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Hereditary Myopathy with Early Respiratory Failure

Synonyms: HMERF, MFM-Titinopathy, Myofibrillar Myopathy with Early Respiratory Failure

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Summary

Clinical characteristics

Hereditary myopathy with early respiratory failure (HMERF) is a slowly progressive myopathy that typically begins in the third to fifth decades of life. The usual presenting findings are gait disturbance relating to distal leg weakness or nocturnal respiratory symptoms due to respiratory muscle weakness. Weakness eventually generalizes and affects both proximal and distal muscles. Most affected individuals require walking aids within a few years of onset; some progress to wheelchair dependence and require nocturnal noninvasive ventilatory support about ten years after onset. The phenotype varies even among individuals within the same family: some remain ambulant until their 70s whereas others may require ventilator support in their 40s.

Diagnosis/testing

The diagnosis of HMERF is established in a proband with typical clinical findings and/or a heterozygous pathogenic variant in the region of *TTN* that encodes the 119th fibronectin-3 domain of titin on molecular genetic testing.

Management

Treatment of manifestations: Management is supportive. For distal leg weakness, use of ankle-foot orthoses can optimize independent ambulation early in the disease course; later in the disease course other mobility aids (canes, walkers, or wheelchairs) may be required. Noninvasive ventilation with bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) may be indicated for nocturnal hypoventilation initially, followed by mechanical ventilatory support as needed. Influenza vaccination, occupational therapy, and social service support are important.

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Surveillance: Reassessment of muscle strength and clinical status annually by a neurologist; pulmonary function testing every six to 12 months, or guided by individual findings.

Pregnancy management: Although the onset of symptoms usually occurs after the age of childbearing, a pregnant woman with early manifestations of HMERF or at risk for HMERF should be considered high-risk because of the associated respiratory muscle weakness and the increased physiologic demands of pregnancy. Consultation with a high-risk maternal-fetal medicine specialist is recommended when possible.

Genetic counseling

HMERF is inherited in an autosomal dominant manner with variable expressivity. Most individuals diagnosed with HMERF have an affected parent; to date, *de novo* pathogenic variants have not been reported in any individuals with genetically confirmed HMERF. Each child of an individual with HMERF has a 50% chance of inheriting the pathogenic variant. If the pathogenic variant has been identified in an affected family member, predictive testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Hereditary myopathy with early respiratory failure (HMERF) is a slowly progressive myopathy with typical onset in adulthood. The diagnosis of this rare disorder is not supported by any formal diagnostic criteria at this time.

Suggestive Findings

Diagnosis of hereditary myopathy with early respiratory failure (HMERF) **should be suspected** in individuals with the following:

- Adult-onset muscle disease with onset typically between ages 30 and 50 years (range 22-71 years)
    - The first symptoms usually relate to weakness of the distal leg muscles and may include foot drop or frequent falls.
    - Weakness may also involve the proximal muscles of the lower extremities, proximal and/or distal muscles of the upper extremities, and axial muscles.
    - Affected individuals may appear quite muscular even when weakness is present [Pfeffer et al 2014a].

      In particular, hypertrophy of the calf muscles is frequently reported [Ohlsson et al 2012]; however, atrophy of the calf muscles has also been reported [Pfeffer et al 2012] and may reflect a more advanced disease stage at the time of examination.
    - Serum creatine kinase is usually mildly elevated (range: normal to 1,000 units/L).
- Evidence of respiratory muscle weakness early in the disease course

  Note: Since affected individuals may not report symptoms, they need to be specifically asked about orthopnea, dyspnea on exertion, and excessive daytime sleepiness.
- Family history consistent with autosomal dominant inheritance

Note: Muscle MRI findings and muscle pathology studies can identify supportive evidence but may not be specific to this disorder (see Clinical Description).

Establishing the Diagnosis

The diagnosis of HMERF **is established** in a proband with typical clinical findings and/or a heterozygous* pathogenic variant in *TTN* identified by molecular genetic testing (see Table 1).

