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Parkin Type of Early-Onset Parkinson Disease

Synonyms: PARK-*Parkin*, *PRKN* Parkinson Disease

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Summary

Clinical characteristics

Parkin type of early-onset Parkinson disease (PARK-*Parkin*) is characterized by the cardinal signs of Parkinson disease (PD): bradykinesia, resting tremor, and rigidity. The median age at onset is 31 years (range: 3-81 years). The disease is slowly progressive: disease duration of more than 50 years has been reported. Clinical findings vary; hyperreflexia is common. Lower-limb dystonia may be a presenting sign and cognitive decline appears to be no more frequent than in the general population. Dyskinesia as a result of treatment with levodopa frequently occurs.

Diagnosis/testing

The diagnosis of PARK-*Parkin* is established in a proband with suggestive findings and biallelic pathogenic variants in *PRKN* identified by molecular genetic testing.

Management

Treatment of manifestations: Levodopa and dopamine agonists, MAO B inhibitors, COMT inhibitors, and amantadine; deep brain stimulation for those experiencing difficulty with levodopa therapy.

Surveillance: Neurologic follow up including assessment of treatment every six to 12 months.

Agents/circumstances to avoid: Use of levodopa therapy that exceeds the dose needed for satisfactory clinical response. Neuroleptic treatment may exacerbate parkinsonism.

Genetic counseling

PARK-*Parkin* is inherited in an autosomal recessive manner. At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Once the *PRKN* pathogenic variants in a family are known, carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

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Diagnosis

Suggestive Findings

Parkin type of early-onset Parkinson disease (PARK-*Parkin*) **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings

- Onset before age 40 years in most individuals (median age: 31 years; range: 3-81 years) or, rarely, juvenile onset (age <20 years).
- Lower-limb dystonia (may be a presenting sign or may occur during disease progression), which sometimes remains an isolated finding for years
- Slow disease progression
- Absence of dementia in most individuals (present in <3%)
- Well-preserved sense of smell
- Marked and sustained response to oral administration of levodopa, which is frequently associated with levodopa-induced motor fluctuations and dyskinesias (abnormal involuntary movements)

Family history consistent with autosomal recessive inheritance, including parental consanguinity

Establishing the Diagnosis

The diagnosis of PARK-*Parkin* **is established** in a proband with suggestive findings and biallelic pathogenic variants in *PRKN* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (typically a multigene panel that includes deletion/duplication analysis) and **gene dosage analysis** (typically multiplex ligation-dependent analysis). Alternatively, *PRKN* variants can be assessed by exome or genome sequencing taking into account copy number variations.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas exome or genome testing does not. Because the phenotype of PARK-*Parkin* is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of PARK-*Parkin* has not been considered are more likely to be diagnosed using exome or genome testing (see Option 2).

Option 1

A Parkinson disease multigene panel that includes *PRKN* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting 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.

Note: Because an approximately equal number of *PRKN* disease-causing variants are detected by sequence analysis and by deletion/duplication analysis [Kasten et al 2018] (see Table 1), use of a multigene panel that also includes deletion/duplication analysis should strongly be considered.

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

Option 2

Comprehensive genomic testing, which does not require the clinician to determine which gene(s) may be involved, can include the following:

- **Exome sequencing.** If exome sequencing is not diagnostic, **exome array** (a microarray designed to determine exon-level copy number variants for as many genes associated with disease as possible) should be strongly considered (when clinically available) to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.
- **Genome sequencing**

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 Parkin Type of Early-Onset Parkinson Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PRKN	Sequence analysis [3]	<50% [4]
	Gene-targeted deletion/duplication analysis [5]	>50% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Kasten et al [2018]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. The frequency of exon rearrangements is likely underestimated given that early variant screening studies did not include methods to detect large deletions and duplications.

Clinical Characteristics

Clinical Description

Parkin type of early-onset Parkinson disease (PARK-*Parkin*) is characterized by the cardinal signs of Parkinson disease (PD): bradykinesia, resting tremor, and rigidity. The median age at onset is 31 years (range: 3-81 years). The disease is slowly progressive and disease duration of more than 50 years has been reported. Clinical findings vary; hyperreflexia is common. Lower-limb dystonia may be a presenting sign and cognitive decline appears to be no more frequent than in the normal population. Dyskinesia as a result of treatment with dopaminergic drugs frequently occurs.

Women and men are affected with equal frequency. Age at onset is highly variable, even among individuals with the same pathogenic variant [Chien et al 2006]; onset is usually before age 40 years; the median age at onset is 31 years (25th %ile: 23 years; 75th %ile: 38 years; range: 3-81 years) (see www.MDSGene.org).

