

REVIEW ARTICLE

Long-Term Outcomes of Genetic Parkinson's Disease

Jan O. Aasly^{1,2}

¹Department of Neurology, St. Olav's Hospital, Trondheim, Norway

²Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 1–2% of people by the age of 70 years. Age is the most important risk factor, and most cases are sporadic without any known environmental or genetic causes. Since the late 1990s, mutations in the genes *SNCA*, *PRKN*, *LRRK2*, *PINK1*, *DJ-1*, *VPS35*, and *GBA* have been shown to be important risk factors for PD. In addition, common variants with small effect sizes are now recognized to modulate the risk for PD. Most studies in genetic PD have focused on finding new genes, but few have studied the long-term outcome of patients with the specific genetic PD forms. Patients with known genetic PD have now been followed for more than 20 years, and we see that they may have distinct and different prognoses. New therapeutic possibilities are emerging based on the genetic cause underlying the disease. Future medication may be based on the pathophysiology individualized to the patient's genetic background. The challenge is to find the biological consequences of different genetic variants. In this review, the clinical patterns and long-term prognoses of the most common genetic PD variants are presented.

Key Words Parkinson's disease; Genes; Long term progression.

The majority of cases of Parkinson's disease (PD) occur in a sporadic manner, although a small percentage of cases are inherited, with causative mutations identified. The first PD gene locus was reported in 1996. This was found among members of a large Greek-Italian family where the disease was followed an autosomal-dominant trait. The mutation was located in the *SNCA* gene, coding for α -synuclein, and this protein was later shown to constitute a major part of Lewy bodies (LBs), the pathological hallmark of Parkinson's disease.^{1,2} A few years later, the first autosomal-recessive gene was found, *PRKN*, the most common gene for early-onset parkinsonism, followed by the identification of mutations in *PINK1* and *DJ-1* as autosomal-recessive causes of PD.^{3–5} Mutations in the *LRRK2* gene were identified in 2004, which today are the most common cause of autosomal-dominant PD and the most common monogenic form of PD.^{6,7} In addition to the specific PD-causing genes, it was rec-

ognized in the 1990s that being a carrier of a heterozygous mutation in the *GBA* gene, known to cause Gaucher disease (GD), significantly increased the risk of developing PD.⁸ By the expansion of the test methods, the number of genetic variants has increased significantly, particularly after the introduction of genome-wide association studies (GWASs).⁹

As the number of cases and controls in large GWASs is expanding, more than 80 loci have been shown to influence the risk of developing PD. Most of these factors have only a minor impact on the risk for the disease. The most important genes are those associated with autosomal-dominant, AD, inheritance, including *LRRK2*, *SNCA*, *VPS35*, *GCH1*, *ATXN2*, *DNAJC13*, *TMEM230*, *GIGYF2*, *HTRA2*, *RIC3*, *EIF4G1*, *UCHL1*, *CHCHD2*, and *GBA*; and autosomal-recessive, AR, inheritance, including *PRKN*, *PINK1*, *DJ-1*, *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, *SYNJ1*, *SPG11*, *VPS13C*, *PODXL*, and *PTRHD1* (Table 1).¹⁰

Received: October 30, 2019 Revised: February 7, 2020 Accepted: March 23, 2020

Corresponding author: Jan O. Aasly, MD, PhD

Department of Neurology, St Olavs Hospital, Edvard Griegs gate 8, 7006 Trondheim, Norway / Tel: +47 7257 5071 / Fax: +47 7257 5774 / E-mail: Jan.Aasly@ntnu.no

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table 1. Most common types of genetic Parkinson's disease

| Synonym | Gene | α -syn pathology | Levodopa responsiveness | DBS effect | Survival |
|------------|-------------------------------|-------------------------|-------------------------|------------|----------------|
| PARK1 | <i>SNCA</i> | LBs | Good | + | Short |
| PARK2 | <i>parkin</i> (<i>PRKN</i>) | No LBs | Very good | ++ | Long |
| PARK6 | <i>PINK1</i> | LBs | Very good | ++ | Long |
| PARK7 | <i>DJ-1</i> | LBs | Very good | ++ | Long |
| PARK8 | <i>LRRK2</i> | LBs +/- | Very good | +++ | Average |
| PARK17 | <i>VPS35</i> | LBs | Very good | NA | NA |
| <i>GBA</i> | <i>GBA</i> | LBs | Good | + | Early dementia |

DBS effect: +, may be of benefit; ++, good response to DBS; +++, excellent response to DBS. DBS: deep brain stimulation, NA: not available, LB: Lewy body, α -syn: α -synuclein.

There are large clinical and neuropathological variabilities among the genes. Most *LRRK2* mutation carriers present with a phenotype similar to that of idiopathic PD. Depending on the *SNCA* mutations, the phenotype within that group ranges from early-onset typical PD to dementia with LBs. *DNAJC6* nonsense mutations lead to a very severe phenotype, whereas *DNAJC6* missense mutations cause a more typical form. Patients with mutations in *PRKN*, *PINK1* and *DJ-1* present with typical early-onset PD with slow progression, whereas patients with AR mutations in other genes present severe atypical Parkinsonism. Mutations in *RAB39B* are responsible for a typical phenotype in women and a variable phenotype in men. Phenotypic data collection and next-generation sequencing of large numbers of cases and controls are needed to differentiate pathogenic dominant mutations with incomplete penetrance from rare, non-pathogenic variants. The expanding number of genes or variants that may increase or decrease the risk of PD may explain only a minority of the cases, but they will add more knowledge to the understanding of pathological mechanisms and to finding new therapeutic strategies. It also challenges health-care professionals for better patient care and genetic counseling.¹¹

The genetic cases are not equally distributed. In some parts of the Middle East, an *LRRK2* mutation may cause 20–30% of the cases, and among some ethnic groups in Asia, a few *LRRK2* variants are major risk factors. The most frequent *GBA* mutation causing PD, N370S, is rather common in patients from Europe, America, and the Middle East, while it is rarely observed in Chinese or Japanese populations.^{12,13} Although the genetic causes of PD may vary between ethnic groups, the prevalence of PD seems to be more or less the same worldwide. The reason for this is still not fully understood.

The quality of life in PD patients was dramatically improved by the introduction of levodopa in the early 1970s. Before that time, PD patients had an almost three times higher mortality than the general population adjusted for age, sex, and race.¹⁴

After the introduction of levodopa, PD patients experienced remarkable symptomatic benefits until some or many of the patients developed drug-related fluctuations. After a disease duration of 10–15 years, the mortality rates almost reached the mortality rates seen before the introduction of levodopa, indicating that although levodopa improved life expectancy during the first 6–7 years of therapy, the protective effect subsequently declined.¹⁵ Only one-third of the people recruited in the Sydney Multicenter Study of Parkinson's Disease were still alive 15 to 18 years after disease onset. No patient was still employed, and 40% of patients lived in aged-care facilities.¹⁶ Therefore, the recognition of genetic causes truly emphasizes the opportunity for a better understanding of disease mechanisms and to develop new drugs.

This review will focus on the long-term prognosis of PD patients carrying a disease-causing mutation. Some of these mutations imply a phenotype with a good prognosis, while others may have a severe impact on the quality of life and life expectancies. A recent worldwide survey from more than 100 researchers from different centers in 43 countries reported 8,453 PD patients with mutations in PD genes.¹⁷ Almost two-thirds of these were *LRRK2* and *GBA* mutation carriers, and one-tenth were *PRKN* mutation carriers. The remaining 20–25% were rare single cases with no follow-up reports in the literature. Here, the long-term outcomes of patients with genetic PD will be reviewed for the most common genetic causes, as these are the absolute majority of patients with PD mutations reported today.¹⁷

METHODS

PubMed searches were performed using key words and strings, such as Parkinson's disease, parkinsonism, monogenic, genetic, survival, mortality, follow-up, and long term, in combination with each gene or variants known to cause PD in a small percentage of cases. The historical nomenclature starting with PARK and followed by a number has been kept for relevant mutations.

SNCA/PARK1

The mutations causing PARK1 PD are located on chromosome 4 in *SNCA*, which codes for the protein α -synuclein. α -Synuclein is abundant in the brain, and smaller amounts are found in the heart, muscles, and other tissues. The function of α -synuclein is not well understood. It is suggested that it plays an important role in maintaining an adequate supply of synaptic vesicles in presynaptic terminals, exocytosis, the regulation of neurite outgrowth, and nerve cell adhesion.

PARK1 was the first gene that could be related to familial PD. Families located in southern Italy demonstrated an autosomal-dominant trait of typical PD through many generations followed

back several centuries. The locus was found in 1996, and one year later, the mutation was shown to be in the α -synuclein gene at chromosome 4.¹⁸ Although this is a rare cause of PD, it is of great importance for understanding the pathology of the disease. It was soon shown that LBs, the hallmark of PD, contain large amounts of α -synuclein.^{1,19,20} The Contursi kindred could trace their ancestry back to a couple who had lived in the late 1600s. The members shared the same A53T mutation in SNCA, and they were all probably related through a common ancestor. Later, additional missense SCNA mutations were shown to cause PD, such as E46K, H50Q, G51D and A53E. In some other families, duplications and triplications of the α -synuclein gene have been found to be rare causes of hereditary PD or PD-like syndromes.²¹⁻²⁶ In homozygous duplication cases, the phenotypes are characterized by early-onset and rapidly progressive parkinsonism followed by dementia, which has been seen to be more aggressive in cases of SNCA triplication.²⁷

Long-term outcome of SNCA-related PD

Most patients with SNCA-related PD present with early and asymmetric onset, initial good response to dopaminergic therapy and early motor complications. A 20-year follow-up was performed among members of the Contursi family.²⁸ A relevant variability was observed in the combination and severity of motor symptoms and nonmotor features. Age at onset (AAO) varied from 26 to 48 years (mean, 32 years), with longer disease duration than previously reported. Cognitive deficits were present in all patients, ranging from frank dementia in those with longer disease duration to moderate cognitive impairment or slight isolated executive dysfunction in those with shorter disease duration. Depression and anxiety were detected in most patients, and behavioral disorders and dysautonomia were present in half of them. Olfaction was impaired in all tested patients. Hyposmia, constipation and REM sleep behavior disorder are all markers for this type of PD and are often referred to as synuclein markers. No mitochondrial defect was detected in extensive biochemical evaluations.²⁹

The "Iowa kindred," a large Iowan family with autosomal-dominant PD, has been followed clinically since the 1920s at the Mayo Clinic. In 2003, the genetic cause was determined to be a 1.7 Mb triplication of the α -synuclein genomic locus. Affected individuals presented with an early-onset, severe parkinsonism-dementia syndrome.^{30,31} Microsatellite variability within the genomic interval was identical to that previously described for a Swedish-American family with an α -synuclein triplication. Subsequent genealogical investigation suggested that both kindreds were ancestrally probably related to the Lister family complex.²⁶

Three family members of a Canadian kindred carrying a heterozygous A53E mutation in SNCA had moderate to severe bra-

dykinesia with rigidity, postural instability, freezing of gait, dyskinesia, and myoclonus, including spontaneous myoclonus. The AAO varied from 25 and 37 to 58 years, with postural myoclonus, focal reflex myoclonus after hand stimulation, and generalized reflex myoclonus. All three individuals developed dementia after a few years.³² Although cognitive dysfunction was not described for Finnish A53E carriers, it has been observed in some individuals with the A53T α -synuclein mutation.³³ There was no cognitive decline among the Finnish patients through the relatively short period of follow-up, which was for 5 years only.³³ They did not share the same allele, showing that these were two distinct families.