Note: All HMERF-associated *TTN* pathogenic variants are located in the 119th fibronectin-3 domain of titin, which corresponds to the following (see Molecular Genetics):

- NM_001267550.2: exon 343
- NM_001256850.1: exon 293
- NM_133378.4: exon 292

* Rare individuals have been reported to be homozygous for the *TTN* pathogenic variant p.Pro30091Leu; such individuals have been born to parents who are both heterozygous and clinically asymptomatic or subclinically symptomatic (i.e., muscle abnormality demonstrable on imaging) [Palmio et al 2014]

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

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

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of HMERF molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TTN* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis can be considered; to date, however, no large deletions or complex rearrangements involving *TTN* have been associated with HMERF.
- **A multigene panel** that includes *TTN* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of HMERF is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely

involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **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 Hereditary Myopathy with Early Respiratory Failure (HMERF)

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

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. To date, all pathogenic variants associated with HMERF are located in the *TTN* 119th fibronectin-3 domain, which is encoded by exon 343 in the Meta-transcript NM_001267550.2, exon 293 in the N2BA transcript NM_001256850.1, and exon 292 in the N2A transcript NM_133378.4 [Ohlsson et al 2012, Pfeffer et al 2012, Izumi et al 2013, Toro et al 2013, Chauveau et al 2014, Palmio et al 2014, Pfeffer et al 2014a, Pfeffer et al 2014b, Uruha et al 2015, Yue et al 2015, Palmio et al 2019].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Hereditary myopathy with early respiratory failure (HMERF) is a slowly progressive myopathy that typically begins in the third to fifth decades of life [Edström et al 1990, Pfeffer et al 2012].

Presentation

The usual presenting findings are gait disturbance relating to distal leg weakness or nocturnal respiratory symptoms due to respiratory muscle weakness. Weakness eventually generalizes and affects both proximal and distal muscles.

Muscle Findings

Muscle weakness can have variability in its distribution and severity, but in general the lower extremities are more affected than the upper extremities. Usually, the earliest and most severely affected muscle is tibialis anterior (ankle dorsiflexion). However, early and predominant hip girdle weakness is also described [Pfeffer et al 2012].

Muscle MRI can be useful earlier in the disease course and is thought to be highly specific, with distinctive early involvement of the semitendinosus muscle [Birchall et al 2005]. Later in the disease course, numerous muscles become affected and this pattern may be nonspecific [Pfeffer et al 2012].

Muscle pathology can demonstrate findings that are considered to be specific to this disorder, but because of the patchy nature of abnormalities in myofibrillar myopathies, these findings are not present in all affected individuals [Selcen 2011].

The specific findings described with this disorder include the presence of "cheetah-print" aggregates [Pfeffer et al 2014a] and "necklace" inclusions [Uruha et al 2015].

Otherwise, features of myofibrillar myopathy such as eosinophilic cytoplasmic inclusions on hematoxylin and eosin staining and cytoplasmic bodies on electron microscopy may be present, but are not specific for HMERF. Other nonspecific myopathic findings may be present.

Respiratory Findings

A distinctive feature of this condition is the early diaphragmatic weakness that often occurs while individuals are still ambulant, which is typical of only a few other rare diseases (see Differential Diagnosis) or may be atypically present in other rare myopathies [Pfeffer & Povitz 2016]. Exertional dyspnea and/or orthopnea are the typical presenting symptoms, and pulmonary function testing demonstrates restrictive impairment. Patients develop progressive reduction in vital capacity and forced expiratory volumes, and often progress to require nocturnal noninvasive ventilatory support [Pfeffer et al 2012].

Progression

Most individuals require walking aids within a few years of onset, most commonly ankle-foot orthoses. Some will progress to wheelchair dependence and require nocturnal noninvasive ventilatory support about ten years after onset.

Weakness of respiratory muscles also progresses with time. Affected individuals become increasingly vulnerable to pulmonary infections as respiratory function deteriorates.

