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Myotonia Congenita

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Summary

Clinical characteristics

Myotonia congenita is characterized by muscle stiffness present from childhood; all striated muscle groups including the extrinsic eye muscles, facial muscles, and tongue may be involved. Stiffness is relieved by repeated contractions of the muscle (the "warm-up" phenomenon). Muscles are usually hypertrophic. Whereas autosomal recessive (AR) myotonia congenita is often associated with more severe manifestations (such as progressive minor distal weakness and attacks of transient weakness brought on by movement after rest), autosomal dominant (AD) myotonia congenita is not. The age of onset varies: in AD myotonia congenita onset is usually in infancy or early childhood; in AR myotonia congenita the average age of onset is slightly older. In both AR and AD myotonia congenita onset may be as late as the third or fourth decade of life.

Diagnosis/testing

The molecular diagnosis of myotonia congenita is established in a proband with suggestive findings of myotonia and sometimes muscle hypertrophy, and either a heterozygous *CLCN1* pathogenic variant or biallelic *CLCN1* pathogenic variants identified on molecular genetic testing.

Management

Treatment of manifestations: Muscle stiffness may respond to sodium channel blockers such as mexiletine (currently the medication with best documented effect), lamotrigine carbamazepine, or phenytoin. Beneficial effects have also been reported with quinine, dantrolene, and acetazolamide.

Agents/circumstances to avoid: Depolarizing muscle relaxants (e.g., suxamethonium), adrenaline, beta-adrenergic agonists, and propranolol may aggravate myotonia.

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Evaluation of relatives at risk: Because individuals with myotonia congenita may be at increased risk for adverse anesthesia-related events, molecular genetic testing of at-risk family members (for the *CLCN1* pathogenic variant[s] identified in the proband) during childhood is appropriate.

Genetic counseling

Myotonia congenita is inherited in either an autosomal recessive (Becker disease) or an autosomal dominant (Thomsen disease) manner; the same pathogenic variant may be associated with both autosomal dominant and autosomal recessive inheritance. Establishing the mode of inheritance in a simplex case (i.e., a single occurrence in a family) may not be possible unless molecular genetic testing reveals two *CLCN1* pathogenic variants *in trans* in a proband with unaffected parents, in which case inheritance can be assumed to be autosomal recessive.

- *Autosomal recessive inheritance*: If both parents are known to be heterozygous for a *CLCN1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- *Autosomal dominant inheritance:* The majority of individuals diagnosed with autosomal dominant myotonia congenita have an affected parent. The proportion of individuals with myotonia congenita caused by a *de novo* pathogenic variant is unknown but is presumably very low. 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%.

Once the *CLCN1* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for myotonia congenita (sometimes referred to as "chloride channel myotonia") have been published.

Suggestive Findings

Myotonia congenita **should be suspected** in individuals with the following clinical and laboratory findings.

Clinical findings and medical history

- Episodes of muscle stiffness (myotonia) or cramps beginning in early childhood
- Alleviation of stiffness by brief exercise (known as the "warm-up" effect)
- Myotonic contraction elicited by percussion of muscles

Laboratory findings

- **Serum creatine kinase concentration** is usually elevated (≤3-4x the upper limits of normal).
- **Electromyography** performed with needle electrodes discloses characteristic showers of spontaneous electrical activity (myotonic bursts). Note that while electrophysiologic tests were an integral part of the diagnosis in the past, they now play a secondary role given the wide-spread availability of molecular genetic testing.

Family history is consistent with either an autosomal recessive (e.g., affected sibs and/or parental consanguinity) or an autosomal dominant (e.g., affected males and females in multiple generations) inheritance pattern. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of myotonia congenita **is established** in a proband with suggestive findings of myotonia and sometimes muscle hypertrophy, and either a heterozygous *CLCN1* pathogenic variant or biallelic *CLCN1* pathogenic variants identified on molecular genetic testing (see Table 1).

