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NLM Citation: Lange LM, Klein C. *PINK1* Type of Young-Onset Parkinson Disease. 2010 Mar 16 [Updated 2024 Apr 25]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

PINK1 Type of Young-Onset Parkinson Disease

Synonym: PARK-*PINK1*

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Created: March 16, 2010; Updated: April 25, 2024.

Summary

Clinical characteristics

PINK1 type of young-onset Parkinson disease is characterized by early onset (median age at onset 32 years) of tremor, bradykinesia, and rigidity that are often indistinguishable from other causes of Parkinson disease. Lower-limb dystonia may be a presenting sign. Postural instability, hyperreflexia, abnormal behavior, and psychiatric manifestations have been described. The disease is usually slowly progressive. Individuals have a marked and sustained response to oral administration of levodopa (L-dopa), frequently associated with L-dopa-induced fluctuations and dyskinesias.

Diagnosis/testing

The diagnosis of *PINK1* type of young-onset Parkinson disease is established by the identification of biallelic *PINK1* pathogenic variants on molecular genetic testing.

Management

Treatment of manifestations: PINK1 type of young-onset Parkinson disease usually responds well to L-dopa and/or other dopamine agonists, which may be used in combination with catechol-O-methyltransferase inhibitors or monoamine oxidase-B inhibitors, anticholinergics, and amantadine. Physical therapy and/or occupational therapy to improve and/or maintain gross motor and fine motor skills as well as speech therapy. Invasive therapies include intrajejunal L-dopa-carbidopa pump, subcutaneous apomorphine pump, or deep brain stimulation. L-dopa-induced dyskinesias can be treated by reducing L-dopa dose, switching to dopamine receptor agonists, deep brain stimulation, or continuous treatment with L-dopa or apomorphine. Atypical neuroleptic agents can be used for neuropsychiatric manifestations; standard treatments for depression. Cholinesterase inhibitors can be used to treat dementia. Consider droxidopa, midodrine, fludrocortisone, and/or supportive measures for orthostasis. Symptomatic treatment for constipation.

Surveillance: Neurologic evaluation every three to 12 months to assess motor and non-motor manifestations and treatment efficacy; in addition, assess for atypical manifestations and therapy needs at each visit.

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Neuropsychiatric evaluation in those with mood disorder / psychotic symptoms or as needed. Cognitive assessment annually or as needed. At each visit, assess nutrition and safety of feeding; assess for symptoms of orthostasis and measure supine and standing blood pressure and pulse; assess for constipation, urinary urgency, or urge incontinence; and assess family needs.

Agents/circumstances to avoid: Neuroleptic treatment may exacerbate parkinsonism.

Genetic counseling

PINK1 type of young-onset Parkinson disease is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PINK1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *PINK1* pathogenic variants. Once the *PINK1* pathogenic variants have been identified in an affected family member, heterozygote testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

Updated guidelines on the molecular diagnosis of Parkinson disease were provided in a joint effort by the European Federation of Neurological Societies (EFNS), the European Section of the International Parkinson and Movement Disorders Society (MDS-ES), and the European Neurological Society (ENS) [Berardelli et al 2013]. Some national societies have also published guidelines on the molecular diagnosis of Parkinson disease, such as the German Society for Neurology.

In addition, new diagnostic criteria using a biological classification referred to as SynNeurGe have been published [Höglinger et al 2024]. This classification has three components: (1) the presence or absence of pathologic alpha-synuclein (Syn) in tissues or cerebrospinal fluid (CSF), (2) evidence of underlying neurodegeneration defined by neuroimaging (Neur), and (3) identification of pathogenic variants that cause or strongly predispose to Parkinson disease (Ge).

Suggestive Findings

PINK1 type of young-onset Parkinson disease **should be suspected** in individuals with the following clinical and family history findings.

