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DCTN1-Related Neurodegeneration

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Summary

Clinical characteristics

The spectrum of *DCTN1*-related neurodegeneration includes Perry syndrome, distal hereditary motor neuronopathy type 7B (dHMN7B), frontotemporal dementia (FTD), motor neuron disease / amyotrophic lateral sclerosis (ALS), and progressive supranuclear palsy. Some individuals present with overlapping phenotypes (e.g., FTD-ALS, Perry syndrome-dHMN7B).

Perry syndrome (the most common of the phenotypes associated with *DCTN1*) is characterized by parkinsonism, neuropsychiatric symptoms, hypoventilation, and weight loss. The mean age of onset in those with Perry syndrome is 49 years (range: 35-70 years), and the mean disease duration is five years (range: 2-14 years). In most affected persons, the reported cause/circumstance of death relates to sudden death/ hypoventilation or suicide.

Diagnosis/testing

The diagnosis of *DCTN1*-related neurodegeneration is established in a proband by identification of a heterozygous *DCTN1* pathogenic variant on molecular genetic testing.

Management

Treatment of manifestations: Dopaminergic therapy in individuals with significant parkinsonism; ventilation support; anti depressants and psychiatric care for depression; high caloric intake for weight loss; feeding tube when needed to prevent aspiration pneumonia and provide adequate caloric intake; arytenoidectomy for vocal cord paralysis to provide a larger airway for respiration; orthosis for neuropathic foot.

Surveillance: Evaluation of weight and calorie intake, respiratory function (particularly at night or during sleep), motor function, and mood/personality changes annually or more frequently as needed.

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Agents/circumstances to avoid: Central respiratory depressants (e.g., benzodiazepines, alcohol, narcotics).

Genetic counseling

DCTN1-related neurodegeneration is inherited in an autosomal dominant manner. Most individuals diagnosed with *DCTN1*-related neurodegeneration have an affected parent. Less commonly, individuals diagnosed with *DCTN1*-related neurodegeneration have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with *DCTN1*-related neurodegeneration has a 50% chance of inheriting the pathogenic variant. Once the *DCTN1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *DCTN1*-related neurodegeneration are possible.

GeneReview Scope

DCTN1-Related Neurodegeneration: Phenotypic Spectrum [1]
• Perry syndrome [2] • Distal hereditary motor neuronopathy type 7B • Frontotemporal dementia • Motor neuron disease / amyotrophic lateral sclerosis • Progressive supranuclear palsy

1. For other genetic causes of these phenotypes, see Differential Diagnosis.
2. The most common phenotype associated with heterozygous *DCTN1* pathogenic variants

Diagnosis

Suggestive Findings

DCTN1-related neurodegeneration **should be suspected** in individuals with any combination of the following clinical features, family history of the following features, or neuroimaging findings.

Clinical findings

- Parkinsonism
- Mood/personality/cognitive changes (depression, apathy, withdrawal, disinhibition, dementia)
- Weight loss
- Breathing disturbances (in particular central hypoventilation)
- Muscle atrophy
- Autonomic dysfunction
- Vocal fold paralysis
- Facial weakness

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Neuroimaging and other studies [Felicio et al 2014, Barreto et al 2015, Hwang et al 2016, Konno et al 2017, Mishima et al 2018, Convery et al 2019, Coughlin & Litvan 2020, Masrori & Van Damme 2020, Saka et al 2010, Tian et al 2020, Mishima et al 2021, Tsuboi et al 2021, Zhang et al 2021]

- Brain CT and MRI may reveal atrophy of the frontal and temporal lobes or the midbrain.
- ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and single-photon emission CT (SPECT) may demonstrate decreased glucose metabolism and blood perfusion in the frontal, temporal, parietal, and occipital lobes.