The effect of subthalamic nucleus deep brain stimulation (STN-DBS) in SNCA/PARK1 patients is probably comparable to what is reported in idiopathic PD patients, with no major adverse events, satisfactory improvement of motor function and a reduction of pharmacological treatment, although the total number of operated patients is low.³⁴

Summary

Although the penetration of disease may vary, SNCA/PARK1 patients usually have severe parkinsonism with rapid progression and the development of dementia. The patients with triplication have on average an earlier onset and a more progressive disease than the patients with duplication and those carrying a single mutation. On average, patients with amplifications of or point mutations in SNCA have a severe PD phenotype. At autopsy, these patients show abundant LB pathology.

PRKN/PARK2-related PD

The PRKN/PARK2 gene encodes the E3-ubiquitin ligase parkin. E3-ubiquitin ligases are involved in the proteasome pathway, which permits the degradation of damaged target proteins by ubiquitin adjunction, and parkin is also essential for maintaining mitochondrial homeostasis.³⁵ PRKN is the most common cause of autosomal-recessive PD and accounts for almost 50% of typical early-onset parkinsonism. Mutations are highly diverse, including missense mutations and nonsense mutations, frameshifts, and rearrangements with exon deletions or multiplications, but all of them lead to protein loss of function or the absence of protein by nonsense mRNA decay. Recently, the number of PRKN disease-causing mutations reached almost 140. This number will probably rise when all new cost-effective, technologically advanced sequencing techniques are implemented and more patients from different ethnic groups are tested. In a recent review of monogenic PD patients from multiple centers around the world, patients with mutations in PRKN made up approximately 80–85% of autosomal-recessive cases. In comparison, patients with PRKN mutations were half as common as

patients with either *LRRK2* or *GBA* mutations.¹⁷

The mean AAO of *PRKN*/*PARK2*-related PD is approximately 30 years, ranging from childhood to over 50 years in some rare cases. *PRKN* mutations are responsible for 77% of cases of juvenile PD, with an AAO before 21 years. Patients present with a typical PD phenotype with the clinical triad and a good response to levodopa. There are, however, differences between patients with *PRKN*/*PARK2*-related PD and those with sporadic PD. *PRKN* patients more often have lower-limb dystonia and more symmetrical symptoms at onset.³ Patients with *PRKN* mutations may present with hyperreflexia and early motor fluctuations.

Furthermore, there are no phenotypical differences between patients with *PRKN* missense mutations and those with disruptive mutations. Although mitophagy is regulated by *PINK1* and parkin proteins, it is quite paradoxical that no PD patients have a better prognosis than those with PD caused by *PRKN* or *PINK1* mutations. The disease progression is very slow, with a sustained response to levodopa. Abrupt and severe fluctuations are common, which makes medical treatment quite challenging. Only a very few patients have cognitive decline; the patients with *PRKN* mutations usually remain cognitively unaffected and do not show typical PD dementia.^{36,37} Additional features such as psychiatric manifestations are rare, and olfaction function is well preserved.³⁸ Dysautonomia and other atypical features are also rare. Heterozygous *PRKN* mutations may be a risk factor for PD, although with an age of onset at much higher age than in homozygous carriers.³⁹ Heterozygous *PRKN* and *PINK1* mutation carriers may show mild PD, being less progressive and responsive to L-dopa administration.⁴⁰

Long-term outcome of *PRKN*-related PD

Long-term survival of patients with *PRKN*-related PD is usually favorable. Although they have a low age at disease onset, most of them have a long disease duration without dementia.^{36,41} The good prognosis of patients with *PRKN* and *PINK1* mutations and parkinsonism has led to the creation of the term “nigropathy,” indicating less deterioration of cognitive function.³⁷ Patients with *PRKN* mutations usually respond well to levodopa therapy, but many patients experience rapid fluctuations with sudden changes in motor function. The freezing of gait, postural deformity, and motor fluctuations are common late features with severe dyskinesias, and sudden on-off episodes are common complications.⁴²

Four family members suffering from young-onset *PRKN*-related PD, located in the Middle East, were followed for 40 years.⁴¹ The patients all had beneficial responses to levodopa, slow progression of the disease, and diurnal fluctuations. They shared similar clinical features to other patients with *PRKN*-related PD, including AAO, symptoms at disease onset, beneficial response

to levodopa, and the occurrence of nonmotor symptoms. However, some features were regarded as unique to that kindred: all members had hypersensitivity to levodopa, responding dramatically to very low doses of levodopa, and they were treated with strikingly low doses of levodopa. The age of onset ranged from 18 to 39 years, which is a typical variation also seen in other families with *PRKN*-related PD. Lower-limb dystonia, often observed among patients with *PRKN*-related PD, was not observed in that family.

An Italian group performed a multicenter, case-control study to investigate the prevalence and severity of impulse-control disorders (ICDs) in a cohort of patients with *PRKN*-related PD. They compared their group of patients with PD patients without *PRKN* mutations, matched for demographic and clinical features. They collected 22 *PRKN*-related PD patients with a mean follow-up of 22 years.⁴³ Although the occurrence of ICDs did not correlate with the parkin genotype, parkin mutations influenced both the onset and the severity of specific behavioral disturbances in the impulsive-compulsive spectrum. In particular, ICDs were overall more severe in *PRKN* mutation carriers, who also disclosed a higher frequency and severity of compulsive shopping, binge eating, and punting. Regarding hypersexuality, patients with parkin-related PD reported a similar frequency but a more severe clinical expression. Moreover, ICDs tended to occur earlier in patients with the *PRKN* mutation, sometimes predating PD onset. Their results also suggested an association between the *PRKN* genotype, smoking status, and ICD severity.⁴³

Depression and anxiety may be common in early-onset PD. A multicenter study of *PRKN*-related PD patients sought to determine the relation between depression, as evaluated by two instruments, the Patient Health Questionnaire and the Beck Depression Inventory II, and genotype in a family-based sample of probands with early-onset PD, EOPD, and their relatives. They did not find any positive association of depression with genotype among EOPD probands, although they had a relatively high prevalence of depression, indicating depressed mood for at least some days to a week over the last two weeks.⁴⁴ DBS has become an important part of the therapeutic armamentarium in complicated PD cases. There are many short reports each describing the favorable effect of DBS on small groups of *PRKN*-related PD patients, and there are some case reports with similar conclusions.⁴⁵⁻⁴⁷ Rizzone et al.⁴⁸ recently published an excellent review of the outcome of DBS in patients with a genetic background of PD. The *PRKN*-related PD patients generally had a favorable outcome with DBS. As in other types of PD, the best results were observed in patients with a good response to levodopa, a younger age and no or few axial, non-levodopa-responsive motor symptoms. The sudden changes in motor func-

tions may still create extra challenges to *PRKN*-related PD patient treatment after DBS surgery.³⁶

The major difference between sporadic PD and *PRKN*-related PD is seen upon autopsy. Patients with *PRKN*-related PD present neuronal loss predominantly in the ventral substantia nigra, and so far, only a few of them have shown LBs. The selectivity of the lesions could explain the lack of cognitive decline. There is a disparity in the severity of nigral loss between patients with sparse LBs and those with no LBs in patients with *PRKN*-related PD, supporting the notion that abnormal α -synuclein deposition is not an integral component of the pathology of *PRKN*-related PD.^{36,49} In a relatively large series of patients with *PRKN*-related PD and a review of the literature, together with autopsy reports of 13 patients with *PRKN*-related PD, only 3 out of 13 had any LBs. Neuronal loss in the substantia nigra was observed in all 13 patients.⁴²

Summary

The disease progression in patients with *PRKN*-related PD is very slow, with a sustained response to levodopa. Abrupt and severe fluctuations are common, which makes medical treatment quite challenging. Patients with *PRKN*-related PD usually remain cognitively unaffected and do not show typical PD dementia.^{36,37} Additional features such as psychiatric manifestations are rare, and olfaction function is well preserved.³⁸ Dysautonomia and other atypical features are also rare. These individuals are probably more prone to develop ICDs. The selectivity of the lesions could explain the lack of cognitive decline. Furthermore, there are no phenotypical differences between patients with *PRKN* missense mutations and those with disruptive mutations.

PINK1/*PARK6*-related PD

PINK1 encodes PTEN-induced putative kinase 1. *PINK1* is the second most frequent gene involved in autosomal-recessive PD, and *PINK1*-related PD has a typical phenotype and early onset. *PINK1* is almost as frequent as *PRKN* in North Africa. The *PINK1*-related PD phenotype is similar to that of the *PRKN*-related PD phenotype, with a slightly later AAO, in the early thirties, a good response to levodopa and rare cognitive decline. However, some differences can be noted, with less spasticity, pyramidal signs or hyperreflexia than patients with *PRKN* mutations. To date, 60 mutations of different types (missense, nonsense, splicing, frameshift and deletions) have been reported. In contrast to patients with *PRKN*-related PD, patients with *PINK1*-related PD may show neuronal loss in the substantia nigra and the presence of LBs.

Kasten et al.⁵⁰ performed an extensive review of 139 *PINK1* mutation carriers from 85 families. In contrast to sporadic PD, the proportion of men in the group with *PINK1*-related PD was

less than that of women, 42%. The *PINK1*-related cases were distributed all over the world, and the majority of patients were of Caucasian ethnicity, followed by mixed/other and Asian ethnicity.⁵⁰ A majority of patients were from Italy (20%), probably because Italian scientists were the first to describe the mutation.⁴ There was a considerable proportion also from Iran (10%) and from Spain (8%).

The median AAO of all *PINK1* mutation carriers was 32 years, with the majority (62%) having an early, 22% a late, and 15% a juvenile PD AAO.⁵⁰ It was long debated whether heterozygous mutation carriers could be at risk for developing PD, although with a later onset.^{51,52} These early observations have not been reproduced, and reports from Tunisia, where *PINK1* mutations are very common, indicate that being a heterozygous mutation carrier does not increase the risk for PD.⁵³

The long list of disease-generating mutations is listed in the paper by Kasten, including a complete listing of the frequencies of signs and symptoms in patients with *PINK1*-related PD.⁵⁰ Eighty-three percent of all patients carried a homozygous mutation, and 17% of these were compound heterozygous mutations. They had all kinds of mutations, including missense mutations, the most frequent type, in 47.6%, followed by structural variants in 19.1% and nonsense mutations in 14%. The most frequent mutation of all was the missense mutation c.1040T>C, resulting in an amino acid change of leucine to proline at position 347. As with most other PD-related genes, the disease-causing potential of *PINK1* genes varies. Only one-fifth of the mutations are classified as definitely pathogenic; the rest are classified as probably or possible pathogenic.

Dyskinesia was reported in 39% of the patients, dystonia in one-fifth, and motor fluctuations in one-third of the patients. Levodopa-induced dyskinesias were very common. Cognitive decline and psychotic symptoms were reported in a small fraction of all patients with *PINK1*-related PD. The majority of patients with *PINK1*-related PD show excellent or very good response to levodopa therapy.

