

# Chapter 2

## Clinical Features of *LRRK2* Carriers with Parkinson's Disease

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**Abstract** *LRRK2* mutations are present in 1% of all sporadic Parkinson's disease (PD) cases and 5% of all familial PD cases. Several mutations in the *LRRK2* gene are associated with PD, the most common of which is the Gly2019Ser mutation. In the following review, we summarize the demographics and motor and non-motor symptoms of *LRRK2* carriers with PD, as well as symptoms in non-manifesting carriers. The clinical features of *LRRK2*-associated PD are often indistinguishable from those of idiopathic PD on an individual basis. However, *LRRK2* PD patients are likely to have less non-motor symptoms compared to idiopathic PD patients, including less olfactory and cognitive impairment. *LRRK2*-associated PD patients are less likely to report REM sleep behavior disorder (RBD) than noncarriers. In addition, it is possible that carriers are more prone to cancer than noncarriers with PD, but larger studies are required to confirm this observation. Development of more sensitive biomarkers to identify mutation carriers at risk of developing PD, as well as biomarkers of disease progression among *LRRK2* carriers with PD, is required. Such biomarkers would help evaluate interventions, which may prevent PD among non-manifesting carriers, or slow down disease progression among carriers with PD.

**Keywords** *LRRK2* • Parkinson's disease • Clinical features

### Introduction

Since 2004 [1], when the association between mutations in the *LRRK2* gene and Parkinson's disease (PD) was first described, numerous studies have been conducted in different populations to define the clinical phenotype of *LRRK2*-associated PD (here and thereafter *LRRK2* PD). Several mutations in the *LRRK2* gene have been shown to be associated with PD, the most common of them being the Gly2019Ser mutation. While tremendous effort has been invested in clinically phenotyping

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*LRRK2* mutation carriers, there are significant limitations to the existing literature. Many of the published studies are single-site studies with small number of participants (and therefore may be underpowered), and the vast majority of the studies are cross-sectional rather than longitudinal.

Although the clinical features of *LRRK2* PD are, in most cases, indistinguishable from idiopathic PD (i.e., PD noncarriers) on an individual basis, recent studies have reported differences in motor and non-motor features between idiopathic PD and *LRRK2* PD. Specifically, *LRRK2* carriers may have slightly slower PD progression, and carriers have fewer non-motor symptoms, including less cognitive impairment and lower frequency of REM sleep behavior disorder and hyposmia when compared to noncarriers with PD. The demographics and motor and non-motor symptoms of *LRRK2* PD carriers, as well as symptoms in non-manifesting carriers, are described in the following review.

## ***LRRK2* Epidemiology**

### ***Ethnic Distribution***

PD is a common neurodegenerative disease affecting 1–2% of people older than 65 years. The etiology of PD has not been fully elucidated, but genetic factors clearly play a role in its pathogenesis. Along with *GBA* mutations, *LRRK2* mutations are to date the most common dominantly inherited (with reduced penetrance) genetic risk factor implicated in late-onset familial and sporadic PD [2]. Several mutations in the *LRRK2* gene have been shown to be associated with PD, the most common of which is the Gly2019Ser mutation [3]. Other mutations and variants in the *LRRK2* gene that have been associated with PD are Arg1441Gly, Arg1441Cys, Arg1441His, Ile2020Thr, Tyr1699Cys [3], Arg1628Pro, and Gly2385Arg [4]. The largest analysis to date [3], in which data from 24 populations worldwide were combined, showed that out of 19,376 unrelated PD patients, approximately 1% of PD patients without a family history of disease and 4% of PD with an affected first-degree relative were carriers of the *LRRK2* Gly2019Ser mutation. The frequency of *LRRK2* mutation carriers among PD patients varies greatly in different populations and is presented in Table 2.1. *LRRK2* mutations are most prevalent among North African Berbers. Lesage et al. [5] reported that 7/17 (41%) of North African families from Morocco, Algeria, and Tunisia with familial PD were carriers of the *LRRK2* Gly2019Ser mutation compared to 5/174 (2.9%) families of European origin, mostly French. Ishihara et al. [6] screened for the *LRRK2* mutation in Tunisian familial PD patients and reported that 38 out of 91 families (42%) were carriers of the *LRRK2* Gly2019Ser mutation compared to only 1 out of 39 (2.6%) North American Caucasian familial PD patients.