Clinical findings vary; however, tremor, bradykinesia, and dystonia are the most common presenting signs. Dystonia is observed in 65% (177/271) of affected individuals for whom this information is available. Almost

half of affected individuals present with hyperreflexia. The diagnosis of PD may be delayed due to unusual clinical features, especially in patients with an early manifestation [Borsche et al 2019, Ruiz-Lopez et al 2019].

PARK-*Parkin* is not associated with specific behavioral, neuropsychological, or psychiatric manifestations [Caccappolo et al 2011, Srivastava et al 2011, Kasten et al 2018]. Cognitive impairment is uncommon, and dementia is observed very rarely [Benbunan et al 2004, Grünewald et al 2013, Kasten et al 2018].

The disease is slowly progressive: disease duration of greater than 50 years has been reported. In later disease stages, freezing of gait, postural deformities, and motor fluctuations may be common features, whereas dementia usually does not develop [Doherty et al 2013].

Neuroimaging

Routine cranial CT and MRI scans are usually normal.

PET/SPECT studies have revealed a reduced striatal ^{18}F-DOPA uptake and a reduced presynaptic dopamine transporter density in individuals with PARK-*Parkin* [van der Vegt et al 2009]. The putamen is predominantly affected, consistent with the findings in Parkinson disease of other etiologies; in contrast, however, the loss of dopaminergic striatal innervation is rather symmetric and the progression rate is considerably slower. The postsynaptic D2 receptor density as assessed with ^{11}C-raclopride PET has been shown to be upregulated in untreated affected individuals and downregulated in affected individuals who receive dopaminergic medication.

Voxel-based morphometry revealed a decrease of putaminal gray matter volume and a slight increase of gray matter in the right pallidum in individuals with PARK-*Parkin* (i.e., those with biallelic *PRKN* pathogenic variants), whereas asymptomatic individuals heterozygous for a *PRKN* pathogenic variant demonstrated an increase of both putaminal and pallidal gray matter volume. Using T_2* relaxometry, an increased substantia nigra iron load was detected in four symptomatic individuals with PARK-*Parkin* and two asymptomatic individuals heterozygous for a *PRKN* pathogenic variant [Pyatigorskaya et al 2015].

Neuropathology

To date, detailed postmortem studies of nine individuals with biallelic *PRKN* pathogenic variants have been published [Poulopoulos et al 2012]. The most prominent and most common feature was the finding of neuronal loss in pigmented nuclei of the brain stem. Unlike Parkinson disease of other etiologies, the neuronal loss was greater in the substantia nigra pars compacta than in the locus coeruleus (see Parkinson Disease Overview). Typical alpha-synuclein-containing Lewy bodies were identified in only two affected individuals, whereas one affected individual had basophilic Lewy body-like pathology of the pedunculopontine nucleus. Tau-containing neurofibrillary tangles were observed in two affected individuals. In summary, the spectrum of postmortem findings is broad and thus reminiscent of the situation in *LRRK2* Parkinson disease [Kasten et al 2018].

Genotype-Phenotype Correlations

No clear-cut genotype-phenotype correlations have been observed.

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 *PRKN* pathogenic variants is "PARK-*Parkin*" [Marras et al 2016].

Families with PARK-*Parkin* were mostly described in Japan in the 1970s as having "autosomal recessive juvenile parkinsonism" (AR-JP).

Prevalence

The population-based prevalence of PARK-*Parkin* is largely unknown. However, in Europe, PARK-*Parkin* accounts for approximately 50% of autosomal recessive parkinsonism and 18% of parkinsonism in simplex cases (i.e., a single occurrence of parkinsonism in a family) with onset before age 45 years [Lücking et al 2000].

The percentage of PARK-*Parkin* rapidly decreases with increasing age at onset: After age 30 years, only a few percent of simplex cases have biallelic *PRKN* pathogenic variants. However, in families with a clear-cut autosomal recessive mode of inheritance, the age-related decrease is less pronounced [Periquet et al 2003].

Prevalence of PARK-*Parkin* appears to be similar in all populations. Individuals with PARK-*Parkin* from many different regions have been reported [Kasten et al 2018].

