U.S. National Library of Medicine
National Center for Biotechnology Information

**NLM Citation:** Ait-El-Mkadem Saadi S, Chaussenot A, Bannwarth S, et al. *CHCHD10*-Related Disorders. 2015 Jul 1 [Updated 2021 May 27]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/


# *CHCHD10*-Related Disorders

Samira Ait-El-Mkadem Saadi, PhD,[1] Annabelle Chaussenot, MD,[1] Sylvie Bannwarth, PhD,[1] Cécile Rouzier, MD, PhD,[1] and Véronique Paquis-Flucklinger, MD, PhD[1]

Created: July 1, 2015; Updated: May 27, 2021.

## Summary

### Clinical characteristics

*CHCHD10*-related disorders are characterized by a spectrum of adult-onset neurologic phenotypes that can include:

- Mitochondrial myopathy (may also be early onset): weakness, amyotrophy, exercise intolerance
- Amyotrophic lateral sclerosis (ALS): progressive degeneration of upper motor neurons and lower motor neurons
- Frontotemporal dementia (FTD): slowly progressive behavioral changes, language disturbances, cognitive decline, extrapyramidal signs
- Late-onset spinal motor neuronopathy (SMA, Jokela type): weakness, cramps, and/or fasciculations; areflexia
- Axonal Charcot-Marie-Tooth neuropathy: slowly progressive lower-leg muscle weakness and atrophy, small hand muscle weakness, loss of tendon reflexes, sensory abnormalities
- Cerebellar ataxia: gait ataxia, kinetic ataxia (progressive loss of coordination of lower- and upper-limb movements), dysarthria/dysphagia, nystagmus, cerebellar oculomotor disorder

Because of the recent discovery of *CHCHD10*-related disorders and the limited number of affected individuals reported to date, the natural history of these disorders (except for SMAJ caused by the p.Gly66Val pathogenic variant) is largely unknown.

### Diagnosis/testing

The diagnosis is established when a heterozygous *CHCHD10* pathogenic variant is detected in an individual with one or more characteristic clinical findings.

**Author Affiliation:** 1 Reference Center of Mitochondrial Disorders, Nice Hospital, Nice, France; Email: saadi.s@chu-nice.fr; Email: chaussenot.a@chu-nice.fr; Email: bannwarth.s@chu-nice.fr; Email: rouzier.c@chu-nice.fr; Email: paquis@unice.fr.

## Management

*Treatment of manifestations:* Adequate nutrition and weight maintenance are essential. Appropriate bracing and stretching can minimize joint contractures, which are often painful and can interfere with caregiving. Those with weakness benefit from assistance with ambulation and posture. Management of ALS, FTD, SMA, and cerebellar ataxia is the same as for other causes of these disorders.

*Surveillance:* Regular evaluations to detect manifestations that can occur with time including neurologic deficits, psychiatric abnormalities, impaired respiratory function, and sensorineural hearing loss.

*Agents/circumstances to avoid:* Baclofen (used to treat spasticity) can sometimes worsen muscle weakness; some drugs used to treat the behavioral manifestations of FTD may worsen dysarthria, dysphagia, and/or respiratory weakness.

## Genetic counseling

*CHCHD10*-related disorders are inherited in an autosomal dominant manner. Many individuals diagnosed with a *CHCHD10*-related disorder have an affected parent. The proportion of probands with a *CHCHD10*-related disorder caused by a *de novo* pathogenic variant is unknown. Each child of an individual with a *CHCHD10*-related disorder has a 50% chance of inheriting the *CHCHD10* pathogenic variant. Because significant clinical heterogeneity is observed within families, it is impossible to accurately predict the age at onset and manifestations that will develop in individuals who inherit a *CHCHD10* pathogenic variant. Once the *CHCHD10* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for a *CHCHD10*-related disorder and preimplantation genetic testing are possible.

# *GeneReview* Scope

With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that heterozygous *CHCHD10* pathogenic variants are associated with a diverse phenotypic spectrum of disorders ranging from mitochondrial myopathy, late-onset spinal motor neuronopathy, and axonal Charcot-Marie-Tooth neuropathy to amyotrophic lateral sclerosis and frontotemporal dementia. The title of this *GeneReview*, *CHCHD10*-related disorders, emphasizes both the need to evaluate an individual found to have a *CHCHD10* pathogenic variant for medically actionable manifestations in the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing) and the importance of counseling families that the finding of a *CHCHD10* pathogenic variant cannot be used to predict clinical outcome in an asymptomatic individual.