The *LRRK2* Gly2019Ser mutation is also common among Ashkenazi Jews (AJ). Orr-Urtreger et al. [7] reported that the frequency of *LRRK2* mutations in 344 AJ PD

**Table 2.1** Frequency of *LRRK2* mutation carriers among different PD patient populations

Reference	Mutation	Ethnicity	Number of participants	Sporadic PD	Familial PD	Comments
Lesage [5]	Gly2019Ser	North African (Algerian, Tunisian, Moroccan)	198		41%	
Ishihara [6]	Gly2019Ser	Tunisian	659		42%	
Hulihan [11]	Gly2019Ser	Tunisian	609	30%		
Orr-Urtreger [7]	Gly2019Ser	Ashkenazi Jewish	126	10.6%	26%	
Alcalay [8]	Gly2019Ser	Ashkenazi Jewish	488	19.9%		Excluding <i>GBA</i> carriers
Ferreira [12]	Gly2019Ser, Arg1441Gly, Arg1441Cys, Arg1441His	Portuguese	138	3.7%	16.1%	
Pulkes [13]	Arg1628Pro	Thai	958	11%		
Sierra [14]	Gly2019Ser	Spanish	493	8.7%		
Cilia [15]	Gly2019Ser, Arg1441Gly, Arg1441Cys, Arg1441His, Ile2020Thr	Italian	2976	1.6%		
Yescas [16]	Gly2019Ser, Arg1441His, Arg1441Cys	Mexican	319	0.9%		
Sanyal [17]	Gly2019Ser, Arg1441Gly, Arg1441Cys, Arg1441His, Tyr1699Cys, Ile2020Thr, Ile2012Thr	East Indian	320	0%		
Chien [18]	Gly2019Ser	Brazilian	200	0%		
Zhang [9]	Arg1628Pro	Chinese	1059	7.2%		
Kim [10]	Gly2385Arg Arg1628Pro	Korean Korean	1345	8.9% 0.8%		
Johnson [19]	Gly2019Ser	North American	79		2.5%	

(continued)

**Table 2.1** (continued)

Reference	Mutation	Ethnicity	Number of participants	Sporadic PD	Familial PD	Comments
Saunders-Pullman [20]	Gly2019Ser	North American (Hispanics, non-Hispanic, non-Jewish Caucasians)	104	2.9%		
Cilia [15]	Gly2019Ser, Arg1441Gly, Arg1441Cys, Arg1441His, Ile2020Thr	Ghana	100		0%	

patients is 14.8%. The frequency ranged from 10.6% of sporadic AJ PD patients to 26% of familial PD, but only 2.7% of non-AJ cases [7]. Alcalay et al. [8] reported that 97 of 488 (19.9%) AJ with PD, excluding carriers of *GBA* mutations, recruited in three medical centers in New York and Tel Aviv were carriers of a *LRRK2* mutation. This cohort contained both familial and nonfamilial PD subjects, but *LRRK2* carriers had a twofold risk of having a first-degree relative with PD compared to noncarriers (39.1% vs. 20.5%, respectively). In other populations worldwide, mutations in the *LRRK2* gene are less common. However, *LRRK2* variants with low PD penetrance are common in East Asian populations. In a cohort of 600 Chinese PD patients, Zhang et al. [9] reported that approximately 7% of PD patients are carriers of the Arg1628Pro *LRRK2* variant compared to 2.4% of controls. Kim et al. [10] reported a twofold increase in Gly2385Arg *LRRK2* variant carrier rate (approximately 9%) in a cohort of 923 Korean PD patients compared to controls.

### ***Gender Distribution***

While idiopathic PD is more common in men, gender distribution is more evenly distributed in *LRRK2* PD. A recently published meta-analysis described 50 studies of *LRRK2* PD where information on sex was available. A total of 1080 *LRRK2* PD patients were identified. The male to female ratio was 1.02:1.00 (50.6% men and 49.4% women), concluding that *LRRK2* PD lacks a sex effect [21]. Some studies report equal gender distribution among *LRRK2* carriers [8], while others report that *LRRK2* mutations were more common in men [7, 22, 23]. In contrast, Marras et al. [24] reported more women than men were carriers of the *LRRK2* mutation. High female frequency of *LRRK2* carriers compared to noncarriers was also reported in an Italian cohort of 2523 unrelated consecutive PD patients [15]. In conclusion, as opposed to idiopathic PD, *LRRK2* PD is probably *not* more common in men. Whether mutations are slightly more penetrant in women or whether PD risk among carriers is similar across genders remains to be studied.