- ^{123}I-Ioflupane SPECT (DaTscan) may show reduced tracer uptake in the striatum, reflecting presynaptic dopaminergic dysfunction.
- ^{18}F-6-fluoro-L-dopa (FDOPA) and ^{11}C-dihydrotetrabenazine (DTBZ) PET may detect a decrease in striatal tracer uptake, reflecting presynaptic dopaminergic dysfunction.
- ^{11}C-raclopride (RAC) PET may find an abnormal striatal tracer uptake, reflecting disturbances of postsynaptic dopaminergic function.
- 3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile (DASB) PET may demonstrate cortical and subcortical disruption of serotonergic neurotransmission.
- Transcranial sonography may show hyperechogenicity in the substantia nigra comparable to that observed in Parkinson disease.
- ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) myocardial scintigraphy may demonstrate reduced cardiac uptake, reflecting autonomic dysfunction.
- Electroneurography may reveal length-dependent predominantly motor neuropathy.
- Electromyography may show evidence of denervation.

Establishing the Diagnosis

The diagnosis of *DCTN1*-related neurodegeneration **is established** in a proband with suggestive findings and a heterozygous *DCTN1* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *DCTN1* variant of uncertain significance does not establish or rule out this diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Therefore, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with parkinsonism are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Perform sequence analysis of *DCTN1*.

Note: *DCTN1*-related neurodegeneration occurs through a dominant-negative mechanism (see Molecular Genetics) and large intragenic deletion or duplication has not been reported; testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant. Detailed genetic studies for intragenic deletions or duplications have not been conducted.

A multigene panel that includes *DCTN1* and other genes of interest (see Differential Diagnosis) may also be considered 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.

Option 2

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 *DCTN1*-Related Neurodegeneration

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DCTN1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [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 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. Data derived from the subscription-based professional view of 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.
6. Since *DCTN1*-related neurodegeneration occurs through a dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Clinical Characteristics

Clinical Description

The spectrum of *DCTN1*-related neurodegeneration includes Perry syndrome, distal hereditary motor neuronopathy type 7B (dHMN7B), frontotemporal dementia (FTD), motor neuron disease / amyotrophic lateral sclerosis (ALS), and progressive supranuclear palsy. Some individuals present with overlapping phenotypes (e.g., FTD-ALS, Perry syndrome-dHMN7B) [Caroppo et al 2014, Konno et al 2017, Zhang et al 2021]. In most families, the phenotype is consistent among affected family members. However, not infrequently, the same *DCTN1* pathogenic variant may manifest with a different clinical phenotype even within the same family.

Perry Syndrome

The cardinal signs of Perry syndrome are parkinsonism, neuropsychiatric symptoms, hypoventilation, and weight loss [Konno et al 2017, Mishima et al 2018]. The mean age of onset is 49 years (range: 35-70 years); the mean disease duration is five years (range: 2-14 years). Psychiatric (depression, apathy, character changes, withdrawal) and motor (parkinsonism) symptoms tend to occur early, whereas severe weight loss and hypoventilation manifest later. In most affected persons, the reported cause/circumstance of death relates to sudden death/hypoventilation or suicide [Konno et al 2017, Mishima et al 2018, Tsuboi et al 2021].

Parkinsonism. Most individuals with Perry syndrome present with parkinsonism, which manifests in rigidity (60%), tremor (52%), bradykinesia (38%), and postural instability (28%). It is relatively symmetric and less responsive to levodopa than that found in Parkinson disease. Some individuals may develop complications of levodopa therapy, including fluctuations and peak dose dyskinesia [Konno et al 2017, Mishima et al 2018].

Hypoventilation. Alveolar hypoventilation manifests particularly at night or during sleep, with tachypnea alternating with normal respiratory cycles, leading to frequent awakenings. Polysomnographic recordings show that hypoxemia and hypercapnia are of central origin; that is, there is no obstructive or structural respiratory tract abnormality. Respiratory symptoms present later in the disease course and slowly worsen over time, leading to respiratory insufficiency and death. However, respiratory failure may occur rapidly without any predictive signs. Of note, hypoventilation was not reported in four of the thirty-one families with confirmed Perry syndrome [Konno et al 2017, Mishima et al 2018, Tsuboi et al 2021].

Sleep difficulties occur in approximately 20% of individuals and probably reflect hypoventilation.

Neuropsychiatric findings. Depression and apathy occur in the majority of affected individuals and are the most common initial presentation. Depression is usually more severe than that observed in Parkinson disease, refractory to treatment, and often associated with suicidal ideations. Apathy is manifested by social withdrawal, loss of interest, and "psychic self-activation" (referred to as "athymhormia" in French literature). Cognitive impairment is associated with the frontostriatal pattern of deficits. In addition, some individuals present with disinhibited behavior, impulsivity, and other psychiatric features overlapping with the behavioral variant of FTD (bvFTD) [Konno et al 2017, Mishima et al 2018, Milanowski et al 2020].

