



## LRRK2 Parkinson Disease

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## Summary

### Clinical characteristics

*LRRK2* Parkinson disease (PD) is characterized by features consistent with idiopathic PD: initial motor features of slowly progressive asymmetric tremor at rest and/or bradykinesia, cogwheel muscle rigidity, postural instability, and gait abnormalities that may include festination and freezing. Certain nonmotor symptoms in *LRRK2*-PD, especially REM sleep behavior disorder and cognitive decline, may occur at similar or slightly reduced frequency compared to typical idiopathic\* PD. Onset is generally after age 50, although early-onset (in the 20s) and late-onset (in the 90s) disease has been described.

\* Idiopathic PD refers to the presence of signs and symptoms of PD for which the etiology is currently unknown and in which there is no known family history of PD.

### Diagnosis/testing

The diagnosis of *LRRK2*-PD relies on clinical findings and the identification of a heterozygous pathogenic variant in *LRRK2*.

### Management

*Treatment of manifestations:* Symptomatic treatment of parkinsonism is the same as for idiopathic Parkinson disease: pharmacologic replacement of dopamine, most commonly accomplished with the precursor of dopamine, L-dopa, combined with carbi-dopa. Dopamine agonists may also be used, as well as monoamine oxidase-B (MAO-B) inhibitors, amantadine, and/or anticholinergics. Physical, occupational, and voice therapy may be beneficial. Exercise is often recommended. Treatment of nonmotor manifestations – e.g., depression, anxiety, sleep disorders, urinary issues, orthostatic hypotension – should be addressed based on individual manifestations.

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*Surveillance:* Annual evaluation for both motor and nonmotor symptoms. Motor evaluation focuses on gait and falls, slowness of movement and dexterity, tremor, and rigidity. Evaluation for nonmotor signs and symptoms includes assessment of constipation, mood disorder, impulse control disorders, other psychiatric disorders, cognitive changes, sleep disturbance, orthostatic hypotension, and urinary frequency. In addition, at least yearly evaluation for melanoma.

*Agents/circumstances to avoid:* Dopamine-blocking therapies may exacerbate parkinsonism.

## Genetic counseling

*LRRK2*-PD is inherited in an autosomal dominant manner. However, given the reduced penetrance associated with *LRRK2*-PD, a high percentage of affected individuals report unaffected parents. *De novo* mutation may occur; its frequency is unknown. Each child of an individual with *LRRK2* Parkinson disease has a 50% chance of inheriting the pathogenic variant. However, the risk of developing disease is lower than 50% because of age-related reduced penetrance. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant in the family is known.

## Diagnosis

While there are subtle group differences between *LRRK2* Parkinson disease (*LRRK2*-PD) and idiopathic PD (IPD), on an individual case basis *LRRK2*-PD is indistinguishable from idiopathic PD. Criteria for probable and clinically established PD were developed by the International Parkinson and Movement Disorders Society [Postuma et al 2015] (see also [Parkinson Disease Overview](#)).

Note: "Idiopathic Parkinson disease" and "sporadic Parkinson disease" are terms used in the Parkinson disease medical literature to describe Parkinson disease of unknown cause diagnosed in an individual with a negative family history. Future advances in the understanding of genetic risk factors are likely to identify genetic causes / risk factors for some Parkinson disease currently considered "idiopathic" or "sporadic."

## Suggestive Findings

*LRRK2* Parkinson disease (*LRRK2*-PD) **should be suspected** in individuals with the following clinical features, neuroimaging findings, and family history.

**Clinical features** include signs of Parkinson disease (PD):

- Bradykinesia (slowness of movement) with decrements in speed or amplitude as movements are continued  
AND
- Rest tremor (4-6-Hz tremor in a fully resting limb) and/or rigidity.

To meet Movement Disorders Society clinical diagnostic criteria [Postuma et al 2015], at least two supportive findings in addition to the signs of PD listed above should be present:

- Clear and dramatic beneficial response to dopaminergic therapy
- Levodopa-induced dyskinesias
- Rest tremor in a limb (prior or current)
- Positive results from an ancillary diagnostic test (e.g.):
  - Cardiac metaiodobenzylguanidine (MIBG) scintigraphy
  - Olfactory abnormality

However: (1) Early and untreated individuals with PD may not meet the supportive criteria, as dopaminergic therapy may not have been tried, and thus no response or dyskinesias documented; (2) attributing olfactory

abnormality to *LRRK2*-PD may be problematic, as the frequency of abnormal olfaction is reduced in individuals with *LRRK2*-PD compared with those who have IPD [Silveira-Moriyama et al 2010, Ruiz-Martínez et al 2011, Saunders-Pullman et al 2014].

**Exclusion criteria.** Early eye movement abnormalities, significant orthostatic hypotension, and signs and symptoms that support atypical parkinsonism are generally exclusionary criteria. However, *LRRK2*-PD may occasionally manifest with atypical features.

**Neuroimaging findings** (brain CT and MRI) are normal. DaT or PET scan may further support the diagnosis, but neither is necessary for diagnosis.

**Family history** for *LRRK2*-PD consistent with autosomal dominant inheritance. However, absence of a family history of *LRRK2*-PD does not preclude the diagnosis (see Genetic Counseling).