*Age at Motor Onset*

Many studies have reported data on the age of onset of motor symptoms in *LRRK2* PD. Disease age of onset is highly variable and has been reported in patients in their 30s as well as after the age of 80 [25]. There are conflicting reports on the effect of *LRRK2* mutations on age of disease onset. In some studies, age of disease onset is similar in *LRRK2* PD and in idiopathic PD and has been shown to be between 52 and 60 years [8, 24–26]; other studies report younger age of disease onset in *LRRK2* carriers [27]. Healy et al. [3] reported an average age of disease onset of 58.1 years in *LRRK2* carriers, which was lower by approximately 3 years than in cases of idiopathic PD at the Queen Square Brain Bank. In this study, 8% of *LRRK2* mutation carriers developed symptoms of PD before the age of 40 (young-onset PD), compared to 4% of idiopathic PD patients.

*Penetrance*

*LRRK2* mutations are associated with autosomal dominant PD with incomplete penetrance. The penetrance varies among different mutations and variants. For example, penetrance is reportedly very low with the Gly2385Arg variant and very high among carriers of the Ile2020Thr mutation. The penetrance of the Gly2019Ser mutation is very controversial, and different studies have reported penetrance estimates ranging from 24 to 100% risk (see Table 2.2) [3]. The reason for such a wide range of penetrance estimation is unclear. Some of the disparity in penetrance estimation may reflect differences in population ethnicity, biases in patient recruitment (familial PD vs. unrelated PD patients’ relatives), differences in statistical methods, and differences between *LRRK2* mutations. A recently published paper by Marder et al. [28] estimated the penetrance of PD among Gly2019Ser mutation carriers, in

**Table 2.2** *LRRK2* Gly2019Ser penetrance estimates for Parkinson’s disease

Author	Penetrance at age 60	Penetrance at age 80	Methods of calculating penetrance
Marder [28]		26%	Kin-cohort method
Lesage [5]	33%	100%	Two highly selected familial autosomal dominant
Healy [3]	28%	74%	In 133 families, mainly familial PD cases
Latourelle [29]	30%	55%	Group of selected familial PD
Goldwurm [30]	15%	32%	Family members of unrelated PD patients
Goldwurm [31]	12%	33%	Kin-cohort study of 24 families of unrelated PD patients
Clark [26]	12%	24%	28 families of unrelated PD patients
Trinh [32]	50%	100%	Kin-cohort analysis

2270 relatives of PD patients from New York and Israel, at 26% by age of 80 using the kin-cohort method. This risk was almost threefold higher for the *LRRK2* carriers than in relatives predicted to be noncarriers of the Gly2019Ser mutation. Healy et al. [3] reported PD risk of 28% at age 59 and 74% at the age of 79. Currently, it is not possible to predict who among unaffected Gly2019Ser carriers will develop PD in the future.

## ***Homozygous Carriers***

Mutations in the *LRRK2* gene can cause autosomal dominant PD. Nearly all reported *LRRK2* PD cases have been heterozygote carriers of one of the mutations associated with PD. In our review we found 32 reported cases of homozygote carriers of the Gly2019Ser mutation. The phenotype of homozygous carriers is similar to that of heterozygote carriers, with regard to age of onset, Unified Parkinson's Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA), Geriatric Depression Scale (GDS), and non-motor symptoms [8, 33].

## **Motor Symptoms**

### ***Motor Phenotype***

Given the heterogeneity of PD, on an individual level, it is often impossible to distinguish a *LRRK2* carrier from a noncarrier. Carriers have a similar response to medical and surgical treatment and have similar rates of side effects and complications [3, 15, 24, 34, 35]. The largest report to date regarding the clinical features of 356 patients with *LRRK2* Gly2019Ser PD stated that the core features were asymmetric parkinsonism with tremor, bradykinesia, and rigidity that responded to dopamine replacement therapy. According to this study, *LRRK2* PD is indistinguishable from idiopathic PD [3], and at some point during the course of the disease, 93% of patients will develop all the cardinal motor symptoms of PD, including rest tremor, rigidity, and bradykinesia. Some reports suggest that tremor as a presenting symptom in *LRRK2* PD was more common than in idiopathic PD, affecting 63–64% compared to 39–52%, respectively [3, 24]. This observation was suggested also by a study focusing on tremor-dominant PD patients [36]. In contrast, other studies report that tremor is less frequent in *LRRK2* PD compared to noncarriers [8, 22]. Alcalay et al. [22] described the motor phenotype of 691 PD patients with early-onset PD (age of onset younger than 51 years). Of these, 26 cases were Gly2019Ser carriers. Gly2019Ser carriers were more likely to manifest the postural instability and gait difficulty (PIGD) phenotype than the tremor-predominant (TD) motor