Long-term outcome of *PINK1*-related PD

There are many reports on *PINK1*-related PD in the literature, but there are very few long-term follow-up studies. Five affected *PINK1* homozygous and 14 heterozygous mutation carriers from two large Italian families were followed over a 12-year period.⁵⁴ Motor, nonmotor, cognitive, psychiatric, and behavioral profiles were systematically assessed. Four homozygotes and eight heterozygotes underwent magnetic resonance imaging. All homozygotes showed a mild progression of motor signs and a persistent excellent response to levodopa. All but one patient complained of nonmotor symptoms and sleep impairment. Three presented with ICDs and two with anxiety and apathy.

All obtained abnormal scores on the Montreal Cognitive Assessment (MoCA) and tests sensitive to frontal lobe functions; one presented global cognitive impairment. Three heterozygotes showed motor signs and were diagnosed as possibly affected. They had nonmotor symptoms and cognitive impairment, and two of them showed mild bilateral temporal atrophy.⁵⁴ This long-term follow-up did not confirm severe hyposmia or impaired color discrimination, as suggested by earlier studies.^{55,56}

These findings are somewhat in contrast to my own experiences with patients with *PINK1*-related PD. In my study of four patients with homozygous or compound heterozygous mutations, the AAO was between 28 and 44 years, with a mean age of 36 years. They have been repeatedly tested over a mean period of 15 years. Their phenotype has been quite identical to that of patients with classic PD. The presenting symptom was unilateral tremor with additional bradykinesia and rigidity. They have had good or excellent levodopa effects, and after some years, they have developed dyskinesias and fluctuations, comparable to what is regularly seen in individuals with classic PD. One of them had mild neuropsychiatric complaints, mainly anxiousness. They all tested normal on cognitive tests and remained cognitively unaffected many years after disease onset.

Several studies have shown that patients with *PINK1* mutations benefit from deep brain stimulation, either in the subthalamic nuclei or in the bilateral globus pallidus internus (GPi). In a study with 5 *PKRN*- and *PINK1*-related PD patients, the clinical response was similar to that observed in nonmutation carriers. These patients have slightly more advanced axial motor symptoms at a relatively early disease stage.^{46,57} This confirms my own experiences with good and maintained effects of STN-DBS and GPi DBS in patients with *PINK1*-related PD.

One of my patients with *PINK1*-related PD was autopsied at age 79 years. At the age of 76, her MoCA score was 30/30 after 32 years of illness duration. One year later, she was taken to the hospital after falls and infection. Her health gradually deteriorated, and she died in a nursing home two years later. At autopsy, there was typical neuronal loss in the substantia nigra with LBs in the brainstem and in the cerebral cortex. There were no amyloid deposits (to be published). This is in accordance with two other single cases of *PINK1*-related PD autopsies. The first case showed neuronal loss in the substantia nigra pars compacta, LBs and aberrant neurites in the reticular nuclei of the brainstem, substantia nigra pars compacta and Meynert nucleus, but the locus coeruleus and the amygdala were spared.⁵⁸ This was similar to what we observed in my patient. The second autopsy report was from an 85-year-old woman with more complex disease, testing positive for a homozygous *PINK1* mutation.⁵⁹ Her brain pathology was, in principle, not different from that of the abovementioned cases.

Summary

The *PINK1*-related PD phenotype is characterized by slow disease progression, and the response to levodopa is good. The sense of smell is less likely to be less affected than in sporadic PD.³¹ Psychiatric comorbidity and gait disturbance are common in *PINK1*-related PD compared to *PRKN*-related PD. This PD variant showed substantia nigra pars compacta neuronal loss, LBs and aberrant neuritis in the brainstem, with amygdala sparing. Although mitophagy is regulated by *PINK1* and parkin proteins, it is quite paradoxical that no PD patients have a better prognosis than those with PD caused by *PRKN* or *PINK1* mutations.

DJ-1/PARK7-related PD

Since the first published report of mutations in the oncogene DJ-1, few patients with DJ-1 mutations have been reported, but it still remains the third most frequent autosomal-recessive early-onset PD-related gene after *PRKN* and *PINK1*.^{50,60,61} The gene is localized to chromosome 1p36 and comprises seven coding exons encoding a DJ-1 protein of 189 amino acids. The DJ protein is expressed in both cerebral and extracerebral tissues and plays a role as a cellular sensor of oxidative stress.⁶² Twenty different disease-causing sequence variants have been reported in the DJ gene, and there are no ethnicity-specific differences.⁵⁰ The median AAO of all patients was 27 years (22–35 years), with the majority (83%) having an early AAO, 13% having a juvenile AAO, and 4% having a late AAO of PD.⁵⁰ To date, there has been a majority of male cases.⁵⁰ Studies from several parts of the world have demonstrated that this is a rare cause of PD.^{63–66} Among patients with early-onset PD, the prevalence of DJ-1 related PD varies between 0.4% and 1%.⁶³ Patients share the same phenotype as those with *PRKN*- or *PINK1*-related PD, but compared to them, more nonmotor signs, including depression, cognitive decline, psychosis and anxiety, have been reported in patients with DJ-1-related PD.⁶¹

Long-term outcome of DJ-1-related PD

Most patients with DJ-1-related PD respond to levodopa therapy, while others may be quite therapy resistant.⁶⁷ In a study from India in patients with early-onset autosomal-recessive PD, PARK2 mutations were most common, accounting for approximately 77% of familial and approximately 20% of EOPD patients in general. DJ-1 mutations were rare, accounting for 1–2% of sporadic cases of EOPD in India.⁶⁸

There have been only a very few reports on neuropathology in PARK7-related PD. They all indicate that this is an α -synucleinopathy associated with LBs.⁶⁷ Patients with DJ-1-related PD usually have more severe anosmia and peripheral synucleinopathy than patients with parkin- and *PINK1*-related

PD.^{50,69} To date, there have been few reports on DBS in *DJ-1*-related PD patients.^{48,70}

Summary

DJ-1-related PD is a very rare, early-onset, recessive form of PD. Its phenotype is similar to that seen in *PKRN*- and *PINK1*-related PD. Most patients respond well to levodopa. One report indicates good outcome from DBS treatment.⁴⁸

LRRK2/PARK8-related PD

The PARK8 locus was described by Funayama et al.⁷¹ in 2002 when analyzing a large Japanese multi-incident PD family. They localized the gene to chromosome 12p11.2-q13.1. Several other groups searched the same area, which led to the discovery of mutations in that locus in 2004.^{6,7} A large Norwegian family could be traced back to 1,580 (Figure 1).

The case of another large multi-incident family had been pub-

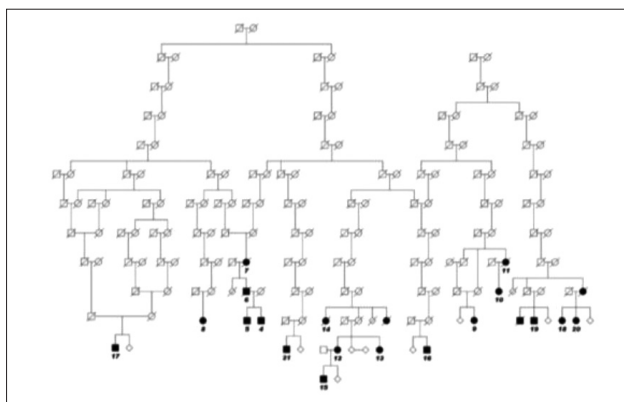


Figure 1. The initial pedigree, presenting six kindreds traced back to a common founder couple, born in approximately 1,580 on a small island off the coast of Central Norway. Later, five more families were identified, more or less intermarried with the others. Adapted from Johansen et al. Parkinsonism Relat Disord 2010;16: 527-530.⁹³ The affected cases are abridged to maintain confidentiality. Later, five more families were identified, and genealogical links to the other *LRRK2* families were found.

lished prior to the identification of the gene. These results showed that family members with identical genetic backgrounds may have typical PD genotypes with quite different pathoanatomical findings at autopsy.⁷² Several other mutations were later discovered, as was the most common, G2019S.^{73,74} The original Japanese family was later found to carry the I2020T mutation.⁷⁵

The *LRRK2* gene encodes a 286 kDa multidomain peptide whose actions include neurite outgrowth, cytoskeletal maintenance, vesicle trafficking, the regulation of autophagy, and immune functioning.⁷⁶ More than 100 *LRRK2* gene variants have been reported, most of which are “rare orphan changes,” and their significance is unknown.⁷⁷ At least eight *LRRK2* mutations are known to increase the risk of familial PD.⁷⁸ These mutations are in the gene’s 1) kinase, 2) Ras of complex protein (ROC)/GTPase, and 3) C-terminal of Ras (COR) domains (Figure 2).⁷⁹ A recent analysis concluded that G2019S, A419V, R1441C/G/H, N1437H, V1699C and I2020T are pathogenic mutations and that G2385R and R1628 are variants significantly associated with increased risk for PD, while the R1398H mutation was associated with a significantly decreased risk for PD.⁸⁰⁻⁸² The G2019S mutation, considered to be the most common PD-associated “pathogenic substitution” *LRRK2* mutation,⁸³ increases *LRRK2* protein kinase (phosphorylation) activity. The frequency of this mutation is highest among Ashkenazi Jews and in North African Arab-Berber populations. Several studies have shown that 15% of PD patients with Ashkenazic Jewish heritage carry this mutation.^{84,85} Estimates of the lifetime penetrance of this mutation have varied from 22% to 100%.^{73,86,87} A study co-authored by the International *LRRK2* Consortium found the risk of PD for G2019S mutation carriers to be 28% at age 59 years, 51% at 69 years, and 74% at 79 years.⁸⁶ The discrepancies between the different estimates of the penetrance of G2019S may be due in part to different populations being studied; the highest estimates were from multi-incident families, whereas lower penetrance was found in ethnically diverse PD populations not selected on the

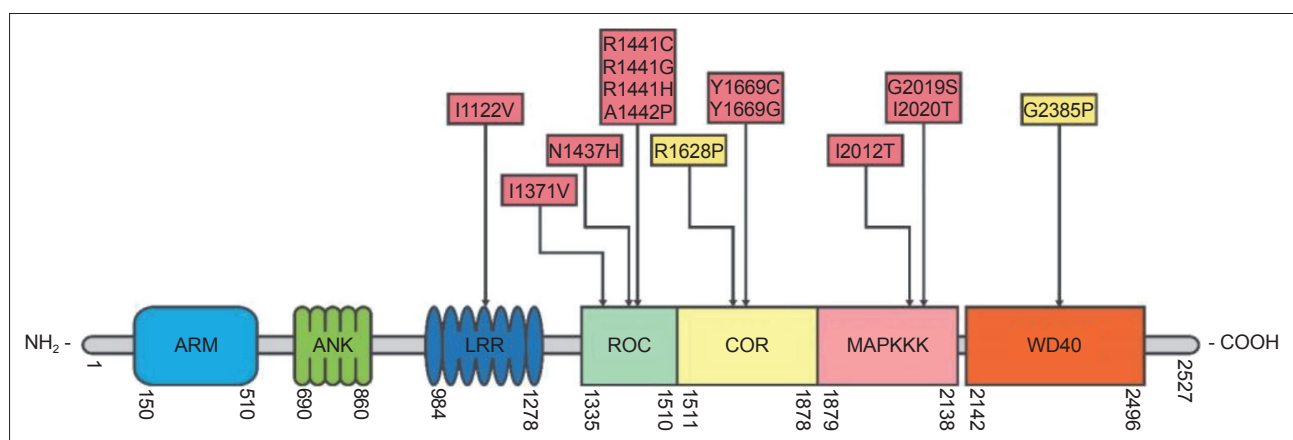


Figure 2. *LRRK2* mutations. Disease-generating mutations (red) and risk variants (yellow).

basis of familial history.⁸⁸ The G2385R and R1628P mutations are susceptibility (risk) variants, rather than penetrant variants, and are found in 3–4% of healthy individuals and 6–8% of PD patients in some Asian populations.^{81,89,90} Recent studies have shown that the G2385R mutation reduces LRRK2 kinase activity,^{91,92} destabilizes LRRK2 and promotes its proteasomal degradation.⁹² The N1437H, R1441C, R1441G, Y1699C, and I2020T mutations are less common mutations and are found in certain areas and ethnic groups.⁸⁶

Independent of mutations, genome-wide association study approaches have also identified LRRK2 as a common genetic risk factor for sporadic PD.⁹⁴ Large-scale genotyping and gene sequencing of LRRK2 have identified risk factors associated with PD. One example is LRRK2 p.G2385R as a risk factor in Asian populations.⁹⁵ There is also evidence of a haplotype in LRRK2 that is inversely associated with PD and other Parkinson-plus syndromes. LRRK2 parkinsonism has pleomorphic pathology.⁹⁶ The precise mechanism by which variations around the LRRK2 gene region contribute to disease risk is not fully determined. However, given that the polymorphisms associated with sporadic PD are in the promoter region of LRRK2, a reasonable hypothesis is that these variants do not change protein structure or function but instead alter the expression levels of the gene. A number of studies support this hypothesis, demonstrating increased LRRK2 protein in the brain⁹⁷ and blood^{79,98} and increased LRRK2 kinase activity in the brain⁹⁹ and urine^{100,101} in patients with sporadic PD compared with controls.