# Diagnosis

## Suggestive Findings

A *CHCHD10*-related disorder **should be suspected** in an individual with **clinical findings** of a mitochondrial myopathy, amyotrophic lateral sclerosis, frontotemporal dementia, late-onset spinal motor neuronopathy, or axonal Charcot-Marie-Tooth neuropathy, especially when the **family history** of these diverse phenotypes is consistent with autosomal dominant inheritance.

### Clinical Findings

**Mitochondrial myopathy.** Signs of muscle weakness (proximal, axial, and/or facial, including ptosis), amyotrophy, or symptoms that suggest respiratory chain dysfunction, such as exercise intolerance

**Amyotrophic lateral sclerosis (ALS).** Characteristic signs and symptoms of progressive degeneration of both upper motor neurons (UMNs) including stiffness, spasticity, hyperreflexia, Babinski sign, and pseudobulbar palsy (dysphagia and dysarthria) and lower motor neurons (LMNs) including weakness accompanied by muscle atrophy, fasciculations, areflexia, and cramping

**Frontotemporal dementia (FTD)**

- Slowly progressive behavioral changes (disinhibition, loss of initiative, loss of interest in environment, psychiatric symptoms)
- Language disturbances (word-finding difficulties and semantic paraphasias, perseveration, echolalia, mutism)
- Cognitive decline (executive dysfunctions, attention disorders, loss of abstract reasoning ability)
- Extrapyramidal signs (rigidity, bradykinesia)

**Late-onset spinal motor neuronopathy (SMN), or spinal muscular atrophy, Jokela type (SMAJ).** LMN manifestations including: weakness, cramps, and/or fasciculations that are more proximal than distal; areflexia

**Axonal Charcot-Marie-Tooth neuropathy**

- Slowly progressive lower leg muscle weakness and atrophy
- Small hand muscles weakness
- Loss of tendon reflexes
- Sensory abnormalities such as loss of sensation for vibration or cold
- Electroneuromyopgraphy (ENMG) showing chronic motor neuropathy with regeneration and sometimes sensory findings

Note: The following signs of **cerebellar ataxia** may be present in combination with mitochondrial myopathy, ALS, and/or FTD:

- Gait ataxia
- Kinetic ataxia (progressive loss of coordination of lower- and upper-limb movements)
- Dysarthria
- Dysphagia
- Nystagmus
- Cerebellar oculomotor disorder

## Establishing the Diagnosis

The diagnosis of a *CHCHD10*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *CHCHD10* 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 *CHCHD10* variant of uncertain significance does not establish or rule out the diagnosis.

Because a *CHCHD10*-related disorder may be associated with a number of different phenotypes (even within a single family) and is indistinguishable from these same phenotypes with other known or unknown causation, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *CHCHD10*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A phenotype-specific multigene panel** that includes *CHCHD10* 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 *CHCHD10*-Related Disorders

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *CHCHD10* | Sequence analysis [3] | ~100% [4, 5] |
| | Gene-targeted deletion/duplication analysis [6] | None reported [4] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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.* Targeted analysis for the p.Gly66Val pathogenic variant can be performed first in individuals of Finnish ancestry with late-onset SMN (SMAJ) [Penttilä et al 2015].
*6.* 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.

# Clinical Characteristics

## Clinical Description

The phenotypic spectrum of *CHCHD10*-related disorders is broad and can include any of the following alone or in any combination: mitochondrial myopathy, amyotrophic lateral sclerosis, frontotemporal dementia (FTD), late-onset spinal motor neuronopathy, and axonal Charcot-Marie-Tooth neuropathy. Cerebellar ataxia may also be found in combination with these disorders, but not as the sole neurologic manifestation.