phenotype. This observation was similarly seen in another study [8] reporting the phenotype of 553 AJ PD patients, of whom 140 were *LRRK2* carriers. *LRRK2* carriers were more likely to have a PIGD phenotype, report their first symptom in the lower extremities, and have persistent levodopa response for more than 5 years. Given the high prevalence of *GBA* mutations among AJ PD patients, in both studies, participants were screened for *GBA* mutations, and *GBA* carriers were excluded from the analysis. *LRRK2* mutation status was not associated with performance on the UPDRS part III (motor part) or presence of dyskinesia. A recent study reported in a Chinese PD population that the *LRRK2* Gly2385Arg variant was associated with motor fluctuations only in women [37]. Another study [38] compared gait and mobility in 50 patients with Gly2019Ser *LRRK2* PD to 50 noncarrier PD patients and found that *LRRK2* PD cases had greater gait variability and less consistent walking patterns than idiopathic PD. Gait parameters, assessed in three walking conditions (usual walking, dual tasking, and fast walking), were quantified by an accelerometer: In all three walking conditions, gait variability was larger, and the walking pattern was less consistent among *LRRK2* PD compared to idiopathic PD. The *LRRK2* carriers also took longer to complete the timed up and go (TUG) task and were more likely to report having fallen in the previous year. This study reported that *LRRK2* carriers were more associated with the PIGD subtype. Marras et al. [24] also reported gait disorder to be more common in *LRRK2* PD compared to idiopathic PD.

Time to first fall (as a marker of motor disease severity) was reported to be longer in patients with a mutation in *LRRK2* and was longer than in the Queen Square Brain Bank (QSBB) series [3].

### ***Response to Treatment and Development of Motor Complications***

The response to treatment with levodopa and development of motor complications in *LRRK2* are generally similar to idiopathic PD, although there is controversy in the literature. Almost all *LRRK2* carriers are reported to have good response of symptoms to levodopa similar to idiopathic PD patients [3, 24]. Drug-induced dyskinesia incidence is similar in *LRRK2* carriers and idiopathic PD, but the time to onset of dyskinesia in *LRRK2* carriers was longer by almost 3 years on average (8.4 years in carriers compared to 5.6 years in noncarriers) [3]. Yahalom et al. [34] reported that the prevalence of levodopa-induced dyskinesia (LID) and the mean duration of therapy from levodopa initiation to the development of LID do not differ between *LRRK2* mutation carriers and noncarriers in a cohort of 349 patients from Israel. Craig et al. [39] further demonstrated that the motor features in *LRRK2* PD and idiopathic PD do not differ in UPDRS scores, frequency of motor symptoms, or levodopa equivalent dose of treatment.

## ***Rate of Disease Progression***

Rate of disease progression in *LRRK2* patients was also described; however, the vast majority of studies are either retrospective or cross-sectional. A retrospective study, which compared the motor progression of AJ PD patients with and without *LRRK2* Gly2019Ser mutation, reported no difference in the time of progression to Hoehn and Yahr (HY) stage 3 (i.e., motor instability) [27]. There are still no published longitudinal studies describing rate of disease progression. Such studies are needed and will provide valuable information.

## ***Deep Brain Stimulation***

In the past 20 years, deep brain stimulation (DBS) has become an important treatment option for PD patients with motor complications and medication refractory tremor. In their review, Healy et al. [3] commented that 22 patients with *LRRK2* PD underwent stereotactic functional neurosurgery. Eighteen of them underwent subthalamic DBS, three had pallidotomy, and one had thalamotomy. The mean time from PD onset to surgery was 11.4 years, and the indications were usually motor fluctuations and dyskinesia (similar to idiopathic PD patients). It is estimated that *LRRK2* carriers are good candidates for DBS given the slower cognitive decline and the reports on dyskinesia [40]. Because of the frequency of Gly2019Ser mutations and the fact that only a fraction of PD patients undergo DBS, the reports on DBS treatment in carriers are limited. Two small studies have been published. One study including 13 *LRRK2* carriers and 26 noncarriers reported no difference in DBS outcomes after follow-up of 3 years post-DBS surgery [35]. The second study, including 15 carriers and 12 noncarriers, reported similar Hoehn and Yahr outcomes, but better improvement on the UPDRS-III (motor exam) among *LRRK2* carriers when patients were “off” medication and “on” DBS [41].

