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DNAJC6 Parkinson Disease

Synonym: PARK-*DNAJC6*

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Summary

Clinical characteristics

DNAJC6 Parkinson disease is a complex early-onset neurologic disorder whose core features are typical parkinsonian symptoms including bradykinesia, resting tremor, rigidity, and postural instability.

The majority of individuals have juvenile onset and develop symptoms before age 21 years. Developmental delay, intellectual disability, seizures, other movement disorders (e.g., dystonia, spasticity, myoclonus), and neuropsychiatric features occur in the majority of individuals with juvenile onset and often precede parkinsonism. The onset of parkinsonian features usually occurs toward the end of the first or beginning of the second decade and the disease course is rapidly progressive with loss of ambulation in mid-adolescence in the majority of individuals. Additional features include gastrointestinal manifestations and bulbar dysfunction.

A minority of individuals with *DNAJC6* Parkinson disease develop early-onset parkinsonism with symptom onset in the third to fourth decade and absence of additional neurologic features.

Diagnosis/testing

The diagnosis of *DNAJC6* Parkinson disease is established in a proband with suggestive phenotypic findings and biallelic pathogenic variants in *DNAJC6* identified by molecular genetic testing.

Management

Treatment of manifestations: Levodopa, dopaminergic agonists, and/or anticholinergics. Medications and/or surgical interventions for dystonia and spasticity. Medications (e.g., sodium valproate, clonazepam, levetiracetam, piracetam) as needed for myoclonus. Multidisciplinary management including physical and occupational therapy, speech and language therapy, and special education services as indicated for developmental delay and intellectual disability. Seizures are treated with anti-seizure medication. Psychiatric disorders are treated as per neuropsychiatry. Sleep aids (e.g., sleep system, conservative measures, melatonin,

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sedative medications) as needed for sleep disorder. Feeding support and medications as needed for constipation, sialorrhea, and reflux. Supportive rehabilitation devices and equipment for orthopedic manifestations. Surgical interventions as needed for hip dislocation or kyphoscoliosis. Low-vision therapy, glasses, and surgical intervention as needed for strabismus and/or vision deficits.

Surveillance: Physical therapy, occupational therapy, and speech and language therapy evaluations every six months or as needed. Assess for new manifestations such as seizures, changes in tone, and movement disorders at each visit. Repeat electroencephalogram as needed. Monitor those with seizures as clinically indicated. Psychiatric assessment as needed. Sleep study/polysomnography as needed. Growth assessment at each visit in children. Assessment of nutritional status at each visit. Swallowing assessment to evaluate risk of aspiration as needed. Gastroenterology evaluation and gastroscopy as needed. Hip and spine radigraphs every six months in individuals older than age two years who are nonambulatory and in individuals with signs and symptoms concerning for spinal deformity. Follow-up ophthalmology evaluation for those with vision concerns.

Agents/circumstances to avoid: Dopamine antagonists and vesicular monoamine transporter 2 (VMAT2) inhibitors should be avoided as they could aggravate dopamine deficiency.

Genetic counseling

DNAJC6 Parkinson disease is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *DNAJC6* 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 *DNAJC6* pathogenic variant. (Note: The risk to heterozygotes of developing manifestations is not yet determined.) Once the *DNAJC6* pathogenic variants have been identified in an affected family member, heterozygote testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

DNAJC6 Parkinson Disease: Included Phenotypes [1]
• *DNAJC6* juvenile Parkinson disease • *DNAJC6* type of early-onset Parkinson disease

For synonyms and outdated names, see Nomenclature.
1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

Suggestive Findings

DNAJC6 Parkinson disease **should be considered** in individuals with the following findings.

Juvenile-onset presentation (onset age <21 years)

- Onset of parkinsonism (bradykinesia, resting tremor, rigidity, postural instability) usually at the end of the first or beginning of the second decade
- Rapid disease progression and neurologic regression after onset of parkinsonism
- Loss of ambulation often in mid-adolescence
- Parkinsonian symptoms often difficult to treat with common medications used for Parkinson disease (e.g., levodopa)
- Additional features that often precede the parkinsonian features: developmental delay, intellectual disability, seizures, other movement disorders (e.g., dystonia, spasticity, myoclonus), and neuropsychiatric features (anxiety, psychosis, behavior disorders, sleep disorders)

Early-onset presentation (onset age 21- 44 years)

- Onset of parkinsonism (bradykinesia, resting tremor, rigidity, postural instability) in the third to fourth decade
- Slower disease progression than juvenile-onset presentation
- Some response to dopaminergic medications

Establishing the Diagnosis

The diagnosis of *DNAJC6* Parkinson disease **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *DNAJC6* 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 *DNAJC6* variants of uncertain significance (or of one known *DNAJC6* pathogenic variant and one *DNAJC6* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *DNAJC6* Parkinson disease is indistinguishable from many other inherited causes of Parkinson disease, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *DNAJC6*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A Parkinson disease multigene panel** that includes *DNAJC6* and other genes of interest (see Differential Diagnosis) 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. 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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **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 *DNAJC6* Parkinson Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
DNAJC6	Sequence analysis [3]	20/21 [4]
	Gene-targeted deletion/duplication analysis [5]	1/21 [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. Edvardson et al [2012], Köroğlu et al [2013], Elsayed et al [2016], Olgiati et al [2016], Li et al [2020], Mittal [2020], Ng 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.
6. To date, one individual has been reported with a *DNAJC6* multiexon deletion including exons 5-19 [Vauthier et al 2012].