To date, approximately 100 individuals have been identified with a pathogenic variant in *CHCHD10* [Bannwarth et al 2014, Ajroud-Driss et al 2015, Auranen et al 2015, Penttilä et al 2015]. The following description of the phenotypes associated with this condition is based on these reports. It should be noted that other individuals

have been reported with *CHCHD10* variants for which the pathogenicity is controversial and there is a need for more studies to classify them as pathogenic or not [Tazelaar et al 2018].

**Mitochondrial myopathy** may present with exercise intolerance; proximal, axial, and/or facial muscle weakness; ptosis; and amyotrophy. Deafness may also be observed.

- **Early onset.** In a Puerto Rican family, affected individuals had myopathy (appearing in the first decade of life) and short stature [Ajroud-Driss et al 2015].
- **Late onset.** In a French family, affected individuals had late-onset myopathy with motor neuron disease, FTD, and cerebellar ataxia [Bannwarth et al 2014].

**Amyotrophic lateral sclerosis (ALS).** *CHCHD10*-related ALS and ALS of other causes (see ALS Overview) are clinically indistinguishable, including in male-to-female ratio, age of onset, symptom distribution, and severity of disease. Most individuals with *CHCHD10*-related ALS meet El Escorial criteria for ALS [Brooks et al 2000] and have both UMN and LMN involvement. Within a family, clinical variability is considerable, especially regarding age of onset and longevity.

- The ALS may occur by itself or in combination with FTD (referred to as FTD-ALS).
- **Onset.** Mean age of onset is 53 years (age range 25-75 years). Upper limb involvement is more frequent at onset of ALS phenotype; bulbar involvement is more predominant at onset in the FTD-ALS phenotype.
- **Progression.** Bulbar dysfunction (atrophy of facial and masticatory muscles, perioral fasciculations, and severe dysphagia leading to frequent aspiration) become prominent in the final stages of the disease. Affected individuals eventually develop respiratory failure, which is the main cause of death. Mean disease duration prior to death is 8.6 years (range 2-17 years).

**Frontotemporal dementia (FTD)** is a presenile dementia affecting the frontal and temporal cortex and some subcortical nuclei. Clinical presentation is variable. Affected individuals may have slowly progressive behavioral changes, cognitive decline with language disturbance, and/or extrapyramidal signs.

- **Onset and duration of disease.** In individuals with *CHCHD10*-related FTD, symptoms start between ages 50 and 67 years. Disease duration is usually between four and 27 years.
- **Behavioral changes.** Disinhibition and loss of initiative are the most common presenting symptoms. Affected individuals lose interest in their environment and neglect their personal hygiene. Obsessive-compulsive behavior and delusions or hallucinations are early clinical features in some. Roaming, restlessness, verbal aggressiveness, hyperorality (including alcohol abuse), and financial mismanagement are frequently seen [Foster et al 1997, Bird et al 1999].

  Persecutory delusions and visual or auditory hallucinations, which occur rarely in FTD in general, are not reported in individuals with *CHCHD10*-related FTD.
- **Cognitive decline.** Word-finding difficulties and semantic paraphasias in conversational speech are common early findings. Orientation in time and place, visuo-constructive functions, and short-term memory remain intact initially. Executive functions, attention, concentration, and abstract reasoning ability become impaired in all affected individuals. Language comprehension remains relatively preserved over the course of the disease. Perseveration, repetitive utterances, and echolalia lead to mutism after several years [Foster et al 1997].
- **Extrapyramidal signs.** Affected individuals may show parkinsonian signs including decreased facial expression, bradykinesia, postural instability, and rigidity without resting tremor.
- **Neuroimaging**. Findings can include the following:
  - Frontal and/or temporal atrophy on brain CT or MRI

- Decrease of cerebral perfusion anteriorly (single-photon emission computed tomography [SPECT])
- Frontotemporal hypometabolism (positron emission tomography with $^{18}$F-fluorodeoxyglucose [FDG-PET])
- Reduced striatal uptake of $^{18}$F-fluoro-L-dopa

**Spinal motor neuronopathy**

- Spinal motor neuronopathy phenotype in *CHCHD10*-related disorders (also known as spinal muscular atrophy, Jokela type or SMAJ) is characterized by cramps and fasciculations, slowly progressive and predominantly lower-limb weakness, and diminished or absent deep tendon reflexes; respiratory symptoms are absent.
- **Onset and progression.** Onset typically occurs between ages 30 and 73 years (mean age 42 years). Progression tends to be slow.

