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Congenital Fiber-Type Disproportion – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: CFTDM, Congenital Myopathy with Fiber-Type Disproportion

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Congenital fiber-type disproportion (CFTD) is usually characterized by hypotonia and mild-to-severe generalized muscle weakness at birth or within the first year of life. Although some individuals remain non-ambulatory throughout life, many eventually develop the ability to walk. In more than 90% of affected individuals, muscle weakness is static or improves; in the remainder it is usually slowly progressive. Mild-to-severe respiratory involvement is seen in approximately 30% of affected individuals; respiratory failure may occur at any age. Ophthalmoplegia, ptosis, and facial and/or bulbar weakness with severe limb/respiratory weakness may predict a poor prognosis. Mild-to-severe feeding difficulties occur in nearly 30% of children. Contractures of the hips, knees, ankles, elbows, and fingers occur in approximately 25% and may be present at birth or occur in older persons with decreased mobility secondary to severe weakness. Spinal deformities including scoliosis, kyphoscoliosis, and lordosis are seen in 25% or more of individuals.

Diagnosis/testing

Diagnosis is based on a combination of clinical presentation and morphologic features observed on skeletal muscle histology. The pathologic and clinical manifestations of CFTD overlap with other neuromuscular and non-neuromuscular diseases that must be ruled out prior to making a diagnosis of CFTD. To date, pathogenic

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variants have been identified in six genes: *ACTA1* (~6% of individuals with CFTD), *MYH7* (unknown), *RYR1* (~10%-20%), *SELENON* (*SEPN1*) (rare), *TPM2* (rare), and *TPM3* (~20%-25% of individuals with CFTD).

Management

Treatment of manifestations: For weakness/contractures: physical therapy and occupational therapy (orthotics or splinting, serial casting, or walking supports/wheelchair); regular low-impact exercise, stretching, and submaximal strength training with sufficient rest to avoid exhaustion; for respiratory issues: breathing exercises, chest physiotherapy, seating assessment, immunizations, antibiotics for chest infections, tracheostomy, or ventilatory support; for feeding/swallowing difficulties: speech therapy, and gavage or gastrostomy feedings; orthopedic evaluation for foot deformities, joint contractures, and scoliosis; bracing or spinal fusion based on progression of the spinal curve and effect on pulmonary and motor function; treatment by a cardiologist as needed; orthodontia as needed.

Prevention of secondary complications: Consider precautions for malignant hyperthermia prior to anesthesia; preoperative assessment of pulmonary and cardiac function; consistent joint movement to prevent contractures.

Surveillance: Regular monitoring of motor abilities/weakness, pulmonary and cardiac function, and spine for scoliosis (especially in childhood and adolescence).

Agents/circumstances to avoid: Extended immobilization.

Genetic counseling

CFTD is a genetically heterogeneous condition that can be inherited in an autosomal recessive, autosomal dominant, or X-linked manner. To date, all identified cases of *ACTA1*, *MYH7*, and *TPM2*-related CFTD have been caused by autosomal dominant pathogenic variants while the *SELENON* and *RYR1*-related cases have been associated with autosomal recessive pathogenic variants. *TPM3*-related CFTD can be inherited in an autosomal dominant or autosomal recessive manner. *ACTA1* and *TPM3* pathogenic variants are often *de novo* dominant. A large portion of individuals with CFTD represent simplex cases (i.e., a single occurrence in a family). It can be difficult to determine inheritance pattern in the family of a simplex case when a pathogenic variant is not identified through testing of known genes. Prenatal testing for pregnancies at risk for CFTD is possible if the pathogenic variant(s) in a family are known.

Diagnosis

Clinical Diagnosis

Diagnosis of congenital fiber-type disproportion (CFTD), a genetically and clinically heterogeneous congenital myopathy, is based on a combination of the following [Brooke 1973, Clarke & North 2003, North 2004]:

- **Clinical presentation** consistent with congenital myopathy
- Morphologic features observed on **skeletal muscle histology**

Most common clinical presentation. CFTD usually presents with hypotonia and varying degrees of skeletal muscle weakness that primarily affects the limbs, generally presenting at birth or within the first year of life and remaining stable over time or improving with age.

Skeletal muscle histology (see Figure 1)

- The original criteria presented by Brooke in 1973 required that type 1 fibers be at least 12% smaller than the mean diameter of type 2A and/or type 2B fibers in the absence of other significant pathologic findings

(e.g., many nemaline bodies, cores, or central nuclei; see Figure 1). In cases with type 2 fiber hypertrophy, type 1 fibers may have a normal diameter for age.

- More recent studies suggest that affected individuals with true congenital fiber size disproportion (i.e., those who do not have another defined neuromuscular condition such as myotonic dystrophy or Ullrich muscular dystrophy) have type 1 fibers that are generally at least 40% to over 80% smaller than type 2 fibers, particularly when the condition is associated with pathogenic variants in *TPM3*, *RYR1*, and *ACTA1* [Laing et al 2004, Clarke et al 2008, Clarke et al 2010, Lawlor et al 2010]. Therefore, a 35%-40% degree of disproportion has been suggested as a better criterion for the diagnosis of CFTD [Clarke 2011]. However, cases of *SELENON*-related CFTD may not meet this stricter criterion [Clarke 2011].

  Note: Multiple males and at least one female without significant muscle weakness have been noted to have fiber-type disproportion on muscle biopsy that was performed in infancy, adolescence, or adulthood [Sobreira et al 2003; Author, personal observation].

- Additional findings that may also be present:
  - Type 1 fiber numeric predominance (Figure 1), not to be confused with fiber-type grouping
  - Decreased presence of 2B/2X fibers
  - One type of type 2 fibers (2A or 2B/2X) possibly larger than the other(s)

- Less frequent abnormalities: central myonuclei, moth-eaten fibers, occasional nemaline rods [Brooke 1973], intramuscular hematopoiesis, infrequent central cores or multicores [Iannaccone et al 1987], and abnormal accumulation of endomysial adipocytes

Ultrastructural findings on electron microscopy (EM) are generally normal; however, fiber size variation may be present. Architectural abnormalities reported in some individuals include: infrequent multiminicores; nemaline bodies; and sub-sarcolemmal sarcomere disarray or glycogen accumulation.

Pathologic findings may change over time, allowing the refinement of the diagnosis through a second biopsy at a later age. Some individuals with a diagnosis of CFTD on first biopsy are later found to have additional findings on second biopsies [De Paula et al 2009, Clarke 2011].

Results of other medical testing

- **Serum creatine phosphokinase (CK) concentration** is generally normal or mildly elevated (i.e., no more than three times the upper limit of normal) [Clarke & North 2003, Laing et al 2004, Clarke et al 2008, Clarke et al 2010].
- **Electromyography (EMG)** is usually normal or myopathic, but neuropathic or mixed findings are also possible [Clarke et al 2008, Clarke et al 2010, Lawlor et al 2010].
- Nerve conduction studies are generally normal.

Muscle imaging. Muscle ultrasound or MRI of the leg or whole body has been shown to be particularly useful in differentiating between congenital myopathies associated with certain genes (see Testing Strategy).

Exclusion of other neuromuscular and non-neuromuscular conditions. The pathologic and clinical manifestations of CFTD overlap with other neuromuscular and non-neuromuscular diseases that must be excluded prior to making a diagnosis of CFTD. The majority of these diseases can be excluded based on a thorough physical examination, family history, and appropriate testing, potentially including serum creatine kinase concentration, EMG, muscle biopsy, and/or genetic testing. A comprehensive list of diseases that may present similarly to CFTD is included in Differential Diagnosis.