Note:

- Identification of a heterozygous *CLCN1* variant of uncertain significance does not establish or rule out the diagnosis of autosomal dominant (AD) myotonia congenita.
- Identification of biallelic *CLCN1* variants of uncertain significance (or identification of one known *CLCN1* pathogenic variant and one *CLCN1* variant of uncertain significance) does not establish or rule out a diagnosis of autosomal recessive (AR) myotonia congenita.
- Distinguishing between AD and AR myotonia congenita depends mainly on the family history (i.e., the presence of an affected parent in autosomal dominant myotonia congenita), as some pathogenic variants can occur in both AR and AD myotonia congenita. (Note: The identification of two *CLCN1* pathogenic variants *in trans* in a proband with unaffected parents establishes a diagnosis of AR myotonia congenita.)

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of myotonia congenita has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *CLCN1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If AR myotonia congenita is suspected and a single heterozygous variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: To date, single-exon, multiexon, or whole-gene deletions/duplications have not been identified in individuals with AD myotonia congenita.

A skeletal muscle channelopathy multigene panel that includes *CLCN1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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 Myotonia Congenita

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CLCN1	Sequence analysis [3]	>97% [4]
	Gene-targeted deletion/duplication analysis [5]	1%-3% [4, 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 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic *CLCN1* deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and gene-targeted microarray designed to detect single-exon deletions or duplications.
6. The published variants are primarily large intragenic deletions. Only one large duplication has been reported.

Clinical Characteristics

Clinical Description

Myotonia congenita is characterized by muscle stiffness present from childhood; all striated muscle groups including the extrinsic eye muscles, facial muscles, and tongue may be involved. Stiffness is relieved by repeated contractions of the muscle (the "warm-up" phenomenon). Muscles are usually hypertrophic. Whereas autosomal recessive (AR) myotonia congenita is often associated with more severe manifestations (such as progressive, minor distal weakness and attacks of transient weakness brought on by movement after rest), autosomal dominant (AD) myotonia congenita is not.

A study of more than 300 affected individuals from the UK revealed a ratio of 70% AR myotonia congenita to 30% AD myotonia congenita among families with a molecularly confirmed diagnosis [Fialho et al 2007]. Comparable distribution has been identified in Italian [Orsini et al 2020], Spanish [Milla et al 2019], and German cohorts [Vereb et al 2020]; in contrast, AD myotonia congenita is more common than AR myotonia congenita in Denmark [Dunø et al 2004].

Table 2. Myotonia Congenita: Comparison of Select Features by Mode of Inheritance

Feature	AR Myotonia Congenita	AD Myotonia Congenita
Age of onset	Early childhood	Early infancy
Muscle stiffness	Generalized, legs>arms	Generalized, arms>legs
Muscle hypertrophy	Generalized	Generalized
Pain	Very common	Common
Transient muscle weakness	Common	Not present
Distal muscle weakness	Rarely	Not present
Proximal muscle weakness	Rarely	Not present

AD = autosomal dominant; AR = autosomal recessive

Age of onset is variable. In AD myotonia congenita, onset of symptoms is usually in infancy or early childhood. In AR myotonia congenita, the average age of onset is slightly older. In both conditions, onset may be as late as the third or fourth decade of life.

Muscle stiffness is present from childhood. All striated muscle groups including the extrinsic eye muscles, facial muscles, and tongue may be involved.

- The physician may note that the individual cannot extend the fingers after shaking hands, or a myotonic contraction may be elicited by percussion of muscles (e.g., the tongue, finger extensors, or thenar muscles).
- The stiffness can be relieved by repeated contractions of the muscle, a feature known as the "warm-up" phenomenon.
- Muscles are usually hypertrophic.
- The AR form is often associated with more severe manifestations than the AD form.

Muscle weakness. Individuals with the AR form may have progressive, minor distal weakness and attacks of transient weakness brought on by movement after rest. Occasionally, proximal weakness or distal myopathy has been reported [Nagamitsu et al 2000].

Extramuscular manifestations are generally absent. Cardiac arrhythmia and conduction defects have been described in a minority of affected individuals; the clinical importance of these findings is as-yet unclear [Vereb et al 2020].