Weight loss is observed in 50% of individuals, progression can vary. The etiology is probably multifactorial, with dysphagia and psychiatric comorbidities being the leading causes; however, a disease-specific mechanism involving central modification of hunger sensation or an increase in metabolic rate cannot be excluded [Konno et al 2017, Mishima et al 2018].

Autonomic failure (e.g., erectile dysfunction, orthostatic hypotension, bladder and bowel incontinence, anhidrosis) has been reported in some individuals; however, it is probably underreported as no information on autonomic function is provided in most reports.

Other Phenotypes

Distal hereditary motor neuronopathy type 7B (dHMN7B) is a length-dependent, primarily motor neuropathy [Hwang et al 2016, Zhang et al 2021]. In most individuals it presents between the third to fifth decades, but it can manifest earlier, even at birth. It is characterized by bilateral vocal cord palsy (leading to breathing difficulties) and progressive atrophy and weakness of the facial and distal limb muscles [Hwang et al 2016, Tian et al 2020, Zhang et al 2021]. However, the clinical presentation varies, and not all features may be present [Zhang et al 2021].

***DCTN1*-related frontotemporal dementia (FTD)** is characterized by the impairment of frontal and temporal lobe functions [Convery et al 2019, Piguet & Kumfor 2020]. FTD can be broadly divided into behavioral (bvFTD) and language (lvFTD) variants. Individuals with bvFTD present with predominant behavioral and personality changes, whereas those with lvFTD develop worsening of speech and language. BvFTD manifests with apathy, disinhibition, impulsivity, loss of empathy, obsessive behaviors, alterations in food preferences, executive function deterioration, and lack of insight. LvFTD, also called primary progressive aphasia, is characterized by gradually progressive disorders of speech and language that disturb the activities of daily living and may be accompanied at later stages by behavioral symptoms similar to those observed in bvFTD [Convery et al 2019]. To date, most individuals with *DCTN1*-related FTD have presented with bvFTD.

***DCTN1*-related motor neuron disease or amyotrophic lateral sclerosis (ALS)** is a multifaceted neurodegenerative disorder predominantly affecting the motor system. It typically presents in adulthood with

weakness and atrophy of the distal limb muscles that gradually spread to adjacent body regions. Muscle weakness and atrophy are often associated with fasciculations, muscle cramps, and stiffness. However, the age and region of onset are variable, and in some individuals the disease may start with bulbar symptoms [Masrori & Van Damme 2020]. Additionally, non-motor symptoms are increasingly recognized, including mood disturbances (depression, anxiety), cognitive decline (most pronounced in executive functions), behavioral symptoms (most commonly apathy and disinhibition), suicidal ideation, pseudobulbar affect, sleep disruption, autonomic dysfunction (bladder incontinence, constipation, excessive secretions), pain, fatigue, and metabolic dysfunction [Mahoney et al 2021]. Despite advances in understanding the disease, the prognosis is ominous: median survival is three years, with most individuals dying of respiratory insufficiency [Masrori & Van Damme 2020].

***DCTN1*-related progressive supranuclear palsy (PSP)** is characterized by supranuclear gaze palsy, postural instability, and increased falls within a year of symptom onset. However, the clinical presentation of PSP is heterogeneous, and it may initially mimic Parkinson disease, frontotemporal dementia, or corticobasal syndrome; rarely, pure akinesia with freezing of gait may be the only manifestation. In such instances, the classic features of PSP appear later in the disease course [Coughlin & Litvan 2020]. Most individuals with *DCTN1*-related PSP presented with dominant parkinsonian and FTD-like symptoms [Caroppo et al 2014, Gustavsson et al 2016, Konno et al 2017, Barreto et al 2021].

