficits in POLG leads to premature aging in mice. Decreased activity in striatal dopaminergic terminals and motor function imperfections have also been observed (30).

Defined mutations in several genes within a common pathway for mitophagy show us the importance of mitochondria in PD (Table 1). One of the mutations concerning mitochondrial autophagy is in the gene PARK2, which encodes parkin protein, and leads to a recessive early-onset PD (31). Parkin protein was firstly known as proteosomal E3 ubiquitousquitin ligase, responsible for K48 substrate polyubiquination and K63 monoubiquination (32). Parkin may also have several functions in neurons, such as the regulation of neuronal apoptosis, and in Eps15 monoubiquination (33) it acts like a SCF complex (34). Regulating the reduction of depolarized or uncoupled mitochondria in coordination with PINK1 and FBXO7, which are also genes accused of playing a role in development of early recessive form of PD, is the most important role of Parkin (35,36). In demonstrated models of Drosophila, Parkin and PINK1 deficiencies have been seen in similar mitochondrial and wing phenotypes; additionally, the importance of PINK1 has been revealed through the experiments for being necessary for the functionality of Parkin in mitochondria (37,38). Parkin's crystal configuration was solved recently, and it has been reported that PINK1 has a mission in the phosphorylation of ubiquitin, which has a critical role in parkin's activation (39,40). Although they have limited overlap, two recent RNA interference experiments clarified the upstream regulators of mitophagy (41,42). STOML2, GRP75, HSP60, LRPPRC, and TUFM have been suggested as downstream targets of the PINK1/parkin pathway (43,44). PINK1-dependent Parkin translocation to depolarized mitochondria may also regulate DJ-1 mutations, which leads to early-onset Parkinsonism (31,45). Deficits in DJ-1 lead to impaired mitochondrial function and cause the production of a large amount of reactive oxygen species (ROS) (45). Accordingly, deficits of Parkin, PINK1, or DJ-1 in mice cause mitochondrial malfunction but do not lead to the progression of locomotor phenotype of PD, death of nigral neurons,

or Lewy body pathology, but they have increased dopaminergic tone due to deficits in D2 presynaptic regulation of release (46,47).

It is know that, mitochondrial activity is the main point of disease pathogenesis and development. For example, mitochondrial activity may be impaired by alpha-synuclein overexpression. It has also been reported that progressive mitochondrial DNA breakdown and degradation lead to neuronal functional loss and death (48).

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