Clinical findings

- Early onset. Onset is age <40 years in 57%; late onset (27%) and juvenile onset (16%) can also occur.
- Parkinsonism (bradykinesia, resting tremor, rigidity)
- Dyskinesia
- Motor fluctuations
- Dystonia
- Cognitive decline
- Psychiatric manifestations
- Good response to levodopa (L-dopa) treatment (in 98% of individuals with a reported L-dopa response)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *PINK1* type of young-onset Parkinson disease **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PINK1* 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 biallelic *PINK1* variants of uncertain significance (or of one known *PINK1* pathogenic variant and one *PINK1* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *PINK1* type of young-onset Parkinson disease is indistinguishable from many other inherited causes of Parkinson disease, recommended molecular genetic testing approaches include the use of a **multigene panel** or **comprehensive genomic testing** (exome sequencing, genome sequencing). A multigene panel requires that the clinician determine which genes are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: (1) *PINK1* single-exon and multiexon deletions/duplications have been identified in individuals with *PINK1* type of young-onset Parkinson disease; molecular genetic testing should include deletion/duplication analysis (see Table 1). (2) Single-gene testing (sequence analysis of *PINK1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A multigene panel that includes *PINK1*, *PRKN*, *PARK7*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting the identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of *PINK1* type of young-onset Parkinson disease is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which genes are likely involved. **Exome sequencing** is most commonly used, **genome sequencing** can also be considered.

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 *PINK1* Type of Young-Onset Parkinson Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PINK1	Sequence analysis [3]	>88% [4]
	Gene-targeted deletion/duplication analysis [5]	<12% [4]

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 the interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of the Human Gene Mutation Database [Stenson et al 2020]
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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

PINK1 type of young-onset Parkinson disease is characterized by typically early-onset Parkinson disease that is often clinically indistinguishable from other genetic causes of Parkinson disease or idiopathic Parkinson disease. Typical features include bradykinesia, rigidity, dyskinesia, motor fluctuations, and dystonia. Some individuals have cognitive decline and psychiatric manifestations. The following information is based on a systematic review of published reports including 205 individuals with *PINK1* type of young-onset Parkinson disease from 136 families (see www.mdsgene.org and references therein).

Table 2. *PINK1* Type of Young-Onset Parkinson Disease: Frequency of Select Features

Feature	% of Persons w/Feature [1]	Comment
Bradykinesia	95%	
Rigidity	90%	
Resting tremor	78%	
Dyskinesia	67%	
Motor fluctuations	79%	
Dystonia	48%	Often of the lower limbs
Cognitive decline	29%	Including mild cognitive impairment & dementia
Autonomic dysfunction	48%	Most commonly including urinary urgency or urge incontinence & orthostatic hypotension
Psychiatric manifestations	33%-56%	Depression in 51%, anxiety in 56%, psychotic symptoms in 33%

1. Data is based on 205 reported individuals identified through the MDSGene *PINK1* Review, previously published by Kasten et al [2018] and updated on the MDSGene website in February 2024 (from www.mdsgene.org; last accessed 2-29-24). Note: Clinical information was often incomplete (e.g., missing data ranged from 7%-79% for the items reported above). Numbers displayed indicate the percentages of individuals with the respective clinical feature out of all individuals for whom this feature was reported (valid percentages); missing data was not taken into account for calculation.

Onset. The majority of individuals (57%) have early onset (age at onset <40 years), 27% have late onset, and 16% have juvenile onset (age at onset <21 years). Note: The age of onset was not specified in 10% of individuals. The median age of onset is 32 years (interquartile range: age 24-40 years; range: age 9-67 years) (see www.mdsgene.org).

Parkinsonian features are usually asymmetric; in some individuals the manifestations at onset are symmetric. *PINK1* type of Parkinson disease clinically resembles other monogenic causes of Parkinson disease, especially those with recessive inheritance, and Parkinson disease of unknown cause. Individuals frequently present with all the typical features of Parkinson disease, including bradykinesia, rigidity, tremor, and postural instability. Tremor and bradykinesia are the most common presenting signs. The disease is slowly progressive. Rigidity and postural instability (60%) frequently occur with disease progression. Sleep benefit was reported for 40% of individuals (see www.mdsgene.org). A clinical presentation resembling atypical parkinsonism is very rare.

Non-motor Parkinson features are frequently reported (92%) in individuals with *PINK1* type of young-onset Parkinson disease and commonly include psychiatric involvement, cognitive impairment, and autonomic dysfunction.

Psychiatric involvement. Abnormal behavior and/or psychiatric manifestations – in particular, depression (51%), anxiety (56%), and psychotic symptoms (33%) (see www.mdsgene.org) – can occur in affected individuals. Related sleep impairment (e.g., falling and staying asleep) is also common in individuals with *PINK1* type of young-onset Parkinson disease [Ricciardi et al 2014].