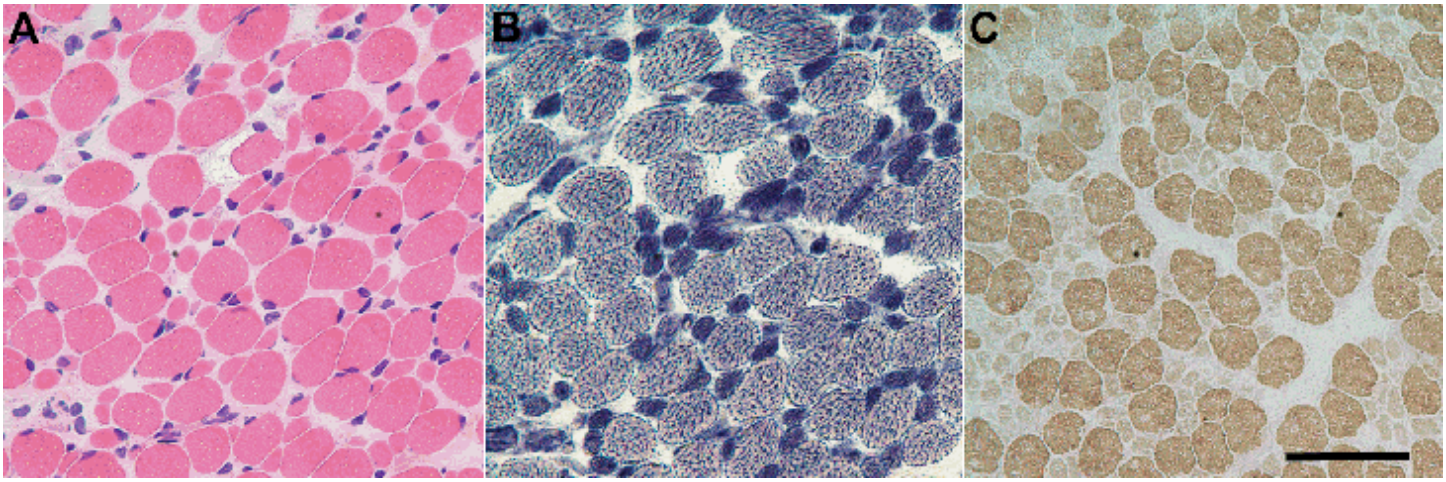

Figure 1. (A) H and E, (B) NADH, and (C) ATPase (pH 9.4) histochemical stains of a biopsy taken from the vastus lateralis of a six-month-old female with CFTD caused by a heterozygous *TPM3* pathogenic variant. The type 1 fibers (dark staining on B. NADH; light staining on C. ATPase) are smaller than the type 2 fibers (inversely stained). Type 1 and type 2 fibers are similar in size in healthy individuals. Bar equals 100 µm.

Molecular Genetic Testing

Genes. To date, the genetic basis of CFTD has been elucidated in only a portion of cases. Pathogenic variants have been identified in the following six genes: *ACTA1*, *MYH7*, *RYR1*, *SELENON* (*SEPN1*), *TPM2*, and *TPM3*.

Evidence for locus heterogeneity. CFTD was identified in an individual with an apparently balanced translocation t(10;17)(p11.2;q25) inherited from the mother, who had subtle findings of myopathy, suggesting a possible autosomal dominant mode of inheritance with variable expressivity [Gerdes et al 1994].

In a kindred of seven males with severe congenital myopathy, biopsies in four of six were suggestive of CFTD. Linkage to the intervals Xp22.13 to Xp11.4 and Xq13.1 to Xq22.1 was found. Of note, Xq28, the locus of *MTM1*, the gene involved in X-linked myotubular myopathy, was excluded. All affected males had ptosis without ophthalmoplegia, low muscle tone, poor suck, and weakness of the facial and respiratory muscles with relatively normal strength in the limbs. Six of the seven died of respiratory failure within the first few months of life. One male walked at age 17 months and developed mild dilated cardiomyopathy at age 3.5 years. Some female carriers had mild myopathic signs [Clarke et al 2005].

A Japanese girl with deletion 1p36, developmental delay, dysmorphic features, and hypotonia had CFTD on muscle biopsy, suggesting that a gene involved in CFTD may exist at this locus [Okamoto et al 2002]. *SELENON*, the gene encoding selenoprotein N and implicated in CFTD and multiminicore disease, resides in this region; however, inheritance of the myopathy associated with *SELENON* alterations is autosomal recessive.

Vorwerk et al [1999] described two brothers with CFTD and insulin-resistant diabetes mellitus who were compound heterozygotes for alterations in the insulin receptor gene (*IR*; *INSR*). A third brother who did not inherit either *INSR* gene alteration did not develop symptoms of CFTD, suggesting a potential association between the mutation of *INSR* and CFTD [Vorwerk et al 1999].

Table 1. Molecular Genetic Testing Used in Congenital Fiber-Type Disproportion

Gene [1]	Proportion of CFTD Attributed to Mutation of Gene	Method	Variants Detected [2]
ACTA1	<6%% [3]	Sequence analysis [4]	Sequence variants
	Unknown	Deletion/duplication analysis [5]	Unknown; none reported [6]
SELENON (*SEPN1*)	Rare [7]	Sequence analysis [4]	Sequence variants
	Unknown	Deletion/duplication analysis [5]	Unknown; none reported [6]
TPM3	~20%-40%	Sequence analysis [4, 8]	Sequence variants
	Unknown	Deletion/duplication analysis [5]	Unknown; none reported [6]
RYR1	10%-20% [9] Likely common	Sequence analysis [4, 10]	Sequence variants
		Deletion/duplication analysis [5]	Unknown; none reported [6]
TPM2	Rare	Sequence analysis [4, 11]	Sequence variants
		Deletion/duplication analysis [5]	Unknown; none reported [6]
MYH7	Unknown [12]	Sequence analysis [4]	Sequence variants
	Unknown	Deletion/duplication analysis [5]	Unknown; none reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Heterozygous pathogenic missense variants were observed in 6% of individuals with CFTD in one series [Laing et al 2004] and have been reported in at least seven families [Laing et al 2009].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.
5. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. No large deletions or duplications that were causative of CFTD have been reported in *ACTA1*, *RYR1*, *TPM2*, or *TPM3*.
7. SELENON homozygous pathogenic missense variants have been reported in two sisters with CFTD [Clarke et al 2006].
8. TPM3 heterozygous pathogenic missense variants have been reported in more than ten families with CFTD, and homozygous pathogenic variants of the stop codon were reported in one family [Clarke et al 2008, Lawlor et al 2010, Munot et al 2010]. Clarke et al [2008] identified *TPM3* alterations in four families from one CFTD cohort, representing approximately 20%-25% of their cases. Lawlor et al [2010] discovered *TPM3* pathogenic variants in five of 13 families in another CFTD cohort, accounting for almost 40% of their cases.
9. Clarke et al [2010] identified recessive *RYR1* alterations in four of seven families with CFTD in whom *ACTA1* and *TPM3* pathogenic variants had been previously excluded, suggesting that *RYR1* pathogenic variants are one of the two most common causes of CFTD, along with *TPM3* alterations. They estimated that *RYR1* alterations are responsible for 10%-20% of cases of CFTD.
10. RYR1 compound heterozygous pathogenic missense, nonsense, and/or splice site variants were identified in four families (5 affected individuals) with CFTD in one study [Clarke et al 2010].
11. A *TPM2* heterozygous pathogenic missense variant was reported in a small number of families with CFTD [Brandis et al 2008, Clarke et al 2012].
12. Heterozygous *MYH7* pathogenic variants have been reported in at least three families (4 affected individuals) with CFTD. All of the families had other affected family members with muscle biopsies that contained additional morphologic features that did not fit the CFTD criteria [Muelas et al 2010, Ortolano et al 2011].

Testing Strategy

To confirm/establish the diagnosis in a proband. The diagnosis of CFTD is currently established by the combination of clinical presentation consistent with congenital myopathy and specific features on muscle biopsy.

Molecular genetic testing can be used to confirm the diagnosis of CFTD in some individuals, but some individuals will have normal testing for all six currently associated genes.

Muscle imaging, including ultrasound or MRI, may be helpful in guiding genetic testing, since some genes are associated with characteristic muscle involvement [Quijano-Roy et al 2012].