  Mild, non-progressive dysphagia appears later in the disease course in 13% of affected individuals. About half of affected individuals develop mild reduction in sensory nerve amplitudes or reduced vibration sense in the distal lower limbs usually later in the disease course. Affected individuals remain ambulant for several decades after onset [Penttilä et al 2015].

**Axonal Charcot-Marie-Tooth neuropathy**

- **Onset and progression.** The onset of symptoms varies from age 30 to 56 years (mean age 44). The typical presenting symptom was slowly progressive lower leg muscle weakness, and small hand muscles were affected later on in the disease. Progression tends to be slow.
- **Clinical examination** has consistently shown loss of tendon reflexes, muscle weakness, and atrophy. Sensory abnormalities such as loss of sensation for vibration or cold were strong enough to be detected on clinical examination in seven of 12 individuals.
- No signs of upper motor neuron disease, bulbar symptoms, or progressive cognitive issues have been observed.
- **Muscular MRI.** Lower-limb muscle MRI showed edema or fatty degeneration that was pronounced distally (particularly in calves) and milder in thighs.
- **Neurophysiologic findings**. ENMG showed chronic motor neuropathy with regeneration; for some, sensory findings (decreased sural nerve action potential amplitude) were evident (consistent with typical CMT2 neuropathy).

**Cerebellar ataxia** in *CHCHD10*-related disorders is characterized by ataxia, dysarthria, and eventual deterioration of bulbar functions. Affected individuals have gait difficulties and slurred speech.

- **Onset** is in the sixth decade. Individuals may first notice balance problems in going down stairs or making sudden turns. In the early stages of disease affected individuals may display brisk deep tendon reflexes, hypermetric saccades, and nystagmus [Schmitz-Hübsch et al 2006]. Mild dysphagia, indicated by choking on food and drink, may also occur early in the disease.
- **Progression.** As the disease progresses saccadic velocity slows and upgaze palsy develops. Nystagmus often disappears with evolving saccadic abnormalities.

  As the ataxia worsens, other cerebellar signs such as dysmetria, dysdiadochokinesia, and hypotonia become apparent.

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

The clinical course of *CHCHD10*-related disorders is highly variable, even within a family, and is not predictable from the type or location of the pathogenic variant.

### Penetrance

Penetrance is difficult to estimate because few unaffected individuals in families with a *CHCHD10*-related disorder have been genotyped or longitudinally followed for the emergence of symptoms.

### Nomenclature

*CHCHD10* was previously referred to as *C22orf16*.

### Prevalence

The prevalence of *CHCHD10*-related disorders is not known at present.

*CHCHD10* pathogenic variants have been identified in individuals from different geographic regions including America, Asia, and Europe.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *CHCHD10*.

## Differential Diagnosis

The differential diagnosis of *CHCHD10*-related disorders spans a wide spectrum of neurodegenerative diseases. All genes known to be associated with the predominant phenotype in an affected individual should be considered in the differential diagnosis. See the following *GeneReviews* for detailed review of genes associated with each phenotype:

- Amyotrophic Lateral Sclerosis Overview
- Charcot-Marie-Tooth Hereditary Neuropathy Overview
- Hereditary Ataxia Overview
- Mitochondrial myopathy (See Mitochondrial Disorders Overview.)

## Management

Consensus clinical management recommendations for *CHCHD10*-related disorders have not been published.

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *CHCHD10*-related disorder, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 2.** Recommended Evaluations Following Initial Diagnosis in Individuals with *CHCHD10*-Related Disorders