Cognitive decline, ranging from mild cognitive impairment to dementia, has been reported for a subset of individuals.

Information on the occurrence of **hyposmia** is scarce (www.mdsgene.org; only available for 24 individuals in total and present in ten).

Autonomic dysfunction was reported for 48% of individuals (see www.mdsgene.org) and most commonly include urinary urgency, urge incontinence, constipation, and orthostatic hypotension.

Other additional neurologic manifestations. Dystonia (often of the lower limbs) and hyperreflexia may also be present or develop as the disease progresses [Bonifati et al 2005]. Dystonia has also been reported as the initial sign in a subset of individuals (18% of individuals with available data).

Neuroimaging. CT and MRI neuroimaging of individuals with *PINK1* type of young-onset Parkinson disease is usually normal. Imaging of dopamine function (using DaTscan) generally demonstrated relatively symmetric loss of radioligand uptake in the striatum, similar to the pattern seen in the Parkin type of young-onset Parkinson disease, *LRRK2* (Gly2019Ser) type of Parkinson disease, and *SNCA* type of Parkinson disease [McNeill et al 2013].

Response to treatment. In general, the vast majority of individuals with *PINK1* type of young-onset Parkinson disease have a good response to L-dopa therapy [Over et al 2021]; it was suggested to be even better than in Parkinson disease of unknown cause [Valente & Ferraris 2010]. Usually, this positive response persists over time, although no systematic longitudinal assessment is available. L-dopa primarily addresses motor features of the disease; additional medication might be needed to address non-motor features, especially psychiatric involvement. Side effects of L-dopa are common and most frequently include L-dopa-induced dyskinesias; motor fluctuations are also reported, and rarely dystonia. Response to non-L-dopa therapies including dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, anticholinergics, and/or amantadine is also good, but information is limited [Over et al 2021]. Surgical therapies, including deep brain stimulation and thalamotomy, have only been reported in a small number of individuals with usually a moderate-to-good response; however, the sample size is too small to draw meaningful conclusions.

Prognosis. Progression is slower compared to Parkinson disease of unknown cause [Kasten et al 2018]. However, detailed and systematic data on disease progression is limited [Kasten et al 2018]. Large, multicenter studies with longitudinal and systematic data collection are needed. In general, the expected life span in individuals with *PINK1* type of young-onset Parkinson disease is similar to Parkinson disease of unknown cause. Common causes of an earlier death include complications related to Parkinson disease (e.g., pneumonia due to severe dysphagia and aspiration, falls resulting in serious injuries due to gait difficulties, or immobility).

Heterozygotes

The evidence of heterozygous *PINK1* variants causing or acting as a risk factor for Parkinson disease remains controversial. Individuals with a heterozygous *PINK1* pathogenic variant usually remain asymptomatic but may show subtle subclinical alterations (e.g., a latent nigrostriatal dopaminergic deficit on functional imaging, premotor-motor excitability changes detected by transcranial magnetic stimulation, reduced arm swing, hyposmia, and/or diminished color discrimination) [Eggers et al 2010, Nürnberger et al 2015, Weissbach et al 2017]. In asymptomatic heterozygotes, voxel-based morphometry revealed an increase of putaminal and pallidal gray matter volume, findings similar to those in the Parkin type of young-onset Parkinson disease [Binkofski et al 2007, Reetz et al 2010].

Several individuals with Parkinson disease and a heterozygous *PINK1* pathogenic variant have been identified, including individuals with young-onset Parkinson disease [Bonifati et al 2005, Abou-Sleiman et al 2006, Hayashida et al 2021]. These studies suggest that age at onset might differ between individuals with biallelic and heterozygous *PINK1* pathogenic variants, with the age at onset of biallelic individuals being slightly younger. The clinical phenotype was similar in both groups, except some features (e.g., dystonia, hyperreflexia, and sleep benefit) seemed to be less common in heterozygous individuals. In one case-control study, heterozygous *PINK1* variant p.Gly411Ser was significantly associated with a markedly increased risk for Parkinson disease (odds ratio = 2.92, P=0.032), a finding that was supported by functional analyses [Puschmann et al 2017]. However, the results of another more recent large-scale meta-analysis suggested that *PINK1* variant p.Gly411Ser is likely benign, that other *PINK1* heterozygous pathogenic variants are not likely associated with an increased risk for Parkinson disease, and that heterozygosity for a *PINK1* pathogenic variant is not a "robust risk factor" for Parkinson disease [Krohn et al 2020].