Several studies have shown that LRRK2 plays an important role in vesicular trafficking, impacting endosomal, lysosomal, and autophagosomal pathways.¹⁰² Importantly, numerous other PD-related genes, including SNCA and VPS35, also converge on these closed loop control pathways, suggesting that these substrates are interacting in the disease pathophysiology. The G2019S mutation may play a role in α -synuclein and/or tau pathology in LRRK2-related PD because α -synuclein in LBs is extensively phosphorylated, and phosphorylated tau colocalizes with α -synuclein in some LBs. Phosphorylation is thought to increase tau neurotoxicity, but the influence of phosphorylation on α -synuclein toxicity is unclear. Although some studies have suggested that LRRK2 may phosphorylate α -synuclein and/or tau,^{103–105} the only presently accepted theory is that the substrates for LRRK2 kinase are LRRK2 protein itself and some Rab GTPases such as Rab10.¹⁰⁵ The current view is that when expressed in the same cell, in disease, α -synuclein and LRRK2 likely interact in response to mitochondrial disruption, in autophagy pathways in the endolysosomal system, and in normal interactions with common protein partners such as 14-3-3 proteins that maintain the homeostasis of a number of systems.¹⁰⁵ Targeting LRRK2 as a therapeutic strategy is supported by re-

cently published studies that have demonstrated that genetically knocking out LRRK2¹⁰⁶ or chronic administration of an LRRK2 kinase inhibitor in rats¹⁰⁷ has been shown to protect against dopamine neuron loss induced by viral-mediated α -synuclein overexpression. This is of vital importance when planning future therapies for retarding disease progression. Preclinical studies have confirmed that the inhibition of LRRK2 may be protective against neuron loss.¹⁰⁸ This implies that antisense therapy could be aimed at either LRRK2 or α -synuclein expression both in PD and in multiple system atrophy.

Interestingly, the mean delay before treatment may be shorter in sporadic PD patients than in LRRK2 patients: 3 years vs. 4 years in LRRK2 patients. Studies in asymptomatic LRRK2 mutation carriers have shown that the premotor or preclinical period may last many years. Multi-incident families with autosomal LRRK2-related PD have, for the first time, made it possible to study the development of PD many years prior to phenoconversion. PET-scan studies with different amine isotopes in asymptomatic mutation carriers have shown that there are up-regulations in dopamine, serotonin and choline receptors in the asymptomatic period.^{109–111} Since only a few of these carriers convert to PD, it is still impossible to estimate the length of the mean premotor or prodromal phase in LRRK2-related PD.

Most patients with LRRK2-related PD show clinical features indistinguishable from those with classic sporadic PD. In the longitudinal The Parkinson's Progression Markers Initiative study, most patients with LRRK2-related PD had cardinal signs and symptoms that were not different from those with sporadic PD. Patients with LRRK2 G2019S mutations have slightly better smell performance than those with sporadic PD.^{112,113} This may reflect a lower burden of LBs and a better prognosis in the majority of cases.

Long-term outcome of LRRK2-related PD

To date, there have been only a few prospective studies on LRRK2-related PD. The largest study spanning 9 years was conducted in 3 centers where they followed patients of Jewish ethnicity with PD with LRRK2 G2019S mutations.¹¹⁴ The groups were rather identical, and the LRRK2-related PD group had a lower increase in Unified Parkinson's Disease Rating Scale (UPDRS) scores than the control group of patients with sporadic PD. The change in MoCA scores was lower in the LRRK2 group, but the difference did not reach statistical significance.¹¹⁴ These results were in accordance with the results from a multicenter cross-sectional survey performed more than 10 years ago.⁸⁶ These were later confirmed in small studies from different ethnic groups.^{115,116} One study also showed that carriers of the G2019S mutation converted to PD 10 years earlier in a population from the Middle East than in a population from Northern Europe.¹¹⁷

Genetic studies have indicated that this difference in phenoconversion may be based on genetic modifiers and not on environmental factors.¹¹⁸ There have been no studies on survival comparing patients with *LRRK2*-related PD to those with sporadic PD, and there are no systematic studies on progression among *LRRK2* gene mutations other than G2019S. There is one study among carriers of *LRRK2* variants. In a study among carriers of risk variants G2385R, R1628P, and S1647T and noncarriers, motor score progression was defined as the difference between UPDRS motor scores at baseline and at follow-up. A total of 184 patients, 122 risk variant carriers and 62 noncarriers, were evaluated and followed up for up to 6.5 years. The risk variant carriers experienced a greater rate of motor progression than noncarriers after 4 years from the date of diagnosis, suggesting that these risk variants may facilitate neurodegeneration with increasing disease duration.¹¹⁹

There have been a number of studies trying to find good biomarkers for PD progression by using preclinical patients with *LRRK2*-related PD and comparing these to patients with *LRRK2*-related PD, patients with sporadic PD and normal controls.

Analytes examined in these studies included A β 1-42, tau, α -synuclein, oxidative stress markers, autophagy-related proteins, pteridines, neurotransmitter metabolites, exosomal *LRRK2* protein, RNA species, inflammatory cytokines, mitochondrial DNA (mtDNA), and intermediary metabolites. Pteridines, α -synuclein, mtDNA, 5-hydroxyindolacetic acid, β -D-glucose, lamp2, interleukin-8, and vascular endothelial growth factor were suggested to differentiate patients with *LRRK2*-related PD from sporadic PD patients; 8-hydroxy-2'-deoxyguanosine (8-OHdG), 8-isoprostane (8-ISO), 2-hydroxybutyrate, mtDNA, lamp2, and neopterin may differentiate between *LRRK2* controls and *LRRK2*-related PD subjects; and soluble oligomeric α -synuclein, 8-OHdG, and 8-ISO might differentiate *LRRK2* controls from unaffected subjects.^{101,120-127} However, the low numbers of investigations of each analyte, small sample sizes, and methodological differences limit conclusions that can be drawn from these studies. Further investigations are indicated to determine the validity of the analytes identified in these studies as possible biomarkers for *LRRK2* PD patients and to obtain markers for PD phenoconversion.

Longitudinal studies in *LRRK2*-related PD families have shown fundamentally different neuropathological findings in phenotypically identical family members.⁷² In a postmortem study with 38 patients with *LRRK2*-related PD with proven pathogenic *LRRK2* mutations, 28 of the patients had symptoms compatible with typical levodopa-responsive parkinsonism, and neuropathological findings in 20 of the subjects were similar to those typically found in patients with idiopathic PD, with substantia nigra LBs. Nigral degeneration without LBs was found in 12 pa-

tients, diffuse LB disease was present in two subjects, tau pathology was found in two subjects, and α -synuclein-immunoreactive glial inclusions and ubiquitin-immunoreactive structures were found in one subject each. Similar findings with and without LBs in *LRRK2*-related PD have been reported by other investigators.¹²⁸ The range of neuropathological findings in *LRRK2* PD might decrease the likelihood that α -synuclein oligomer, amyloid or tau concentrations in cerebrospinal fluid (CSF) or peripheral body fluids could offer biomarkers for *LRRK2*-related PD diagnosis or progression.

The most striking difference between groups of *LRRK2* mutation carriers is seen after DBS treatment. *LRRK2*-related PD patients develop levodopa-induced fluctuations and dyskinesias as patients do in the sporadic PD groups. The percentage of *LRRK2* mutation carriers among those qualifying for DBS surgery is significantly higher than that among patients with sporadic PD.¹²⁹ The outcome from DBS surgery seems to depend on the location of the *LRRK2* mutation at the gene. There have been a number of studies demonstrating superior efficiency and good outcome after DBS surgery in *LRRK2* G2019S mutation carriers.¹²⁹⁻¹³² There are only a few cases published on patients carrying mutations in the ROC domain.^{78,133,134} The results from these studies are all negative. Patients with *LRRK2*-related PD with mutations in the ROC domain seem to have less optimal outcome than those carrying mutations in the kinase domain. This might explain why there are so few reports after DBS in patients with *LRRK2* ROC-domain mutations. There is a tendency not to report negative results and vice versa. There is only one report on DBS in patients with mutations in the *LRRK2* COR domain.¹³⁵ These patients seem to experience a good outcome after DBS, comparable to that generally seen in G2019S patients.

The long-term prognosis of *LRRK2* mutation carriers might reflect the underlying neuropathology among the different mutations, which is quite heterogeneous.^{72,128,136} Approximately half of *LRRK2*-related PD patients show no LB pathology, although the highest percentage is found in G2019S mutation carriers.¹²⁸ This is in some ways a paradox since the G2019S patients have the most favorable outcome after DBS, they have the best scores on smell tests and they seem to have the lowest rate of progression measured by annual increase in UPDRS scores.^{114,137,138}

Summary

Autosomal-dominant mutations within the *LRRK2* gene account for a small percentage of all cases of PD and a much higher proportion in some populations in the Middle East/North Africa. *LRRK2*-associated PD closely resembles idiopathic disease in terms of late age of onset, signs, and symptoms. The penetrance of *LRRK2* mutations is incomplete and dependent on age and each specific mutation. Up to half of the *LRRK2* pa-

tients do not show any LBs at autopsy.

Long-term follow-up indicates that carriers of the most common mutation, G2019S, have slightly better prognosis than those with sporadic PD without any known mutation. Patients carrying the G2019S mutation selected for deep brain stimulation, DBS, seem to have very good long-term outcomes compared to cases with *LRKK2* mutations in the ROC domain. The latter group should probably not be selected as good candidates for DBS.

PARK17, VPS35-related PD

The *VPS35* gene was first discovered in a large Swiss family with multiple members affected by PD. At the same time, a group in Austria had similar cases with the D620N (p.Asp620Asn, c.1858G>A) mutation in the vacuolar protein sorting 35, *VPS35*, gene.^{139,140} To date, there are only very few cases and families with this mutation published.