Genotype-Phenotype Correlations

While there are no clear-cut phenotype-genotype correlations, loss-of-function variants are expected to associate primarily with AR myotonia congenita.

The phenotypic manifestations of *CLCN1* pathogenic variants can vary even within the same family [Sun et al 2001, Colding-Jørgensen 2005, Orsini et al 2020].

Penetrance

Pathogenic variants identified in AD myotonia congenita can be associated with variable expression and reduced penetrance [Sun et al 2001, Colding-Jørgensen 2005, Brugnoni et al 2013, Orsini et al 2020].

Nomenclature

AD myotonia congenita is also known as Thomsen disease.

AR myotonia congenita is also known as Becker disease.

Myotonia congenita may also be referred to as chloride channel myotonia.

Myotonia levior is essentially the same as myotonia congenita.

Prevalence

Worldwide prevalence of myotonia congenita has been estimated at 1:100,000 [Emery 1991, Coote et al 2018], supported by national population studies in the Netherlands [Stunnenberg et al 2018] and England [Horga et al 2013]. In northern Scandinavia, the prevalence of myotonia congenita has been estimated at 1:10,000 [Papponen et al 1999].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CLCN1*.

Differential Diagnosis

The differential diagnosis of myotonia congenita includes other disorders in which myotonia is a prominent finding. Myotonia congenita can usually be distinguished from these disorders based on the following:

- Factors that provoke or alleviate myotonia
- Presence or absence of extramuscular manifestations
- Findings on electrodiagnostic and molecular genetic testing

***SCN4A*-related myotonias.** The autosomal dominant *SCN4A*-related myotonias may be difficult to distinguish from myotonia congenita (chloride channel myotonia) on clinical grounds alone. A significant proportion of individuals suspected of having myotonia congenita may in fact have pathogenic variants in *SCN4A* [Trip et al 2008]. Among confirmed probands with nondystrophic myotonias, a *CLCN1* defect was identified in 45% of probands [Sasaki et al 2020], 68.5% of probands [Vereb et al 2020], and 89% of probands [Milla et al 2019], and the remaining had an *SCN4A* variant. Clinicakl findings that may be helpful in distinguishing the disorders are summarized in Table 3.

Note: Pathogenic variants in *CLCN1* have been identified in individuals with sodium channel myotonia (an *SCN4A*-related myotonia). This coexistence may modulate the *SCN4A*-related myotonia phenotype and exaggerate the clinical manifestations of the disorder [Furby et al 2014, Kato et al 2016, Zhao et al 2020].

Table 3. *SCN4A*-Related Myotonias Compared with Myotonia Congenita (Chloride Channel Myotonia)

Clinical Characteristics in *SCN4A*-Related Myotonias		Compared w/Myotonia Congenita (Chloride Channel Myotonia)
Paramyotonia congenita (OMIM 168300)	Episodes of generalized stiffness in early childhood	Also observed in MC
	Cold sensitivity w/cold-induced severe stiffness usually followed by true weakness	May be assoc w/some aggravation of stiffness in the cold
	Repeated muscle contractions may aggravate stiffness (paradoxic myotonia).	Repeated muscle contractions relieve myotonia ("warm-up" phenomenon).
Sodium channel myotonias known as potassium-aggravated myotonia [1] (OMIM 608390)	Myotonia may be assoc w/episodes of hyperkalemic periodic paralysis.	MC is not assoc w/episodes of periodic paralysis.
	Symptoms of sodium channel disorders typically worsen w/potassium ingestion.	Not observed in MC
	May be assoc w/exercise-induced, delayed-onset myotonia, in which muscle contractions induce myotonia after period of delay	Contrasts w/the "warm-up" phenomenon seen in MC
	Eye closure myotonia is more frequent in sodium channel myotonia.	Falls are more frequent in MC.
	Painful myotonia is common.	Painful myotonia is less common.