Genotype-Phenotype Correlations

No correlation between the type of variant and age at onset, clinical presentation, or disease progression has yet been observed.

Modifiers. Recently, it has been shown that somatic mitochondrial variant load is a disease-onset modifier for *PINK1* (and Parkin) type of young-onset Parkinson disease. By investigating mitochondrial DNA (mtDNA) integrity in individuals with biallelic (n=84) and heterozygous (n=170) *PINK1 or PRKN* pathogenic variants compared to individuals with Parkinson disease of unknown cause (n=67) and controls (n=90), it was shown that affected and unaffected individuals with a heterozygous *PINK1 or PRKN* pathogenic variant can be distinguished by heteroplasmic mtDNA variant load; and individuals with biallelic *PINK1* or *PRKN* pathogenic variants contain more heteroplasmic mtDNA variants in blood than individuals with a heterozygous *PINK1* or *PRKN* variant [Trinh et al 2023].

Further, one individual with biallelic *PINK1* pathogenic variants and homoplasmy for pathogenic variants in two mitochondrial genes encoding subunits of complex I (*MT-ND5* and *MT-ND6*) was reported with very early-onset Parkinson disease [Piccoli et al 2008]; thus, it was hypothesized that the combination of pathogenic variants in *MT-ND5* and *MT-ND6* accelerated the disease onset.

Penetrance

Biallelic *PINK1* pathogenic variants are considered fully penetrant [Höglinger et al 2024]. Penetrance of heterozygous variants is under debate (see Heterozygotes).

Nomenclature

Based on the International Parkinson and Movement Disorder Society Task Force for Nomenclature of Genetic Movement Disorders, the recommended name for Parkinson disease caused by *PINK1* pathogenic variants is "PARK-*PINK1*" [Marras et al 2016, Lange et al 2022].

Prevalence

The prevalence is not known. *PINK1* pathogenic variants are a rare cause of early-onset Parkinson disease but are the second most common form of autosomal recessive Parkinson disease [Jia et al 2022].

The proportion of women among individuals with *PINK1* type of young-onset Parkinson disease is 54%. The majority of families are of Asian (36%), White/European (31%), or mixed (21%) ancestry; reports of individuals of Arab, African, or Indian ancestry are rare (see www.mdsgene.org).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic germline pathogenic variants in *PINK1*.

Differential Diagnosis

Clinically, *PINK1* type of young-onset Parkinson disease and **idiopathic Parkinson disease** are difficult to differentiate (see Parkinson Disease Overview). More than 80% of individuals with Parkinson disease have no family history of the disorder. A monogenic cause of Parkinson disease can be identified in some individuals with a positive family history or a young age at disease onset.

Early-onset autosomal recessive Parkinson disease. *PINK1* type of young-onset Parkinson disease and early-onset Parkinson disease of other etiologies (see Table 3) are difficult to distinguish by clinical examination.

Table 3. Genes Associated with Early-Onset Autosomal Recessive Parkinson Disease in the Differential Diagnosis of *PINK1* Type of Young-Onset Parkinson Disease

Gene	PD Designation [1]	Median Age at Onset (Range) [2]	Selected Features
PRKN	Parkin type of early-onset Parkinson disease (PARK-*Parkin*)	31 yrs (3-81)	• Most common cause of EOPD • PARK-*PINK1* & PARK-*Parkin* are clinically indistinguishable.
PARK7 (DJ1)	PARK-*PARK7* (OMIM 606324)	27 yrs (15-40)	• Phenotype similar to PARK-*Parkin* • IDD &/or seizures occasionally
DNAJC6	PARK-*DNAJC6*	11 yrs (7-42)	• Pyramidal signs • IDD / early cognitive impairment • Early & vivid hallucinations on intake of dopamine agonists • Early falls • Saccadic abnormalities • Pyramidal signs

Table 3. continued from previous page.