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Neurologic** | Complete neurologic eval | To assess:<br>• UMN involvement: spasticity, Babinski signs, hyperreflexia<br>• LMN involvement: weakness, amyotrophy, fasciculations<br>• Muscle strength<br>• Coordination & balance |
| | EMG/NCS | To document regions of involvement & indicate LMN &/or myopathic involvement |
| | Brain MRI | |
| | Neuropsychological exam | To evaluate extent & profile of cognitive disturbance |
| | Speech & swallowing eval | For those w/frequent choking or severe dysphagia, also assess:<br>• Nutritional status;<br>• Aspiration risk. |
| | PT & OT | To evaluate for need for adaptive devices to maximize function |
| **Neuropsychiatric** | Screening for depression &/or behavioral concerns | Assess need for psychosocial support & behavioral therapy. |
| **Pulmonary** | Pulmonary function testing | To detect & stage respiratory involvement |
| **Hearing** | Audiologic exam | Incl auditory brain stem response & evoked otoacoustic emission testing |
| **Nutrition** | Nutrition eval | Consider involving a gastroenterology/nutrition/feeding team, incl formal swallowing eval. |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & their families re nature, MOI, & implications of *CHCHD10*-related disorders to facilitate medical & personal decision making |

Piguet et al [2017], Oskarsson et al [2018], Masrori & Van Damme [2020]
EMG = electromyogram; LMN = lower motor neuron; MOI = mode of inheritance; NCS = nerve conduction studies; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron
*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

Many individuals benefit from care by a multidisciplinary team that includes a neurologist, specially trained nurses, pulmonologist, speech therapist, physical therapist, occupational therapist, respiratory therapist, nutritionist, psychologist, social worker, and genetic counselor.

**Table 3.** Treatment of Manifestations in Individuals with *CHCHD10*-Related Disorders

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **General** | Adequate nutrition & weight maintenance | Percutaneous gastrostomy may be needed to maintain caloric intake in those w/significant bulbar involvement. |
| | Minimize contractures w/appropriate bracing & stretching | Contractures are often painful & can interfere w/caregiving. |
| **Mitochondrial myopathy** | Treatment does not typically require multisystem management as may be seen in other forms of mitochondrial myopathy. See Mitochondrial Disorders Overview. | |

*Table 3. continued from previous page.*

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Amyotrophic lateral sclerosis (ALS)** | Identical to that for ALS of other causes [Andersen et al 2012, Oskarsson et al 2018, Masrori & Van Damme 2020]. See ALS Overview. | |
| **Frontotemporal dementia (FTD)** | Treatment follows routine practices for FTD [Piguet et al 2017]. | |
| **Late-onset spinal motor neuronopathy (or SMA, Jokela type)** | Treatment identical to that for adult-onset SMA of other causes | |
| **Axonal Charcot-Marie-Tooth neuropathy** | Treatment identical to that for axonal CMT neuropathy of other causes. See CMT Overview. | |

CMT = Charcot-Marie-Tooth; SMA = spinal muscular atrophy

## Surveillance

**Table 4.** Recommended Surveillance for Individuals with *CHCHD10*-Related Disorders

| System/Concern | Evaluation | Frequency by Phenotype |
|---|---|---|
| **Neurologic deficits** | Neurologic exam incl assessment of memory, personality changes, dysphagia | • Mitochondrial myopathy: undefined; depends on disease progression & presenting symptoms<br>• ALS: every 2-3 mos<br>• FTD: undefined; depends on disease progression & presenting symptoms<br>• SMAJ or axonal CMT: annually initially, then depending on person's progress |
| **Psychiatric abnormalities** | Assessment for signs incl depression & suicidal ideation | • ALS: every 2-3 mos<br>• FTD: undefined; depends on disease progression & presenting symptoms<br>• Other phenotypes: NA |
| **Impaired respiratory function** | Monitoring of FVC & other aspects of respiratory function to determine appropriate time to offer noninvasive ventilation | • ALS: every 2-3 mos<br>• Other phenotypes: NA |
| **Sensorineural hearing loss** | Audiologic exam incl speech discrimination testing | • Mitochondrial myopathy: annually<br>• Other phenotypes: NA |

ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; FVC = forced vital capacity; NA = not applicable; SMAJ = spinal muscular atrophy, Jokela type

## Agents/Circumstances to Avoid

The following should be noted:

- Baclofen used to treat spasticity can sometimes worsen muscle weakness.
- Some drugs used to treat the behavioral manifestations of FTD may worsen dysarthria, dysphagia, and/or respiratory weakness.