Genetically Related (Allelic) Disorders

Role of heterozygous *PRKN* pathogenic variants in disease causation. Heterozygous *PRKN* pathogenic variants have been detected in a large number of individuals with Parkinson disease, raising the question of whether a heterozygous *PRKN* pathogenic variant may contribute to the development of parkinsonism [Klein et al 2007]. Case-control studies revealed a frequency of 0% to 7.9% in people with Parkinson disease and 0% to 3.7% in neurologically healthy controls [Grünewald & Klein 2012]. In a comprehensive case-control study the frequency of heterozygous *PRKN* exon rearrangements was the same among affected persons and controls [Kay et al 2010]. Notably, however, the frequency of heterozygous *PRKN* pathogenic variants in presumably healthy individuals in public exome databases is only 0.17%.

Multimodal neuroimaging and electrophysiologic studies disclosed latent nigrostriatal impairment, compensatory hypertrophy of the putamen and pallidum, and increased iron deposition in the substantia nigra in asymptomatic individuals heterozygous for a *PRKN* pathogenic variant, supporting the assumption that heterozygous *PRKN* pathogenic variants are a genetic susceptibility factor for Parkinson disease [van der Vegt et al 2009, Pyatigorskaya et al 2015].

PET/SPECT studies have revealed that asymptomatic individuals heterozygous for a *PRKN* pathogenic variant have a slight and subclinical impairment of dopaminergic neurotransmission. A longitudinal PET study demonstrated a very subtle progression rate, indicating that only a marginal number of asymptomatic individuals heterozygous for a *PRKN* pathogenic variant may develop clinically overt parkinsonism if no other risk factors are present [Pavese et al 2009].

Using functional MRI, asymptomatic individuals heterozygous for a *PRKN* pathogenic variant showed an increased activation of motor-related brain regions when they performed repetitive finger movements [van Nuenen et al 2009]. The same mechanism of an increased neuronal recruitment has been illustrated for a facial emotion recognition task [Anders et al 2012].

However, based on the currently available data (and lack of prospective evaluations), the role of heterozygous *PRKN* pathogenic variants in disease causation cannot be determined conclusively.

Sporadic tumors (e.g., ovarian cancer) occurring as single tumors in the absence of any other findings of PARK-*Parkin* frequently harbor *PRKN* somatic variants that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. However, the involvement of *PRKN* pathogenic variants in oncogenesis is ambiguous, as the association with cancer could not be replicated in a population-based study [Alcalay et al 2012].

Differential Diagnosis

Early-Onset Parkinson Disease

Parkin type of early-onset Parkinson disease (PARK-*Parkin*) is often clinically indistinguishable from Parkinson disease of other etiologies (see Parkinson Disease Overview). Rigidity, bradykinesia, and resting tremor are variably combined in both disorders.

PARK-*Parkin* 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 PARK-*Parkin*

Gene	PD Designation [1]	Median Age at Onset (Range) [2]	# of Persons w/ Clinical Information in the Literature [2]	Comment
PINK1	PARK-*PINK1*	32 yrs (9-67)	151	• 2nd most common cause of EOPD, after *PRKN* • PARK-*PINK1* & Parkin type EOPD are clinically indistinguishable. • Non-motor manifestations incl psychiatric features may be more common. • Heterozygotes may have ↑ risk for PD.
DJ-1	PARK-*DJ1* (OMIM 606324)	27 yrs (15-40)	33	• Phenotype similar to PARK-*Parkin* • IDD &/or seizures occasionally • Risk to heterozygotes unknown
DNAJC6	PARK-*DNAJC6*	11 yrs (7-42)	11	• Pyramidal signs • IDD / early cognitive impairment • Early & vivid hallucinations on intake of dopamine agonists • Early falls • Saccadic abnormalities • Pyramidal signs
FBXO7	PARK-*FBXO7* (OMIM 260300)	17 yrs (10-52)	27	• 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)	15	• Early cognitive impairment • Early falls • Saccadic abnormalities • Gaze palsy • Pyramidal signs • Ataxia • Autonomic dysfunction

Table 3. continued from previous page.

Gene	PD Designation [1]	Median Age at Onset (Range) [2]	# of Persons w/ Clinical Information in the Literature [2]	Comment
VPS13C	PARK-*VPS13C* (OMIM 616840)	29 yrs (0-70)	4	• 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]
2. Data from www.MDSGene.org (accessed 4-10-2020)

Dopa-Responsive Dystonia

For individuals with juvenile-onset parkinsonism, especially those with prominent dystonia, dopa-responsive dystonia should be considered:

- GTP cyclohydrolase 1-deficient dopa-responsive dystonia caused by heterozygous pathogenic variants in *GCH1*
- Tyrosine hydroxylase-deficient dopa-responsive dystonia caused by biallelic pathogenic variants in *TH*
- Sepiapterin reductase-deficient dopa-responsive dystonia caused by biallelic pathogenic variants in *SPR*

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Parkin type early-onset Parkinson disease (PARK-*Parkin*), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Assess the presence and the severity of parkinsonian signs, non-motor features, and treatment-related complications using the Unified Parkinson's disease rating scale (UPDRS) [Fahn & Elton 1987] or the Movement Disorder Society (MDS) UPDRS [Goetz et al 2008].
- Assess the presence of atypical signs, such as hyperreflexia and dystonia.
- Evaluate the degree of response to treatment.
- Assess for cognitive or behavioral problems.
- Consider consultation with a clinical geneticist and/or genetic counselor.