## Establishing the Diagnosis

The diagnosis of *LRRK2*-PD is **established** in a proband with clinical features consistent with PD and a heterozygous pathogenic (or likely pathogenic) variant in *LRRK2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *LRRK2* variant of uncertain significance does not establish or rule out the diagnosis.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *LRRK2*-PD overlaps with IPD and other genetic forms of PD, the best approach to understanding the genetic cause in an individual usually includes testing for *LRRK2* as well as other genes that lead to PD.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

### Single-gene testing

- **Targeted analysis for specific pathogenic variants** can be performed first in individuals with PD of certain ancestries, including Ashkenazi (Eastern European) Jewish, North African Berber, Spanish/Hispanic, Belgian, Portuguese, and Asian (see Molecular Genetics, **Pathogenic Variants**), or when the family-specific pathogenic variant is known. However, additional testing to evaluate for other causative genes may also be indicated. Ashkenazi Jews may occasionally have both the *LRRK2* p.Gly2019Ser variant and a *GBA1* (formerly *GBA*) Parkinson-related variant [Yahalom et al 2019].
- **Sequence analysis** of *LRRK2* may be performed in individuals who are not of any of the ancestries listed above if the suspicion of *LRRK2*-PD is high.

A **multigene panel** that includes *LRRK2* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-

sequencing-based tests. (4) Currently some PD panels do not include testing for variants in glucocerebrosidase resulting from pathogenic variants in *GBA1*, the most frequent cause of genetic PD, for which clinical trials are ongoing. Therefore, single-gene testing for *GBA1* may be needed if not included on the panel.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Comprehensive genomic testing.** When the phenotype is indistinguishable from many other inherited disorders characterized by features of Parkinson disease, comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in *LRRK2* Parkinson Disease

Gene <sup>1</sup>	Method	Proportion of Proband with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>LRRK2</i>	Sequence analysis <sup>3</sup>	~100% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	See footnote 6.

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. *LRRK2*-PD is defined by the presence of a pathogenic variant in *LRRK2*; thus, the pathogenic variant detection rate approaches 100% for nucleotide changes, small deletions/insertions, and pathogenic variants in splice site consensus motifs.

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. To date, no deletions or duplications involving *LRRK2* have been reported to cause *LRRK2* Parkinson disease [Mata et al 2005a, Di Fonzo et al 2006].

7. Homozygous p.Gly2019Ser cases are not phenotypically different from heterozygous cases [Ishihara et al 2006, Ben Romdhan et al 2018].

## Clinical Characteristics

### Clinical Description

*LRRK2* Parkinson disease (PD) is characterized by features consistent with idiopathic PD (IPD), including initial symptoms of slowness, decreased arm swing, rest tremor, and initial motor signs of bradykinesia, associated with rigidity and/or resting tremor. Gait abnormalities and postural instability also occur, particularly with progression of the disease [Alcalay et al 2013, Mirelman et al 2013, Trinh et al 2014b]. While indistinguishable individually from IPD, motor and cognitive features suggest that as a group, signs and symptoms of *LRRK2*-PD may be milder than in IPD [Kestenbaum & Alcalay 2017, Ben Romdhan et al 2018, Saunders-Pullman et al 2018] (see Phenotype Correlations by Cause).

*LRRK2*-PD disease onset is insidious with a slowly progressive course.

- Age at onset is typically in the 50s and 60s but varies, even within the same family. The range of disease onset is 28-95 years with a mean of 58-61 years – similar to or slightly younger than in individuals with

IPD [Ishihara et al 2006, Healy et al 2008, San Luciano et al 2010, Trinh et al 2014b, Marder et al 2015, San Luciano et al 2017].

- The percentage of men and women with *LRRK2*-PD is approximately equal, although individuals with *LRRK2*-PD of Tunisian descent demonstrated a male predominance [Ben Romdhan et al 2018].
- Clinical features are overall similar in men and women; however, women may have more complications related to therapy [San Luciano et al 2017, Ben Romdhan et al 2018].

**Motor features.** Data conflict regarding the predominant motor features specific to *LRRK2*-PD. Some have reported more tremor at onset [Healy et al 2008, Marras et al 2011], while others have reported more gait-predominant features, postural instability, and rigidity at onset [Alcalay et al 2009, Gan-Or et al 2010]. Motor features are overall similar to IPD and include the following:

- Slowness and difficulty with dexterity (bradykinesia)
- Tremor, which may occur at rest or during action, although this sign may not be present
- Slow walk or shuffling gait
- Unsteadiness and falls
- Low vocal volume, with difficulty projecting
- Facial hypomimia (masking)

As with other forms of Parkinson disease, the disorder is slowly progressive, and generally spreads from unilateral to bilateral involvement. Disease progression varies significantly among individuals and is related to age of onset.