Clinical Characteristics

Clinical Description

DNAJC6 Parkinson disease is a complex early-onset neurologic disorder characterized by typical parkinsonian symptoms including bradykinesia, resting tremor, rigidity, and postural instability. To date, 20 individuals with biallelic *DNAJC6* pathogenic variants have been identified, 19 of whom have prominent motor features [Edvardson et al 2012, Vauthier et al 2012, Köroğlu et al 2013, Elsayed et al 2016, Olgiati et al 2016, Mittal 2020, Ng et al 2020]. One additional individual with early-onset parkinsonism and other findings consistent with *DNAJC6* Parkinson disease was compound heterozygous, with one *DNAJC6* variant predicted to be pathogenic and one *DNAJC6* variant that may potentially be associated with disease manifestations; further study is needed to determine if this variant is benign or pathogenic [Li et al 2020].

The following description of the phenotypic features associated with this condition is based on reports of the 20 individuals with biallelic *DNAJC6* pathogenic variants.

Table 2. *DNAJC6* Parkinson Disease: Frequency of Select Features

Feature	Proportion of Persons w/Feature		Comment
	Juvenile onset (age <21 yrs)	Early onset (age 21-50 yrs)	
Parkinsonism (bradykinesia, resting tremor, rigidity, postural instability)	14/14	6/6	1/19 not classified as juvenile or early-onset (Person had no signs of parkinsonism.) [1]
Developmental delay	10/14	–	
Intellectual disability	12/14	1/6	
Dystonia	9/14	–	Additional motor features reported in 9/14 persons w/juvenile onset
Spasticity	6/14	–	
Myoclonus	2/14	–	
Seizures	7/14	–	

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature		Comment
	Juvenile onset (age <21 yrs)	Early onset (age 21-50 yrs)	
Anxiety	3/14	–	Neuropsychiatric features occurred predominantly in those w/juvenile onset (8/14); psychosis reported in 1 person w/early-onset parkinsonism (attributed to levodopa)
Behavior disorders	3/14		
Psychosis	2/14	1/6	
Gastrointestinal &/or bulbar dysfunction	5/14	–	

– = not reported in this group
1. One person, age seven years, with seizures, developmental delay, obesity, and no signs of a movement disorder, had a homozygous *DNAJC6* deletion of exons 8-19 [Vauthier et al 2012]. Given the young age of this person, it is possible that a movement disorder may become apparent at an older age.

Parkinsonism is the predominant motor phenotype in individuals with *DNAJC6* Parkinson disease. Bradykinesia and resting tremor were the motor features at the time of presentation, followed by rigidity and gait abnormalities. Hypomimia and postural instability often occurred later in the disease course.

Juvenile-Onset Parkinsonism

The majority of individuals reported to date (14/21) developed symptoms before age 21 years [Edvardson et al 2012, Vauthier et al 2012, Köroğlu et al 2013, Elsayed et al 2016, Mittal 2020, Ng et al 2020]. The onset of parkinsonian features usually occurred toward the end of the first or beginning of the second decade (median age of onset 10 years, range 7-14 years) and the disease course was then rapidly progressive with loss of ambulation in mid-adolescence in the majority of individuals. Loss of ambulation is likely due to multiple factors including developmental motor regression, progressive bradykinesia leading to akinesia, and also limb rigidity and postural instability.

Developmental delay, intellectual disability, seizures, other movement disorders (e.g., dystonia, spasticity, myoclonus), and neuropsychiatric features are observed in the majority of individuals with juvenile onset and often precede the movement disorder [Edvardson et al 2012, Vauthier et al 2012, Köroğlu et al 2013, Elsayed et al 2016, Mittal 2020, Ng et al 2020].

Detailed developmental history was available for six individuals with juvenile-onset parkinsonism. They showed delay in motor and language development but ultimately reached independent walking and achieved spoken language between ages three and four years. These individuals had slow developmental progress over time and manifested learning difficulties requiring special educational support. Three individuals suffered cognitive decline; of these, two became nonverbal in the second decade of life in tandem with progression of the movement disorder. The remaining three individuals were reported to have mild-to-moderate intellectual disability (IQ range 40-63).

Seizures were classified as generalized (5/7) and/or atypical absences (4/7), when specified [Köroğlu et al 2013, Elsayed et al 2016, Ng et al 2020, Mittal 2020]. Seizure onset was reported to occur in the first decade of life. Seizures were treated with lamotrigine, zonisamide, or sodium valproate, which led to clinical improvement in four individuals.