- Those with *RYR1* pathogenic variants show particular involvement of the gluteus maximus muscle, adductor magnus, vastus lateralis, sartorius, and soleus muscle with sparing of the rectus femoris and gracilis muscles.
- Affected individuals with *ACTA1* pathogenic variants show particular involvement of the gluteus maximus, medial muscles, tibial anterior and peroneal muscles, and posterior thigh, including the sartorius, adductor magnus, and semitendinosus muscles, with sparing of the adductor longus, rectus femoris, and gracilis muscles.
- Those with *SELENON* pathogenic variants show involvement of the sartorius, posterior thigh, posterior tibial, and medial and lateral gastrocnemius muscles with sparing of the rectus femoris, adductor longus, and gracilis muscles.
- Those with pathogenic variants in *MYH7* may show particular involvement of the tibial anterior and peroneal muscles, milder involvement of the soleus muscle, and sparing of the medial gastrocnemius muscle [Quijano-Roy et al 2012].

Based on variant frequency and gene size, it is recommended that sequence analysis be performed sequentially or in tiers of two to three genes at a time unless there are clinical/pathologic features or family history suggesting a different testing order.

- Sequential testing may be considered in the following order: *TPM3*, *ACTA1*, *RYR1*, *MYH7*, *TPM2*, *SELENON*
- *RYR1* pathogenic variants appear to be the most common cause of recessive CFTD, while *TPM3* pathogenic variants appear to be the most common cause of autosomal dominant CFTD. Given the size of *RYR1*, testing can be more time consuming and costly than testing of the other genes, which may influence decisions about the order of testing.
- In individuals with ophthalmoplegia and/or a personal or family history of malignant hyperthermia, *RYR1* screening could be considered first.
- *MYH7*, *TPM2*, and particularly *SELENON* pathogenic variants appear to be rarer causes of CFTD and therefore could be considered for a second tier.
- In individuals with cardiomyopathy, *MYH7* testing may be considered first.
- In individuals with spinal rigidity or early-onset scoliosis, *SELENON* testing may be considered first.
- To date, no large deletions or duplications in the six known genes have been identified to be causative of CFTD; however, disease-causing *RYR1* and *SELENON* deletions have been identified in individuals with other related diagnoses. Therefore, there may be some clinical utility to pursuing deletion/duplication testing if sequencing is normal.

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

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder. However, the risk for malignant hyperthermia (MH) in individuals with a heterozygous pathogenic variant in *RYR1* is not well understood. Therefore, it is recommended that individuals with a heterozygous pathogenic variant in *RYR1* follow appropriate restrictions for MH.

Prenatal testing and preimplantation genetic testing for at-risk pregnancies require prior identification of the pathogenic variant(s) in the family.

Clinical Characteristics

Clinical Description

Clarke & North [2003], North & Goebel [2003], and North [2004] provide summaries of the natural history of congenital fiber-type disproportion (CFTD), while Sobrido et al [2005], Clarke et al [2008], Clarke et al [2010], and Lawlor et al [2010] present clinical data on the largest number of affected individuals with known pathogenic variants. Together, these citations are the primary references for the majority of this section. Findings are summarized in Table 2.

Most children present with hypotonia, mild-to-severe generalized muscle weakness, and/or delayed motor milestones at birth or within the first year of life. Poor head control is also common. Limb weakness may be greatest in the limb girdle and proximal limb muscles, but weakness is not usually solely distal. Facial weakness is often present, resulting in a long face, high-arched palate, and tented upper lip. Ptosis, ophthalmoplegia, and bulbar weakness can be seen. Tendon reflexes are often decreased or absent.

Motor milestones are often delayed. Although some individuals remain non-ambulatory throughout life, many eventually develop the ability to walk. In more than 90% of affected individuals, muscle weakness becomes static or shows improvement, and in 9% it is slowly progressive [Brooke 1973, Clarke & North 2003]. Progression may result in loss of independent ambulation in some individuals.

Table 2. Clinical Features Seen in CFTD Based on Frequency of Occurrence

Frequency of Occurrence (% of Affected Individuals)	Clinical Features
Primary (>50%-75%)	Hypotonia Mild-to-severe generalized or proximal muscle weakness Height and/or weight below the 3rd percentile Decreased or absent deep tendon reflexes Normal or mildly elevated CK levels Normal or myopathic EMG Normal intelligence
Common (10%-50%)	Facial weakness/myopathic facies: long face, high-arched palate, and tented upper lip Mild-to-severe respiratory issues Mild-to-severe feeding difficulties Ophthalmoplegia Joint contractures or arthrogryposis multiplex congenital Congenital hip dislocation Spinal abnormalities, including scoliosis, kyphoscoliosis, and lordosis Joint laxity
Rarely reported (<10%)	Cardiac involvement Cognitive impairment Cryptorchidism

At least 30% of individuals with CFTD have mild-to-severe respiratory involvement, which may not develop until adulthood. The majority of severely affected children develop significant respiratory weakness; however, the severity of respiratory muscle weakness and limb muscle weakness do not always correlate. Respiratory failure may occur at any age with some affected children succumbing to respiratory failure during infancy or childhood. Respiratory failure can occur without evidence of respiratory distress. In more mildly affected individuals, respiratory insufficiency may manifest as nocturnal hypoxia, potentially resulting in frequent chest infections, morning headaches, daytime fatigue, decreased appetite, reduced weight gain, and/or sleep disturbances. Severe respiratory involvement in infancy does not always predict poor prognosis.

Approximately 25% of individuals with CFTD show a more severe clinical course with significant and persistent weakness of limb or respiratory muscles at birth. The association in particular of ophthalmoplegia, ptosis, and facial and/or bulbar weakness with severe limb and respiratory weakness has previously been suggested to predict a poor prognosis.

Mild-to-severe feeding difficulties occur in almost 30% of children with CFTD. Bulbar weakness may result in chewing and swallowing problems and aspiration of secretions. Infants with severe facial and bulbar weakness may have significant feeding issues and may require intervention (gavage feeding, and/or gastrostomy with or without fundoplication) if symptoms continue beyond the first few months of life. Milder feeding issues often resolve over time.

Contractures of the ankles, fingers, hips, elbows, and knees occur in approximately 25% of affected children. Contractures may be present at birth or occur in older individuals who have decreased mobility secondary to severe weakness. Congenital hip dislocation and talipes equinovarus may also be present.

Spinal deformities, including scoliosis, kyphoscoliosis, and lordosis, are seen in 25% or more of individuals. Spinal rigidity has also been reported.

Contractures and spinal abnormalities are not necessarily associated with increased disease severity.

Other. Most individuals have normal intelligence, but cognitive impairment has been reported in a few individuals.

Cryptorchidism has been seen in a few males with CFTD.

Dilated cardiomyopathy or other cardiac abnormalities have been identified in several individuals with CFTD:

- One required cardiac transplantation at age 12 years [Banwell et al 1999].
- A male with X-linked CFTD and dilated cardiomyopathy was medically stable during follow-up from age 3.5 years to age 5.5 years [Clarke et al 2005].
- One individual required a pacemaker for cardiomyopathy presenting with nocturnal and exertional dyspnea at age 28 years [Fujita et al 2005].
- A nine-month-old with CFTD had atrial fibrillation and an atrial septal defect [Banwell et al 1999].

Dental crowding and high-arched palate, seen in other congenital myopathies, may be observed in CFTD.

Genotype-Phenotype Correlations

Some genotype-phenotype correlations have been established. See Testing Strategy for more information on muscle imaging-related genotype-phenotype correlations.

ACTA1. Laing et al [2004] reported three individuals with *ACTA1*-associated CFTD who did not have ophthalmoplegia, but did have severe disease with significant muscle weakness and respiratory insufficiency requiring ventilator support [Laing et al 2004]. *ACTA1*-associated myopathies have a variable phenotype ranging from severe infantile onset to milder weakness, but they appear to be more frequently associated with a more severe presentation. There is considerable phenotypic variability, even with the same pathogenic variant, making specific predictions difficult [Laing et al 2009].