**Nonmotor features** may appear prior to the movement disorder or emerge with motor disease progression. They include the following [Healy et al 2008, Saunders-Pullman et al 2011, Alcalay et al 2013, Gaig et al 2014, Alcalay et al 2015]:

- Cognitive decline, including mild cognitive impairment and dementia
- Constipation
- Hyposmia/anosmia
- Depression, anxiety, and other neuropsychiatric features [Brockmann et al 2011, Marras et al 2011, Shanker et al 2011]
- Seborrhea
- Sexual dysfunction
- Sleep complaints, including poor sleep quality, excessive daytime sleepiness, sleep fragmentation, early awakening, daytime sleepiness, and insomnia [Pont-Sunyer et al 2015]
- Urinary frequency
- Orthostatic hypotension

### **Risk of malignancy**

- An association between melanoma and PD of any etiology has been reported [Huang et al 2015, Dalvin et al 2017]. Compared to individuals without PD, those with PD due to any cause have a 3.8-fold increased likelihood of having a preexisting melanoma [Dalvin et al 2017]. The rate of melanoma in individuals with *LRRK2*-PD who have a heterozygous p.Gly2019Ser pathogenic variant is similar or increased compared to the risk of melanoma in individuals with other forms of Parkinson disease [Agalliu et al 2015, Agalliu et al 2019].
- Non-skin cancer, especially leukemia and colon cancer, may be increased in individuals with a heterozygous pathogenic variant in *LRRK2*, although not all studies support this association (see Phenotype Correlations by Cause) [Agalliu et al 2015, Agalliu et al 2019].

**Atypical Parkinson disease phenotypes.** For a small number of individuals with a *LRRK2* pathogenic variant, clinical features and/or pathology support an atypical parkinsonian syndrome. These atypical phenotypes include progressive supranuclear palsy (PSP), multiple-system atrophy, corticobasal syndrome, amyotrophic lateral sclerosis-like signs, and frontotemporal dementia [Zimprich et al 2004a, Ross et al 2006, Dächsel et al 2007, Chen-Plotkin et al 2008, Santos-Rebouças et al 2008, Lee et al 2018b]. See also **Neuropathology** (below).

**DaT and PET scanning.** In general, PET scan results in individuals with *LRRK2*-PD are similar to those in others with adult-onset PD from a variety of causes.

- There is typically significant reduction in uptake of  $^{18}\text{F}$ -dopa (PET) and dopamine transporter (DaT-SPECT).
- Studies of these and other tracers support abnormalities of both dopaminergic and serotonergic metabolism [Lin et al 2008, Fu et al 2018].

Infrequently, normal PET scanning early in the disease course has been observed in both *LRRK2*-PD and non-*LRRK2*-PD and does not preclude a PD diagnosis [Wile et al 2016].

**Neuropathology.** The hallmark pathologic features of the common idiopathic form of PD are neuronal loss and gliosis in the substantia nigra and the presence of intracytoplasmic inclusions (or Lewy bodies). The majority of individuals with *LRRK2*-PD exhibit these characteristics [Ross et al 2006]. However, a significant subset of individuals with *LRRK2*-PD, particularly those with the p.Gly2019Ser pathogenic variant, have substantia nigra dopaminergic neuronal loss and gliosis *without* accompanying Lewy body inclusion. Of great interest, the pathology correlates with the extent of nonmotor clinical features. Kalia et al [2015] correlated the presence of Lewy bodies with nonmotor features of cognitive impairment / dementia, anxiety, orthostatic hypotension, and the absence of Lewy bodies with a predominantly motor phenotype.

*LRRK2*-PD has also been documented with alternate pathologies. Of particular note, three out of six individuals with parkinsonism and a heterozygous *LRRK2* pathogenic variant identified in a large brain bank series were found to have pathology suggestive of PSP or pre-PSP with tau-positive neurons, neuropil threads, and tufted astrocytes [Blauwendraat et al 2019]. Additional series include those with PSP pathology and neurofibrillary tangles, as well as ubiquitin-immunopositive inclusions (Marinesco bodies) and TDP-43 inclusions [Wszolek et al 2004, Zimprich et al 2004b, Funayama et al 2005, Ross et al 2006, Covy et al 2009, Ujji et al 2012].

Click [here](#) (pdf) for more information on neuropathology.

## Phenotype Correlations by Cause

Among the confirmed pathogenic variants in *LRRK2*, the pathogenic p.Gly2019Ser variant is the most common. The numerous published reports related to its associated clinical features are the focus of this section. See Genotype-Phenotype Correlations for differences associated with other *LRRK2* variants.

Most studies have shown that individual clinical features are indistinguishable between individuals with *LRRK2*-PD and idiopathic PD (IPD) [Healy et al 2008, Alcalay et al 2013]. However, mild differences are observed in many studies. These cluster overall on a slightly milder clinical motor course for individuals with *LRRK2*-PD who have the p.Gly2019Ser variant compared to those with IPD. Some of the difference in nonmotor features may be attributable to neuropathologic heterogeneity, as individuals with fewer or less severe nonmotor features are more likely to have isolated nigral degeneration without associated Lewy bodies [Kalia et al 2015].

## Reported Clinical Differences Between Individuals with *LRRK2*-PD and IPD

While *LRRK2*-PD typically has late-onset disease (mean of 58 years [Marder et al 2015] or 61.6 years [San Luciano et al 2017]), a subset of individuals have very early-onset disease (in the 20s). This may be related to other genes that modify the expression of *LRRK2* [Trinh et al 2016].