## 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.

# 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

*CHCHD10*-related disorders are inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband**

- Many individuals diagnosed with a *CHCHD10*-related disorder have an affected parent.
- A proband with a *CHCHD10*-related disorder may have the disorder as the result of a *de novo CHCHD10* pathogenic variant; however, the proportion of probands who have a *de novo* pathogenic variant is unknown.
- Clinical examination and molecular genetic testing for the *CHCHD10* pathogenic variant identified in the proband are 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, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Although no instances of germline mosaicism have been reported, it remains a possibility. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of some individuals diagnosed with a *CHCHD10*-related disorder may appear to be negative because of failure by health care professionals to recognize the disorder in family members and/or milder phenotypic presentation, 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 pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because significant clinical heterogeneity is observed within families, it is impossible to accurately predict the age at onset and

manifestations that will develop in sibs who inherit a *CHCHD10* pathogenic variant [Bannwarth et al 2014].
- If the *CHCHD10* pathogenic variant detected in the proband cannot be detected in the leukocyte DNA of either parent, the 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 *CHCHD10* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for a *CHCHD10*-related disorder because of the possibility of age-related penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with a *CHCHD10*-related disorder has a 50% chance of inheriting the *CHCHD10* pathogenic variant.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *CHCHD10* 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 *CHCHD10* 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.
- See also 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 a *CHCHD10*-related disorder, 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. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *CHCHD10* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: The clinical course of *CHCHD10*-related disorders is highly variable and cannot be predicted based on family history or the presence of a pathogenic variant identified on prenatal testing.

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 for 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.*

- **ALS Association**
  **Phone:** 800-782-4747
  **Email:** alsinfo@alsa-national.org
  www.alsa.org
- **Amyotrophic Lateral Sclerosis Society of Canada**
  Canada
  **Phone:** 800-267-4257 (toll-free); 416-497-2267
  **Email:** communityservices@als.ca
  www.als.ca
- **Association for Frontotemporal Degeneration (AFTD)**
  **Phone:** 866-507-7222
  **Email:** info@theaftd.org
  www.theaftd.org
- **Mito Foundation**
  Australia
  **Phone:** 61-1-300-977-180
  **Email:** info@mito.org.au
  www.mito.org.au

# 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.** CHCHD10-Related Disorders: Genes and Databases

| Gene | Chromosome Locus | Protein | HGMD | ClinVar |
|---|---|---|---|---|
| *CHCHD10* | 22q11.23 | Coiled-coil-helix-coiled-coil-helix domain-containing protein 10, mitochondrial | CHCHD10 | CHCHD10 |

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 CHCHD10-Related Disorders (View All in OMIM)

| | |
|---|---|
| 615048 | SPINAL MUSCULAR ATROPHY, JOKELA TYPE; SMAJ |
| 615903 | COILED-COIL-HELIX-COILED-COIL-HELIX DOMAIN-CONTAINING PROTEIN 10; CHCHD10 |
| 615911 | FRONTOTEMPORAL DEMENTIA AND/OR AMYOTROPHIC LATERAL SCLEROSIS 2; FTDALS2 |
| 616209 | MYOPATHY, ISOLATED MITOCHONDRIAL, AUTOSOMAL DOMINANT; IMMD |

## Molecular Pathogenesis

The precise function of CHCHD10 in mitochondria is unclear. Fibroblasts of individuals with p.Ser59Leu variant in *CHCHD10* have displayed respiratory chain deficiency, fragmentation of the mitochondrial network, and mitochondrial ultrastructural alterations with loss of cristae [Bannwarth et al 2014]. CHCHD10 interacts with Mitofilin/MIC60, a central component of mitochondrial contact site and cristae organizing system (MICOS) complex, the integrity of which is required for the maintenance of mitochondrial cristae. The p.Ser59Leu variant in human cells leads to MICOS complex disassembly and loss of cristae junctions [Genin et al 2016]. In mice, *Chchd10* knockout does not cause disease, indicating that *CHCHD10* phenotypes associated with the p.Ser59Leu variant are caused by gain of function of the variant protein rather than by loss of function [Anderson et al 2019].