Gene	PD Designation [1]	Median Age at Onset (Range) [2]	Selected Features
FBXO7	PARK-*FBXO7* (OMIM 260300)	17 yrs (10-52)	• IDD / early cognitive impairment • Early & vivid hallucinations & behavioral abnormalities on intake of dopamine agonists • Early falls • Saccadic abnormalities • Gaze palsy • Oculogyric spasms • Pyramidal signs • Autonomic dysfunction
SYNJ1	PARK-*SYNJ1* (OMIM 615530)	21 yrs (12-31)	• Early cognitive impairment • Early falls • Saccadic abnormalities • Gaze palsy • Pyramidal signs • Ataxia • Autonomic dysfunction
VPS13C	PARK-*VPS13C* (OMIM 616840)	29 yrs (0-70)	• Early cognitive impairment • Early falls • Pyramidal signs • Autonomic dysfunction

EOPD = early-onset Parkinson disease; IDD = intellectual developmental disorder
1. Nomenclature based on Marras et al [2016] and Lange et al [2022].
2. Data based on Kasten et al [2018], Wittke et al [2021], and the MDSGene website (www.mdsgene.org).

Levodopa-responsive dystonia. For individuals with juvenile-onset Parkinson disease, especially those with prominent dystonia, L-dopa-responsive dystonia should be considered, including:

- GTP cyclohydrolase 1-deficient dopa-responsive dystonia caused by heterozygous pathogenic variants in *GCH1*;
- Tyrosine hydroxylase-deficient dopa-responsive dystonia (see Tyrosine Hydroxylase Deficiency) caused by biallelic pathogenic variants in *TH*;
- Sepiapterin reductase-deficient dopa-responsive dystonia (see Sepiapterin Reductase Deficiency) caused by biallelic pathogenic variants in *SPR*.

In general, the phenotype of tyrosine hydroxylase-deficient dopa-responsive dystonia and sepiapterin reductase-deficient dopa-responsive dystonia is much more severe.

Management

No clinical practice guidelines specifically for *PINK1* type of young-onset Parkinson disease have been published. Some national societies (e.g., the German Society for Neurology) recommend treating *PINK1* type of young-onset Parkinson disease similar to Parkinson disease of unknown cause. In the absence of internationally published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PINK1* type of young-onset Parkinson disease, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *PINK1* Type of Young-Onset Parkinson Disease: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Detailed neurologic exam focusing on presence & extent of movement disorder	Using the Unified Parkinson Disease Rating Scale [1]
	Assessment for presence/severity of atypical manifestations	
	Eval by PT, OT, & SLP if required	
Autonomic	Assessment for presence/severity of urinary urgency, urge incontinence, constipation, & orthostatic hypotension	
Neuropsychiatric	Formal neuropsychiatric assessment w/neuropsychiatrist	
Cognition	Formal cognitive testing	
Sleep	Assessment for presence/severity of sleep disturbances, e.g., difficulties falling asleep, staying asleep, or rapid eye movement sleep behavior disorder (RBD)	Consider polysomnography for persons w/ suspected RBD.
Smell	Assessment for presence/severity of hyposmia	
Nutrition/ Gastrointestinal	• Nutritional eval by dietician to monitor & ensure adequate caloric intake • SLP assessment of safety of feeding	
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *PINK1* type of young-onset Parkinson disease to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources • Social work referral • Home nursing referral

MOI = mode of inheritance; OT = occupational therapist; PT = physical therapist; SLP = speech-language therapist
1. Goetz et al2008]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

To date, the treatment of *PINK1* type of young-onset Parkinson disease does not differ from that of Parkinson disease of other etiologies (e.g., other monogenic forms, Parkinson disease of unknown etiology), and no gene-specific guidelines or recommendations have been developed. Updated treatment guidelines for Parkinson disease have been published by national and international neurologic societies, such as the European or American Academy of Neurology (EAN or AAN), often in cooperation with the Movement Disorder Society (MDS).

To date, no therapy can slow or stop the progression of Parkinson disease; available treatment options are purely symptomatic. In general, optimal management should begin at diagnosis and involve a multidisciplinary team approach, including pharmacologic and non-pharmacologic interventions [Bloem et al 2021].