Affected male-to-female ratio is similar, compared to 60% male and 40% female for IPD [Gan-Or et al 2015, San Luciano et al 2017].

Overall survival is longer in those with *LRRK2*-PD [Thaler et al 2018].

### Motor features

- Generally a milder motor course, including slower motor progression, reported in those with *LRRK2*-PD [Ben Romdhan et al 2018, Saunders-Pullman et al 2018]
- Note: Some longitudinal studies do not support this finding [Yahalom et al 2014, Nabli et al 2015].
- Postural instability and gait difficulty may be slightly worse in individuals with *LRRK2*-PD [Alcalay et al 2013, Mirelman et al 2013], although a lower rate of falls has also been reported [Healy et al 2008, Brockmann et al 2011].

### Nonmotor features

- **Cognition** may be slightly less impaired in individuals with *LRRK2*-PD, although dementia may still occur [Alcalay et al 2013, Alcalay et al 2015, Somme et al 2015, Srivatsal et al 2015].
- Note: Some studies have not found any significant differences in cognition between individuals with *LRRK2*-PD and those with IPD [Aasly et al 2005, Goldwurm et al 2006, Belarbi et al 2010, Ben Sassi et al 2012].
- More difficulty with **color discrimination** in those with *LRRK2*-PD [Marras et al 2011]
- **Constipation** is less severe in the Tunisian Berber cohort with *LRRK2*-PD [Trinh et al 2014a] compared to those with IPD.
- **Olfaction** is impaired to a lesser extent in those with *LRRK2*-PD [Silveira-Moriyama et al 2010, Marras et al 2011, Ruiz-Martínez et al 2011, Saunders-Pullman et al 2014].
- Possibly a slightly lower risk of **depression** in those with *LRRK2*-PD [Marras et al 2016]
- **Sleep-onset insomnia** may occur more frequently in those with *LRRK2*-PD, although the frequency of excessive daytime sleepiness may not differ [Pont-Sunyer et al 2015].
- **REM sleep behavior disorder** is less frequent in Ashkenazi Jews and Tunisian Berbers with the *LRRK2* p.Gly2019Ser variant [Saunders-Pullman et al 2014, Trinh et al 2014a] and in Spanish individuals with p.Gly2019Ser, p.Arg1441Cys, and p.Arg1441Gly variants [Pont-Sunyer et al 2015] compared to those with idiopathic PD.
- **Heart rate variability** may be normal in individuals with *LRRK2*-PD (i.e., less impaired than in those with IPD) [Visanji et al 2017] and there may be less sympathetic denervation and orthostasis [Quattrone et al 2008, Tijero et al 2013].
- **Non-skin cancer** may be more common in those with *LRRK2*-PD, although this is not consistently observed across all studies [Saunders-Pullman et al 2010, Inzelberg et al 2012, Agalliu et al 2015, Warø & Aasly 2017].

### Co-Occurring Pathogenic Variants in *LRRK2* and *GBA1*

Among 12 Ashkenazi Jewish individuals who had both the *LRRK2* pathogenic p.Gly2019Ser variant and a heterozygous pathogenic *GBA1* (formerly *GBA*) variant, no significant differences in phenotype were observed when compared to those with just the *LRRK2* variant [Yahalom et al 2019].

### Genotype-Phenotype Correlations

Differences in phenotype have been observed for the rarer pathogenic *LRRK2* variants as compared to the p.Gly2019Ser variant [Domingo & Klein 2018]:

- Individuals with the p.Arg1441Gly pathogenic variant may be more likely to have excessive tremor, although they may also present with bradykinesia [Paisán-Ruíz et al 2004, Mata et al 2005b].

However, one systematic review found more frequent tremor in individuals with the p.Gly2019Ser variant compared to those with the p.Arg1441Gly variant.

The same review found that individuals with a pathogenic variant at residue 1441 (p.Arg1441Gly, p.Arg1441Cys, p.Arg1441His, p.Arg1441Ser) have more frequent motor fluctuations compared to individuals with the p.Gly2019Ser variant [Trinh et al 2018].

- Individuals with a p.Gly2385Arg variant appear to have more rapidly progressive parkinsonism with greater subjective and objective scores of motor decline, as well as more motor fluctuations, compared to individuals with the p.Gly2019Ser variant [Marras et al 2016].
- Individuals with at least one risk-factor variant (p.Gly2385Arg, p.Arg1628Pro, or p.Ser1647Thr) showed greater motor progression over a four-year period than those with the p.Gly2019Ser variant [Oosterveld et al 2015, Saunders-Pullman et al 2018].
- Individuals with the pathogenic p.Tyr1699Cys variant may present with a variety of signs and symptoms. This variant was identified in a large Korean family who had clinical features similar to those with idiopathic PD, although interfamilial clinical heterogeneity was described [Kim et al 2012]. Atypical presentations initially reported include symptoms of dementia and amyotrophy [Zimprich et al 2004a; Family A] or behavior disorder characterized by depression and anxiety [Khan et al 2005; Lincolnshire kindred].