The *VPS35* phenotype varies, but in the few cases published to date, most of them have tremor-dominant PD with some tendency toward depression and other neuropsychiatric features. Members from one large Taiwanese family presented with a classic PD phenotype responding well to levodopa.¹⁴¹

Other polymorphisms in the *VPS35* gene have since been identified, but these variants still need to be definitively linked to PD. *VPS35* was originally identified in yeast as a member of the retromer complex. This complex is involved in the intracellular trafficking of proteins, where it may interact with parkin and may be involved in the retromer-mediated endosomal sorting process.¹⁴²

There have been no systematic follow-up studies in patients with *VPS35*-related PD, with only a few single reports.^{143,144}

One member of the Taiwanese family with *VPS35*-related PD had STN-DBS, and the outcome was reported as very successful.¹⁴²

GBA mutations and variants causing PD

It has been noted for many years that there is an increased frequency of parkinsonism among patients with GD (Table 2), and that there is an increased frequency of typical parkinsonism among healthy heterozygous mutation carriers of *GBA* gene mutations.⁸ GD is a lysosomal storage disorder and results from the deficiency of the lysosomal enzyme glucocerebrosidase, GCase, localized to lysosomes. It is an autosomal-recessive disorder caused by mutations in the human β -glucocerebrosidase gene, *GBA*. Low GCase levels lead to the accumulation of its major substrate, glucosylceramide, GL-1, localized in lysosomes. In GD, large amounts of GL-1 accumulate in many cell types, including macrophages and neurons, which may lead to white matter accumulation, cell death and neurodegeneration.^{11,145}

The *GBA* gene is located on chromosome 1q21 and comprises 11 exons and 10 introns, spanning 7.6 kb of sequence. A non-

Table 2. *GBA* mutations and variants causing Parkinson's disease

| | Percentage of cases | Mean age at onset |
|----------------|-------------------------|-------------------|
| Mutation | | |
| No mutations | 90 | - |
| N370S | 22 of mutation carriers | ≈ 55 years |
| L444P | 8 | ≈ 50 years |
| Variants | | |
| E326K | 30 | ≈ 55–60 years |
| T369M | 22 | ≈ 55–60 years |
| E388K | 3 | ≈ 55–60 years |
| Other variants | 15 | ≈ 55–60 years |

processed pseudogene (*GBAP*) that shares 96% exonic sequence homology is located 16 kb downstream of the functional *GBA* gene. The presence of this highly homologous pseudogene along with another 6 genes at the locus increases the occurrence of chromosomal rearrangements and misalignments in this region. These processes provide an explanation for the high number of complex recombinant alleles that have been detected in patients with GD.¹⁴⁶

Mutations in the gene for GD are probably the most common familial variant of PD. The age-specific estimates of PD penetrance in patients with GD and *GBA* heterozygous carriers is still debated. Although *GBA* mutations may increase the risk for PD, the vast majority of patients with GD who are heterozygotes may not develop the disease.^{147–149} Studies are ongoing to identify what modifies the risk of PD in *GBA* mutation carriers.

In a French study, approximately 10% of PD patients were carriers of some GD mutation. PD was strongly associated with the neuropathic GD mutation and to a lesser degree to the more common GD variants.¹⁵⁰ The latter are correlated with PD, but they do not cause GD in homozygous carriers. In a large multicenter study, it was shown that the prevalence of *GBA* mutations strongly varies between ethnic groups.¹³

GBA patients are usually grouped on the basis of their mutations as having benign variants or mild or severe mutations. The most common variants are E326K, T369M and T297S. N370S is a milder mutation than L444P, which is regarded as a severe mutation. In addition, there are a high number of rare variants/mutations, which makes the genetic testing for *GBA* parkinsonism technically complicated and the interpretation of the results difficult. Future diagnostics for *GBA* mutations may be of importance for neuroprotective therapy. These biomarkers could include CSF glucocerebrosidase activity or some other CSF or plasma levels of glucosylceramide substrates.

The mean age of onset of *GBA*-related PD is to some degree related to the type of mutation. The onset in neuropathic mutation carriers is approximately 50 years and is 5–10 years later in patients with the more benign N370S mutation. Patients carry-

ing one of the *GBA* variants have an age of onset comparable to those carrying the N370S mutation.

The phenotype is often quite typical and clinically not easy to separate from that seen in patients with sporadic PD, with resting tremor, bradykinesia, rigidity and postural instability in patients with advanced cases. Nonmotor features include cognitive impairment, hallucinations, autonomic dysfunction and sleep disorders. *GBA* PD patients typically have severe anosmia.¹⁵¹ Most *GBA*-related PD patients show a good response to levodopa, and the development of levodopa-related complications such as dyskinesias and off-periods is probably comparable to that seen in sporadic PD patients. The progression of patients with *GBA*-related PD is quite fast; therefore, many patients may be candidates for DBS treatment. This may not always be a good choice since studies have shown that patients with *GBA*-related PD deteriorate faster and develop cognitive deficits after fewer years than patients with sporadic PD.^{132,151}

Long-term prognosis of *GBA*-related PD

PD in the context of GD seems to resemble idiopathic PD more closely in terms of its clinical heterogeneity than PD associated with *GBA* heterozygous mutations.¹⁵² Heterozygous *GBA* mutation carriers develop a more severe phenotype, including dyskinesias, than those with sporadic PD.^{153,154}

There have been several studies in *GBA*-related PD and the risk of developing dementia. Three studies investigated the effects of *GBA* variation on PD dementia, Parkinson's disease dementia (PDD), and risk. Four addressed the effects of *GBA* mutations on PDD risk, two explored the effects of *GBA* polymorphism on PDD risk, two investigated the effects of the *GBA* L444P mutation on PDD risk, and two studied the effects of the *GBA* N370S mutation on the risk of cognitive decline. These studies came from different ethnic groups located in Europe and North America, and one was from Japan. One study predicted cognitive decline and dementia in half of the patients after 8–10 years of disease duration.^{150,155} They made an algorithm, and the main indicators were age, education, depression and UPDRS.¹⁵⁵ Most studies indicate that PD patients carrying a *GBA* mutation seem to have a 3–5 times higher risk of developing dementia than noncarriers.^{154,156,157}

Well-preserved cognitive function is also a crucial factor for survival in PD. After the discovery of the connection between *GBA* mutations and PD pathology, many reports have described cortical and/or hippocampal LBs in the majority of the subjects with *GBA* mutations, corresponding to the more aggressive parkinsonism described in probands with both GD and parkinsonism.^{158–160} PD patients with GD-associated mutations develop dementia and psychosis significantly earlier than those without mutations, but wearing-off does not significantly differ from

that observed in patients with mutation.¹⁵⁴ The risk for dementia is strongly modulated by the type of mutation. In the clinical continuum between PD and DLB, patients with *GBA* mutations seem to localize midway, with carriers of severe mutations closer to DLB than to idiopathic PD.¹⁵⁷

The difference in the risk of developing so-called sporadic PD and *GBA*-related PD is particularly important in regard to the treatment of late-stage complications. The selection of patients for advanced PD therapy, including deep brain stimulation, is based on international consensus.¹⁶¹ PD patients with GD-associated mutations develop wearing-off and dyskinesia following the same timeline as sporadic PD patients.¹⁵⁴ Many patients with *GBA*-related PD are thus, in principle, excellent candidates for DBS surgery. However, the shorter time to cognitive deterioration after DBS makes these patients less optimal for advanced treatment. In retrospect, many patients who have developed dementia and other neuropsychiatric complications not long after DBS have been shown to be *GBA* mutation carriers.^{48,131,132,162,163}

Summary

GBA patients exhibit classic symptoms, including tremor, rigidity and bradykinesia. There are 2 relatively common *GBA* mutations, N370S and L444P, and there are a high number of rare mutations and variants. *GBA* mutations are most common among Ashkenazi Jewish PD patients, 15%, compared to as low as 3% of PD patients of other ethnic origin. Low levels of GCase may promote the stabilization of α -synuclein into oligomers similar to those found in LBs. This may explain why *GBS* patients have an earlier onset of PD symptoms with faster cognitive and motor decline than sporadic PD patients. *GBA*-associated PD patients present with more rapid disease progression of motor impairment, cognitive decline and lower survival rates than PD patients without mutations.

Mutations not covered in this review

Other rare mutations may cause PD but are not included in this review. These include mutations in EIF4G1 (eukaryotic translation initiation factor 4 gamma 1), *DCTN1* (dynactin 1) in Perry syndrome, *ATP13A2* (ATPase type 13A2), *PARK9* in Kufor-Rakeb syndrome, *PLA2G6* (phospholipase A2, group 6) (*PARK14*), and *FBXO7* (F-box protein 7) (*PARK15*). There are no follow-up reports on these patients.

CONCLUSIONS

During the last twenty years, there has been continued success in the identification of genetic causes and contributors to PD. There are now a high number of mutations and gene vari-

ants that may affect the risk for developing PD; the majority are very rare. This review describes the long-term outcome in PD patients carrying the most common mutations. **The genotype-phenotype relations that vary between different genetic mutations have provided excellent information for selecting patients for specific therapies.** SNCA mutation carriers have a younger onset than LRRK2 mutation carriers and have a more severe prognosis. The early-onset recessive patients respond well to levodopa and are less prone to cognitive decline. The GBA-related PD phenotype is similar to that seen in sporadic PD, but patients with GBA-related PD have more nonmotor symptoms, including cognitive impairment and hallucinations, making them less optimal candidates for advanced treatments such as DBS.

The clinical and basic research in genetic PD has given increasing insight into the genetic and molecular basis of this complex disease. This is a prerequisite for revealing the molecular pathogenesis of PD and identifying a therapy based on etiology.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

None.