Table 5. *PINK1* Type of Young-Onset Parkinson Disease: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Neurologic	**Medication** Levodopa (L-dopa) in combination w/peripheral dopa decarboxylase inhibitor (carbidopa, benserazide):	• Response to L-dopa is usually significant & sustained for low doses even after long

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
	1. Immediate-release (IR) tablets 2. Disintegrating tablets 3. Controlled-release (CR) tablets 4. Extended-release (ER) capsules 5. Inhalation powder Dopamine agonists: 1. IR & CR tablets 2. Subcutaneous injections (apomorphine) 3. Transdermal patch (rotigotine) Other drugs used in combination w/L-dopa & dopamine agonists: COMT inhibitors or MAO-B inhibitors, anticholinergics, & amantadine.	disease duration in persons w/*PINK1* type of young-onset Parkinson disease. • The major problem is the early occurrence of severe L-dopa-induced dyskinesias (abnormal involuntary movements) & fluctuations. Fluctuations can be ↓ by a combination of dopamine therapies (e.g., dopamine agonists), adding COMT inhibitors, & keeping the doses of L-dopa as low as possible.
	Supportive non-pharmacologic options • PT &/or OT to improve &/or maintain gross motor & fine motor skills. • Speech therapy	
	Invasive therapies • Intrajejunal L-dopa-carbidopa pump • Subcutaneous apomorphine pump • DBS (preferably STN-DBS)	• Can be considered for advanced stages w/fluctuations not satisfactorily controlled w/oral medications. [1] • STN-DBS improves motor symptoms & quality of life. [1] • The use of DBS was reported to be successful in 4/5 persons w/*PINK1* type of young-onset Parkinson disease. [2]
Dyskinesias	**Treatment options:** • Reduction of L-dopa dose • Dopamine receptor agonists • DBS • Continuous application of L-dopa or apomorphine (pump therapies)	
Neuropsychiatric manifestations	• Atypical neuroleptic agents such as low-dose clozapine, quetiapine, or pimavanserin & reduction of dopaminergic therapy can ↓ delusions & hallucinations. • Standard treatments for depression	
Dementia	Consider treatment w/cholinesterase inhibitor (rivastigmine).	
Orthostasis	Consider treatment w/droxidopa, midodrine, fludrocortisone.	Consider supportive measures (e.g., compression stockings, abdominal belts).
Constipation	Symptomatic treatment	Consider dietary adjustments before using medication.

COMT = catechol-O-methyltransferase; DBS = deep brain stimulation; MAO-B = monoamine oxidase-B; OT = occupational therapy; PT = physical therapy; STN = subthalamic nucleus

1. Treatment recommendations on invasive therapies based on the recent EAS/MDS-ES guidelines [Deuschl et al 2022].

2. According to the most recent review [Kuusimäki et al 2020]

Surveillance

Table 6. *PINK1* Type of Young-Onset Parkinson Disease: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Neurologic eval to assess motor & non-motor manifestations & treatment efficacy	Every 3-12 mos to modify treatment as needed
	• Assessment of presence/severity of atypical manifestations • Assessment of need for PT, OT, & speech therapy	At each visit
Psychiatric	Neuropsychiatric eval	In those w/mood disorder or psychotic symptoms, or as needed
Cognition	Cognitive assessment	Annually or as needed
Nutrition/ Gastrointestinal	• Nutritional eval by dietician to monitor & ensure adequate caloric intake • SLP assessment of safety of feeding	As needed
Autonomic dysfunction	• Assess for symptoms of orthostasis. • Measure supine & standing blood pressure & pulse. • Assess for constipation, urinary urgency, or urge incontinence.	At each visit
Family support & resources	Assess need for: • Community or online resources • Social work support; • Home nursing referral.	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Neuroleptic treatment may exacerbate parkinsonism.

Evaluation of Relatives at Risk

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

Pregnancy Management

There is only a single case report of a woman with biallelic *PINK1* pathogenic variants who became pregnant [Li et al 2021]. During pregnancy, symptoms neither worsened nor improved, and the individual continued to take very low doses of L-dopa. The pregnancy and birth were without complications.