## Penetrance

Penetrance of *LRRK2* pathogenic variants is age dependent and may vary based on pathogenic variant and population ethnicity (including ancestral background and country of origin [Hentati et al 2014]). Both Marder et al [2015] and Lee et al [2017a] employed the kin-cohort method to estimate genotypes of family members whose genotypes were unknown. In these two studies penetrance in Jews and non-Jews was not statistically different. Penetrance in men and women was also not statistically different.

The most frequent variant is p.Gly2019Ser; it exists as a founder variant in both Eastern European (Ashkenazi) Jews and North African Berbers.

- In Ashkenazi Jews with this variant, penetrance is estimated at 25%-30% up to age 80 [Ozelius et al 2006, Goldwurm et al 2007, Marder et al 2015].
- In North African Berbers, lifetime penetrance is estimated at 45% [Hulihan et al 2008], and the risk to heterozygotes and rarer homozygotes was equivalent [Ishihara et al 2006].
- In non-Jewish individuals, penetrance associated with this variant is estimated at 42% by age 80 [Lee et al 2017a].

**Other variants.** High penetrance was reported for some of the rarer pathogenic *LRRK2* variants [Lee et al 2017a]:

- The p.Arg1441Cys variant has been associated with penetrance of 95% by 75 years [Haugarvoll et al 2008, Klein & Westenberger 2012] in a group of mostly familial cases and penetrance of 80% by 80 years in another study [Ruiz-Martínez et al 2010].
- A study of the original *LRRK2*-linked family with the p.Ile2020Thr variant similarly estimated a 70% penetrance by age 70 [Funayama et al 2002].



## Nomenclature

Alternate nomenclature for *LRRK2*-PD includes the following:

- PARK8, which refers to the chromosomal region of 12q12 linked to disease in a large Japanese PD kindred [Funayama et al 2002].
- "Dardarin," the Basque word for "tremor," has been used to refer to *LRRK2*-PD caused by the pathogenic p.Arg1441Gly variant.

## Prevalence

In the US, *LRRK2*-PD causes approximately 1% of simplex PD (i.e., single occurrences in a family) and approximately 5%-6% of familial PD.

- A founder effect exists for certain pathogenic variants, such as p.Gly2019Ser (**North African Berber and Ashkenazi Jewish populations**). p.Gly2019Ser is also common in individuals of **Portuguese, Brazilian, Spanish, and Italian ancestry** and has been reported in **Puerto Rican, British, Norwegian, Japanese, Chinese, and Indian** populations.
- A founder effect exists for the p.Arg1441Gly variant in the **Basque** population.
- p.Arg1441Cys may be more common in the **southern Italian** and **Belgian** populations.

Further information about the prevalence of certain variants in different populations can be accessed [here](#) (pdf).

## Differential Diagnosis

The differential diagnosis of *LRRK2* Parkinson disease includes other genes associated with inherited forms of Parkinson disease, neurologic entities that commonly mimic Parkinson disease, and autosomal dominant neurologic conditions and genetic disorders in which parkinsonism can be a prominent feature (see [Parkinson Disease Overview](#)).

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *LRRK2* Parkinson disease, the evaluations below (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Assessment of motor symptoms and signs, including motor functioning and falls
- Assessment of nonmotor symptoms and signs, including:
  - Cognition
  - Constipation
  - Mood
  - Illusions/hallucinations
  - Sexual dysfunction
  - Pain
  - Sleep disturbance
  - Urinary difficulties, including frequency
  - Orthostatic hypotension
  - Baseline skin evaluation for evidence of melanoma
- Consider referral to a clinical geneticist and/or genetic counselor.

## Treatment of Manifestations

The treatment of individuals with *LRRK2*-PD does not differ from that of idiopathic PD (IPD), and should be tailored to the individual (see also [Parkinson Disease Overview](#)), with referral to a neurologist with training in movement disorders, a rehabilitation medicine specialist, psychiatrist, sleep medicine specialist, gastroenterologist, urologist, and pain medicine specialist, as indicated.

**Pharmacotherapy**, if needed, is symptomatic and may include the following:

- Pharmacologic replacement of dopamine
  - Different formulations of levodopa may be considered, including l-dopa combined with cardi-dopa.
  - Multiple formulations of l-dopa (which may be immediate release or longer acting) exist, as well as multiple routes of delivery, including oral (the major one), sublingual, and enteric.
  - Utilization of l-dopa should be driven by clinical need, and the clinician should consider using the lowest dose that yields a satisfactory clinical effect [Olanow & Stocchi 2018, Bressman & Saunders-Pullman 2019].
- Monoamine oxidate B (MAO-B) inhibitors, including selegiline and rasagiline
- Amantadine (Symmetrel®)
- Dopamine receptor agonists
- Anticholinergics

### Supportive treatment

- Exercise, as safe for the particular affected individual; often recommended [Giladi et al 2016, Lee et al 2018a]
- Physical and occupational therapy
- Voice therapy, particularly the Lee Silverman Voice Treatment
- Cognitive behavioral therapy; potentially beneficial either with or without pharmacologic treatment
- For those with hallucinations, consideration of non-dopamine-blocking medications (particularly pimavanserin; see Gaig et al [2014])