Treatment of Manifestations

To date, the treatment of PARK-*Parkin* does not differ from that of Parkinson disease of other etiologies. No specific guidelines are currently available.

- The motor impairment usually responds very well to low doses of dopaminergic medication; the response is typically sustained even after long disease duration. To reduce or delay side effects, levodopa doses should not exceed the levels required for satisfactory clinical response.

  On average, the response to low doses of levodopa is excellent and sustained. The likelihood of developing levodopa-induced dyskinesias is higher than in individuals with parkinsonism resulting from other etiologies.

- The most relevant treatment-related problem is the early occurrence of levodopa-induced dyskinesias (abnormal involuntary movements) and motor fluctuations. The management of treatment-related complications is not different from the strategies applied in Parkinson disease of other etiologies, and includes deep brain stimulation (DBS) in selected cases. Given its rarity, PARK-*Parkin* appears to be overrepresented in patient populations undergoing DBS.
- The response to DBS is favorable, including in patients with a long disease duration [Ligaard et al 2019].

Surveillance

Neurologic follow up every six to 12 months to modify treatment as needed is appropriate.

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

Pregnancy is rare in women with Parkinson disease. Only one instance of a successful pregnancy in a woman with PARK-*Parkin* has been reported [Serikawa et al 2011]. The woman successfully gave birth to spontaneously conceived dichorionic/diamnionic male twins at age 27 years. Exacerbation of her motor disabilities occurred during late pregnancy. She was treated with levodopa/carbidopa only during the period of organogenesis. Both babies were born healthy, without any evidence of psychomotor impairment at age two years.

Both levodopa and carbidopa have the ability to cross the placenta. Limited data from case reports and pregnancy registries do not suggest an increased risk of major malformations in fetuses exposed to levodopa [Seier & Hiller 2017]. Currently, levodopa is considered a first-line therapy for pregnant women with PD who experience progressive motor symptoms during pregnancy.

Data on the risk of adverse fetal outcome from the use of other medications (e.g., dopamine agonists and anticholinergics) to treat PD manifestations during pregnancy are limited, but generally reassuring [Seier & Hiller 2017]. Some reports have suggested an increased risk of adverse fetal outcome with the use of amantadine during pregnancy; therefore, this medication is generally avoided.

Worsening of parkinsonian manifestations could in part be explained by the reduction of dopaminergic replacement therapy. If possible, dopaminergic medication should be limited to levodopa/decarboxylase inhibitor to minimize the potential risk for teratogenicity at least over the course of the embryonic phase.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

PRKN variants result in impaired mitochondrial function and clearance of dysfunctional mitochondria. Thus, individuals PARK-*Parkin* may preferentially benefit from mitochondrial enhancers that are currently being tested in clinical trial in a gene-targeted fashion [Prasuhn et al 2019].

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

Parkin type of early-onset Parkinson disease (PARK-*Parkin*) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *PRKN* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm the genetic status of each parent and to allow reliable recurrence risk assessment. Although the parents of a proband with PARK-*Parkin* are typically heterozygous, in rare families:
  - Only one parent is heterozygous for a *PRKN* pathogenic variant and the proband has PARK-*Parkin* as the result of one inherited and one *de novo PRKN* pathogenic variant [Williams et al 2018].
  - One parent is affected (based on the presence of biallelic *PRKN* pathogenic variants) and the other parent is heterozygous for one *PRKN* pathogenic variant [Maruyama et al 2000, Bonifati et al 2001, Lücking et al 2001, Kobayashi et al 2003, Pellecchia et al 2007]. This occurrence in any autosomal recessive disorder is termed pseudodominant inheritance.
- The risk to heterozygotes of developing manifestations is not yet conclusively determined (see Genetically Related Disorders, **Role of heterozygous *PRKN* pathogenic variants**).