MYH7. Only a few families with *MYH7* pathogenic variants have been reported to have a muscle biopsy and clinical presentation consistent with CFTD. Individuals with *MYH7*-associated CFTD have a variable phenotype, with age of onset ranging from birth to adulthood. However, life expectancy is not significantly shortened, and the course is generally slowly progressive. Delayed motor milestones or abnormal gait are common presenting symptoms, but may not bring the individual to medical attention until adulthood [Sobrido et al 2005, Muelas et al 2010, Ortolano et al 2011]. Cardiac abnormalities, including cardiomyopathy and rhythm

abnormalities, have been reported in a small subset of individuals with *MYH7* myopathy, including those who have one of the pathogenic variants known to be associated with CFTD [Muelas et al 2010].

- In affected individuals with the recurrent p.Lys1729del variant associated with myosin storage myopathy and CFTD, the anterior compartment of the lower leg is particularly involved, and weakness of the lower leg is sometimes the only identifiable muscle weakness [Muelas et al 2010].
- In a single large family with CFTD caused by a frameshift variant in exon 39, weakness was primarily proximal [Sobrido et al 2005, Ortolano et al 2011]. Interestingly, this family had several members with a muscle biopsy consistent with CFTD, while at least one family member had a later biopsy consistent with myosin storage myopathy [Ortolano et al 2011].

RYR1. Ophthalmoplegia appears to be particularly suggestive of underlying *RYR1* pathogenic variants, although it can be subtle or absent, particularly in younger individuals or in individuals with milder disease [Clarke et al 2010].

- The five individuals reported with homozygous or compound heterozygous *RYR1* pathogenic variants had the following findings: symptoms at birth or within the first two years of life with hypotonia, muscle weakness, or difficulty running; particularly weak axial muscles; variable requirements for feeding and breathing support from an early age; variable clinical course with death in infancy or early childhood from respiratory failure in some and retained ambulation for short distances into adulthood in others.
- Delayed motor milestones, respiratory weakness, ophthalmoplegia, ptosis, and facial weakness were all reported in multiple affected individuals; however, none were present in all five cases.

***SELENON* (*SEPN1*).** The two sisters with CFTD caused by homozygous *SELENON* pathogenic missense variants had findings typical of *SELENON*-related myopathy, including truncal hypotonia, neck weakness, progressive scoliosis, respiratory involvement, and relatively preserved strength in the extremities [Clarke et al 2006].

TPM2. Thus far, *TPM2* pathogenic variants have been reported in only a small number of families with onset ranging from severe hypotonia in infancy to difficulty running in childhood [Brandis et al 2008, Clarke et al 2012].

- Unlike other cases of CFTD associated with mutation of other genes, one mother and son had two populations of type 1 fibers: one population that was hypotrophic and a second population that was relatively normal in size [Donner et al 2002, Brandis et al 2008].
- *TPM2* pathogenic variants can also cause CFTD with neonatal onset of severe hypotonia, weakness, respiratory weakness and arthrogryposis [Author, personal observation].

TPM3. *TPM3*-associated CFTD generally causes early onset of mild proximal and/or distal weakness, allowing for ambulation into adulthood without the need for invasive ventilation, and no ophthalmoplegia.

- Individuals with CFTD caused by heterozygous pathogenic missense variants in *TPM3* who have been described thus far generally presented with hypotonia and/or delayed motor milestones within the first year of life [Clarke et al 2008, Lawlor et al 2010, Munot et al 2010]. A few affected individuals presented with difficulty running or keeping up with peers in childhood or adolescence [Lawlor et al 2010]. Many of these individuals walked within the normal age range and had mild-to-moderate muscle weakness of proximal and/or distal muscles. All individuals who had reached adulthood at the time of the studies were ambulatory.
- Respiratory difficulties during sleep were common and sometimes insidious, presenting in childhood or early adulthood, making respiratory monitoring particularly important for this subset of individuals [Clarke et al 2008, Lawlor et al 2010, Munot et al 2010, Clarke 2011].
- Extraocular muscle weakness was not reported in this group of affected individuals [Clarke et al 2008, Lawlor et al 2010].

- The single person with CFTD caused by homozygous *TPM3* pathogenic variants had a more severe presentation: she never walked and required full-time respiratory and feeding support from early childhood [Lawlor et al 2010].

Prevalence

CFTD is rare; prevalence is unknown. Studies suggest that CFTD is less common than nemaline myopathy [Wallgren-Pettersson et al 1990, Fardeau & Tomé 1994], which has an estimated incidence of 1:50,000 live births in Finland [Wallgren-Pettersson et al 1990].

Genetically Related (Allelic) Disorders

***ACTA1*-related myopathies.** Heterozygous pathogenic variants in *ACTA1* most commonly cause nemaline myopathy (NM). Homozygous pathogenic variants in *ACTA1* have also been identified in a small number of individuals with NM [Laing et al 2009].

- Nemaline myopathy is characterized by rod-like structures on muscle biopsy with clinical features similar to those seen in CFTD.
- Less frequently, *ACTA1* pathogenic variants can also cause actin filament aggregate myopathy (characterized by accumulation of actin-contacting filaments), intranuclear rod myopathy (characterized by rod-like bodies in the nuclei), and congenital myopathy with core-like areas (without rods), as well as CFTD. A mixture of these pathologic findings can also be seen in a single individual.

***MYH7*-related myopathies.** Heterozygous pathogenic variants in *MYH7* have been associated with isolated hypertrophic/dilated cardiomyopathy, Laing distal myopathy, and myosin storage myopathy (previously known as hyaline body myopathy) [Tajsharghi & Oldfors 2013].

- Cardiac abnormalities have been reported in individuals with *MYH7* pathogenic variants without a diagnosis of CFTD [Muelas et al 2010].
- Laing early-onset distal myopathy generally presents with distal weakness, starting with weakness of the ankle dorsiflexors in childhood through early adulthood, and later progresses to include proximal limb muscle weakness. Muscle biopsy shows nonspecific findings, including type 1 predominance and hypotrophy [Tajsharghi & Oldfors 2013].
- Myosin storage myopathy presents with variable proximal, distal, or scapuloperoneal weakness during early childhood to mid-to-late adulthood (4th-6th decade) [Goebel & Laing 2009, Tajsharghi & Oldfors 2013]. Inheritance is generally dominant, but recessive inheritance has been reported in at least one family with a more severe presentation that included cardiomyopathy. Muscle biopsy shows characteristic aggregation of unstructured material called hyaline bodies [Tajsharghi & Oldfors 2013].

***RYR1*-related myopathies.** Heterozygous alterations in *RYR1* cause central core disease (CCD), as well as core-rod myopathy and malignant hyperthermia without myopathy. All *RYR1*-related myopathies have clinical presentations that overlap with CFTD, with ophthalmoplegia often being a prominent feature [Treves et al 2005].

- Rare recessive *RYR1* pathogenic variants have been associated with CCD [Treves et al 2005].
- Homozygous or compound heterozygous alterations in *RYR1* can cause other congenital myopathies, including congenital myopathies with central nuclei [Wilmshurst et al 2010], multiminicore disease [Treves et al 2005], and a form of congenital myopathy with internalized nuclei and myofibrillar disorganization [Bevilacqua et al 2011]. A large heterozygous deletion of *RYR1* was reported in one individual with recessive multiminicore disease [Monnier et al 2009].
- There has been one reported case of a heterozygous *RYR1* pathogenic variant causing centronuclear myopathy [Jungbluth et al 2007].

***SELENON*-related myopathies.** Homozygous or compound heterozygous alterations in *SELENON* can also cause multiminicore disease (MmD) [Ferreiro et al 2002], rigid spine muscular dystrophy (RSMD) [Moghadaszadeh et al 2001], and desmin-related myopathy with Mallory body-like inclusions [Ferreiro et al 2004].

- MmD is diagnosed based on the presence of multiple minicores on muscle biopsy. Clinical features generally include the onset of axial and proximal weakness and hypotonia at birth or in infancy. Scoliosis and respiratory involvement are also common. Most individuals with classic MmD develop spinal rigidity, and thus the classic form is believed to be synonymous with RSMD [Ferreiro et al 2002].
- Desmin-related myopathy with Mallory body-like inclusions is defined histologically by the presence of hyaline plaques in approximately 10% of muscle fibers. Clinical features are similar to MmD/RSMD [Ferreiro et al 2004]. Deletions of approximately 90 to 100 base pairs have been reported to be associated with other *SELENON*-related myopathies [Ferreiro et al 2004, Maiti et al 2009, Cagliani et al 2011].