**Treatment of complications of levodopa therapy.** With disease progression, up to approximately half of individuals with PD develop complications of levodopa therapy within the first two years of treatment [PSG 2000, Stocchi et al 2010]; complications may include the following:

- Troubling dyskinesias
  - Dyskinesias in individuals with *LRRK2*-PD occur at a similar or lower frequency than in those with IPD [Healy et al 2008], with no difference in prevalence or latency to dyskinesia [Yahalom et al 2012].
  - In general, women with *LRRK2*-PD have a higher rate of dyskinesias than men [San Luciano et al 2017].
  - While dyskinesia is related to l-dopa dose, decisions regarding dosing should be guided by the clinician [Olanow & Stocchi 2018].
- Significant wearing-off of doses
- Delayed onset of medication action
- Refractory rest tremor

Neurosurgical procedures such as deep brain stimulation (DBS) of the subthalamic nucleus (STN) / globus pallidus interna (GPi) may be considered if there is good response to but complications from l-dopa therapy.

- [Guidelines](#) for choice of DBS target are described by the Congress of Neurological Surgeons.
- Whether target selection should be guided by *LRRK2* genotype is under investigation.

- Response to both STN and GPi have been reported in individuals with *LRRK2*-PD [Breit et al 2010, Greenbaum et al 2013, Stefani et al 2013, Artusi et al 2019, Leaver et al 2019, Kuusimäki et al 2020].

Further, disease-modifying clinical trials are under way for *LRRK2*-PD (see Therapies Under Investigation).

## Surveillance

**Table 2.** Recommended Surveillance for Individuals with *LRRK2* Parkinson Disease

System/Concern	Annual Evaluation
<b>Neurologic</b>	Neurologic exam: <sup>1</sup> incl bradykinesia, rigidity, tremor, & gait & postural stability assessment (MDS-UPDRS) <sup>2</sup>
<b>Gastrointestinal</b>	Assess for signs & symptoms of constipation.
<b>Psychiatric</b>	Assess for symptoms of depression, anxiety, apathy, hallucinations, illusions, impulse control disorders, or other psychiatric condition.
<b>Sleep disorder</b>	Assess for signs & symptoms.
<b>Cardiovascular</b>	Assess for orthostatic hypotension.
<b>Urologic/Gynecologic</b>	Assess for urinary frequency & sexual dysfunction.
<b>Skin</b>	Full skin exam by dermatologist for signs of melanoma. <sup>3</sup>

1. To assess effect of motor therapies (including wearing off and dyskinesias) and need for symptomatic treatment

2. Systematic assessment of history of motor and nonmotor features including associated disability as well as examination of motor features are captured in the Movement Disorder Society Sponsored Revision of the [Unified Parkinson's Disease Rating Scale](#) (MDS-UPDRS) [Goetz et al 2008].

3. Dalvin et al [2017]

## Agents/Circumstances to Avoid

Dopamine-blocking therapies (both typical and atypical dopamine-blocking psychiatric medications as well as dopamine blockers for gastrointestinal causes) may exacerbate parkinsonism in *LRRK2*-PD and should be avoided, when possible.

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

While the data are restricted to case reports and registries, most support treatment with L-dopa during pregnancy (reviewed by Seier & Hiller [2017]).

See [MotherToBaby](#) for further information on medication use during pregnancy.

## Therapies Under Investigation

The *Lrrk2* protein is a fusion of Rab (Roc), COR, and kinase (MAPK) domains, and pathogenic variants are postulated to augment kinase activity [Kachergus et al 2005, West et al 2005, Gloeckner et al 2006, Greggio et al 2006]. Hence, the development of specific **kinase inhibitors** offers an attractive therapeutic target for neuroprotection in asymptomatic and affected *LRRK2* heterozygotes, as well as for IPD [Albrecht 2005, Toft et al 2005]. A number of inhibitors are being developed; however, selectivity, specificity, and delivery into the central nervous system remain difficult issues to address [Lee et al 2010]. *LRRK2* kinase inhibition had been associated with pulmonary complications in rodents and non-human primates [Herzig et al 2011, Baptista et al 2013, Fuji

et al 2015]. However, more recent data suggest that this effect is reversible, and that toxicity is not significant (see [bioRxiv](#)). Initial studies of the drug DNL201 have proceeded to a Phase I clinical trial ([ClinicalTrials.gov](#)).

In addition to kinase inhibitors, **antisense oligonucleotides** have been evaluated preclinically [Zhao et al 2017], and may have therapeutic potential. Such therapies are reviewed in Sardi & Simuni [2019] and in Shihabuddin et al [2018].

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*LRRK2* Parkinson disease (PD) is inherited in an autosomal dominant manner with reduced penetrance.