Knock-in (KI) mice with a punctual pathogenic variant in *Chchd10* corresponding to the p.Ser59Leu variant in human *CHCHD10* are a relevant model for the disease [Genin et al 2019]. *Chchd10*$^{S59L/+}$ mice appear normal at birth but fail to gain weight normally beginning at age ten weeks. Around age one year, they present a typical mitochondrial myopathy. Their condition worsens rapidly with severe weight loss and tremors and they develop a fatal mitochondrial cardiomyopathy. At the end stage of the disease, around age one year, *Chchd10*$^{S59L/+}$ animals display neuromuscular junction and motor neuron (MN) degeneration with hyperfragmentation of the motor end plate and significant MN loss in lumbar spinal cord. In addition, TDP-43 cytoplasmic aggregates are observed in spinal neurons, corresponding to TDP-43 proteinopathy found in individuals with ALS [Genin et al 2019].

**Mechanism of disease causation.** From the mouse model, pathogenic variants in *CHCHD10* appear to cause disease via a gain-of-function mechanism [Anderson et al 2019].

***CHCHD10*-specific laboratory technical considerations.** The genomic region of *CHCHD10*, particularly a part of exon 2 (5' end), may have low-to-moderate coverage using exome sequencing as currently available in the clinical laboratory, potentially making the diagnosis more challenging.

**Table 5.** Notable *CHCHD10* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|
| NM_213720.3<br>NP_998885.1 | c.197G>T | p.Gly66Val | Founder variant in Finnish population, assoc w/late-onset SMN (or SMAJ) [Penttilä et al 2015] & axonal CMT disease [Auranen et al 2015] |
| | c.176C>T | p.Ser59Leu | Variant assoc w/late-onset complex phenotype incl motor neuron disease, cognitive decline resembling FTD, cerebellar ataxia, & myopathy [Bannwarth et al 2014] |
| | c.[43C>A;172G>C] | p.[Arg15Ser;Gly58Arg] | Variants reported *in cis* in persons w/early-onset isolated mitochondrial myopathy [Ajroud-Driss et al 2015] |
| | c.44G>T | p.Arg15Leu | Variant observed to segregate w/ALS in several families; likely responsible for <1% of familial ALS [Tazelaar et al 2018]. |

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.
ALS = amyotrophic lateral sclerosis; CMT = Charcot-Marie-Tooth; FTD = frontotemporal dementia; SMAJ = spinal muscular atrophy, Jokela type; SMN = spinal motor neuropathy

# Chapter Notes

## Author Notes

Authors belong to the Department of Medical Genetics and the Reference Center for Rare Diseases on "Mitochondrial Disorders," at the Teaching Hospital of Nice (CHU de Nice) and UCA (Université Côte d'Azur). This reference center is affiliated with the Filnemus rare disease healthcare network and the Euro-NMD (Newcastle) European reference network. Authors also belong to the research team "Genetics of Mitochondrial Disease" at the Institute for Research on Cancer and Aging (IRCAN).

## Acknowledgments

We thank the ANR (Agence Nationale de la Recherche, ANR-16-CE16-0024-01), the AFM-Téléthon (Association Française contre les Myopathies, #20947), and the Fondation Maladies Rares for financial support.

## Revision History

- 27 May 2021 (ha) Comprehensive update posted live
- 1 July 2015 (me) Review posted live
- 20 January 2015 (saem) Original submission

# References

## Published Guidelines / Consensus Statements

- Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 2-9-23.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 2-9-23.

## Literature Cited

Ajroud-Driss S, Fecto F, Ajroud K, Lalani I, Calvo SE, Mootha VK, Deng HX, Siddique N, Tahmoush AJ, Heiman-Patterson TD, Siddique T. Mutation in the novel nuclear-encoded mitochondrial protein CHCHD10 in a family with autosomal dominant mitochondrial myopathy. Neurogenetics. 2015;16:1–9. PubMed PMID: 25193783.

Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, Hardiman O, Kollewe K, Morrison KE, Petri S, Pradat PF, Silani V, Tomik B, Wasner M, Weber M, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012;19:360–75. PubMed PMID: 21914052.

Anderson CJ, Bredvik K, Burstein SR, Davis C, Meadows SM, Dash J, Case L, Milner TA, Kawamata H, Zuberi A, Piersigilli A, Lutz C, Manfredi G. ALS/FTD mutant CHCHD10 mice reveal a tissue-specific toxic gain-of-function and mitochondrial stress response. Acta Neuropathol. 2019;138:103–21. PubMed PMID: 30877432.