MC = myotonia congenita
1. Shapiro & Ruff [2002], Tan et al [2011]

Myotonic dystrophy type 1 (DM1) and **myotonic dystrophy type 2 (DM2)**, autosomal dominant disorders associated with pathogenic variants in *DMPK* and *CNBP*, respectively, should always be considered in the

differential diagnosis of myotonia congenita, as the extramuscular manifestations of DM1 and DM2 have important implications for prognosis and management. Although some degree of muscular weakness and wasting may be observed in autosomal recessive myotonia congenita, the pattern of muscle weakness is very different, and extramuscular manifestations including early cataracts, cardiac arrhythmias, and endocrine dysfunction found in DM1 and DM2 are not observed in myotonia congenita. However, absence of these extramuscular features does not rule out (for example) a mild form of DM1.

Pathogenic variants in *CLCN1* have been identified in individuals with molecularly confirmed DM2. This coexistence may modulate the DM2 phenotype and exaggerate the clinical manifestations of the disorder [Cardani et al 2012].

Management

No specific clinical practice guidelines for myotonia congenita have been published. However, a general guideline on clinical presentation and management of nondystrophic myotonias is available [Stunnenberg et al 2020].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with myotonia congenita, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Consultation with a neurologist or other relevant specialist to evaluate the need for pharmacologic treatment. Severity of myotonia can be assessed by a myotonia questionnaire (e.g., the Myotonia Behavior Scale [Andersen et al 2017b]) and by timed assessments of myotonia, for instance, time to open tightly closed eyes, time to open a clinched hand, testing of myotonia walking on a staircase, or a timed-up-and-go test.
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of myotonia congenita in order to facilitate medical and personal decision making

Treatment of Manifestations

Some individuals with minor complaints may only need to accommodate their activities and lifestyles to reduce symptoms [Shapiro & Ruff 2002]. Exercise temporarily alleviates myotonia (the "warm-up" effect). Note that a long-term beneficial effect of gymnastics is doubtful, as a small training study of six individuals with myotonia congenita showed good improvement in fitness but no change in severity of myotonia assessed clinically and on the Myotonia Behavior Scale [Andersen et al 2017b].

Myotonic stiffness may respond to sodium channel blockers or other pharmacologic treatment options:

- **Mexiletine**, a lidocaine derivative, is the best documented treatment option and the only FDA-approved drug for this indication. In a double-blind randomized trial, mexiletine (200 mg 3x/day) significantly reduced stiffness in a group of 59 individuals with myotonia, 34 of whom had myotonia congenita [Statland et al 2012]. In clinical practice, doses generally begin at 150 mg/2x/day, increasing slowly as needed up to 200-300 mg/3x/day. The most common potential side effects, including epigastric discomfort, nausea, lightheadedness, dizziness, tremor, and ataxia, are reversible with dose reduction.
- Lamotrigine, another sodium channel blocker, also significantly reduced myotonia in a randomized controlled trial in patients with both sodium and chloride channelopathies [Andersen et al 2017a].
- Other sodium channel blockers such as **phenytoin** and **carbamazepine** have been reported to have beneficial effects [Conravey & Santana-Gould 2010].

- Compounds with other presumed modes of action such as **quinine**, **dantrolene**, or **acetazolamide** may be beneficial in some cases [Shapiro & Ruff 2002].

See Conravey & Santana-Gould [2010] for a detailed description of these treatment options.

Agents/Circumstances to Avoid

In general, anesthesia should be used with caution [Bandschapp & Laizzo 2013]. Particular care must be taken with the use of **depolarizing muscle relaxants** during anesthesia because they may cause adverse anesthesia-related events. Because life-threatening muscle spasms and secondary ventilation difficulties occurred following a preoperative injection of **suxamethonium**, Farbu et al [2003] recommended that suxamethonium be avoided in individuals with myotonia congenita.

Note: Non-depolarizing muscle relaxants appear to act normally in individuals with myotonia congenita but do not counteract a myotonic response caused by suxamethonium [Farbu et al 2003].

In rare cases, injections of **adrenaline** or **selective beta-adrenergic agonists** in high doses may aggravate myotonia.

The beta-antagonist **propranolol** has likewise been reported to worsen myotonia [Blessing & Walsh 1977]. Accordingly, beta-agonists and beta-antagonists should be used with caution, and particular care should be taken with the use of intravenous **fenoterol** or **ritodrine**.