Additional movement disorders often occurred as the disease progressed, with dystonia being the most frequent feature, followed by spasticity and myoclonus. Dystonia and spasticity also increased the risk of secondary complications such as limb contractures, hip dislocation, and kyphoscoliosis. To date, eye movement abnormalities have only been reported in one individual, who had hypometric saccades [Edvardson et al 2012];

given that this feature often correlates with hypokinesia (and is eventually present in almost all individuals with Parkinson disease), it is possible that it is underrecognized in this condition.

Neuropsychiatric features included anxiety disorder, behavior disorders (e.g., emotional lability, aggressive behavior, perseveration behavior, attention-deficit disorder), and psychosis. Behavioral features and psychosis emerged after levodopa therapy in two individuals. Disrupted sleep pattern in tandem with neuropsychiatric features was observed in three individuals.

Systemic features, in particular gastrointestinal (neonatal/infantile feeding difficulties, recurrent vomiting, sialorrhea) and bulbar dysfunction (dysphagia, dysarthria, drooling), were associated with a more severe disease course [Ng et al 2020].

CSF neurotransmitter analysis showed low CSF homovanillic acid (HVA) in three individuals and borderline CSF HVA in one individual. A reduced CSF HVA:5-HIAA ratio was identified in four individuals with juvenile-onset parkinsonism. Other CSF neurotransmitter metabolites (pterins species, 5-methyltetrahydrofolate) were normal in these four individuals [Ng et al 2020].

Treatment with levodopa showed a moderate-to-good response in six of fourteen individuals – although in two individuals, levodopa had to be discontinued due to intolerable motor and neuropsychiatric side effects.

Other

- Scoliosis (1 individual)
- *Pes cavus* (1 individual)
- Primary non-progressive microcephaly (3 sibs from a consanguineous family); the possibility of a second condition causing microcephaly cannot be fully excluded.

Early-Onset Parkinsonism

Six individuals from four families have been reported with symptom onset in the third to fourth decade. The median age of onset was 32 years (range 21-44 years). Additional neurologic features were not observed in this group, although psychosis was described in one individual. In this group, there appears to be slower disease progression [Olgiati et al 2016] with better clinical response to dopaminergic treatments [Olgiati et al 2016]. Three individuals underwent surgical procedures with good outcome (bilateral subthalamic nucleus deep brain stimulation in two individuals and pallidotomy in the other) [Olgiati et al 2016, Li et al 2020].

Neuroradiographic Features

Fourteen individuals had a normal brain MRI. Mild-to-moderate generalized cerebral atrophy was reported in five individuals with juvenile-onset disease, and two of these five individuals also had cerebellar atrophy [Edvardson et al 2012, Köroğlu et al 2013, Elsayed et al 2016, Olgiati et al 2016, Mittal 2020, Ng et al 2020.

^{123}I-FP-CIT SPECT (DaTScan™) imaging performed in three individuals with juvenile-onset parkinsonism showed reduced or absent tracer uptake in the basal ganglia [Ng et al 2020].

F-DOPA-PET performed in two individuals with early-onset parkinsonism showed striatonigral abnormalities [Olgiati et al 2016].

Heterozygotes

Five individuals with Parkinson disease (representing both simplex and multiplex cases) have been reported with heterozygous *DNAJC6* variants (mean age of onset 33 years, range 29-58 years) [Olgiati et al 2016]. There are no further details of the disease presentation and course. Although these variants were classified as pathogenic by several variant prediction programs, their clinical relevance and contribution to disease needs to be further investigated. It is possible that these rare variants may confer risk of Parkinson disease, similar to other

Parkinson disease-related genes (*LRRK2*, *SNCA*, *GBA1* [*GBA*]) [Blauwendraat et al 2020]. Of note, obligate carrier parents of individuals with biallelic *DNAJC6* variants have not been reported to develop Parkinson disease.

Genotype-Phenotype Correlations

Though data are limited, there is some evidence of a genotype-phenotype correlation.

Nonsense variants throughout the gene (e.g., c.2410C>T, c.2365C>T, c.766C>T, c.2416C>T) and **splice site variants located toward the 5' end** (e.g., c.801-2A>G in intron 6). Individuals homozygous for these variants predicted to cause complete protein deficiency or a nonfunctional protein, showed a rapidly progressive, juvenile-onset parkinsonism with a complex neurologic phenotype [Edvardson et al 2012, Köroğlu et al 2013, Elsayed et al 2016, Mittal 2020, Ng et al 2020]. Treatment proved difficult in these individuals: only a few demonstrated a mild-to-moderate clinical response to levodopa (6/14). Also, a rapidly developing sensitivity to levodopa was evident in this group.

Missense variants located throughout the gene (e.g., c.2779A>G) and **splice site variants located toward the 3' end** (e.g., c.2223A>T in exon 15, c.2038+3A>G in intron 13). Individuals homozygous for these variants showed later disease onset, with early-onset parkinsonism with a milder disease course [Olgiati et al 2016]. All had a good clinical response to levodopa, though the dose had to be frequently adjusted due to intolerable side effects. Two individuals underwent surgical procedures – subthalamic nucleus deep brain stimulation and pallidotomy – with marked improvement of motor manifestations.