## ***Cognition***

Several studies compared the cognitive function of *LRRK2* carriers to idiopathic PD. Studies of cognition are prone to epidemiological challenges, as cognitive performance is highly correlated with level of education, age, and longer PD duration. Differences between carriers and noncarriers are subtle and not always identified by screening tests such as the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Exam (MMSE) tests.

In contrast, the following studies support the notion of milder cognitive changes in *LRRK2* PD patients compared to idiopathic PD patients:



A study assessing the neuropsychological performance in *LRRK2* Gly2019Ser PD patients and noncarrier PD patients from three movement disorder centers in New York and Tel Aviv reported that carriers performed better than noncarriers in attention (Stroop word reading test), executive function (Stroop interference test), and language (category fluency) [46]. Srivatsal et al. [47] also reported that *LRRK2* mutation carriers have better performance on certain cognitive tests, as well as lower rates of dementia compared to idiopathic PD patients. This study was conducted in eight sites and 1447 participants underwent a battery of seven cognitive tests. Twenty-nine of them had *LRRK2* mutations (24 with Gly2019Ser mutation and 5 with Arg1441Cys mutation). Mutation carriers demonstrated better performance in the MMSE and Letter-Number Sequencing test and had significantly lower frequency of dementia (4% compared to 19.6% in noncarriers). The motor UPDRS scores were also better in the mutation carriers. This study suggests that *LRRK2* carriers might have an overall milder disease course, although these findings require replication.

In addition, Somme et al. [48] described that *LRRK2* PD patients showed less impairment on scales for general cognition (Mattis Dementia Rating Scale) and episodic verbal memory (Rey's auditory verbal learning test, immediate recall, and delayed recall) and had less apathy and hallucinations compared to idiopathic PD.

Healy et al. [3] reported that the proportion of PD patients that develop cognitive impairment within 2 years of symptom onset is less than half in the *LRRK2* carriers than in idiopathic PD. Aasly et al. [49] also reported the *LRRK2* carriers in a Norwegian cohort have only mild cognitive changes even after many years of disease. Cognitive studies are summarized in Table 2.3

## ***Depression/Anxiety***

Findings on depression and anxiety among carriers with PD have been inconsistent. Several studies reported no difference in the Geriatric Depression Scale (GDS) between *LRRK2* carriers and noncarrier PD patients [8, 38]. Alcalay et al. [8] reported similar GDS scores in 97 *LRRK2* PD compared to 391 idiopathic PD in a cohort of AJ. Craig et al. [39] also reported no difference in the frequency of depression and anxiety between carriers and noncarriers. Shanker et al. [44] reported no difference in lifetime affective disorders between *LRRK2* carriers and noncarriers, but did report a trend toward a greater risk of premorbid mood disorder in the carriers.

On the other hand, a study comparing 25 *LRRK2* PD patients to 84 idiopathic PD patients from four movement disorder centers in Germany, Canada, the USA, and Brazil reported higher Beck Depression Inventory scores in *LRRK2* carriers but no difference in the State-Trait Anxiety Inventory (STAI) [24]. Belarbi et al. [45] also reported higher frequency of depression in the *LRRK2* carriers than in noncarriers. Goldwurm et al. [25] reported that 69% of *LRRK2* carriers in their cohort were depressed according to the Hamilton Depression Rating Scale scores.