Evaluation of Relatives at Risk

Because individuals with myotonia congenita may be at increased risk for adverse anesthesia-related events, molecular genetic testing of at-risk family members (for the *CLCN1* pathogenic variant[s] identified in the proband) during childhood is appropriate.

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

Pregnancy Management

A comprehensive birth plan is recommended for a pregnant woman with myotonia congenita to minimize the risks of muscular spasms due to factors such as medications, intramuscular injections, and cold [Gorthi et al 2013].

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

Myotonia congenita can be inherited in either an autosomal recessive (Becker disease) or an autosomal dominant (Thomsen disease) manner.

Distinguishing between autosomal dominant and autosomal recessive myotonia congenita depends mainly on the family history (i.e., the presence of an affected parent in autosomal dominant myotonia congenita). However, a clear distinction can be difficult because the same *CLCN1* pathogenic variant may occur in families with autosomal recessive inheritance and those with autosomal dominant inheritance (see Molecular Genetics).

In a simplex case (i.e., the occurrence of a single individual with myotonia congenita in a family), establishing the mode of inheritance may not be possible unless molecular genetic testing reveals two *CLCN1* pathogenic variants *in trans* in a proband with unaffected parents, demonstrating autosomal recessive inheritance. Confirmation of phase by segregation analysis is important, as a single allele with two pathogenic variants has been described [Brugnoni et al 2013].

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual with autosomal recessive myotonia congenita are obligate heterozygotes (i.e., presumed to be carriers of one *CLCN1* 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 *CLCN1* 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.
- Occasionally, the heterozygous parent of a proband with autosomal recessive myotonia congenita (i.e., the proband has two *CLCN1* pathogenic variants *in trans*) can show subtle evidence of myotonia on EMG testing. However, the parent is not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *CLCN1* pathogenic variant, each sib of an affected individual has a 25% risk of being affected at conception, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier.
- Intrafamilial clinical variability may be observed in sibs who inherit the same biallelic pathogenic variants [Sun et al 2001, Colding-Jørgensen 2005, Orsini et al 2020].
- Occasionally, the heterozygous sibs of a proband with autosomal recessive myotonia congenita (i.e., the proband has two *CLCN1* pathogenic variants *in trans*) can show subtle evidence of myotonia on EMG testing. However, the sibs are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive myotonia congenita are obligate heterozygotes (carriers of a *CLCN1* pathogenic variant).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CLCN1* pathogenic variant.

Heterozygote Detection

Carrier testing for at-risk relatives requires prior identification of the *CLCN1* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with autosomal dominant myotonia congenita have an affected parent.
- A proband with autosomal dominant myotonia congenita may potentially have the disorder as the result of a *de novo CLCN1* pathogenic variant. The proportion of individuals with myotonia congenita caused by a *de novo* pathogenic variant is unknown but presumably very low.
- 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, 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. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of some individuals diagnosed with autosomal dominant myotonia congenita may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, or early death of the parent before the onset of symptoms. Therefore, an apparent 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 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%. Intrafamilial clinical variability may be observed in sibs who inherit the same pathogenic variant [Sun et al 2001, Colding-Jørgensen 2005, Orsini et al 2020].
- If the *CLCN1* 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 *CLCN1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for myotonia congenita 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 autosomal dominant myotonia congenita has a 50% chance of inheriting the *CLCN1* 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 *CLCN1* pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CLCN1* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for myotonia congenita are possible. The prenatal identification of a *CLCN1* pathogenic variant(s) is not useful in predicting age of onset, severity, type of symptoms, or rate of progression.