***TPM2*-related myopathies and arthrogryposis.** Heterozygous pathogenic missense variants in *TPM2* are a rare cause of nemaline myopathy, characterized by nemaline rods [Donner et al 2002], and a common cause of cap disease/myopathy, characterized by cap-like structures composed of disorganized thin filaments that resemble a cap [Ohlsson et al 2008]. These myopathies have a clinical presentation that overlaps with CFTD [Donner et al 2002, Ohlsson et al 2008], but they differ from CFTD on muscle biopsy.

- Clarke et al [2012] described an individual whose initial muscle biopsy was consistent with CFTD, but electron microscopy identified cap structures, indicating that electron microscopy can be a useful tool in clarifying a diagnosis of CFTD. Cardiomyopathy has been reported in at least one individual with *TPM2*-associated cap myopathy [Clarke 2011].
- Alterations in *TPM2* can also cause distal arthrogryposis, including type 1 (DA1) and Sheldon-Hall syndrome (DA2B), both of which are characterized by prominence of distal contractures and lack of an obvious myopathic or neurogenic cause.
- Recessive *TPM2* pathogenic variants have also been associated with Escobar syndrome with nemaline myopathy in at least one family. Affected individuals presented with hypotonia and multiple pterygium syndrome [Tajsharghi et al 2012].

***TPM3*-related myopathies.** Heterozygous, homozygous, and compound heterozygous pathogenic variants in *TPM3* can cause nemaline myopathy with rod-like structures on biopsy and clinical features similar to those seen in CFTD [Pénisson-Besnier et al 2007].

- A heterozygous *TPM3* pathogenic variant has also been reported in one individual who had features of CFTD on first muscle biopsy, but on a later muscle biopsy had features consistent with cap myopathy (characterized by abnormally arranged myofibrils resembling a cap) [De Paula et al 2009].

Differential Diagnosis

Congenital myopathies. The primary differential diagnoses are other congenital myopathies, including centronuclear/X-linked myotubular myopathy, multiminicore disease, and nemaline myopathy [Clarke & North 2003].

Since congenital myopathies often present similarly, congenital fiber-type disproportion (CFTD) cannot be distinguished from other congenital myopathies solely on clinical findings. Muscle biopsy can often help establish the appropriate diagnosis, since other congenital myopathies have specific associated histologic features, such as increased central nuclei, multiminicores, and nemaline bodies.

Other neuromuscular disorders. Muscular dystrophies and diseases of the anterior horn cell may also present with fiber size disproportion and clinical findings similar to CFTD. The disorders that have been specifically associated with fiber size disproportion include the following:

- Type 1 spinal muscular atrophy (SMA)
- Congenital muscular dystrophy, including Ullrich muscular dystrophy [Schessl et al 2008]
- Emery-Dreifuss muscular dystrophy
- Myotonic dystrophy type 1, particularly the congenital form
- Becker muscular dystrophy, and rarely, Duchenne muscular dystrophy (see Dystrophinopathies)

These dystrophies can be distinguished from CFTD based on physical examination, serum CK concentrations (often significantly increased), and muscle biopsy findings, including dystrophic changes (fiber degeneration and regeneration with necrosis and infiltration of fatty and connective tissue) and immunohistochemistry staining indicative of decreased protein expression [Kang & Kunkel 2014].

Congenital myotonic dystrophy (DM1), and congenital muscular dystrophies in particular, may present very similarly to CFTD and appear indistinguishable on muscle biopsy. Furthermore, sensitive molecular genetic testing is not possible for all congenital muscular dystrophies.

- Molecular genetic testing detects a CTG expansion of *DMPK* in all individuals with DM1.
- Brain MRI and ophthalmologic examination may help to differentiate between CFTD and other types of congenital muscular dystrophy.
- Ullrich muscular dystrophy may be differentiated from CFTD based on the unique pattern of hyperlaxity of distal joints with contractures of more proximal joints, as well as immunohistochemical studies identifying abnormal amounts and/or localization of collagen VI.
- Spinal muscular atrophy (SMA) can often be differentiated from CFTD by physical examination, abnormal brain MRI, neurogenic EMG, and neurogenic muscle pathology displaying reinnervation and fiber type grouping. Molecular genetic testing using targeted analysis for pathogenic variants and sequence analysis identifies two *SMN1* pathogenic variants in virtually all individuals with SMA.

Other conditions with fiber size disproportion. Fiber size disproportion of 12% or more may be a nonspecific finding on muscle biopsy, and secondary fiber size disproportion can be seen with various other neuromuscular and non-neuromuscular conditions. A more complete list of conditions associated with fiber size disproportion is provided by Iannaccone et al [1987], Imoto & Nonaka [2001], Clarke & North [2003], and North [2004].

Fiber size disproportion has also been seen in healthy individuals, including healthy infants younger than age two months [Vogler & Bove 1985] and normal healthy young adult males [Staron et al 2000].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital fiber-type disproportion, the following evaluations are recommended:

- Medical history and physical examination with particular attention to the following:
  - Weakness
  - Hypotonia
  - Failure to thrive
  - Scoliosis
  - Contractures

- Comprehensive respiratory evaluation in individuals with and without respiratory symptoms including the following:
  - Respiratory rate
  - Signs of respiratory distress
  - History of recurrent chest infections
  - Ability to maintain oxygen saturation
  - Pulmonary function studies
  - Sleep study to evaluate for nocturnal hypoxia and assess the need for ventilator support

    Note: Some individuals with CFTD who have nocturnal hypoxia without symptoms can develop respiratory failure without warning.
- Feeding evaluation including assessment of suck and swallow and gastroesophageal reflux
- Speech therapy assessment, particularly if dysarthria and/or hypernasal speech are present
- Cardiac evaluation for heart disease, including *cor pulmonale* and cardiomyopathy, particularly for those with pathogenic variants in*TPM2* or *MYH7* or those with an unknown genetic etiology. Evaluation should include echocardiogram and electrocardiogram.
- Physical therapy and occupational therapy assessment
- Screening for skeletal and orthopedic issues, including skeletal examination for scoliosis (after the child starts sitting), joint contractures, congenital hip dislocations, and foot deformities
- Examination by a general dentist with referral for orthodontic evaluation if dental crowding becomes apparent
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

It is recommended that care be provided by a multidisciplinary team coordinated by a clinician familiar with treatment of neuromuscular conditions [North & Goebel 2003, North 2004]. Teams often include a pulmonologist, neurologist, physical therapist and/or rehabilitation medicine specialist, orthopedist, and clinical geneticist.

Hypotonia, weakness, and joint contractures may benefit from physical therapy, occupational therapy, and/or orthopedic intervention. Interventions may include exercise and stretching programs, orthotics or splinting, serial casting, or walking supports/wheelchairs [North 2004]. Regular low-impact exercise, stretching, and submaximal strength training may be helpful. These activities should be balanced with sufficient rest time to avoid exhaustion [North 2004].

Respiratory issues may benefit from breathing exercises, chest physiotherapy for handling secretions, seating assessment, immunization against influenza and other respiratory infections, antibiotics for chest infections, tracheostomy, or ventilatory support [North 2004].

Feeding and swallowing difficulties may benefit from speech therapy, diet supplementation, and feeding by gavage or gastrostomy. Gastrostomy and fundoplication should be considered if feeding issues continue beyond a few months of age [North 2004].

Referral to an orthopedist for evaluation of scoliosis and joint contractures is recommended. If scoliosis is present, serial x-rays can be used to define and monitor the degree of curve. The need for bracing or corrective (spinal fusion) surgery is based on the progression of the curve, the effect on pulmonary function, and the likelihood that surgery could affect motor function [North 2004].

Foot deformities may benefit from physical therapy, splinting/casting, or corrective surgery by an orthopedic surgeon [North 2004].

Cardiac involvement should be monitored by a cardiologist and treated as necessary [North 2004].

Orthodontic evaluation and appropriate intervention may be necessary.