**Table 2.3** Studies assessing differences between *LRRK2* PD and idiopathic PD on cognitive tasks

Reference	Cognitive task	Findings
<i>Cognitive screens</i>		
Alcalay et al. [8]	MoCA	No significant differences
Alcalay et al. [22, 42]	MMSE	No significant differences
Trinh et al. [32]	MMSE, MoCA, FAB	No significant differences
Lesage et al. [5]	MMSE	Mildly worse performance among carriers
<i>Neuropsychological testing</i>		
Ben Sassi et al. [43]	MMSE, MoCA, FAB	No significant differences
Shanker et al. [44]	FAB	No significant differences
Mirelman et al. [38]	MoCA, trail making tests A and B, verbal fluency, digit span, and Stroop test	No significant differences
Belarbi et al. [45]	Neuropsychological battery	No significant differences in cognitive performance. Higher rates of depression and hallucinations among carriers
Alcalay et al. [46]	Neuropsychological battery	<i>LRRK2</i> Gly2019Ser PD patients performed better than idiopathic PD patients on attention (Stroop word reading test), executive function (Stroop interference test), and language (category fluency) tasks.
Srivatsal et al. [47]	Neuropsychological battery, MMSE, clinical diagnosis of dementia	<i>LRRK2</i> Gly2019Ser PD patients performed better than idiopathic PD patients on the MMSE and Letter-Number Sequencing test and had significantly lower frequency of dementia (4% compared to 19.6% in noncarriers)
Somme et al. [48]	Neuropsychological battery and the Mattis Dementia Rating Scale	<i>LRRK2</i> PD patients showed less impairment on scales for general cognition ( Mattis Dementia Rating Scale) and episodic verbal memory (Rey's auditory verbal learning test, immediate recall, and delayed recall)

## Olfaction

The majority of studies reported less olfactory disturbance in *LRRK2* PD compared to idiopathic PD. A study from four movement disorder centers in Europe and the USA comparing olfaction with the Brief Smell Identification Test (B-SIT) reported significantly better olfactory identification in *LRRK2* PD subjects compared to idiopathic PD [24]. Saunders-Pullman et al. [50] also reported that *LRRK2* PD patients had significantly better University of Pennsylvania Smell Identification

Test (UPSIT) scores than idiopathic PD patients, by an average of six points, but had lower UPSIT scores than healthy controls. An additional study by Saunders-Pullman et al. [51] recently reaffirmed that *LRRK2* PD had better olfactory scores compared to idiopathic PD. Silveira-Moriyama et al. [52] reported higher scores on the “Sniffin’ sticks” and better odor identification in *LRRK2* PD compared to idiopathic PD, but lower scores compared to controls. Johansen et al. [53] showed that sporadic PD had significantly lower scores in olfaction (assessed by B-SIT) compared with *LRRK2* PD. Craig et al. [39] showed that UPSIT scores in *LRRK2* Gly2019Ser PD were higher than those in idiopathic PD by an average of five points.

However, some studies reported similarly impaired olfaction in *LRRK2* PD and idiopathic PD in mean UPSIT scores [54] and in the “Sniffin’ sticks” test [32]. Silveira-Moriyama et al. [54] reported that 19 *LRRK2* PD patients did not differ in their UPSIT scores from 145 idiopathic PD patients in a cohort from Portugal and the UK and that *LRRK2* PD patients’ UPSIT scores were lower than those of healthy controls. Valldeoriola et al. [55] reported that UPSIT scores in 14 *LRRK2* PD patients do not differ from those of 14 idiopathic PD patients in a Spanish cohort. Healy et al. [3] reported that abnormal olfaction was common and found in 51% of *LRRK2* PD patients after an average disease duration of 5 years.

## *Sleep Disorders*

Sleep disorders are frequently seen in *LRRK2* PD. Goldwurm et al. [25] reported that 56% of *LRRK2* PD patients had sleep disorders mainly manifesting as repeated awakenings and insomnia. Healy et al. [3] reported that 69% of *LRRK2* Gly2019Ser patients had sleep disturbances, but there was no significant difference from idiopathic PD patients. The most common sleep disturbances were insomnia and sleep fragmentation, but rapid eye movement (REM) sleep behavior disorder (RBD) and restless legs syndrome were also noted. When *LRRK2* carriers were compared to noncarriers in three different cohorts [8, 32, 56], carriers were less likely to report RBD. This observation was not observed by others [39, 45].

## *Autonomic Dysfunction*

Most reports on autonomic dysfunction did not observe a difference between carriers and noncarriers. Gaig et al. [39] reported that dysautonomic symptoms in *LRRK2* Gly2019Ser PD were not significantly different from those in idiopathic PD in a cohort of 1251 Spanish PD patients. They described a cohort of 33 *LRRK2* PD patients and compared them to idiopathic PD patients. Hao et al. [57] and Li et al. [4] found non-motor symptoms to be very common in PD patients, but did not find a difference in two different studies using the non-motor symptom questionnaire

(NMSQ) in a Chinese cohort comparing *LRRK2* PD (with Arg1628Pro or Gly2385Arg variants) and idiopathic PD. Alcalay et al. also reported no difference in NMS questionnaires in *LRRK2* carriers and noncarriers [8] in a cohort of AJ PD patients. Trinh et al. [32] reported no differences between *LRRK2* carriers and noncarriers in the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) questionnaires in a large cohort of Tunisian PD patients. Healy et al. [3] reported that 48% of *LRRK2* carriers had constipation, 28% were affected with urinary symptoms (mainly frequency and urge incontinence), and 11% of men reported erectile dysfunction; however, there was no comparison to idiopathic PD in this study.