ORCID iD

Jan O. Aasly <https://orcid.org/0000-0002-0558-7686>

REFERENCES

- Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 1997;276:2045-2047.
- Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. *Nature* 1997;388:839-840.
- Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 1998;392:605-608.
- Valente EM, Bentivoglio AR, Dixon PH, Ferraris A, Ialongo T, Frontali M, et al. Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35-p36. *Am J Hum Genet* 2001;68:895-900.
- Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science* 2003;299:256-259.
- Paisán-Ruiz C, Jain S, Evans EW, Gilks WP, Simón J, van der Brug M, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron* 2004;44:595-600.
- Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* 2004;44:601-607.
- Neudorfer O, Giladi N, Elstein D, Abrahamov A, Turekzite T, Aghai E, et al. Occurrence of Parkinson's syndrome in type I Gaucher disease. *QJM* 1996;89:691-694.
- Chang D, Nalls MA, Hallgrímsdóttir IB, Hunkapiller J, van der Brug M, Cai F, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat Genet* 2017;49:1511-1516.
- Lunati A, Lesage S, Brice A. The genetic landscape of Parkinson's disease. *Rev Neurol (Paris)* 2018;174:628-643.
- Stirnermann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Cailaud C, et al. A review of gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci* 2017;18:441.
- Mitsui J, Mizuta I, Toyoda A, Ashida R, Takahashi Y, Goto J, et al. Mutations for Gaucher disease confer high susceptibility to Parkinson disease. *Arch Neurol* 2009;66:571-576.
- Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med* 2009;361:1651-1661.
- Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427-442.
- Curtis L, Lees AJ, Stern GM, Marmot MG. Effect of L-dopa on course of Parkinson's disease. *Lancet* 1984;2:211-212.
- Hely MA, Morris JG, Reid WG, Trafficante R. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord* 2005;20:190-199.
- Vollstedt EJ, Kasten M, Klein C, MJFF Global Genetic Parkinson's Disease Study Group. Using global team science to identify genetic parkinson's disease worldwide. *Ann Neurol* 2019;86:153-157.
- Golbe LI, Di Iorio G, Sanges G, Lazzarini AM, La Sala S, Bonavita V, et al. Clinical genetic analysis of Parkinson's disease in the Contursi kindred. *Ann Neurol* 1996;40:767-775.
- Trinh J, Zeldenrust FMJ, Huang J, Kasten M, Schaake S, Petkovic S, et al. Genotype-phenotype relations for the Parkinson's disease genes SNCA, LRRK2, VPS35: MDSGene systematic review. *Mov Disord* 2018;33:1857-1870.
- Spellman GG. Report of familial cases of parkinsonism. Evidence of a dominant trait in a patient's family. *JAMA* 1962;179:372-374.
- Zarranz JJ, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann Neurol* 2004;55:164-173.
- Appel-Cresswell S, Vilarino-Guell C, Encarnacion M, Sherman H, Yu I, Shah B, Weir D, et al. Alpha-synuclein p.H50Q, a novel pathogenic mutation for Parkinson's disease. *Mov Disord* 2013;28:811-813.
- Krüger R, Kuhn W, Müller T, Woitalla D, Graeber M, Kösel S, et al. Ala-30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat Genet* 1998;18:106-108.
- Pasanen P, Myllykangas L, Siitonen M, Raunio A, Kaakkola S, Lyytinen J, et al. Novel alpha-synuclein mutation A53E associated with atypical multiple system atrophy and Parkinson's disease-type pathology. *Neurobiol Aging* 2014;35:2180.e1-2180.e5.
- Elia AE, Petrucci S, Fasano A, Guidi M, Valbonesi S, Bernardini L, et al. Alpha-synuclein gene duplication: marked intrafamilial variability in two novel pedigrees. *Mov Disord* 2013;28:813-817.
- Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schüle B, et al. Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. *Neurology* 2007;68:916-922.
- Ross OA, Braithwaite AT, Skipper LM, Kachergus J, Hulihan MM, Middleton FA, et al. Genomic investigation of alpha-synuclein multiplication and parkinsonism. *Ann Neurol* 2008;63:743-750.
- Ricciardi L, Petrucci S, Di Giuda D, Serra L, Spanò B, Sensi M, et al. The Contursi family 20 years later: intrafamilial phenotypic variability of the SNCA p.A53T mutation. *Mov Disord* 2016;31:257-258.
- Swerdlow RH, Parks JK, Cassarino DS, Binder DR, Bennett JP Jr, Di Iorio G, et al. Biochemical analysis of cybrids expressing mitochondrial DNA from Contursi kindred Parkinson's subjects. *Exp Neurol* 2001;169:479-485.
- Muenter MD, Forno LS, Hornykiewicz O, Kish SJ, Maraganore DM, Caselli RJ, et al. Hereditary form of parkinsonism--dementia. *Ann Neurol* 1998;43:768-781.
- Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, et al. alpha-Synuclein locus triplication causes Parkinson's disease. *Science* 2003;302:841.
- Picillo M, Lizarraga KJ, Friesen EL, Chau H, Zhang M, Sato C, et al. Parkinsonism due to A53E alpha-synuclein gene mutation: clinical, genetic, epigenetic, and biochemical features. *Mov Disord* 2018;33:1950-1955.

33. Martikainen MH, Päiväranta M, Hietala M, Kaasinen V. Clinical and imaging findings in Parkinson disease associated with the A53E SNCA mutation. *Neurol Genet* 2015;1:e27.
34. Antonini A, Pilleri M, Padoan A, Landi A, Ferla S, Biundo R, et al. Successful subthalamic stimulation in genetic Parkinson's disease caused by duplication of the α -synuclein gene. *J Neurol* 2012;259:165-167.
35. Cartelli D, Amadeo A, Calogero AM, Casagrande FVM, De Gregorio C, Gioria M, et al. Parkin absence accelerates microtubule aging in dopaminergic neurons. *Neurobiol Aging* 2018;61:66-74.
36. Johansen KK, Torp SH, Farrer MJ, Gustavsson EK, Aasly JO. A Case of Parkinson's disease with no Lewy body pathology due to a homozygous exon deletion in Parkin. *Case Rep Neurol Med* 2018;2018:6838965.
37. Ahlskog JE. Parkin and PINK1 parkinsonism may represent nigral mitochondrial cytopathies distinct from Lewy body Parkinson's disease. *Parkinsonism Relat Disord* 2009;15:721-727.
38. Aasly JO, Sæther O, Johansen KK, Bathen TF, Giskeødegård GF, White LR. Changes to intermediary metabolites in sporadic and LRRK2 Parkinson's disease demonstrated by proton magnetic resonance spectroscopy. *Parkinsons Dis* 2015;2015:264896.
39. Mellick GD, Siebert GA, Funayama M, Buchanan DD, Li Y, Imamichi Y, et al. Screening PARK genes for mutations in early-onset Parkinson's disease patients from Queensland, Australia. *Parkinsonism Relat Disord* 2009;15:105-109.
40. Weissbach A, König IR, Hükelheim K, Pramstaller PP, Werner E, Brüggemann N, et al. Influence of L-dopa on subtle motor signs in heterozygous Parkin- and PINK1 mutation carriers. *Parkinsonism Relat Disord* 2017;42:95-99.
41. Clarimon J, Johnson J, Djaldetti R, Hernandez D, Hattori N, Sroka H, et al. Mutation of the Parkin gene in a Persian family: clinical progression over a 40-year period. *Mov Disord* 2005;20:887-890.
42. Doherty KM, Silveira-Moriyama L, Parkkinen L, Healy DG, Farrell M, Mencacci NE, et al. Parkin disease: a clinicopathologic entity? *JAMA Neurol* 2013;70:571-579.
43. Morgante F, Fasano A, Ginevrino M, Petrucci S, Ricciardi L, Bove F, et al. Impulsive-compulsive behaviors in parkin-associated Parkinson disease. *Neurology* 2016;87:1436-1441.
44. Srivastava A, Tang MX, Mejia-Santana H, Rosado L, Louis ED, Caccapolo E, et al. The relation between depression and parkin genotype: the CORE-PD study. *Parkinsonism Relat Disord* 2011;17:740-744.
45. Kim HJ, Yun JY, Kim YE, Lee JY, Kim HJ, Kim JY, et al. Parkin mutation and deep brain stimulation outcome. *J Clin Neurosci* 2014;21:107-110.
46. Moro E, Volkman J, König IR, Winkler S, Hiller A, Hassin-Baer S, et al. Bilateral subthalamic stimulation in Parkin and PINK1 parkinsonism. *Neurology* 2008;70:1186-1191.
47. Romito LM, Contarino MF, Ghezzi D, Franzini A, Garavaglia B, Albanese A. High frequency stimulation of the subthalamic nucleus is efficacious in Parkin disease. *J Neurol* 2005;252:208-211.
48. Rizzone MG, Martone T, Balestrino R, Lopiano L. Genetic background and outcome of Deep Brain Stimulation in Parkinson's disease. *Parkinsonism Relat Disord* 2019;64:8-19.
49. Doherty KM, Hardy J. Parkin disease and the Lewy body conundrum. *Mov Disord* 2013;28:702-704.
50. Kasten M, Hartmann C, Hampf J, Schaake S, Westenberger A, Vollstedt EJ, et al. Genotype-phenotype relations for the Parkinson's disease genes Parkin, PINK1, DJ1: MDSGene systematic review. *Mov Disord* 2018;33:730-741.
51. Bonifati V, Rohé CF, Breedveld GJ, Fabrizio E, De Mari M, Tassorelli C, et al. Early-onset parkinsonism associated with PINK1 mutations: frequency, genotypes, and phenotypes. *Neurology* 2005;65:87-95.
52. Toft M, Myhre R, Pielsticker L, White LR, Aasly JO, Farrer MJ. PINK1 mutation heterozygosity and the risk of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:82-84.
53. Ishihara-Paul L, Hulihan MM, Kachergus J, Upmanyu R, Warren L, Amouri R, et al. PINK1 mutations and parkinsonism. *Neurology* 2008;71:896-902.
54. Ricciardi L, Petrucci S, Guidubaldi A, Ialongo T, Serra L, Ferraris A, et al. Phenotypic variability of PINK1 expression: 12 years' clinical follow-up of two Italian families. *Mov Disord* 2014;29:1561-1566.
55. Ferraris A, Ialongo T, Passali GC, Pellicchia MT, Brusa L, Laruffa M, et al. Olfactory dysfunction in Parkinsonism caused by PINK1 mutations. *Mov Disord* 2009;24:2350-2357.
56. Kertelge L, Brüggemann N, Schmidt A, Tadic V, Wisse C, Dankert S, et al. Impaired sense of smell and color discrimination in monogenic and idiopathic Parkinson's disease. *Mov Disord* 2010;25:2665-2669.
57. Borellini L, Cogiamanian F, Carrabba G, Locatelli M, Rampini P, Di Fonzo A, et al. Globus pallidus internus deep brain stimulation in PINK-1 related Parkinson's disease: a case report. *Parkinsonism Relat Disord* 2017;38:93-94.
58. Samaranch L, Lorenzo-Betancor O, Arbelo JM, Ferrer I, Lorenzo E, Irigoyen J, et al. PINK1-linked parkinsonism is associated with Lewy body pathology. *Brain* 2010;133:1128-1142.
59. Steele JC, Guella I, Szu-Tu C, Lin MK, Thompson C, Evans DM, et al. Defining neurodegeneration on Guam by targeted genomic sequencing. *Ann Neurol* 2015;77:458-468.
60. Bonifati V. Autosomal recessive parkinsonism. *Parkinsonism Relat Disord* 2012;18 Suppl 1:S4-S6.
61. Clark LN, Afridi S, Mejia-Santana H, Harris J, Louis ED, Cote LJ, et al. Analysis of an early-onset Parkinson's disease cohort for DJ-1 mutations. *Mov Disord* 2004;19:796-800.
62. Klein C, Westenberger A. Genetics of Parkinson's disease. *Cold Spring Harb Perspect Med* 2012;2:a008888.
63. Gustavsson EK, Trinh J, McKenzie M, Bortnick S, Petersen MS, Farrer MJ, et al. Genetic identification in early onset parkinsonism among Norwegian patients. *Mov Disord Clin Pract* 2017;4:499-508.
64. Bozi M, Papadimitriou D, Antonellou R, Moraitou M, Maniati M, Vasilatis DK, et al. Genetic assessment of familial and early-onset Parkinson's disease in a Greek population. *Eur J Neurol* 2014;21:963-968.
65. García S, López-Hernández LB, Suarez-Cuenca JA, Solano-Rojas M, Gallegos-Arreola MP, Gama-Moreno O, et al. Low prevalence of most frequent pathogenic variants of six PARK genes in sporadic Parkinson's disease. *Folia Neuropathol* 2014;52:22-29.
66. Alcalay RN, Caccapolo E, Mejia-Santana H, Tang MX, Rosado L, Ross BM, et al. Frequency of known mutations in early-onset Parkinson disease: implication for genetic counseling: the consortium on risk for early onset Parkinson disease study. *Arch Neurol* 2010;67:1116-1122.
67. Taipa R, Pereira C, Reis I, Alonso I, Bastos-Lima A, Melo-Pires M, et al. DJ-1 linked parkinsonism (PARK7) is associated with Lewy body pathology. *Brain* 2016;139(Pt 6):1680-1687.
68. Abbas MM, Govindappa ST, Sudhaman S, Thelma BK, Juyal RC, Behari M, et al. Early onset Parkinson's disease due to DJ1 mutations: an Indian study. *Parkinsonism Relat Disord* 2016;32:20-24.
69. Narendera DP, Isonaka R, Nguyen D, Schindler AB, Kokkinis AD, Ehrlich D, et al. Peripheral synucleinopathy in a DJ1 patient with Parkinson disease, cataracts, and hearing loss. *Neurology* 2019;92:1113-1115.
70. Kuusimäki T, Korpela J, Pekkonen E, Martikainen MH, Antonini A, Kaasinen V. Deep brain stimulation for monogenic Parkinson's disease: a systematic review. *J Neurol* 2020;267:883-897.
71. Funayama M, Hasegawa K, Kowa H, Saito M, Tsuji S, Obata F. A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. *Ann Neurol* 2002;51:296-301.
72. Wszolek ZK, Pfeiffer RF, Tsuboi Y, Uitti RJ, McComb RD, Stoessl AJ, et al. Autosomal dominant parkinsonism associated with variable synuclein and tau pathology. *Neurology* 2004;62:1619-1622.
73. Kachergus J, Mata IF, Hulihan M, Taylor JP, Lincoln S, Aasly J, et al. Identification of a novel LRRK2 mutation linked to autosomal dominant parkinsonism: evidence of a common founder across European populations. *Am J Hum Genet* 2005;76:672-680.
74. Aasly JO, Toft M, Fernandez-Mata I, Kachergus J, Hulihan M, White LR, et al. Clinical features of LRRK2-associated Parkinson's disease in