Prevention of Secondary Complications

Although malignant hyperthermia has not been described in CFTD, it has been seen in other congenital myopathies, particularly *RYR1*-associated myopathies; therefore, precautions for malignant hyperthermia prior to anesthesia should be considered (see Malignant Hyperthermia Susceptibility.)

Preoperative assessment of pulmonary and cardiac function is recommended to avoid complications.

Prevention of scoliosis, respiratory and feeding issues, and cardiac disease may be possible with comprehensive early screening and regular monitoring as described in Treatment of Manifestations.

Contractures may be avoided by consistent joint movement or therapy.

Surveillance

The following are appropriate:

- Regular monitoring for scoliosis [North 2004], particularly in childhood and adolescence
- Regular pulmonary monitoring including assessment for evidence of decreased nocturnal ventilation, such as morning headaches, daytime drowsiness, and decreased appetite or school performance; sleep studies; and lung function tests, including FEV1 and FVC
- After an initial cardiac evaluation, consideration of ongoing cardiac monitoring on a case-by-case basis. Monitoring is advisable in those who have been found to have pathogenic variants in *MYH7* and *TPM2* and/or baseline cardiac abnormalities. Other subsets of individuals with CFTD may require cardiac monitoring in the future as more data are gathered regarding the incidence of cardiac complications in these people.
- Regular assessment of motor abilities to determine need for physical therapy, occupational therapy, and physical support, such as walkers or wheelchairs

Agents/Circumstances to Avoid

Extended immobilization following surgery can exacerbate muscle weakness and thus should be avoided [North 2004].

Evaluation of Relatives at Risk

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

Pregnancy Management

Pregnancy has not been specifically studied in women or fetuses with CFTD. Women with congenital myopathies generally do not experience significant complications during pregnancy or delivery; however,

gestation may lead to an increase in symptoms in some women with CFTD and other congenital myopathies, including exacerbation of fatigue and muscle weakness [Rudnik-Schöneborn et al 1997, Sobrido et al 2005].

The pregnancy of a fetus with a congenital myopathy is at an increased risk for complications such as polyhydramnios and reduced fetal movements and the delivery is at an increased risk for breech presentation, fetal distress, failure to progress, and/or prematurity [North & Goebel 2003, North 2004].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

Congenital fiber-type disproportion (CFTD) is a genetically heterogeneous condition that can be inherited in an autosomal recessive, autosomal dominant, or X-linked manner.

To date, the majority of known cases of *ACTA1*-related CFTD have been the result of a *de novo* dominant pathogenic variant. A single CFTD-associated *ACTA1* pathogenic variant has shown dominant inheritance in a father and son. The father did not report clinical symptoms but had a histopathologic diagnosis of CFTD based on muscle biopsy [Laing et al 2009].

MYH7-associated CFTD has been reported to be inherited in an autosomal dominant manner [Sobrido et al 2005, Muelas et al 2010, Ortolano et al 2011]. However, recessive and *de novo* dominant *MYH7* pathogenic variants have been reported to be associated with other *MYH7*-diagnoses (see Genetically Related Disorders) and thus such inheritance may also occur with CFTD.

RYR1-associated CFTD has been reported to be inherited in an autosomal recessive manner.

SELENON (*SEPN1*)-related CFTD is inherited in an autosomal recessive manner.

TPM2-related CFTD can be inherited in an autosomal dominant manner or result from a *de novo* dominant pathogenic variant.

TPM3-related CFTD has been inherited in an autosomal dominant manner in at least three families and is the result of a *de novo* dominant pathogenic variant in at least eight individuals [Clarke et al 2008, Lawlor et al 2010]. *TPM3*-related CFTD has also been inherited in an autosomal recessive manner in a single family [Lawlor et al 2010].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with CFTD have an affected parent.

- A proband with CFTD may have the disorder as the result of a *de novo* pathogenic variant. The exact proportion of cases caused by *de novo* variants is unknown. However, *de novo* variants in *TPM3* and *ACTA1* appear to be a common cause of CFTD.
- Although some individuals diagnosed with CFTD have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, late onset of the disease in the affected parent, or decreased penetrance. In addition, if the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.
- For probands with no apparent family history, parental disease status may be clarified through medical evaluation; i.e., physical examination and follow-up with appropriate studies (e.g., EMG, muscle biopsy) for any positive findings. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband

- The risk to sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected and/or has a pathogenic variant in a gene associated with autosomal dominant CFTD, the risk to sibs is 50%.
- If both parents are clinically unaffected, the risk to sibs, while low, is greater than that in the general population because:
  - Although the incidence of germline mosaicism is unknown, it remains a possibility;
  - Autosomal dominant inheritance with significant variable expressivity has been suggested in multiple families [Laing et al 2009, Lawlor et al 2010].

Offspring of a proband. Each child of an individual with autosomal dominant CFTD has a 50% chance of inheriting the 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, his or her family members may be at risk.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutated allele.
- Heterozygotes (carriers) are generally asymptomatic. Because parents of children with other congenital myopathies have had subtle clinical and pathologic findings when examined closely [Wallgren-Pettersson et al 1990], the possibility of mild manifestations in individuals who are carriers for a pathogenic variant causing CFTD cannot be excluded.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are generally asymptomatic. Because parents of children with other congenital myopathies have had subtle clinical and pathologic findings when examined closely [Wallgren-Pettersson et al 1990], the possibility of mild manifestations in individuals who are carriers for a pathogenic variant causing CFTD cannot be excluded.

Offspring of a proband. The offspring of an individual with autosomal recessive CFTD are obligate heterozygotes (carriers) for a pathogenic variant.

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

Carrier (Heterozygote) Detection

Carrier testing for at-risk family members is possible if the pathogenic variants have been identified in the proband.

X-Linked Inheritance

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the pathogenic variant.
- If X-linked inheritance is established through pedigree analysis, the mother of an affected male is an obligate carrier. If X-linked inheritance cannot be established through pedigree analysis, a mother of more than one affected male may be a carrier or may have germline mosaicism. Although germline mosaicism has not been reported in X-linked CFTD, it has been reported in other X-linked congenital myopathies [Häne et al 1999].
- Female carriers of X-linked CFTD may have mild muscle weakness [Clarke et al 2005].
- When an affected male is the only affected individual in the family, several possibilities regarding his mother's carrier status need to be considered:
  - He has a *de novo* pathogenic variant and his mother is not a carrier.
  - His mother has a *de novo* pathogenic variant either (a) as a "germline variant" (i.e., present at the time of her conception and therefore in every cell of her body); or (b) as "germline mosaicism" (i.e., present in some of her germ cells only).
  - His mother has a pathogenic variant that she inherited from a maternal female ancestor.

Sibs of a proband. The risk to sibs depends on the carrier status of the mother:

- If the mother of the proband is a carrier, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Male sibs who inherit the variant will be affected; female sibs who inherit the variant will be carriers and will usually not be affected. Female carriers of X-linked CFTD may have mild muscle weakness [Clarke et al 2005].
- If the mother of the only affected male in the family is not a carrier, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Males with X-linked CFTD are not known to have reproduced [Clarke et al 2005].

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing for X-linked CFTD is not possible as the gene in which mutation is causative has not been identified.