Nomenclature

Other terms used to refer to *DNAJC6* Parkinson disease:

- PARK-*DNAJC6*. 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 *DNAJC6* pathogenic variants is "PARK-*DNAJC6*" [Marras et al 2016].
- "Autosomal recessive juvenile-onset Parkinson's disease" [Edvardson et al 2012, Vauthier et al 2012, Köroğlu et al 2013, Elsayed et al 2016, Mittal 2020, Ng et al 2020] and "autosomal-recessive early-onset Parkinson's disease" [Olgiati et al 2016].
- *DNAJC6* parkinsonism-dystonia [Ng et al 2020]

Prevalence

The prevalence of *DNAJC6* Parkinson disease is not yet established. To date, 20 individuals with biallelic *DNAJC6* pathogenic variants have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DNAJC6*.

Differential Diagnosis

Early-Onset Parkinson Disease

DNAJC6 Parkinson disease is often clinically indistinguishable from early-onset Parkinson disease and parkinsonism of other etiologies (see Parkinson Disease Overview and Table 3). Rigidity, bradykinesia, and resting tremor are variably combined in these disorders.

Table 3. Genes Associated with Early-Onset Autosomal Recessive Parkinson Disease and Parkinsonism in the Differential Diagnosis of *DNAJC6* Parkinson Disease

Gene	PD Designation [1]	Median Age at Onset (Range) [2]	Number of Persons [2, 3]	Comment
ATP13A2	PARK-*ATP13A2* (Kufor-Rakeb syndrome) (OMIM 606693)	14 (0-30) yrs	36	Pyramidal signs, eye movement abnormalities, T_2-weighted basal ganglia hypointensity, cerebral & cerebellar atrophy, brain stem atrophy
DJ-1	PARK-*DJ-1* (OMIM 606324)	27 (15-40) yrs	33	Phenotype similar to PARK-*Parkin*; ID, DD &/or seizures occasionally; risk to heterozygotes unknown
FBXO7	PARK-*FBXO7* (OMIM 260300)	17 (10-52) yrs	27	ID/DD/early cognitive impairment, early & vivid hallucinations & behavioral abnormalities w/intake of dopamine agonists, early falls, saccadic abnormalities, gaze palsy, oculogyric spasms, pyramidal signs, autonomic dysfunction
GBA1 (*GBA*)	PARK-*GBA*	May be <50 yrs; median onset: ~60 yrs [4]	>100	Severe motor impairment & rapid progression (akinetic-rigid onset), early onset of cognitive decline, neuropsychiatric & autonomic vulnerability
PINK1	PARK-*PINK1*	32 (9-67) yrs	151	2nd most common cause of EOPD; heterozygotes may have ↑ PD risk [5].
PRKN	PARK-*Parkin*	31 (3-81) yrs	>1000	Most common cause of EOPD; dystonia, hyperreflexia [5]
SYNJ1	PARK-*SYNJ1* (OMIM 615530)	21 (12-31) yrs	15	Early cognitive impairment, early falls, saccadic abnormalities, gaze palsy, pyramidal signs, ataxia, autonomic dysfunction
VPS13C	PARK-*VPS13C* (OMIM 616840)	29 (0-70) yrs	4	Early cognitive impairment, early falls, pyramidal signs, autonomic dysfunction
SPG11	Spastic paraplegia 11 (SPG11)	Typically in infancy or adolescence [6]; median onset of parkinsonism: ~15 yrs	5 (atypical parkinsonism)	Progressive spastic paraparesis, cognitive impairment, axonal neuropathy, MRI abnormalities (thin corpus callosum, T_2 periventricular white matter hyperintensities)

Table 3. continued from previous page.

Gene	PD Designation [1]	Median Age at Onset (Range) [2]	Number of Persons [2, 3]	Comment
ZFYVE26	Spastic paraplegia 15	Childhood or early adulthood; median onset of parkinsonism: ~15 (14-30) yrs	6 (atypical parkinsonism)	Progressive spastic paraparesis, levodopa responsive, MRI abnormalities (thin corpus callosum)

DD = developmental delay; EOPD = early-onset Parkinson disease; ID = intellectual disability; PD = Parkinson disease
1. Nomenclature based on Marras et al [2016]
2. Data from MDSGene.org (accessed 10-10-2023)
3. Based on persons with clinical information reported in the literature
4. Malek et al [2018]
5. PARK-*PINK1* & PARK-*Parkin* EOPD are clinically indistinguishable; non-motor manifestations including psychiatric features may be more common in PARK-*PINK1* than in PARK-*Parkin*.
6. Other features of this disorder typically manifest before the onset of parkinsonism.

Juvenile-Onset Parkinsonism with Prominent Dystonia

For individuals with juvenile-onset parkinsonism, especially those with prominent dystonia, dystonia-parkinsonism phenotypes should be considered (see Table 4 and the Hereditary Dystonia Overview).