- central Norway. *Ann Neurol* 2005;57:762-765.
75. Funayama M, Hasegawa K, Ohta E, Kawashima N, Komiyama M, Kowa H, et al. An LRRK2 mutation as a cause for the parkinsonism in the original PARK8 family. *Ann Neurol* 2005;57:918-921.
 76. Rideout HJ, Stefanis L. The neurobiology of LRRK2 and its role in the pathogenesis of Parkinson's disease. *Neurochem Res* 2014;39:576-592.
 77. Shu L, Zhang Y, Pan H, Xu Q, Guo J, Tang B, et al. Clinical Heterogeneity Among LRRK2 Variants in Parkinson's Disease: A Meta-Analysis. *Front Aging Neurosci* 2018;10:283.
 78. Aasly JO, Vilarinho-Güell C, Dachsel JC, Webber PJ, West AB, Haugarvoll K, et al. Novel Pathogenic Lrrk2 p.Asn1437His substitution in familial Parkinson's disease. *Mov Disord* 2010;25:2156-2163.
 79. Cook DA, Kannarkat GT, Cintron AF, Butkovich LM, Fraser KB, Chang J, et al. LRRK2 levels in immune cells are increased in Parkinson's disease. *NPJ Parkinsons Dis* 2017;3:11.
 80. Shu L, Zhang Y, Sun Q, Pan H, Tang B. A comprehensive analysis of population differences in LRRK2 variant distribution in Parkinson's disease. *Front Aging Neurosci* 2019;11:13.
 81. Farrer MJ, Stone JT, Lin CH, Dächsel JC, Hulihan MM, Haugarvoll K, et al. Lrrk2 G2385R is an ancestral risk factor for Parkinson's disease in Asia. *Parkinsonism Relat Disord* 2007;13:89-92.
 82. Liang D, Shu L, Pan H, Xu Q, Guo J, Yan X, et al. Clinical characteristics of PD patients with LRRK2 G2385R and R1628P variants. *Neurosci Lett* 2018;685:185-189.
 83. Kelly K, Wang S, Boddu R, Liu Z, Moukha-Chafiq O, Augelli-Szafran C, et al. The G2019S mutation in LRRK2 imparts resiliency to kinase inhibition. *Exp Neurol* 2018;309:1-13.
 84. Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med* 2006;354:424-425.
 85. Orr-Urtreger A, Shifrin C, Rozovski I, Rosner S, Bercovich D, Gurevich T, et al. The LRRK2 G2019S mutation in Ashkenazi Jews with Parkinson disease: is there a gender effect? *Neurology* 2007;69:1595-1602.
 86. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol* 2008;7:583-590.
 87. Clark LN, Wang Y, Karlins E, Saito L, Mejia-Santana H, Harris J, et al. Frequency of LRRK2 mutations in early- and late-onset Parkinson disease. *Neurology* 2006;67:1786-1791.
 88. Latourelle JC, Sun M, Lew MF, Suchowersky O, Klein C, Golbe LI, et al. The Gly2019Ser mutation in LRRK2 is not fully penetrant in familial Parkinson's disease: the GenePD study. *BMC Med* 2008;6:32.
 89. Tan EK, Tang M, Tan LC, Wu YR, Wu RM, Ross OA, et al. Lrrk2 R1628P in non-Chinese Asian races. *Ann Neurol* 2008;64:472-473.
 90. Ross OA, Wu YR, Lee MC, Funayama M, Chen ML, Soto AI, et al. Analysis of Lrrk2 R1628P as a risk factor for Parkinson's disease. *Ann Neurol* 2008;64:88-92.
 91. Rudenko IN, Kaganovich A, Hauser DN, Beylina A, Chia R, Ding J, et al. The G2385R variant of leucine-rich repeat kinase 2 associated with Parkinson's disease is a partial loss-of-function mutation. *Biochem J* 2012;446:99-111.
 92. Rudenko IN, Kaganovich A, Langston RG, Beilina A, Ndukwe K, Kumaran R, et al. The G2385R risk factor for Parkinson's disease enhances CHIP-dependent intracellular degradation of LRRK2. *Biochem J* 2017;474:1547-1558.
 93. Johansen KK, Hasselberg K, White LR, Farrer MJ, Aasly JO. Genealogical studies in LRRK2-associated Parkinson's disease in central Norway. *Parkinsonism Relat Disord* 2010;16:527-530.
 94. Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet* 2014;46:989-993.
 95. Ross OA, Soto-Ortolaza AI, Heckman MG, Aasly JO, Abahuni N, Annesi G, et al. Association of LRRK2 exonic variants with susceptibility to Parkinson's disease: a case-control study. *Lancet Neurol* 2011;10:898-908.
 96. Yuan X, Chen Y, Cao B, Zhao B, Wei Q, Guo X, et al. An association analysis of the R1628P and G2385R polymorphisms of the LRRK2 gene in multiple system atrophy in a Chinese population. *Parkinsonism Relat Disord* 2015;21:147-149.
 97. Cho HJ, Liu G, Jin SM, Parisiadou L, Xie C, Yu J, et al. MicroRNA-205 regulates the expression of Parkinson's disease-related leucine-rich repeat kinase 2 protein. *Hum Mol Genet* 2013;22:608-620.
 98. Bliederhaeuser C, Zondler L, Grozdanov V, Ruf WP, Brenner D, Melrose HL, et al. LRRK2 contributes to monocyte dysregulation in Parkinson's disease. *Acta Neuropathol Commun* 2016;4:123.
 99. Di Maio R, Hoffman EK, Rocha EM, Keeney MT, Sanders LH, De Miranda BR, et al. LRRK2 activation in idiopathic Parkinson's disease. *Sci Transl Med* 2018;10:ear5429.
 100. Fraser KB, Rawlins AB, Clark RG, Alcalay RN, Standaert DG, Liu N, et al. Ser(P)-1292 LRRK2 in urinary exosomes is elevated in idiopathic Parkinson's disease. *Mov Disord* 2016;31:1543-1550.
 101. Wang S, Liu Z, Ye T, Mabrouk OS, Maltbie T, Aasly J, et al. Elevated LRRK2 autophosphorylation in brain-derived and peripheral exosomes in LRRK2 mutation carriers. *Acta Neuropathol Commun* 2017;5:86.
 102. Roosen DA, Cookson MR. LRRK2 at the interface of autophagosomes, endosomes and lysosomes. *Mol Neurodegener* 2016;11:73.
 103. Wang S, West AB. Caught in the act: LRRK2 in exosomes. *Biochem Soc Trans* 2019;47:663-670.
 104. Zhang M, Yao C, Cai J, Liu S, Liu XN, Chen Y, et al. LRRK2 is involved in the pathogenesis of system lupus erythematosus through promoting pathogenic antibody production. *J Transl Med* 2019;17:37.
 105. Cresto N, Gardier C, Gubinelli F, Gaillard MC, Liot G, West AB, et al. The unlikely partnership between LRRK2 and α -synuclein in Parkinson's disease. *Eur J Neurosci* 2019;49:339-363.
 106. Daher JP, Volpicelli-Daley LA, Blackburn JP, Moehle MS, West AB. Abrogation of α -synuclein-mediated dopaminergic neurodegeneration in LRRK2-deficient rats. *Proc Natl Acad Sci U S A* 2014;111:9289-9294.
 107. Daher JP, Abdelmotilib HA, Hu X, Volpicelli-Daley LA, Moehle MS, Fraser KB, et al. Leucine-rich Repeat Kinase 2 (LRRK2) Pharmacological Inhibition Abates α -Synuclein Gene-induced Neurodegeneration. *J Biol Chem* 2015;290:19433-19444.
 108. Nucifora FC Jr, Nucifora LG, Ng CH, Arbez N, Guo Y, Roby E, et al. Ubiquitination via K27 and K29 chains signals aggregation and neuronal protection of LRRK2 by WSB1. *Nat Commun* 2016;7:11792.
 109. Sossi V, de la Fuente-Fernández R, Nandhagopal R, Schulzer M, McKenzie J, Ruth TJ, et al. Dopamine turnover increases in asymptomatic LRRK2 mutations carriers. *Mov Disord* 2010;25:2717-2723.
 110. Wile DJ, Agarwal PA, Schulzer M, Mak E, Dinelle K, Shahinfard E, et al. Serotonin and dopamine transporter PET changes in the premotor phase of LRRK2 parkinsonism: cross-sectional studies. *Lancet Neurol* 2017;16:351-359.
 111. Liu SY, Wile DJ, Fu JF, Valerio J, Shahinfard E, McCormick S, et al. The effect of LRRK2 mutations on the cholinergic system in manifest and premanifest stages of Parkinson's disease: a cross-sectional PET study. *Lancet Neurol* 2018;17:309-316.
 112. Gaig C, Vilas D, Infante J, Sierra M, García-Gorostiaga I, Buongiorno M, et al. Nonmotor symptoms in LRRK2 G2019S associated Parkinson's disease. *PLoS One* 2014;9:e108982.
 113. Johansen KK, Warø BJ, Aasly JO. Olfactory dysfunction in sporadic Parkinson's Disease and LRRK2 carriers. *Acta Neurol Scand* 2014;129:300-306.
 114. Saunders-Pullman R, Mirelman A, Alcalay RN, Wang C, Ortega RA, Raymond D, et al. Progression in the LRRK2-associated Parkinson disease population. *JAMA Neurol* 2018;75:312-319.
 115. Alcalay RN, Mirelman A, Saunders-Pullman R, Tang MX, Mejia-Santana H, Raymond D, et al. Parkinson disease phenotype in Ashkenazi Jews with and without LRRK2 G2019S mutations. *Mov Disord* 2013;28:1966-1971.
 116. Yahalom G, Orlev Y, Cohen OS, Kozlova E, Friedman E, Inzelberg R, et