## Risk to Family Members

### Parents of a proband

- To date, all individuals with *LRRK2*-PD inherited an *LRRK2* pathogenic variant from a parent. However, because penetrance of *LRRK2*-PD is reduced, a high percentage of probands report unaffected parents.
- The probability that an asymptomatic parent with a pathogenic variant will become symptomatic increases with age.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. (See also Related Genetic Counseling Issues, **Considerations in families with an apparent *de novo* pathogenic variant.**)
  - Although no instances of germline mosaicism have been reported, it remains a possibility.
  - Similarly, *de novo* mutation has not been seen, but remains a possibility. Some sites within *LRRK2* may be highly mutable – notably, the arginine codon at residue 1441, in which four sometimes recurring amino acid changes have been reported to be pathogenic [Mata et al 2016].
- The family history of some individuals diagnosed with *LRRK2*-PD may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, reduced penetrance, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or has an *LRRK2* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. However, the risk to sibs of developing disease is lower than 50% because of reduced, age-related penetrance (see Penetrance).
- The probability that an asymptomatic sib who has the pathogenic variant will become symptomatic increases with age.

### Offspring of a proband

- Each child of an individual with *LRRK2*-PD has a 50% chance of inheriting the pathogenic variant.
- The probability that an offspring with a pathogenic variant will become symptomatic increases with age.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent is affected or has an *LRRK2* pathogenic variant, the parent's family members may be at risk.

## Related Genetic Counseling Issues

### Testing of asymptomatic at-risk individuals

- Testing for at-risk relatives is possible once the *LRRK2* pathogenic variant has been identified in an affected family member. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result), as well as the capabilities and limitations of such testing, should be discussed in the context of formal genetic counseling prior to testing. The Genetic Information Non-Discrimination Act (GINA) does not provide protection against genetic discrimination for life insurance, long-term insurance, or disability insurance.

### Testing of asymptomatic at-risk individuals younger than age 18 years

- Testing of asymptomatic minors for adult-onset disorders for which treatment of an asymptomatic individual does not decrease morbidity or mortality is not considered appropriate. Such testing negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors [position statement](#) on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics [policy statement](#): ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *LRRK2*-PD, it is appropriate to consider testing of symptomatic individuals regardless of age.

**Considerations in families with an apparent *de novo* pathogenic variant.** When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *LRRK2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **American Parkinson Disease Association (APDA)**  
**Phone:** 800-223-2732  
**Fax:** 718-981-4399  
**Email:** [apda@apdaparkinson.org](mailto:apda@apdaparkinson.org)  
[www.apdaparkinson.org](http://www.apdaparkinson.org)
- **Fox Trial Finder**  
[foxtrialfinder.michaeljfox.org](http://foxtrialfinder.michaeljfox.org)
- **MedlinePlus**  
 Parkinson disease
- **Michael J. Fox Foundation for Parkinson's Research**  
**Phone:** 800-708-7644 (toll-free)  
**Email:** [info@michaeljfox.org](mailto:info@michaeljfox.org)  
[www.michaeljfox.org](http://www.michaeljfox.org)
- **Parkinson's Foundation**  
**Phone:** 800-4PD-INFO (473-4636)  
**Email:** [contact@parkinson.org](mailto:contact@parkinson.org)  
[www.parkinson.org](http://www.parkinson.org)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A.** LRRK2 Parkinson Disease: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PARK8	<a href="#">LRRK2</a>	12q12	Leucine-rich repeat serine/threonine-protein kinase 2	Parkinson's disease Mutation Database (LRRK2)	LRRK2	LRRK2

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for LRRK2 Parkinson Disease ([View All in OMIM](#))

168600	PARKINSON DISEASE, LATE-ONSET; PD
607060	PARKINSON DISEASE 8, AUTOSOMAL DOMINANT; PARK8
609007	LEUCINE-RICH REPEAT KINASE 2; LRRK2

## Molecular Pathogenesis

*LRRK2*, which comprises 144 kb and 51 exons, encodes a leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2). LRRK2 is a 2,527-amino acid protein (286 kd) that shares homology with the Roco family of proteins. The six conserved domains are the following [Bosgraaf & Van Haastert 2003, Mata et al 2006]:

- Ankyrin repeat
- Leucine-rich repeat
- Roc
- COR
- Kinase
- WD40

See Figure 1.

Several biochemical studies have confirmed kinase activity for LRRK2 wild type protein [West et al 2005, Gloeckner et al 2006, Greggio et al 2006, Iaccarino et al 2007]. Additionally, LRRK2 has GTPase activity [Ito et al 2007, Li et al 2007, Liu et al 2016]. Given the size, domain composition, and organization of LRRK2, and the potential for protein-protein interactions, it is likely to be part of a higher molecular-weight complex involved in cellular signaling. Monomers of LRRK2 protein may also dimerize [Guaitoli et al 2016, Civiero et al 2017].

*LRRK2* pathogenic variants have been reported through the gene including in the ROC, COR, kinase, and WD40 domains.