Table 4. Genes Associated with Dystonia-Parkinsonism in the Differential Diagnosis of *DNAJC6* Parkinson Disease

Gene	Disorder (Designation [1])	MOI	Dystonia-Parkinsonism	Other Key Clinical Features
Neurotransmitter disorders				
DDC	Aromatic L-amino acid decarboxylase deficiency (DYT-*DDC*) [2]	AR	Infantile-onset parkinsonism & dystonia	Bulbar dysfunction, oculogyric crisis, autonomic dysfunction, ID, DD
GCH1	GTP cyclohydrolase 1-deficient dopa-responsive dystonia (DYT/PARK-*GCH1*)	AD	Adult-onset dystonia-parkinsonism; childhood-onset L-dopa-responsive dystonia	Diurnal fluctuation, female predominance
PTS	6-pyruvoyl-tetrahydropterin synthase deficiency [3] (DYT/PARK-*PTS*)	AR	Infantile-onset dystonia & parkinsonism	DD, ID, seizures, autonomic dysfunction, hyperphenylalaninemia
QDPR	Dehydropteridin reductase deficiency [4] (DYT/PARK-*QDPR*)	AR	Infantile-onset dystonia & parkinsonism	DD, ID, hypotonia, seizures, autonomic dysfunction, hyperphenylalaninemia
SLC6A3	Dopamine transporter deficiency syndrome (DYT/PARK-*SLC6A3*)	AR	Infantile-onset dystonia & parkinsonism; atypical onset w/juvenile-onset dystonia/ parkinsonism	Mild DD, hypotonia, oculogyric crisis, bulbar dysfunction
SLC18A2	Brain dopamine-serotonin transport disease [5]	AR	Childhood-onset parkinsonism	Mood disturbance, autonomic instability, DD
SPR	Sepiapterin reductase deficiency (DYT/PARK-*SPR*)	AR	Infantile-onset L-dopa-responsive dystonia, infantile-onset parkinsonism	DD, ID, spastic paraparesis, autonomic dysfunction, oculogyric crisis, psychiatric symptoms

Table 4. continued from previous page.

Gene	Disorder (Designation [1])	MOI	Dystonia-Parkinsonism	Other Key Clinical Features
TH	Tyrosine hydroxylase deficiency (DYT/PARK-*TH*)	AR	Mild infantile- to childhood-onset L-dopa-responsive dystonia, moderate-to-severe infantile-onset parkinsonism	Hypotonia, limb spasticity, oculogyric crisis, severe autonomic dysfunction
Disorders of heavy metal metabolism				
SLC30A10	Dystonia/parkinsonism, hypermanganesemia, polycythemia, & chronic liver disease (DYT/PARK-*SLC30A10*)	AR	Infantile- to childhood-onset dystonia & parkinsonism	Polycythemia, chronic liver disease, MRI brain abnormalities w/T_1-weighted basal ganglia hyperintensity
SLC39A14	SLC39A14 deficiency (hypermanganesemia w/dystonia 2)	AR	Infantile- to childhood-onset dystonia & parkinsonism	MRI brain abnormalities, w/T_1-weighted basal ganglia hyperintensity
ATP7B	Wilson disease (DYT-*ATP7B*)	AR	Adolescent-/adult-onset parkinsonism, dystonia	Tremor, psychiatric symptoms, liver disease, ocular Kayser-Fleischer rings; on MRI: features of basal ganglia heavy metal deposition ("face of giant panda" sign)
Inherited metabolic disorders				
GLB1	GM1 gangliosidosis type III - chronic/adult form (See *GLB1*-Related Disorders.) (DYT/PARK-*GLB1*)	AR	Adolescent-/adult-onset dystonia & parkinsonism	Mild ID/DD, pyramidal signs, dysarthria, skeletal abnormalities, cardiomyopathy, cataract, vacuolated lymphocytes
NPC1 *NPC2*	Niemann-Pick disease type C	AR	Childhood-/adolescent-/adult-onset dystonia, adolescent-/adult-onset parkinsonism	Vertical supranuclear gaze palsy, oculomotor apraxia, cerebellar ataxia, gelastic cataplexy
SLC19A3	Biotin-thiamine-responsive basal ganglia disease (DYT-*SLC19A3*)	AR	Childhood-onset dystonia & parkinsonism	Subacute encephalopathy/coma, cerebellar signs, pyramidal signs, ID/DD, epilepsy
HPRT1	Lesch-Nyhan disease (See *HPRT1* Disorders.)	XL	Infantile-/adolescent-/adult-onset dystonia & parkinsonism	Variety of neurologic & behavioral problems (incl self-mutilation), ID/DD
Mitochondrial disorders [6]				
DLAT *DLD* *PDHA1* *PDHB* *PDHX* *PDK3* *PDP1*	Primary pyruvate dehydrogenase complex deficiency	AR XL	Adult-onset parkinsonism & dystonia	Chorea, ataxia, dysarthria, dementia
POLG	*POLG*-related disorders	AR (AD)	Juvenile-/adult-onset parkinsonism	Continuum of overlapping phenotypes [7]
mtDNA	Leber hereditary optic neuropathy	Mat	Adult-onset parkinsonism	Optic atrophy
Early-onset neurodegeneration with brain iron accumulation (NBIA) disorders [8]				
C19orf12	Mitochondrial membrane protein-associated neurodegeneration (HSP/NBIA-*C19orf12*)	AR (AD)	Early childhood-onset parkinsonism & dystonia	Spasticity, dystonia, dementia, psychiatric features, motor axonopathy, optic atrophy; on MRI: features of BIA in basal ganglia (globus pallidus, substantia nigra)

Table 4. continued from previous page.