Auranen M, Ylikallio E, Shcherbii M, Paetau A, Kiuru-Enari S, Toppila JP, Tyynismaa H. CHCHD10 variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease. Neurol Genet. 2015;1:e1. PubMed PMID: 27066538.

Bannwarth S, Ait-El-Mkadem S, Chaussenot A, Genin EC, Lacas-Gervais S, Fragaki K, Berg-Alonso L, Kageyama Y, Serre V, Moore DG, Verschueren A, Rouzier C, Le Ber I, Augé G, Cochaud C, Lespinasse F, N'Guyen K, de Septenville A, Brice A, Yu-Wai-Man P, Sesaki H, Pouget J, Paquis-Flucklinger V. A mitochondrial origin for frontotemporal dementia and amyotrophic lateral sclerosis through CHCHD10 involvement. Brain. 2014;137:2329–45. PubMed PMID: 24934289.

Bird TD, Nochlin D, Poorkaj P, Cherrier M, Kaye J, Payami H, Peskind E, Lampe TH, Nemens E, Boyer PJ, Schellenberg GD. A clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). Brain. 1999;122:741–56. PubMed PMID: 10219785.

Brooks BR, Miller RG, Swash M, Munsat TL. World Federation of Neurology Research Group on Motor Neuron Diseases; El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:293–9. PubMed PMID: 11464847.

Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. Ann Neurol. 1997;41:706–15. PubMed PMID: 9189031.

Genin EC, Madji Hounoum B, Bannwarth S, Fragaki K, Lacas-Gervais S, Mauri-Crouzet A, Lespinasse F, Neveu J, Ropert B, Augé G, Cochaud C, Lefebvre-Omar C, Bigou S, Chiot A, Mochel F, Boillée S, Lobsiger CS, Bohl D, Ricci JE, Paquis-Flucklinger V. Mitochondrial defect in muscle precedes neuromuscular junction degeneration and motor neuron death in CHCHD10S59L/+ mouse. Acta Neuropathol. 2019;138:123. PubMed PMID: 30874923.

Genin EC, Plutino M, Bannwarth S, Villa E, Cisneros-Barroso E, Roy M, Ortega-Vila B, Fragaki K, Lespinasse F, Pinero-Martos E, Augé G, Moore D, Burté F, Lacas-Gervais S, Kageyama Y, Itoh K, Yu-Wai-Man P, Sesaki H, Ricci JE, Vives-Bauza C, Paquis-Flucklinger V. CHCHD10 mutations promote loss of mitochondrial cristae junctions with defect in mitochondiral genome maintenance and apoptosis. EMBO Mol Med. 2016;8:58. PubMed PMID: 26666268.

Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;27:1918–29. PubMed PMID: 32526057.

Oskarsson B, Gendron TF, Staff NP. Amyotrophic lateral sclerosis: an update for 2018. Mayo Clin Proc. 2018;93:1617–28. PubMed PMID: 30401437.

Penttilä S, Jokela M, Bouquin H, Saukkonen AM, Toivanen J, Udd B. Late onset spinal motor neuronopathy is caused by mutation in CHCHD10. Ann Neurol. 2015;77:163–72. PubMed PMID: 25428574.

Piguet O, Kumfor F, Hodges J. Diagnosing, monitoring and managing behavioural variant frontotemporal dementia. Med J Aust. 2017;207:303–8. PubMed PMID: 28954617.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Schmitz-Hübsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, Giunti P, Globas C, Infante J, Kang JS, Kremer B, Mariotti C, Melegh B, Pandolfo M, Rakowicz M, Ribai P, Rola R, Schöls L, Szymanski S, van de Warrenburg BP, Dürr A, Klockgether T, Fancellu R. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology. 2006;66:1717–20. PubMed PMID: 16769946.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Tazelaar GHP, Boeynems S, De Decker M, van Vugt JJFA, Kool L, Goedee HS, McLaughlin RL, Sproviero W, Iacoangeli A, Moisse M, et al. CHCHD10 variants in amyotrophic lateral sclerosis: Where is the evidence? Ann Neurol. 2018;84:110–6. PubMed PMID: 30014597.

## License