Neuroimaging and Other Studies

Reported findings [Felicio et al 2014, Barreto et al 2015, Hwang et al 2016, Konno et al 2017, Mishima et al 2018, Convery et al 2019, Coughlin & Litvan 2020, Masrori & Van Damme 2020, Saka et al 2010, Tian et al 2020, Mishima et al 2021, Tsuboi et al 2021, Zhang et al 2021]:

- Brain CT and MRI may reveal atrophy of the frontal and temporal lobes or the midbrain.
- ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and single-photon emission CT (SPECT) may demonstrate decreased glucose metabolism and blood perfusion in the frontal, temporal, parietal, and occipital lobes.
- ^{123}I-Ioflupane SPECT (DaTscan) may show reduced tracer uptake in the striatum, reflecting presynaptic dopaminergic dysfunction.
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- Electroneurography may reveal length-dependent predominantly motor neuropathy.
- Electromyography may show evidence of denervation.

Neuropathology

The neuropathology of *DCTN1*-related neurodegeneration is not well studied, and most autopsies were conducted on individuals with Perry syndrome.

Histology showed severe neuronal loss and gliosis in the substantia nigra, and to a lesser degree in locus ceruleus, striatum, hypothalamus, periaqueductal gray matter, ventrolateral medulla, dorsal raphe nucleus, and brain stem reticular formation. Lewy bodies and neurofibrillary tangles were not present in most individuals.

Immunohistochemistry showed abnormal deposition of transactive response DNA-binding protein 43 (TDP-43) in the form of neuronal cytoplasmic inclusions, dystrophic neurites, glial cytoplasmic inclusions, and axonal spheroids. If present, TDP-43 pathology was morphologically similar in Perry syndrome, FTD, motor neuron disease, and other disorders. However, its distribution was distinct in individuals with Perry syndrome, who had most lesions located in the extrapyramidal system [Konno et al 2017, Mishima et al 2017, Mishima et al 2018].

In *DCTN1*-related dHMN7B, neuropathologic studies revealed decreased density of large myelinated nerve fibers and neurogenic changes in the muscles [Tian et al 2020, Zhang et al 2021]. TDP-43 aggregation was not observed [Mishima et al 2017]; however, it was detected in a cell model [Deshimaru et al 2021].

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been identified. While affected family members often share the same phenotype, intrafamilial variability has also been reported. For example, individuals from one Chinese family with the same *DCTN1* pathogenic variant presented with dHMN7B, Perry syndrome, or overlapping features of dHMN7B-Perry syndrome [Zhang et al 2021].

Penetrance

Although precise estimates have not been calculated given the limited number of families reported, penetrance is age related and high, with all asymptomatic heterozygotes being younger than or within the range of age of onset.

Prevalence

Since the discovery of *DCTN1*-related neurodegeneration [Puls et al 2003], more than 30 families and approximately 200 affected individuals have been reported. The majority of reports included individuals with Perry syndrome (~80%).

Genetically Related (Allelic) Disorders

To date, no phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DCTN1*.

Differential Diagnosis

Table 2. Disorders of Interest in the Differential Diagnosis of *DCTN1*-Related Neurodegeneration

Phenotype	Gene	Disorder	MOI	Comment
Early-onset parkinsonism (See also Parkinson Disease Overview.)	*DNAJC6*	PARK-D*NAJC6* (OMIM 615528)	AR	Findings of personality changes, weight loss, & hypoventilation in Perry syndrome tend to distinguish it from other forms of early-onset PD. Also, response to standard doses of levodopa is usually poorer or of shorter duration in Perry syndrome than in other forms of early-onset PD.
	FBXO7	PARK-*FBXO7* (OMIM 260300)	AR	
	LRRK2	PARK-*LRRK2*	AD	
	PARK7 (*DJ-1*)	PARK-*DJ1* (OMIM 606324)	AR	
	PINK1	PARK-*PINK1*	AR	
	PRKN	PARK-*Parkin*	AR	
	SYNJ1	PARK-*SYNJ1* (OMIM 615530)	AR	
	VPS13C	PARK-*VPS13C* (OMIM 616840)	AR	
Frontotemporal dementia	*C9orf72*	*C9orf72*-FTD/ALS	AD	*DCTN1*-related FTD & other causes of FTD may share mood/personality changes, similar age of onset, & levodopa-resistant parkinsonism. Weight loss, breathing disturbances, muscle atrophy, & dysautonomia suggest *DCTN1*-related disorder.
	GRN	*GRN*-FTD	AD	
	MAPT [1]	*MAPT*-FTD	AD	
Progressive supranuclear palsy	*MAPT*	Progressive supranuclear palsy 1 (See *MAPT*-FTD.)	AD	*MAPT*- & *DCTN1*-related PSP may share features of bvFTD. Weight loss, breathing disturbances, muscle atrophy, & dysautonomia suggest *DCTN1*-related disorder.

AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; bv = behavioral variant; FTD = frontotemporal dementia; MOI = mode of inheritance; PD = Parkinson disease; PSP = progressive supranuclear palsy

1. An individual of Japanese ancestry who showed symptoms reminiscent of Perry syndrome had an *MAPT* pathogenic variant. On autopsy examination, the brain showed tau-positive inclusions; transactive response DNA-binding protein 43 (TDP-43)-positive inclusions were not present [Omoto et al 2012].

Distal hereditary motor neuronopathy. In addition to a family history consistent with autosomal dominant inheritance, the most significant diagnostic clues in distinguishing dHMN7B from other distal hereditary motor neuronopathies include the presence of breathing difficulties due to bilateral vocal cord palsy, atrophy and weakness of the facial and distal limb muscles, and a family history of parkinsonism, depression/apathy, weight loss, or behavioral symptoms. See Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview for a review of disorders that may mimic the neuropathy-dominant phenotype of *DCTN1*-related neurodegeneration.

Note: Only a few individuals with distal hereditary motor neuronopathy type 7B (dHMN7B) have been reported to date.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *DCTN1*-related neurodegeneration, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *DCTN1*-Related Neurodegeneration

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval of motor & non-motor function	
Pulmonary	• Sleep study • Eval by pulmonologist or sleep disorders consultant for ventilation support if required	
Psychiatric	• Psychiatric eval • Neuropsychological exam if indicated	
Weight & nutrition	Assessment of swallowing & caloric intake	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *DCTN1*-related neurodegeneration to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources; • Social work involvement; • Home nursing referral.	

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Parkinsonism. Dopaminergic therapy (particularly carbidopa/levodopa) should be considered in all individuals with significant parkinsonism. Response to levodopa is usually absent, erratic, or transient in Perry syndrome [Konno et al 2017, Mishima et al 2018]. However, large doses of carbidopa/levodopa (>2g) have been used successfully to reduce rigidity, tremor, and other symptoms in two individuals [Newsway et al 2010; J Stoessl, personal communication].

Hypoventilation. Ventilation support (invasive or noninvasive) may prolong life expectancy and have a significant effect on quality of life. Several persons without evidence of daytime central hypoventilation or respiratory compromise died suddenly at night, most likely as a result of nocturnal hypoventilation. Therefore, ventilation support may be needed only during sleep [Wider & Wszolek, personal observation]. A bilateral diaphragmatic pacemaker may be helpful for respiratory insufficiency [Konno & Wszolek 2018].

Depression. Psychiatric manifestations may require antidepressants and management by a psychiatrist to reduce the risk of suicide.

Weight loss. Careful weight monitoring is indicated and high caloric intake should be considered if weight loss is present.

Dysphagia. Nasogastric or preferably percutaneous endoscopic gastrostomy (PEG) feeding should be considered to prevent aspiration pneumonia and provide adequate caloric intake.

Vocal cold paralysis. Arytenoidectomy should be considered to provide larger airway for respiration.

Neuropathic foot. Orthosis should be considered to improve the function of the foot.

Surveillance

Evaluate weight and calorie intake, respiratory function (particularly at night or during sleep), motor function, and mood/personality changes annually or more frequently as needed.

Agents/Circumstances to Avoid

Use of central respiratory depressants (e.g., benzodiazepines, alcohol, narcotics) should be minimized.