Gene	Disorder (Designation [1])	MOI	Dystonia-Parkinsonism	Other Key Clinical Features
CP	Aceruloplasminemia (NBIA/DYT/PARK-*CP*)	AR	Adult-onset dystonia & parkinsonism	Ataxia, chorea, diabetes mellitus, retinal degeneration, psychiatric symptoms, anemia, ↑ serum ferritin, ↓ serum copper, absent ceruloplasmin, liver iron storage; on MRI: features of BIA (basal ganglia & dentate nuclei on MRI)
PANK2	Pantothenate kinase-associated neurodegeneration (NBIA/DYT-*PANK2)*	AR	Childhood-onset dystonia & parkinsonism	Neuropsychiatric features, pyramidal signs, pigmentary retinopathy; on MRI: features of BIA (globus pallidus) w/"eye of the tiger" sign)
PLA2G6	*PLA2G6*-associated neurodegeneration (NBIA/DYT/PARK-*PLA2G6*)	AR	Adolescent/adult-onset dystonia & parkinsonism	ID/DD (in early-onset disease)/dementia, pyramidal signs, ataxia, psychiatric features; on MRI: features of progressive cerebellar atrophy, cerebellar gliosis & BIA (globus pallidus & substantia nigra)
WDR45	Beta-propeller protein-associated neurodegeneration (NBIA/PARK-*WDR45*)	XL	Adolescent-onset parkinsonism & dystonia	DD/ID, spasticity, seizures, abnormal behavior; on MRI: features of BIA (substantia nigra & globus pallidus), T_1-weighted hyperintense "halo" midbrain, cerebral & cerebellar atrophy
Other monogenic disorders with prominent parkinsonism				
ATP1A3	Rapid-onset dystonia-parkinsonism (See *ATP1A3*-Related Neurologic Disorders.) (DYT/PARK-*ATP1A3*)	AD	Adolescent-/adult-onset dystonia & parkinsonism	Pyramidal degeneration w/spasticity, supranuclear palsy; symptoms can be triggered by fever, infection, physical/emotional stress, alcohol consumption
HTT	Childhood or juvenile-onset Huntington disease	AD	Childhood-/juvenile-onset parkinsonism (rigid-hypokinetic)	Severe mental deterioration, prominent motor & cerebellar symptoms, rapid progression, seizures
PRKRA	Young-onset dystonia-parkinsonism (See Hereditary Dystonia Overview.) (DYT-*PRKRA*)	AR	Infantile-/childhood-onset dystonia (lower limb) & parkinsonism	Severe laryngeal dystonia in most persons
TAF1	X-Linked dystonia-parkinsonism (DYT/PARK-*TAF1*)	XL	Adult-onset dystonia (craniofacial, lower limb, cervical) & parkinsonism	Most frequent in Filipino males of Panay Islander ancestry

AD = autosomal dominant; AR = autosomal recessive; BIA = brain iron accumulation; DD = developmental delay; DYT = dystonia; HSP = hereditary spastic paraplegia; ID = intellectual disability; Mat = maternal; MOI = mode of inheritance; mtDNA = mitochondrial DNA; PARK = parkinsonism; XL = X-linked

1. Movement disorder nomenclature is based on Marras et al [2016].

2. OMIM 608643

3. OMIM 261640

4. OMIM 261630

5. OMIM 618049

6. Mitochondrial dysfunction can be associated with infantile-onset parkinsonism, pyramidal signs, and axonal neuropathy and should be considered in the differential diagnosis of any progressive multisystem disorder. Many nuclear and mitochondrial genes are known to be associated with respiratory chain defects; see Mitochondrial Disorders Overview).

7. Most affected individuals have some, but not all, of the features of a given phenotype. Associated phenotypes are: Alpers-Huttenlocher syndrome, childhood myocerebrohepatopathy spectrum, myoclonic epilepsy myopathy sensory ataxia, ataxia neuropathy spectrum, autosomal recessive progressive external ophthalmoplegia, and autosomal dominant progressive external ophthalmoplegia.