- al. Motor progression of Parkinson's disease with the leucine-rich repeat kinase 2 G2019S mutation. *Mov Disord* 2014;29:1057-1060.
117. Hentati F, Trinh J, Thompson C, Nosova E, Farrer MJ, Aasly JO. *LRRK2* parkinsonism in Tunisia and Norway: a comparative analysis of disease penetrance. *Neurology* 2014;83:568-569.
118. Trinh J, Gustavsson EK, Vilariño-Güell C, Bortnick S, Latourelle J, McKenzie MB, et al. *DNM3* and genetic modifiers of age of onset in *LRRK2* Gly2019Ser parkinsonism: a genome-wide linkage and association study. *Lancet Neurol* 2016;15:1248-1256.
119. Oosterveld LP, Allen JC Jr, Ng EY, Seah SH, Tay KY, Au WL, et al. Greater motor progression in patients with Parkinson disease who carry *LRRK2* risk variants. *Neurology* 2015;85:1039-1042.
120. Klaver AC, Coffey MP, Aasly JO, Loeffler DA. CSF lamp2 concentrations are decreased in female Parkinson's disease patients with *LRRK2* mutations. *Brain Res* 2018;1683:12-16.
121. Shi M, Furay AR, Sossi V, Aasly JO, Armaly J, Wang Y, et al. DJ-1 and α SYN in *LRRK2* CSF do not correlate with striatal dopaminergic function. *Neurobiol Aging* 2012;33:836.e5-836.e7.
122. Aasly JO, Johansen KK, Brønstad G, Warø BJ, Majbour NK, Varghese S, et al. Elevated levels of cerebrospinal fluid α -synuclein oligomers in healthy asymptomatic *LRRK2* mutation carriers. *Front Aging Neurosci* 2014;6:248.
123. Vilas D, Shaw LM, Taylor P, Berg D, Brockmann K, Aasly J, et al. Cerebrospinal fluid biomarkers and clinical features in leucine-rich repeat kinase 2 (*LRRK2*) mutation carriers. *Mov Disord* 2016;31:906-914.
124. Loeffler DA, Klaver AC, Coffey MP, Aasly JO, LeWitt PA. Increased oxidative stress markers in cerebrospinal fluid from healthy subjects with Parkinson's Disease-associated *LRRK2* gene mutations. *Front Aging Neurosci* 2017;9:89.
125. Ichinose H, Inoue KI, Arakawa S, Watanabe Y, Kurosaki H, Koshiba S, et al. Alterations in the reduced pteridine contents in the cerebrospinal fluids of *LRRK2* mutation carriers and patients with Parkinson's disease. *J Neural Transm (Vienna)* 2018;125:45-52.
126. Aasly JO, Shi M, Sossi V, Stewart T, Johansen KK, Wszolek ZK, et al. Cerebrospinal fluid amyloid β and tau in *LRRK2* mutation carriers. *Neurology* 2012;78:55-61.
127. Podlesniy P, Vilas D, Taylor P, Shaw LM, Tolosa E, Trullas R. Mitochondrial DNA in CSF distinguishes *LRRK2* from idiopathic Parkinson's disease. *Neurobiol Dis* 2016;94:10-17.
128. Kalia LV, Lang AE, Hazrati LN, Fujioka S, Wszolek ZK, Dickson DW, et al. Clinical correlations with Lewy body pathology in *LRRK2*-related Parkinson disease. *JAMA Neurol* 2015;72:100-105.
129. Johansen KK, Jørgensen JV, White LR, Farrer MJ, Aasly JO. Parkinson-related genetics in patients treated with deep brain stimulation. *Acta Neurol Scand* 2011;123:201-206.
130. Schüpbach M, Lohmann E, Anheim M, Lesage S, Czernecki V, Yaici S, et al. Subthalamic nucleus stimulation is efficacious in patients with Parkinsonism and *LRRK2* mutations. *Mov Disord* 2007;22:119-122.
131. Pal GD, Hall D, Ouyang B, Phelps J, Alcalay R, Pauciulo MW, et al. Genetic and clinical predictors of deep brain stimulation in young-onset Parkinson's disease. *Mov Disord Clin Pract* 2016;3:465-471.
132. Angeli A, Mencacci NE, Duran R, Aviles-Olmos I, Kefalopoulou Z, Candelario J, et al. Genotype and phenotype in Parkinson's disease: lessons in heterogeneity from deep brain stimulation. *Mov Disord* 2013;28:1370-1375.
133. Gómez-Esteban JC, Lezcano E, Zarranz JJ, González C, Bilbao G, Lambarri I, et al. Outcome of bilateral deep brain subthalamic stimulation in patients carrying the R1441G mutation in the *LRRK2* dardarin gene. *Neurosurgery* 2008;62:857-862.
134. Hatano T, Funayama M, Kubo SI, Mata IF, Oji Y, Mori A, et al. Identification of a Japanese family with *LRRK2* p.R1441G-related Parkinson's disease. *Neurobiol Aging* 2014;35:2656.e17-2656.e23.
135. Perju-Dumbrava LD, McDonald M, Kneebone AC, Long R, Thyagarajan D. Sustained response to deep brain stimulation in *LRRK2* parkinsonism with the Y1699C mutation. *J Parkinsons Dis* 2012;2:269-271.
136. Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain* 2011;134(Pt 5):1493-1505.
137. Thaler A, Kozlovski T, Gurevich T, Bar-Shira A, Gana-Weisz M, Orr-Urtreger A, et al. Survival rates among Parkinson's disease patients who carry mutations in the *LRRK2* and *GBA* genes. *Mov Disord* 2018;33:1656-1660.
138. Clarimón J, Pagonabarraga J, Paisán-Ruiz C, Campolongo A, Pascual-Sedano B, Martí-Massó JF, et al. Tremor dominant parkinsonism: clinical description and *LRRK2* mutation screening. *Mov Disord* 2008;23:518-523.
139. Vilariño-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lincoln SJ, et al. *VPS35* mutations in Parkinson disease. *Am J Hum Genet* 2011;89:162-167.
140. Zimprich A, Benet-Pagès A, Struhal W, Graf E, Eck SH, Offman MN, et al. A mutation in *VPS35*, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. *Am J Hum Genet* 2011;89:168-175.
141. Chen YF, Chang YY, Lan MY, Chen PL, Lin CH. Identification of *VPS35* p.D620N mutation-related Parkinson's disease in a Taiwanese family with successful bilateral subthalamic nucleus deep brain stimulation: a case report and literature review. *BMC Neurol* 2017;17:191.
142. Williams ET, Glauser L, Tsika E, Jiang H, Islam S, Moore DJ. Parkin mediates the ubiquitination of *VPS35* and modulates retromer-dependent endosomal sorting. *Hum Mol Genet* 2018;27:3189-3205.
143. Sheerin UM, Charlesworth G, Bras J, Guerreiro R, Bhatia K, Foltynie T, et al. Screening for *VPS35* mutations in Parkinson's disease. *Neurobiol Aging* 2012;33:838.e1-838.e5.
144. Kumar KR, Weissbach A, Heldmann M, Kasten M, Tunc S, Sue CM, et al. Frequency of the D620N mutation in *VPS35* in Parkinson disease. *Arch Neurol* 2012;69:1360-1364.
145. Romero R, Ramanathan A, Yuen T, Bhowmik D, Mathew M, Munshi LB, et al. Mechanism of glucocerebrosidase activation and dysfunction in Gaucher disease unraveled by molecular dynamics and deep learning. *Proc Natl Acad Sci U S A* 2019;116:5086-5095.
146. Martínez-Arias R, Comas D, Mateu E, Bertranpetit J. Glucocerebrosidase pseudogene variation and Gaucher disease: recognizing pseudogene tracts in *GBA* alleles. *Hum Mutat* 2001;17:191-198.
147. Rana HQ, Balwani M, Bier L, Alcalay RN. Age-specific Parkinson disease risk in *GBA* mutation carriers: information for genetic counseling. *Genet Med* 2013;15:146-149.
148. Alcalay RN, Dinur T, Quinn T, Sakanaka K, Levy O, Waters C, et al. Comparison of Parkinson risk in Ashkenazi Jewish patients with Gaucher disease and *GBA* heterozygotes. *JAMA Neurol* 2014;71:752-757.
149. Sidransky E, Lopez G. The link between the *GBA* gene and parkinsonism. *Lancet Neurol* 2012;11:986-998.
150. Liu G, Boot B, Locascio JJ, Jansen IE, Winder-Rhodes S, Eberly S, et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's. *Ann Neurol* 2016;80:674-685.
151. McNeill A, Duran R, Proukakis C, Bras J, Hughes D, Mehta A, et al. Hyposmia and cognitive impairment in Gaucher disease patients and carriers. *Mov Disord* 2012;27:526-532.
152. Collins LM, Williams-Gray CH, Morris E, Deegan P, Cox TM, Barker RA. The motor and cognitive features of Parkinson's disease in patients with concurrent Gaucher disease over 2 years: a case series. *J Neurol* 2018;265:1789-1794.
153. Kim HJ, Mason S, Foltynie T, Winder-Rhodes S, Barker RA, Williams-Gray CH. Motor complications in Parkinson's disease: 13-year follow-up of the CamPaIGN cohort. *Mov Disord* 2020;35:185-190.
154. Oeda T, Umemura A, Mori Y, Tomita S, Kohsaka M, Park K, et al. Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. *Neurobiol Aging* 2015;36:3306-3313.
155. Liu G, Locascio JJ, Corvol JC, Boot B, Liao Z, Page K, et al. Prediction of cognition in Parkinson's disease with a clinical-genetic score: a longi-

- tudinal analysis of nine cohorts. *Lancet Neurol* 2017;16:620-629.
156. Winder-Rhodes SE, Evans JR, Ban M, Mason SL, Williams-Gray CH, Foltynie T, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. *Brain* 2013;136(Pt 2):392-399.
 157. Cilia R, Tunesi S, Marotta G, Cereda E, Siri C, Tesei S, et al. Survival and dementia in *GBA*-associated Parkinson's disease: the mutation matters. *Ann Neurol* 2016;80:662-673.
 158. Lwin A, Orvisky E, Goker-Alpan O, LaMarca ME, Sidransky E. Glucocerebrosidase mutations in subjects with parkinsonism. *Mol Genet Metab* 2004;81:70-73.
 159. Brockmann K, Srulijes K, Pflederer S, Hauser AK, Schulte C, Maetzler W, et al. *GBA*-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. *Mov Disord* 2015;30:407-411.
 160. Pal G, Robertson E, O'Keefe J, Hall D. The neuropsychiatric and motor profile of *GBA*-associated Parkinson's disease: a review. *Mov Disord Clin Pract* 2015;3:4-8.
 161. Munhoz RP, Picillo M, Fox SH, Bruno V, Panisset M, Honey CR, et al. Eligibility criteria for deep brain stimulation in Parkinson's disease, tremor, and dystonia. *Can J Neurol Sci* 2016;43:462-471.
 162. Lythe V, Athauda D, Foley J, Mencacci NE, Jahanshahi M, Cipolotti L, et al. *GBA*-associated Parkinson's disease: progression in a deep brain stimulation cohort. *J Parkinsons Dis* 2017;7:635-644.
 163. Singleton AB, Farrer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. *Mov Disord* 2013;28:14-23.