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

DCTN1-related neurodegeneration is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *DCTN1*-related neurodegeneration have an affected parent. Affected family members typically have a similar phenotype. However, intrafamilial variability has been reported and family members who are heterozygous for the same *DCTN1* pathogenic variant may not infrequently manifest a different clinical phenotype within the spectrum of *DCTN1*-related neurodegeneration.
- Less commonly, individuals diagnosed with *DCTN1*-related neurodegeneration have the disorder as the result of a *de novo* pathogenic variant. The proportion of probands who have a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

- The family history of some individuals diagnosed with *DCTN1*-related neurodegeneration may appear to be negative because of failure to recognize the disorder in family members because of a milder phenotypic presentation, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the *DCTN1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. In most families, heterozygous sibs have a similar phenotype; however, not infrequently, the same *DCTN1* pathogenic variant may manifest with a different clinical phenotype within the spectrum of *DCTN1*-related neurodegeneration.
- If the *DCTN1* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *DCTN1* pathogenic variant but are clinically unaffected, the risk to sibs of the proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *DCTN1*-related neurodegeneration because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *DCTN1*-related neurodegeneration has a 50% chance of inheriting the *DCTN1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a *DCTN1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *DCTN1* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *DCTN1*-related neurodegeneration, it is appropriate to consider testing of symptomatic individuals regardless of age.

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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DCTN1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *DCTN1*-related neurodegeneration 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. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

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.

- **MedlinePlus**
  Perry syndrome
- **American Parkinson Disease Association (APDA)**
  Phone: 800-223-2732
  Email: apda@apdaparkinson.org
  apdaparkinson.org
- **Michael J. Fox Foundation for Parkinson's Research**
  Phone: 212-509-0995
  Email: info@michaeljfox.org
  michaeljfox.org
- **Parkinson's Foundation**
  Phone: 800-473-4636
  Email: Helpline@Parkinson.org
  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. DCTN1-Related Neurodegeneration: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

DCTN1	2p13.1	Dynactin subunit 1	alsod/DCTN1 genetic mutations DCTN1 homepage - Leiden Muscular Dystrophy pages	DCTN1	DCTN1

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 DCTN1-Related Neurodegeneration (View All in OMIM)

168605	PERRY SYNDROME
601143	DYNACTIN 1; DCTN1
607641	NEURONOPATHY, DISTAL HEREDITARY MOTOR, AUTOSOMAL DOMINANT 14; HMND14

Molecular Pathogenesis

DCTN1 encodes dynactin subunit 1, the major subunit of the dynactin protein complex [Deshimaru et al 2021]. The dynactin protein complex plays a major role in retrograde axonal and cytoplasmic transport of vesicles, organelles, and other cargos through binding to its complex structure. Dynactin subunit 1 contains the cytoskeleton-associated protein glycine-rich (CAP-Gly) domain that is essential for microtubule binding. All *DCTN1* variants found in individuals with Perry syndrome and most variants associated with dHMN7B are located in this domain. However, some *DCTN1* variants identified in individuals with dHMN7B and motor neuron disease are located in the C-terminal half of the protein [Zhang et al 2021]. In vitro, *DCTN1* variants alter the ability of dynactin to bind microtubules, thereby impairing its function as a transport protein [Konno et al 2017, Mishima et al 2018].

Under physiologic conditions, dynactin subunit 1 interacts with TDP-43 and regulates its localization and aggregation. Dysfunction of dynactin subunit 1 may disrupt this process and underlie abnormal TDP-43 aggregation [Deshimaru et al 2021].

The link between *DCTN1* pathogenic variants and neuronal dysfunction/death remains to be elucidated. For example, the fact that the same pathogenic variants cause Perry syndrome and dHMN7B constitutes a challenging puzzle.

Mechanism of disease causation. Most reported *DCTN1* pathogenic variants are missense variants (26/29). Splicing alterations (2/29) and frameshift changes (1/29) have also been identified. *DCTN1* variants alter the ability of dynactin to bind microtubules, thereby impairing its function as a transport protein. The most frequently reported variant, p.Gly71Arg, has a dominant-negative effect on the initiation of retrograde transport [Moughamian & Holzbaur 2012]. Several variants on the C-terminal half have been linked to reduced *DCTN1* expression [Tian et al 2020].

***DCTN1*-specific laboratory technical considerations.** Alternative splicing results in multiple transcript variants encoding distinct isoforms. The reference sequence NM_004082.4 is known as isoform 1; details of other isoforms are available at Entrez Gene.

Table 4. Notable *DCTN1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_004082.4 NP_004073.2	c.211G>A	p.Gly71Arg	Most common variant reported

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.

Chapter Notes

Author Notes

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