## ***Vision***

Marras et al. reported worse performance on the 100-hue test of color discrimination in 25 *LRRK2* PD patients compared with 84 idiopathic PD patients from four movement disorder centers in Europe, Brazil, Canada, and the USA [24].

## ***Cancer***

Cancer frequency among idiopathic PD patients is probably lower than in the general population with the exception of melanomas [58, 59] and possibly breast cancer. Epidemiological studies of cancer frequency among *LRRK2* carriers face many challenges, including small numbers, mechanism by which cancer history is collected, and selection bias (those with cancer may have died and are not available to provide history). In contrast to idiopathic PD patients, the Gly2019Ser *LRRK2* mutation may not be overrepresented in patients with melanoma [60]. A study from three movement disorder centers in Israel reported a higher prevalence (odds ratio of 3.38) of non-skin cancers in 79 AJ *LRRK2* PD patients (carriers of the Gly2019Ser mutation) compared to 401 noncarrier PD patients [61]. Cancer history was obtained by personal interview and reviewing patients' files. The most common non-skin cancers were breast and prostate cancers. The study did not include a control group, so it remains unclear whether cancer frequency among *LRRK2* carriers is higher than in controls without PD. Another study reported a higher (almost threefold) prevalence of non-skin cancers (primarily breast and prostate cancers) as seen by chart reviews in 32 Gly2019Ser PD mutation carriers compared to 132 idiopathic PD in a cohort of 163 AJ [62]. Sixty-seven percent of the *LRRK2* carriers in that study were diagnosed with cancer before the onset of PD, whereas only 40% of noncarriers developed their first non-skin cancer before onset of PD.

Agalliu et al. [63] reported in a recently published multinational study from five centers in Europe, Israel, and the USA that Gly2019Ser *LRRK2* mutation carriers

have an overall increased risk of cancer compared to noncarriers, especially for hormone-related cancer and breast cancer in women. Gly2019Ser *LRRK2* mutation carriers had a 1.62-fold risk of developing non-skin cancers and a 2.3-fold risk of developing breast cancer compared to noncarriers. The cancer history was self-reported by the patients and confirmed by medical record review and tumor registry databases.

Ruiz-Martinez et al. [64] reported on cancer prevalence using population-based cancer registry in 732 Spanish PD patients with Arg1441Gly or Gly2019Ser mutations and in idiopathic PD. In this study cancer prevalence did not differ between PD Gly2019Ser carriers, PD Arg1441Gly carriers, and PD noncarriers, with the exception of a high prevalence of hematological cancers in the Arg1441Gly group.

The underlying biological mechanism that links the *LRRK2* Gly2019Ser mutation and cancer remains largely unknown. Proposed mechanisms include mitogenic kinase activity (given that Gly2019Ser mutations increase *LRRK2* activity) and possible modification of the immune system. The gain-of-function carcinogenic theory is supported by the findings that amplification and overexpression of the *LRRK2* gene have been reported in papillary renal and thyroid carcinomas [65].

## *Pathology*

The neuropathology of *LRRK2* PD was previously reviewed [66, 67]. Briefly, the most common pathology in autopsies of Gly2019Ser carriers is Lewy body pathology. However, as in the case of the clinical studies of *LRRK2* mutation carriers, the literature may be biased because of study design. First, the vast majority of Gly2019Ser autopsies were obtained from patients with neurodegenerative disorders in spite of an estimated penetrance of 30%. This is because brain banks are skewed toward collection from patients with neurodegeneration rather than healthy controls. Among autopsies of patients with parkinsonism, there may be additional bias. On one hand, in many cases, only Lewy body brain banks were genotyped in order to estimate Gly2019Ser mutation frequency in these banks; on the other hand, there is likely a publication bias where Gly2019Ser autopsies with Lewy body pathology are less likely to be reported as compared with brains with unusual pathology. For example, the Columbia University Brain Bank has six Gly2019Ser autopsies. All manifest Lewy body pathology, but one of them also contains tau inclusion bodies consistent with progressive supranuclear palsy pathology. Most of the non-Lewy body brain bank was not genotyped for the Gly2019Ser mutation. When the clinical features of those with Lewy body pathology were compared to those with other pathology (e.g., neuronal loss in substantia nigra), Kalia et al. [67] reported that the presence of Lewy bodies was associated with non-motor features of PD, while cases without Lewy body were more likely to manifest a more pure motor deficit. Carriers of mutations other than Gly2019Ser are less likely to have Lewy bodies, which were present only in 35% of the reported autopsies (8 out of