Sibs of a proband

- If each parent is known to be heterozygous for a *PRKN* 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 *PRKN* pathogenic variant. Age of onset is highly variable; sibs who inherit two pathogenic variants may have an earlier or later age of onset than the proband.
- The risk to heterozygotes of developing symptoms is not yet conclusively determined (see Genetically Related Disorders, **Role of heterozygous *PRKN* pathogenic variants**).

Offspring of a proband

- Unless an individual with PARK-*Parkin* has children with an affected individual or heterozygote, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *PRKN*.
- The empiric recurrence risk to offspring of a proband depends on the frequency of heterozygotes, which is ≤3.7% in the general population [Grünewald & Klein 2012], thus generating a risk of ≤1% to offspring of being affected. As for other autosomal recessive disorders, the risk is higher when the proband and his/her reproductive partner are related.

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

Heterozygote Detection

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, 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, heterozygous, or at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PRKN* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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
  www.apdaparkinson.org
- **Fox Trial Finder**
  foxtrialfinder.michaeljfox.org
- **Michael J. Fox Foundation for Parkinson's Research**
  Phone: 800-708-7644 (toll-free)
  Email: info@michaeljfox.org
  www.michaeljfox.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Parkinson's Disease Information Page
- **Parkinson's Disease Society (UK)**
  United Kingdom
  Phone: 0808 800 0303
  Email: hello@parkinsons.org.uk
  www.parkinsons.org.uk
- **Parkinson's Foundation**

Phone: 800-4PD-INFO (473-4636)
Email: contact@parkinson.org
www.parkinson.org

- **MedlinePlus**
  Parkinson disease

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. Parkin Type of Early-Onset Parkinson Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PRKN	6q26	E3 ubiquitin-protein ligase parkin	Parkinson's disease Mutation Database (PARK2) Movement Disorder Society Genetic mutation database - PRKN	PRKN	PRKN

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 Parkin Type of Early-Onset Parkinson Disease (View All in OMIM)

600116	PARKINSON DISEASE 2, AUTOSOMAL RECESSIVE JUVENILE; PARK2
602544	PARKIN RBR E3 UBIQUITIN PROTEIN LIGASE; PRKN

Molecular Pathogenesis

PRKN encodes parkin, which comprises a ubiquitin-like domain at the N terminus and a RING (*r*eally *i*nteresting *n*ew *g*ene) domain composed of three RING finger motifs (RING0, 1, and 2). Like other RING finger proteins, parkin exhibits E3 ubiquitin ligase activity [Imai et al 2000, Shimura et al 2000, Zhang et al 2000] targeting a number of proteins for proteasomal degradation. Parkin can additionally mediate nondegradative modes of ubiquitination, which appear to be required for the survival of nigrostriatal dopaminergic neurons [Moore 2006].

Parkin is also involved in the maintenance of mitochondrial function and integrity, and protection from multiple stressors, hence acting as neuroprotectant. Parkin works in a pathway with its companion protein PINK1, another protein associated with autosomal recessive early-onset parkinsonism [Valente et al 2004]. They are jointly responsible for mitochondrial quality control and removal of dysfunctional mitochondria [Narendra et al 2012, Rakovic et al 2013, Rakovic et al 2019]. Parkin also triggers mitochondrial-induced inflammation through activation of the STING pathway [Sliter et al 2018].

Mechanism of disease causation. It is postulated that the vast majority of *PRKN* pathogenic variants result in loss of function of normal E3 ubiquitin ligase activity by loss (truncating variants) or inactivation (missense variants) of the protein.

Pathogenic variants may result in the accumulation of its substrates no longer appropriately targeted for degradation; however, this has not been confirmed.

***PRKN*-specific laboratory technical considerations.** Gene-targeted deletion/duplication testing should be considered due to the high rate of exon rearrangements (deletions and duplications of whole exons accounting for about half of *PRKN* variants; see Table 1).

Table 5. Notable *PRKN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_004562.2 NP_004553.2	c.155delA	p.Asn52MetfsTer29	The most common pathogenic variants [Kasten et al 2018]
	c.337_376del (438-477del)	p.Pro113ThrfsTer51	
	c.823C>T (924C>T)	p.Arg275Trp	
	c.(7+1_8-1)_(171+1_172-1)del [Deletion of exons 2 & 3]		
	c.(171+1_172-1)_(412+1_413-1)del [Deletion of exon 3]		
	c.(171+1_172-1)_(534+1_534-1)del [Deletion of exons 3 & 4]		
	c.(412+1_413-1)_(534+1_534-1)del [Deletion of exon 4]		

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). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

References

Published Guidelines / Consensus Statements

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