Related Genetic Counseling Issues

Determining the mode of inheritance

- A large proportion of individuals with CFTD represent simplex cases (i.e., a single occurrence in a family), most likely attributed to autosomal recessive inheritance, X-linked recessive inheritance, or a heterozygous *de novo* dominant or *de novo* X-linked recessive pathogenic variant. In a review of inheritance patterns of 39 individuals with CFTD [Clarke & North 2003], 22 of 39 individuals (56%) represented simplex cases, 11 of 39 individuals (28%) had a family history consistent with autosomal dominant inheritance, and six of 39 individuals (15%) had a family history consistent with autosomal recessive inheritance. Since publication of that review, a large kindred with X-linked inheritance of CFTD has also been reported [Clarke et al 2005].
- It can be difficult to determine an inheritance pattern in the family of an individual representing a simplex case (i.e., a single occurrence in a family). Detailed family history, medical history, and physical examination, EMG, and muscle biopsies of parents may or may not be helpful in differentiating among the various possibilities. For example, autosomal dominant inheritance with significant variable expressivity has been suggested in at least one family, in which the mother was clinically healthy but had subtle EMG and pathology findings suggestive of myopathy. The daughter had biopsy findings consistent with CFTD and muscle weakness, hypotonia, and joint contractures [Gerdes et al 1994]. Since the father was not evaluated, it is possible that the family had autosomal recessive CFTD and the mother's subclinical findings resulted from her heterozygous status. In another family, a child with *ACTA1*-associated CFTD had an asymptomatic father who carried an *ACTA1* pathogenic variant and had histopathologic features of CFTD [Laing et al 2009].
- In some families with a simplex case, both parents have subtle myopathic findings clinically and/or on biopsy, indicating that heterozygotes of a recessive neuromuscular condition may have mild clinical or pathologic manifestations [Wallgren-Pettersson et al 1990]. Therefore, if only one parent is evaluated and found to have myopathic findings, it does not necessarily eliminate the possibility of autosomal recessive inheritance.
- If one parent is clinically healthy and has a normal muscle biopsy and the second parent has clinical signs of myopathy and/or myopathic findings on biopsy, inheritance is most likely autosomal dominant or X-linked (if no male-to-male transmission has occurred).
- If both parents are healthy without clinical or muscle biopsy findings suggestive of myopathy, inheritance may be autosomal recessive, *de novo* autosomal dominant, *de novo* X-linked recessive, or familial X-linked recessive.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

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

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.

- **Muscular Dystrophy Association - Canada**
  2345 Yonge Street
  Suite 900
  Toronto Ontario M4P 2E5
  Canada
  Phone: 866-687-2538 (toll-free); 416-488-0030
  Fax: 416-488-7523
  Email: info@muscle.ca
  www.muscle.ca
- **Muscular Dystrophy Association - USA (MDA)**
  222 South Riverside Plaza
  Suite 1500
  Chicago IL 60606
  Phone: 800-572-1717
  Email: mda@mdausa.org
  www.mda.org
- **Muscular Dystrophy UK**
  61A Great Suffolk Street
  London SE1 0BU
  United Kingdom
  Phone: 0800 652 6352 (toll-free); 020 7803 4800
  Email: info@musculardystrophyuk.org
  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. Congenital Fiber-Type Disproportion: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ACTA1	1q42.13	Actin, alpha skeletal muscle	ACTA1 homepage - Leiden Muscular Dystrophy pages	ACTA1	ACTA1
MYH7	14q11.2	Myosin-7	MYH7 homepage - Leiden Muscular Dystrophy pages	MYH7	MYH7
RYR1	19q13.2	Ryanodine receptor 1	Leiden Muscular Dystrophy pages (RYR1)	RYR1	RYR1

Table A. continued from previous page.

SELENON	1p36.11	Selenoprotein N	SEPN1 homepage - Leiden Muscular Dystrophy pages	SELENON	SELENON
TPM2	9p13.3	Tropomyosin beta chain	TPM2 homepage - Leiden Muscular Dystrophy pages	TPM2	TPM2
TPM3	1q21.3	Tropomyosin alpha-3 chain	TPM3 homepage - Leiden Muscular Dystrophy pages	TPM3	TPM3

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 Congenital Fiber-Type Disproportion (View All in OMIM)

102610	ACTIN, ALPHA, SKELETAL MUSCLE 1; ACTA1
160760	MYOSIN, HEAVY CHAIN 7, CARDIAC MUSCLE, BETA; MYH7
180901	RYANODINE RECEPTOR 1; RYR1
190990	TROPOMYOSIN 2; TPM2
191030	TROPOMYOSIN 3; TPM3
255310	MYOPATHY, CONGENITAL, WITH FIBER-TYPE DISPROPORTION; CFTD
606210	SELENOPROTEIN N; SELENON

ACTA1

Gene structure. *ACTA1* comprises seven exons and is approximately 3.8 kb in length. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Multiple benign variants (single-nucleotide polymorphisms SNPs) have been identified in *ACTA1*.

Pathogenic variants. At least seven heterozygous variants in *ACTA1* have been associated with congenital fiber-type disproportion (CFTD) [Laing et al 2004], as shown in Table 3. Numerous other *ACTA1* pathogenic variants causing nemaline or actin myopathy have also been reported [Laing et al 2009].

Table 3. *ACTA1* Pathogenic Variants Associated with Congenital Fiber-Type Disproportion Discussed in This *GeneReview*

Nucleotide Change	Predicted Protein Change	Reference Sequences
c.16G>A	p.Glu6Lys	NM_001100.3 NP_001091.1
c.143G>A	p.Gly48Asp	
c.621G>C	p.Glu207Asp	
c.668T>C	p.Leu223Pro	
c.727G>A	p.Glu243Lys	
c.881A>T	p.Asp294Val	
c.1000C>T	p.Pro334Ser	

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.

Normal gene product. *ACTA1* codes for the actin, alpha skeletal muscle protein (skeletal muscle α-actin). The resulting encoded 377-amino-acid protein plays an important role in skeletal muscle contraction through interaction with myosin. The α-actin isoform is uniquely expressed in skeletal muscle.

Abnormal gene product. The seven identified *ACTA1* base changes associated with CFTD cause single amino acid substitutions. Most of these pathogenic variants are found on the same face of the actin protein, suggesting that they impact a specific protein interaction or similar muscle function [Laing et al 2009]. One hypothesis suggests that these variants affect the ability of α-actin to interact with tropomyosin, most likely interfering with the relationship between the two proteins and affecting sarcomere function [Clarke et al 2007]. In contrast, heterozygous pathogenic variants in *ACTA1* that are associated with nemaline myopathy act through a dominant-negative effect: the mutated α-actin hinders the normal role of the wild type protein.

MYH7

Gene structure. *MYH7* comprises 39 exons (38 coding exons) [NM_000257.2] and is approximately 23 kb in length. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Multiple single-nucleotide polymorphisms (SNPs) have also been identified in *MYH7*.

Pathogenic variants. At least two heterozygous variants in *MYH7* have been associated with congenital fiber-type disproportion (CFTD) [Muelas et al 2010, Ortolano et al 2011], as shown in Table 4. The p.Lys1729del variant causes deletion of one out of three consecutive AAG triplet repeats. This pathogenic variant has also been associated with Laing distal myopathy and reported as a founder variant in the Safor region of Spain [Muelas et al 2010]. Other *MYH7* pathogenic variants have also been reported to cause Laing distal myopathy, myosin storage myopathy, and hypertrophic and dilated cardiomyopathy [Tajsharghi & Oldfors 2013].

Table 4. *MYH7* Pathogenic Variants Associated with Congenital Fiber-Type Disproportion Discussed in This *GeneReview*

Nucleotide Change	Predicted Protein Change	Reference Sequences
c.5186_5188delAGA	p.Lys1729del	NM_000257.2 NP_000248.2
c.5807A>G	p.Ter1936TrpextTer31 [1]	

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. Ter indicates nucleotide(s) are 3' of the translation stop codon; "extTer#" is used to indicate the extension of a protein sequence until a new stop codon is reached at "#" amino acids downstream as a consequence of a variant changing the natural stop codon into an amino acid.

Normal gene product. *MYH7* codes for the beta-myosin heavy chain protein. The resulting 1,935-amino-acid protein plays an important role in cardiac and skeletal muscle contraction. It is expressed in slow, type 1 fibers and the ventricles of the heart.

Abnormal gene product. Most previously identified pathogenic variants in *MYH7* have been missense changes located in the globular myosin head (possibly impacting actin binding sites) or the rod region of the protein [Tajsharghi & Oldfors 2013]. Pathogenic variants in the tail of the myosin heavy chain, such as p.Lys1729del, affect the tail's ability to form a coiled coil dimer or its interaction with other proteins [Goebel & Laing 2009]. The p.Ter1936TrpextTer31 variant is predicted to cause the stop codon to be replaced by a tryptophan resulting in the elongation of the protein tail by 31 amino acids [Ortolano et al 2011].