Of note, the phenotype varies even among individuals within the same family [Pfeffer et al 2012]: some affected individuals remain ambulant until their 70s whereas others may require ventilator support in their 40s.

Life Expectancy

Presumably life expectancy is decreased in this disorder, but because of the rarity of the condition, studies have not formally addressed this question. From the experience of the authors, individuals with this condition are more susceptible to pulmonary complications (due to the respiratory muscle weakness), which may result in early morbidity and mortality [Pfeffer et al 2014b].

Genotype-Phenotype Correlations

Although clinical variability is observed with HMERF-related *TTN* variants, no relationship between the pathogenic variant and phenotype is evident.

Penetrance

Penetrance appears to depend on the pathogenic variant.

For the common p.Cys30071Arg variant, penetrance appears to be complete, although individuals with very late-onset disease have been described (as late as age 71 years); therefore, it is possible that some affected individuals may die from other causes before the disease becomes manifest.

The p.Pro30091Leu variant appears to have reduced penetrance [Pfeffer et al 2014a] in at least one family, where only one of two heterozygous family members developed the disease.

Because the other pathogenic variants have only been described in a few individuals to date [Izumi et al 2013, Toro et al 2013, Palmio et al 2014, Uruha et al 2015, Yue et al 2015, Palmio et al 2019], data are insufficient to draw conclusions regarding their penetrance; however, current observations suggest complete penetrance.

Nomenclature

Hereditary myopathy with early respiratory failure (HMERF) has previously been termed:

- Myopathy with respiratory failure and myofibrillar aggregates [Kinoshita et al 1975, Edström et al 1990];
- Hereditary cytoplasmic body myopathy with early respiratory failure [Jerusalem et al 1979];
- Hereditary inclusion body myopathy with early respiratory failure [Chinnery et al 2001].

The authors prefer the term "myofibrillar myopathy-titinopathy" [Pfeffer et al 2014a] because of the clinical, MRI, and pathologic similarities of HMERF with the myofibrillar myopathies. For pragmatic purposes this term is useful because future cases of HMERF are most likely to be identified among persons with myofibrillar myopathy.

Prevalence

The prevalence of HMERF is not known, but it is most likely under-recognized because of its broad phenotypic spectrum and relatively recent discovery of its underlying genetic etiology.

Two studies have indicated that about 5% of persons with an undiagnosed myofibrillar myopathy have a *TTN* pathogenic variant and a phenotype consistent with HMERF [Toro et al 2013, Pfeffer et al 2014a]. This suggests that HMERF is a fairly common subtype of myofibrillar myopathy, which itself is rare. Of note, the estimated prevalence of desminopathy in the northeastern United Kingdom (accounting for 3% of myofibrillar myopathy in that population [Pfeffer et al 2014a]) is 0.17:100,000 [Norwood et al 2009].

Genetically Related (Allelic) Disorders

Phenotypes other than those discussed in this *GeneReview* that are known to be associated with pathogenic variants in *TTN*:

- Udd distal myopathy – tibial muscular dystrophy
- Autosomal recessive limb-girdle muscular dystrophy LGMDR10, titin-related (OMIM 608807)
- Hypertrophic cardiomyopathy (rare)
- Dilated cardiomyopathy
- Early-onset myopathy with fatal cardiomyopathy (also known as Salih myopathy)

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Hereditary Myopathy with Early Respiratory Failure

Disorder	Gene(s)	MOI	Clinical Features of Differential Disorder	
			Overlapping w/HMERF	Distinguishing from HMERF
Amyotrophic lateral sclerosis	>30 genes [1]	AD AR XL	Presents w/respiratory failure in ~3% of cases [2]	• Presence of combined upper & lower motor neuron signs • Early atrophy of hand muscles • Characteristic neurophysiologic abnormalities