In general, data on pregnancy in individuals with Parkinson disease is rare, since age of onset is often after the childbearing years. Historically, it was reported that parkinsonian symptoms may exacerbate during pregnancy, but this may be because antiparkinsonian medications were not recommended or were underdosed [Seier & Hiller 2017]. Reviewing data from case reports and drug registries, L-dopa seems to be the safest option in pregnancy. Amantadine should be avoided in women who are pregnant or trying to become pregnant [Seier & Hiller 2017]. Data on other pharmacologic and surgical treatments is limited. To date, there is no evidence that women with Parkinson disease have higher rates of birth or fetal complications [Seier & Hiller 2017].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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

PINK1 type of young-onset Parkinson disease is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *PINK1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PINK1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- The risk to heterozygotes of developing symptoms is not yet determined; however, several individuals with parkinsonism who have a single *PINK1* pathogenic variant have been reported (see Clinical Description, Heterozygotes).

Sibs of a proband

- If both parents are known to be heterozygous for a *PINK1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *PINK1* pathogenic variants.
- The risk to heterozygotes of developing symptoms is not yet determined; however, several individuals with parkinsonism who have a single *PINK1* pathogenic variant have been reported (see Clinical Description, Heterozygotes).

Offspring of a proband. The offspring of an individual with *PINK1* type of young-onset Parkinson disease are obligate heterozygotes for a pathogenic variant in *PINK1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *PINK1* pathogenic variant.

Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the *PINK1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is 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, are heterozygous, or are at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PINK1* pathogenic variants have 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 decisions 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
  www.apdaparkinson.org
- **MedlinePlus**
  Parkinson disease
- **Michael J. Fox Foundation for Parkinson's Research**
  Phone: 800-708-7644 (toll-free)
  Email: info@michaeljfox.org
  www.michaeljfox.org
- **Parkinson's Foundation**
  Phone: 800-4PD-INFO (473-4636)
  Email: contact@parkinson.org
  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. PINK1 Type of Young-Onset Parkinson Disease : Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PARK6	*PINK1*	1p36.12	Serine/threonine-protein kinase PINK1, mitochondrial	Parkinson's disease Mutation Database (PINK1) Movement Disorder Society Genetic mutation database (PINK1)	PINK1	PINK1

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 PINK1 Type of Young-Onset Parkinson Disease (View All in OMIM)

605909	PARKINSON DISEASE 6, AUTOSOMAL RECESSIVE EARLY-ONSET; PARK6
608309	PTEN-INDUCED KINASE 1; PINK1

Molecular Pathogenesis

PINK1 encodes serine/threoninep-protein kinase PINK1, mitochondrial (also called PTEN-induced putative kinase 1, or PINK1). PINK1 spans the outer mitochondrial membrane, with the C-terminal kinase domain facing the cytoplasm and the N-terminal inside the mitochondria. PINK1 presumably exerts its neuroprotective effect by phosphorylating specific mitochondrial proteins and modulating their functions [Sim et al 2006]. PINK1 and E3 ubiquitin-protein ligase parkin (parkin; see Parkinson Disease Overview) have been mapped to a shared pathway, with PINK1 acting upstream of parkin. PINK1 detects mitochondrial dysfunction, initiates the translocation of parkin to mitochondria, and signals parkin to ubiquitinate the damaged mitochondria, leading to their removal by autophagy [Pickrell & Youle 2015]. Thus, PINK1 and parkin acting together constitute a mitochondrial quality control function.

Most of the known pathogenic variants are localized within the serine/threonine kinase domain of *PINK1*, as expected [Valente et al 2004] (see www.mdsgene.org). *PINK1* pathogenic variants or PINK1 silencing result in reduced mitochondrial DNA (mtDNA) levels, defective ATP production, impaired mitochondrial calcium handling, and increased free radical generation. This in turn results in a reduction of mitochondrial membrane potential and an increased susceptibility to apoptosis in neuronal cells, animal models, and patient-derived fibroblasts [Valente et al 2004, Gegg et al 2009, Abramov et al 2011].