RYR1

Gene structure. *RYR1* comprises 106 exons, and the cDNA is approximately 15,117 kb in length. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Multiple benign variants (single-nucleotide polymorphisms) have been identified in *RYR1* [Robinson et al 2002].

Pathogenic variants. Eight compound heterozygous variants in *RYR1* have been reported to be associated with CFTD [Clarke et al 2010], as shown in Table 5. Other recessive and/or dominant *RYR1* variants causing centronuclear myopathy, multiminicore myopathy, malignant hyperthermia, central core disease, and congenital myopathy with internalized nuclei and myofibrillar disorganization have also been reported [Treves et al 2005, Robinson et al 2002, Jungbluth et al 2007, Wilmshurst et al 2010, Bevilacqua et al 2011].

Table 5. *RYR1* Pathogenic Variants Associated with Congenital Fiber-Type Disproportion Discussed in This *GeneReview*

Nucleotide Change	Predicted Protein Change	Reference Sequences
c.738T>G	p.Tyr246Ter	NM_000540.2 NP_000531.2
c.1205T>C	p.Met402Thr	
c.5333C>A	p.Ser1778Ter	
c.6104A>T	p.His2035Leu	
c.9000+1G>T	Splice site	
c.9978C>A	p.Asn3326Lys	
c.10204T>G	p.Cys3402Gly	
c.13480G>T	p.Glu4494Ter	

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.

Normal gene product. *RYR1* codes for the skeletal muscle isoform ryanodine receptor protein. The resulting 5,038-amino-acid protein plays an important role in excitation-contraction coupling and skeletal muscle calcium homeostasis. It is predominantly expressed in skeletal muscle [Treves et al 2005].

Abnormal gene product. Nonsense variants are predicted to cause lack of production of the full-length protein. The splice site variant c.9000+1G>T eliminates a donor splice site, causing exon skipping and resulting in an out-of-frame transcript that is predicted to produce a truncated nonfunctional protein. The exact impact of the missense variants is unknown.

SELENON (*SEPN1*)

Gene structure. *SELENON* comprises 13 exons and is approximately 18.5 kb in length. Selenoprotein N, like other selenoproteins, contains a selenocysteine encoded by UGA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Several SNPs have been identified in *SELENON*. Current data are available in online databases (see Table A), such as the SNP database provided by the National Center for Biotechnology Information) NCBI.

Pathogenic variants. Only one pathogenic variant in *SELENON* has been associated with CFTD in the literature [Clarke et al 2006] (see Table 6). This variant has also been identified in two families from Belgium and the United Kingdom affected with multiminicore disease and rigid spine muscular dystrophy; a founder effect has been suggested. Numerous other *SELENON* pathogenic variants causing multiminicore disease and rigid spine muscular dystrophy have also been reported [Ferreiro et al 2002].

Table 6. *SELENON* Pathogenic Variants Associated with Congenital Fiber-Type Disproportion Discussed in This *GeneReview*

Nucleotide Change	Predicted Protein Change	Reference Sequences
c.943G>A	p.Gly315Ser	NM_020451.2 NP_065184.2

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

Normal gene product. *SELENON* codes for selenoprotein N, a 590-amino-acid protein that plays an important role in skeletal muscle [Moghadaszadeh et al 2001]. Two *SELENON* isoforms have been identified, both of which are widely expressed in many different tissues. Based on the structure of selenoprotein N and the enzymatic function of several other selenoproteins, it is hypothesized that selenoprotein N may also function as an enzyme, but its role is not yet known [Moghadaszadeh et al 2001]. The fiber size variation in cases of *SELENON*-related CFTD is not as striking as the disproportion seen in most patients with CFTD associated with *TPM3*, *ACTA1*, or *RYR1* pathogenic variants, perhaps accounting for the observation that *SELENON* pathogenic variants are not a common cause of CFTD [Clarke 2011].

Abnormal gene product. The identified base change causes a substitution of an evolutionarily conserved amino acid [Ferreiro et al 2002], which does not affect the level of expression of the protein in skeletal muscle tissue [Clarke et al 2005].

TPM2

Gene structure. *TPM2* comprises 11 exons and is approximately 8-10 kb in length [Wang & Coluccio 2010]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Multiple single-nucleotide polymorphisms (SNPs) have been identified in *TPM2*. Current data are available in online databases (see Table A), such as the SNP database provided by NCBI.

Pathogenic variants. At least one heterozygous variant in *TPM2* has been associated with congenital fiber-type disproportion (CFTD) [Brandis et al 2008], as shown in Table 7. Other *TPM2* pathogenic variants causing nemaline or cap myopathy, distal arthrogryposis, and Escobar syndrome have also been reported [Tajsharghi et al 2012].

Table 7. *TPM2* Pathogenic Variants Associated with Congenital Fiber-Type Disproportion Discussed in This *GeneReview*

Nucleotide Change	Predicted Protein Change	Reference Sequences
c.349G>A	p.Glu117Lys	NM_003289.3 NP_003280.2

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.

Normal gene product. *TPM2* codes for β-tropomyosin, which is expressed in the sarcomere of striated muscle, where it associates with α-actin in the thin filament. β-tropomyosin is primarily expressed in the slow type 1 muscle fibers but also has some expression in fast muscle fibers and cardiac muscle [Tajsharghi et al 2012].

Abnormal gene product. Pathogenic variants in *TPM2* may influence the formation of the coiled-coil structure of the protein and/or its ability to interact with proteins in the thin filament [Tajsharghi et al 2012].

TPM3

Gene structure. *TPM3* comprises 13 exons and is at least 42 kb in length. The gene produces multiple transcripts, one of which is muscle specific. The muscle-specific slow muscle α-tropomyosin is coded for by ten exons, producing a transcript 1.3 kb in length [Laing et al 1995]. The NM_152263.2 variant is transcribed from the distal promoter, and is predominantly expressed in slow-twitch skeletal muscle. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Ten different variants in *TPM3* have been reported to be associated with CFTD in the literature; at least two of these ten have also been associated with nemaline myopathy [Clarke et al 2008, Lawlor

et al 2010]. Several other homozygous, heterozygous, and compound heterozygous *TPM3* variants have also been described as causative of nemaline myopathy [Pénisson-Besnier et al 2007].

Table 8. *TPM3* Pathogenic Variants Associated with Congenital Fiber-Type Disproportion Discussed in This *GeneReview*

Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.11C>T	p.Ala4Val	NM_152263.2 NP_689476.2
c.272G>C	p.Arg91Pro	
c.298C>A	p.Leu100Met	
c.502C>G	p.Arg168Gly	
c.502C>T	p.Arg168Cys	
c.503G>A	p.Arg168His	
c.505A>G	p.Lys169Glu	
c.721G>A	p.Glu241Lys	
c.733A>G	p.Arg245Gly	
c.857A>C	p.Ter286SerextTer57 [2] (Ter286Ser)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Ter indicates nucleotide(s) are 3' of the translation stop codon; "extTer#" is used to indicate the extension of a protein sequence until a new stop codon is reached at "#" amino acids downstream as a consequence of a variant changing the natural stop codon into an amino acid.

Normal gene product. The muscle-specific slow muscle α-tropomyosin contains 285 amino acids, producing a protein that is solely expressed in the slow type 1 muscle fibers. The TPM3 protein is a component of the thin filament and plays a role in muscle contraction.

Abnormal gene product. All dominant heterozygous pathogenic variants in *TPM3* reported to date are missense variants hypothesized to affect the protein's ability to interact with other proteins in the muscle thin filament, including actin and β-tropomyosin, thus affecting the muscle's ability to contract [Clarke et al 2008].

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Chapter Notes

Author Notes

Dr Beggs' website

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Revision History

- 18 April 2019 (ma) Chapter retired: histologic diagnosis without strong genetic correlation
- 11 April 2013 (me) Comprehensive update posted live
- 23 October 2008 (cd) Revision: prenatal diagnosis for *ACTA1* mutations available clinically
- 13 August 2008 (cd) Revision: sequence analysis and prenatal testing for *TPM3* mutations as a cause of CFTD available clinically
- 12 January 2007 (me) Review posted live
- 12 April 2006 (et) Original submission

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