Abnormal LRRK2 has been implicated in a number of different pathways [Berwick & Harvey 2011, Berwick & Harvey 2012, Friedman et al 2012, Gómez-Suaga & Hilfiker 2012, Tong et al 2012, Bravo-San Pedro et al 2013, Howlett et al 2017, Lee et al 2017b, Pan et al 2017, Verma et al 2017], including the following:

- Autophagy
- Endosomal-lysosomal function
- Mitochondrial dysfunction
- Immune signaling microglial motility
- Synaptic vesicle trafficking and Wnt signaling

**Mechanism of disease.** In general, pathogenic variants tend to result in overactivity of LRRK2 [Cookson 2015].

While the precise mechanism of action of *LRRK2* pathogenic variants is unknown, most (e.g., p.Gly2019Ser) appear to disrupt kinase or GTPase activity. *LRRK2* p.Gly2019Ser is within exon 41 and the "activation hinge" of the kinase domain and is associated with increased intra- and intermolecular phosphorylation [Luzón-Toro et al 2007, Anand et al 2009]. While in vitro assays have provided conflicting information on whether enhanced kinase activity represents a characteristic feature shared by all pathogenic *LRRK2* variants, several well-known pathogenic variants have been shown to increase phosphorylation of known LRRK2 substrates [Greggio & Cookson 2009, Sheng et al 2012, Steger et al 2016].

***LRRK2*-specific laboratory technical considerations.** Penetrance of *LRRK2* pathogenic variants is age dependent and may vary based on pathogenic variant and population ethnicity (including ancestral background and country of origin [Hentati et al 2014]). In addition, some disease-associated *LRRK2* variants are common in specific populations. Therefore, interpretation of *LRRK2* variants requires careful review of all relevant literature.

Of note, reported risk-factor variants (which are not associated with mendelian disease) include p.Arg1628Pro, p.Ser1647Thr, and p.Gly2385Arg [Oosterveld et al 2015].

**Table 3.** Notable *LRRK2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_198578.4 NP_940980.4	c.4321C>T	p.Arg1441Cys	May be more common in southern Italian & Belgian populations – see Prevalence
	c.4321C>G	p.Arg1441Gly	<ul style="list-style-type: none"> <li>• Founder variant in the Basque population – see Prevalence</li> <li>• Associated with excessive tremor – see Genotype-Phenotype Correlations [Paisán-Ruiz et al 2004, Mata et al 2005b]</li> </ul>
	c.4322G>A	p.Arg1441His	See Genotype-Phenotype Correlations.
	c.4321C>A	p.Arg1441Ser	
	c.6059T>C	p.Ile2020Thr	The change found in the original <i>LRRK2</i> family [Funayama et al 2005]
	c.6055G>A	p.Gly2019Ser	<ul style="list-style-type: none"> <li>• Most frequent pathogenic variant – see Prevalence</li> <li>• See Genotype-Phenotype Correlations and Penetrance [West et al 2005, Greggio et al 2006, MacLeod et al 2006, Smith et al 2006, Jaleel et al 2007].</li> </ul>
	c.5096A>G	p.Tyr1699Cys	A range of clinical presentations have been reported – see Genotype-Phenotype Correlations [Kim et al 2012].

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

### Author Notes

Dr Saunders-Pullman is the Bachmann-Strauss Chair of Neurology at Mount Sinai. Her research interests focus on the clinical-genetic spectrum of Parkinson disease (PD) and dystonia, including the study of biomarkers and molecular pathways implicated in PD. Ms Raymond is a genetic counselor and clinical research manager. Ms Elango is also a genetic counselor at Mount Sinai. The authors have no financial disclosures.

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### Author History

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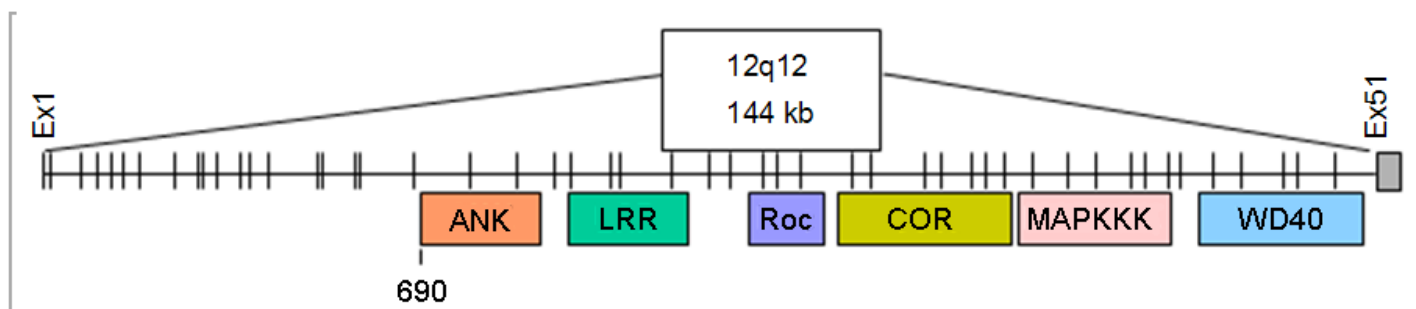
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**Figure 1.** Schematic representation of the 144-kb *LRRK2* loci on chromosome 12q12. The estimated start of the *Lrrk2* domain structure is indicated by the residue number (690) below the exonic-intronic (Ex1-Ex51) and domain scheme. Domains:

ANK = ankyrin repeat region

LRR = leucine-rich repeat

Roc = Ras of complex; GTPase

COR = C terminal of Ras

MAPKKK = MAPK kinase kinase

WD40

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- 29 April 2010 (me) Comprehensive update posted live
- 2 November 2006 (me) Review posted live
- 6 July 2006 (mf) Original submission

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