23). No autopsy with the common Asian variant Gly2385Arg has been reported to date.

In summary, pathological features of different *LRRK2* mutations may vary considerably. The majority of G2019S carriers with PD had Lewy body containing neurons, which may also correlate with the presence (or lack thereof) of non-motor symptoms. Autopsies of mutation carriers without PD are sparse and may be extremely informational for our understanding of the pathogenesis of the *LRRK2* mutations and their incomplete penetrance.

### ***Symptoms in Non-manifesting LRRK2 Carriers***

A few groups studied non-manifesting *LRRK2* mutation carriers. Study design often includes analyses of families with *LRRK2* mutations, where family member carriers and noncarriers are compared. To date, there are no studies which can clinically distinguish carriers without PD from their noncarrier family members.

A recently published study [68] assessed non-motor symptoms in 256 family relatives of AJ PD patients (non-manifesting Gly2019Ser *LRRK2* mutation carriers and noncarriers of the Gly2019Ser mutation). Non-manifesting carriers had higher non-motor symptom score on the non-motor symptom (NMS) questionnaire (questions relating to constipation and urinary urgency) than noncarriers. Differences between groups were more pronounced with older subject age and also included anxiety and daytime sleepiness. No differences between groups were found in motor scores (UPDRS part III), cognitive function (MoCA), or olfaction (UPSIT) [68].

Saunders-Pullman et al. reported that non-manifesting carriers of the *LRRK2* mutation had lower UPSIT scores compared to healthy controls but higher UPSIT scores compared to *LRRK2* PD patients [50]. Another study by Saunders-Pullman et al. [51] reported that non-manifesting *LRRK2* carriers had higher UPSIT scores than healthy controls, but their olfaction did not differ from first-degree family members of idiopathic PD patients.

Mirelman et al. assessed gait in 52 first-degree relatives of PD patients, in whom 25 were non-manifesting *LRRK2* mutation carriers and 27 were noncarriers. Mutation carriers had subtle gait changes. Although the groups did not differ in gait speed, stride time, or stride length, mutation carriers had altered gait variability (measure of gait consistency and stability) during fast walking and dual tasking [69]. The groups did not differ in the UPDRS part III scores.

Thaler et al. [70] reported that non-manifesting *LRRK2* carriers demonstrated poorer performance on computerized measure of executive functioning (Stoop test score and response time) compared with that of noncarriers. The groups did not differ in their MoCA scores, GDS scores, or UPDRS part III motor scores.

The only notable difference Marras et al. [24] reported between non-manifesting *LRRK2* mutation carriers and noncarriers was a marginally higher frequency of postural and action tremor in the former.

## Conclusions and Future Directions

In this review we highlighted the current data available on the demographics, motor and non-motor symptoms of *LRRK2* PD carriers, and symptoms in non-manifesting carriers. *LRRK2* is the most common dominantly inherited genetic factor implicated in late-onset familial and sporadic PD identified to date. Several mutations in the *LRRK2* gene have been shown to be associated with PD. The clinical phenotype of *LRRK2* PD is variable, similar to idiopathic PD, but is probably slightly milder, with less non-motor involvement compared to idiopathic PD patients. There is considerable variability in the literature regarding the epidemiology, penetrance, and symptoms of *LRRK2* PD. This heterogeneity may be partially explained by phenotypic variations of the different mutations in the *LRRK2* gene and the differences in experimental methods applied to identify motor and non-motor symptoms. Development of more sensitive biomarkers for identifying and monitoring motor and non-motor symptom progression is needed. Longitudinal studies and pathological data of *LRRK2* PD will likely help to shed light on the disease characteristics of this intriguing subgroup of PD patients.

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