8. See also Neurodegeneration with Brain Iron Accumulation Disorders Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *DNAJC6* Parkinson disease, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *DNAJC6* Parkinson Disease

System/Concern	Evaluation	Comment
Neurologic	Detailed neurologic exam focusing on presence & extent of movement disorder	Unified Parkinson Disease [Fahn & Elton 1987] or Movement Disorder Society [Goetz et al 2008] rating scale may be helpful.
	Detailed neurologic exam for movement abnormalities	To identify any additional movement disorders (e.g., dystonia) & seizures
	Eval by PT, OT, speech & language therapy if required	
Development & Cognition	• Detailed developmental assessment in those w/juvenile onset • Formal IQ testing w/psychologist	
Neuropsychiatric	Formal neuropsychiatric assessment w/neuropsychiatrist	
Nutrition/ Gastrointestinal	• Nutritional eval by dietician to monitor & ensure adequate caloric intake • Speech-language therapist to assess safety of feeding	
Musculoskeletal	Detailed orthopedic exam	For secondary complications (e.g., fixed contractures, hip & spine abnormalities)
Vision	Ophthalmology eval for eye movement abnormalities & vision assessment	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *DNAJC6* Parkinson disease to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; OT = occupational therapist/therapy; PT = physical therapist/therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with *DNAJC6* Parkinson Disease

Manifestation/ Concern	Treatment	Considerations/ Other
Parkinsonism	• Levodopa, started at low dosage, & cautiously titrated & adjusted, esp in those w/juvenile onset • If levodopa is not effective, other agents incl dopaminergic agonists or anticholinergics may be used.	Surgical procedures have been applied w/good outcome in 2 persons w/an early-onset milder disease course [Olgiati et al 2016].

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/ Other
Dystonia	• Oral medications: dopamine-related medications (levodopa, dopaminergic agonists), anticholinergics, benzodiazepines, gabapentin, baclofen, clonidine • Surgical interventions: Deep brain stimulation, pallidotomy	
Spasticity	• Oral medications: baclofen, benzodiazepines, dantrolene, local botulinum toxin • PT & OT • Surgical interventions: tenotomy	
Myoclonus	Oral medications: sodium valproate, clonazepam, levetiracetam, piracetam	
DD/ID	• Multidisciplinary mgmt per PT, OT, speech & language therapy • Special education services as indicated	
Seizures	Anti-seizure medication depending on type & frequency of seizures	
Psychiatric disorders	Treatment per neuropsychiatrist to determine need for antidepressants, antipsychotic medications, &/or anxiolytics	
Sleep disorder	Sleep aids (e.g., sleep system, conservative measures, melatonin, sedative medications) depending on underlying sleep disorder	
GI manifestations	• Supportive feeding measures (e.g., gastrostomy) if needed for ↓ oral intake or aspiration risk • Treatment of constipation (laxatives, diet) • Sialorrhea therapy w/hyoscine patches, glycopyrronium bromide, or (if severe) botulinum toxin or surgical approaches • Treatment of reflux w/proton pump inhibitors	
Orthopedic manifestations	• Supportive rehab devices & equipment • Surgical interventions may be needed for hip dislocation or kyphoscoliosis.	
Vision deficits	• Low vision therapy • Glasses • Surgical intervention for strabismus if needed	

DD = developmental delay; GI = gastrointestinal; ID = intellectual disability; OT = occupational therapist/therapy; PT = physical therapist/therapy

Surveillance

Table 7. Recommended Surveillance for Individuals with *DNAJC6* Parkinson Disease

System/Concern	Evaluation	Frequency
Movement disorder	PT, OT, speech & language therapy evals	Every 6 mos or more frequently as needed
Seizures	Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).	At each visit
	EEG	At 1st manifestation of symptoms, then as frequently as needed
	Monitor those w/seizures as clinically indicated.	Incl assessment & adjustment of anti-seizure medication as needed
Psychiatric disorders	Psychiatric assessment	At 1st manifestation of symptoms, then as frequently as needed
Sleep disorder	Sleep study/polysomnography	

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Nutrition	Growth assessment	At each visit in children
	Assessment of nutritional status to evaluate dietary requirements	At each visit
Dysphagia	Swallowing assessment to evaluate risk of aspiration	At 1st manifestation of symptoms, then as frequently as needed
Gastrointestinal manifestations	Gastroenterology eval; gastroscopy if needed	
Orthopedic manifestations	Hip & spine radiographs	Every 6-12 mos in persons: • Who are nonambulatory at age >2 yrs • W/signs/symptoms concerning for spinal deformity
Vision deficits	Ophthalmology eval	At 1st manifestation of symptoms, then as frequently as needed

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Though there are no data available to date, dopamine antagonists and vesicular monoamine transporter 2 (VMAT2) inhibitors should be avoided as they could aggravate dopamine deficiency. VMAT2 inhibitors prevent reuptake and storage of neurotransmitters into synaptic vesicles and thus could theoretically cause further depletion of presynaptic dopamine.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. 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

DNAJC6 Parkinson disease is inherited in an autosomal recessive manner.

Note: The identification of heterozygous *DNAJC6* variants in five individuals with Parkinson disease has raised the question of whether heterozygous *DNAJC6* variants may contribute to the development of parkinsonism [Olgiati et al 2016]. Further studies are needed to determine if these variants confer Parkinson disease risk.