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)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 00-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Myotonia Congenita Information Page
- **National Library of Medicine Genetics Home Reference**
  Myotonia congenita
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  www.musculardystrophyuk.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. Myotonia Congenita: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

CLCN1	7q34	Chloride channel protein 1	Chloride channel 1, skeletal muscle (CLCN1) @ LOVD	CLCN1	CLCN1

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 Myotonia Congenita (View All in OMIM)

118425	CHLORIDE CHANNEL 1, SKELETAL MUSCLE; CLCN1
160800	MYOTONIA CONGENITA, AUTOSOMAL DOMINANT
255700	MYOTONIA CONGENITA, AUTOSOMAL RECESSIVE

Molecular Pathogenesis

CLCN1 encodes the voltage-gated chloride channel ClC-1 (chloride channel protein 1), which is primarily expressed in the sarcolemma, where its main function is to regulate excitability and to stabilize the resting potential. Normally, the chloride conductance contributes 85% to the resting membrane conductance of human muscle, ensuring its electrical stability. The chloride conductance is crucial for countering the depolarizing effect of potassium (K^+) accumulation in T tubules. If the chloride conductance is reduced to 40% or less, K^+ accumulation in the T-tubular lumen depolarizes the surface membrane sufficiently to initiate self-sustaining action potentials causing a prolonged (myotonic) contraction [Barchi 2001]. A reduction of chloride conductance to 50% apparently does not cause myotonia, because heterozygotes (i.e., carriers) of nonfunctional ("autosomal recessive") pathogenic variants are usually asymptomatic.

Mechanism of disease causation. The voltage-gated chloride channel ClC-1 (chloride channel protein 1) functions as a homodimer. The functional ClC-1 channel contributes approximately 80% of the total resting conductance and determines membrane excitability.

Pathogenic variants associated with autosomal recessive (AR) inheritance are presumed to cause loss of function of the channel; pathogenic variants associated with autosomal dominant (AD) inheritance presumably act through a dominant-negative mechanism by primarily affecting dimerization [Skálová et al 2013].The latter variants are therefore mainly located in the dimer interface, whereas variants associated with AR myotonia congenita can be located throughout the protein [Skálová et al 2013]. A subset of presumed loss-of-function variants located downsteam of the dimer interface domain have been associated with AD inheritance.

***CLCN1*-specific laboratory technical considerations.** The majority of the more than 318 different *CLCN1* pathogenic variants identified to date are associated with AR myotonia congenita. Pathogenic variants associated with AR inheritance appear to be scattered throughout the coding sequence and are mostly missense or nonsense variants (Table 4).

Pathogenic variants causing AD myotonia congenita are often located in exon 8 [Fialho et al 2007], which encodes part of the dimer interface domain. Apart from c.2680C>T (p.Arg894Ter), all variants associated with AD inheritance are missense.

Approximately 20 pathogenic variants have been solely associated with AD myotonia congenita, whereas approximately 12 pathogenic variants associate with both AR and AD myotonia congenita, making it difficult to predict mode of inheritance.

Unambiguous pedigrees with AR inheritance and AD inheritance have been described only for p.Gly230Glu, p.Thr310Met, p.Ala531Val, and p.Arg894Ter. This peculiar phenomenon may be explained by the following [Koty et al 1996, Mailänder et al 1996, Zhang et al 1996, Plassart-Schiess et al 1998, Dunø et al 2004, Bernard et al 2008, Richardson et al 2014]:

- Reduced penetrance of dominant-negative pathogenic variants
- Incomplete dominance
- Haplotype background
- Incomplete pathogenic variant detection
- Differences in variant expression

Table 4. Notable CLCN1 Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000083.2 NP_000074.2	c.689G>A	p.Gly230Glu	Assoc w/AR & AD MOI [1]
	c.929C>T	pThr310Met	Assoc w/AR & AD MOI [1]
	c.1592C>T	p.Ala531Val	Assoc w/AR & AD MOI [1]
	c.2680C>T	p.Arg894Ter	Most common variant assoc w/both AR & AD MOI. [1] Interpretation should be performed w/caution: variant is frequently found in persons presumed to be healthy, an indication of ↓ penetrance. [2]

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
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. Most of the following reports regarding the p.Arg894Ter variant predate the gnomAD data set (see footnote 2): Koty et al [1996], Mailänder et al [1996], Zhang et al [1996], Plassart-Schiess et al [1998], Dunø et al [2004], Bernard et al [2008], Richardson et al [2014].
2. See gnomAD.broadinstitute.org.

Chapter Notes

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