Overexpression of parkin can rescue the effects of a *PINK1* pathogenic variant in *Drosophila* and mammalian cells [Pickrell & Youle 2015]. Studies in fibroblasts from individuals with Parkinson disease revealed impaired ubiquitination of mitofusins and confirmed the link between the PINK1 and parkin pathways [Rakovic et al 2010, Rakovic et al 2011, Seibler et al 2011, Rakovic et al 2013, Koyano et al 2014]. A link with leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2) [Azkona et al 2018] and alpha-synuclein levels [Chung et al 2016] has also been demonstrated. PINK1-patient-specific induced pluripotent stem cell-derived midbrain dopamine neurons exhibit mitochondrial dysfunction with increased susceptibility to mitochondrial toxins [Chung et al 2016]. Animal studies of *Pink1* knockout mice showed defects in mitochondrial depolarization and synaptic transmission that were rescued by phosphomimetic NdufA10 in knockout mouse cells and in pink^{B9}-null mutated *Drosophila* [Morais et al 2014]. Complex I deficits and adenosine triphosphate synthesis were also rescued in cells derived from individuals with *PINK1* type of young-onset Parkinson disease [Morais et al 2014]. Heterozygous *Pink1* knockout (Pink$^{+/-}$) mice show subtle alterations of dopamine-dependent striatal synaptic plasticity [Madeo et al 2014]. While chronic exposure to low doses of rotenone was not sufficient to alter mitochondrial integrity and ATP production in this model, the rotenone led to profound impairment in expression of long-term plasticity at corticostriatal synapses, suggesting that disruption of synaptic plasticity

may represent an early feature of a premanifesting state of the disease [Martella et al 2016]. Findings of possible translational and treatment relevance include the role of vitamin K_2 as a mitochondrial electron carrier rescuing PINK1 deficiency [Vos et al 2012] and the observation that cardiolipin promotes electron transport between ubiquinone and complex I to rescue PINK1 deficiency [Vos et al 2017].

Mechanism of disease causation. Loss of function

Neuropathology. Data in individuals with *PINK1* type of young-onset Parkinson disease is limited [Samaranch et al 2010, Poulopoulos et al 2012]. Brain autopsy data are available for four individuals with biallelic *PINK1* pathogenic variants [Samaranch et al 2010, Poulopoulos et al 2012, Steele et al 2015, Takanashi et al 2016, Nybø et al 2020], all of which had characteristic neuronal loss in the substantia nigra. Lewy bodies were present in on histopathology in three of four individuals, although distribution varied. One individual had Lewy bodies in the substantia nigra, the temporal cortex, and locus coeruleus [Nybø et al 2020]; the second in the reticular nuclei in the brain stem, substantia nigra, and basal nucleus of Meynert, with sparing of the locus coeruleus and amygdala [Samaranch et al 2010]; and the third only in the amygdala, with only minimal neurites in the substantia nigra [Steele et al 2015]. A fourth individual had no Lewy body pathology [Takanashi et al 2016]. In addition, tau depositions were present in two individuals [Steele et al 2015, Nybø et al 2020]. In a Parkinson disease brain bank study, four individuals with Parkinson disease and heterozygous *PINK1* pathogenic variants had pathologic findings consistent with typical Parkinson disease, with Lewy bodies distributed in the brain stem and cortical areas, neuronal loss affecting the substantia nigra pars compacta, and neurofibrillary tangles stage I to V [Gandhi et al 2006].

Chapter Notes

Author Notes

Lara M Lange, MD (la.lange@uni-luebeck.de), and Christine Klein, MD (christine.klein@uni-luebeck.de), are actively involved in clinical and genetic research regarding individuals with Parkinson disease. They would be happy to communicate with persons who have any questions regarding the diagnosis of Parkinson disease or other considerations.

Lara M Lange and Christine Klein are also interested in hearing from clinicians treating families affected by Parkinson disease in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Lara M Lange or Prof Christine Klein to inquire about the review of *PINK1* variants of uncertain significance.

Acknowledgments

Lara M Lange and Christine Klein would like to thank Susanne Schneider for her previous engagement in the *PINK1 GeneReviews* and Johanna Junker and Maria Leila M Doquenia for their work on the MDSGene *PINK1* update.

Lara M Lange acknowledges support from the Bachmann-Strauss Dystonia and Parkinson Foundation.

Christine Klein acknowledges support from the Aligning Science Across Parkinson's (ASAP) Global Parkinson's Genetics Program (GP2), The Michael J Fox Foundation (MJFF), and the German Research Foundation (FOR2488).

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Revision History

- 25 April 2024 (sw) Comprehensive update posted live
- 24 May 2018 (sw) Comprehensive update posted live
- 18 September 2014 (me) Comprehensive update posted live
- 6 September 2012 (me) Comprehensive update posted live
- 16 March 2010 (me) Review posted live
- 1 December 2009 (ck) Original submission

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