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *DNAJC6* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *DNAJC6* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- The risk to heterozygotes of developing manifestations is not yet determined (see Clinical Characteristics, Heterozygotes).

Sibs of a proband

- If both parents are known to be heterozygous for a *DNAJC6* 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 *DNAJC6* pathogenic variant.
- In sibs who inherit biallelic *DNAJC6* variants, the range in onset of Parkinson disease reported to date is:
  - Onset between ages seven and 14 years in juvenile-onset disease [Edvardson et al 2012, Köroğlu et al 2013, Elsayed et al 2016, Mittal 2020, Ng et al 2020];
  - Onset between ages 21 and 44 years in early-onset disease [Olgiati et al 2016, Li et al 2020].
- The risk to heterozygotes of developing manifestations is not yet determined (see Clinical Characteristics, Heterozygotes).

Offspring of a proband. The offspring of an individual with *DNAJC6* Parkinson disease are obligate heterozygotes (carriers) for a pathogenic variant in *DNAJC6*.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *DNAJC6* pathogenic variant.

Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the *DNAJC6* 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, heterozygous, or are at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DNAJC6* 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 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.

- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Parkinson's Disease Information Page
- **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
- **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 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

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. DNAJC6 Parkinson Disease: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
DNAJC6	1p32.1-p31.3	Auxilin	DNAJC6

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 DNAJC6 Parkinson Disease (View All in OMIM)

608375	DNAJ/HSP40 HOMOLOG, SUBFAMILY C, MEMBER 6; DNAJC6
615528	PARKINSON DISEASE 19A, JUVENILE-ONSET; PARK19A

Molecular Pathogenesis

DNAJC6 encodes for the protein auxilin 1, which is a co-chaperone protein involved in clathrin-mediated synaptic vesicle endocytosis. It specifically recruits the molecular chaperone protein heat shock cognate (Hsc70) to the nascent clathrin-coated vesicle. Auxilin induces Hsc70-mediated ATP hydrolysis, which leads to subsequent uncoating of the clathrin lattice and release of cargo [Kaksonen & Roux 2018, Milosevic 2018]. Clathrin-mediated endocytosis is involved in a variety of cellular processes including synaptic neurotransmission, regulation of surface protein expression, and plasma membrane homeostasis, as well as developmental and synaptic signaling [Kaksonen & Roux 2018].

Auxilin deficiency has been investigated in several animal models. The auxilin knockout mouse model demonstrated increased early postnatal mortality and a significantly reduced body weight in one-week old mice [Yim et al 2010]. In cortical and hippocampal neurons, synaptic vesicle endocytosis was impaired, most likely due to accumulation of clathrin-coated vesicles (CCVs) and empty clathrin cages. The mice also showed upregulation of the ubiquitously expressed homolog protein cyclin-G-associated kinase (GAK) in brain lysates, probably as a compensatory mechanism for auxilin deficiency. The auxilin knockdown *Drosophila* model showed reduced locomotion and longevity [Song et al 2017]. The flies exhibited an age-dependent, α-synuclein-mediated loss of dopaminergic neurons and showed increased sensitivity to paraquat, a toxin widely used to induce parkinsonism in animal and cell models.

Altogether, these findings suggest that auxilin deficiency leads to impaired synaptic vesicle endocytosis, which in turn negatively impacts synaptic neurotransmission, synaptic homeostasis, and signaling. However, the exact pathogenic mechanisms by which auxilin deficiency leads to dopaminergic neurodegeneration and a complex neurologic phenotype still remain to be fully elucidated.

Mechanism of disease causation. *DNAJC6* Parkinson disease is caused by loss-of-function variants including nonsense, missense, and splice site variants.

Table 8. Notable *DNAJC6* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_001256864.2 NP_001243793.1	c.766C>T	p.Arg256Ter	Juvenile-onset parkinsonism (founder variant identified in 2 unrelated families originating from the same region in Pakistan [Ng et al 2020])
	c.2416C>T	p.Arg806Ter	Juvenile-onset parkinsonism [Ng et al 2020]
	c.2410C>T (2200C>T)	p.Gln804Ter (Gln734Ter)	Juvenile-onset parkinsonism [Köroğlu et al 2013]
	c.2365C>T	p.Gln789Ter	Juvenile-onset parkinsonism [Elsayed et al 2016]
NM_001256864.2	c.801-2A>G	--	Juvenile-onset parkinsonism [Edvardson et al 2012]

Table 8. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_001256864.2 NP_001243793.1	c.2779A>G	p.Arg927Gly	Early-onset parkinsonism [Olgiati et al 2016]
NM_001256864.2	c.2038+3A>G	--	
NM_001256864.2 NP_001243793.1	c.2223A>T	See footnote 2.	
	c.2687C>T	p.Thr896Met	Early-onset parkinsonism [Li et al 2020]

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.
2. Predicted to introduce an aberrant spice acceptor site

Chapter Notes

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