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of Differential Disorder	
			Overlapping w/HMERF	Distinguishing from HMERF
Facioscapulohumeral muscular dystrophy (FSHD)	*DNMT3B* *SMCHD1* [3]	AD	• Typically presents w/ weakness of facial & proximal arm muscles (esp shoulder & hip girdle) • Highly variable disease severity	• Absence of early respiratory failure • Presence of facial weakness
Late-onset Pompe disease (late-onset glycogen storage disease type II)	*GAA*	AR	• Proximal muscle weakness • Respiratory insufficiency • Early diaphragmatic weakness while still ambulant	• Pathologic findings • Muscle MRI abnormalities
Limb-girdle muscular dystrophy type 2 (LGMD2; OMIM PS253600)	~29 genes [4]	AR	• Weakness & wasting restricted to limb musculature (proximal > distal) • Subtypes LGMD2I (*FKRP*) & the sarcogylcanopathies (LGMD2C-LGMD2F) affect the respiratory muscles early in disease course. [5]	LGMD2I is distinguished by presence of degenerating/ regenerating muscle fibers on muscle biopsy.
Myofibrillar myopathy (MFM) (OMIM PS601419)	*BAG3* *CRYAB* *DES* *FLNC* *KY* *LDB3* *MYOT* *PYROXD1*	AD AR	• Significant overlap in clinical, MRI, & pathologic features w/HMERF; some individuals w/HMERF meet diagnostic criteria for MFM on muscle biopsy. [6] • Slowly progressive weakness that can involve both proximal & distal muscles • Distal muscle weakness present in ~80% of individuals • Respiratory muscle weakness can occur esp in *DES*-, *CRYAB*-, or *BAG3*-related MFM. [7]	Some pathology findings may be specific to HMERF (necklace inclusions, cheetah-skin aggregates).
Myotonic dystrophy type 1 (DM1)	*DMPK* [8]	AD	• Highly variable muscle disease • May present w/distal muscle weakness & respiratory muscle involvement	• Distribution of muscle weakness, usually incl face or eyelids • Variable multisystem features incl: myotonia; cataracts; cognitive deficits; cardiac arrhythmia; endocrine & GI dysfunction
Oculopharyn-godistal myopathy 1 (OMIM 164310)	*LRP12*	AD AR	Early diaphragmatic weakness while still ambulant	Ocular, facial, & pharyngeal weakness

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of Differential Disorder	
			Overlapping w/HMERF	Distinguishing from HMERF
Myasthenia gravis	NA	NA	May present w/respiratory failure & skeletal muscle weakness [9]	• Fatigability • Bulbar muscles often affected • Electrodecremental response demonstrated on nerve conduction studies • Jittery motor unit potentials on single-fiber electromyography • Most affected individuals are seropositive for AchR or MuSK antibodies.

AD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; HMERF = hereditary myopathy with early respiratory failure; MOI = mode of inheritance; NA = not applicable; XL = X-linked

1. See Amyotrophic Lateral Sclerosis: Phenotypic Series to view genes associated with this phenotype in OMIM.

2. Gautier et al [2010]

3. The diagnosis of FSHD1 is established in a proband with characteristic clinical features by identification of a heterozygous pathogenic contraction of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on a chromosome 4 permissive haplotype. The diagnosis of FSHD2 is established in a proband by identification of hypomethylation of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on a chromosome 4 permissive haplotype. Hypomethylation of the D4Z4 repeat array can be due to a heterozygous pathogenic variant in *SMCHD1* or *DNMT3B*.

4. See Muscular dystrophy, limb-girdle, autosomal recessive for a list of genes associated with this phenotype in OMIM.

5. Poppe et al [2004]

6. Pfeffer et al [2014a]

7. Selcen & Engel [2003], Walter et al [2007], Selcen et al [2009]

8. DM1 is caused by expansion of a CTG trinucleotide repeat in the noncoding region of *DMPK*.

9. Qureshi et al [2004]

Other similar clinical presentations may occur atypically with other disorders and may be considered on a case-by-case basis. The individual should be evaluated in the context of coexisting medical conditions, medication use, and/or toxic exposures. Reversible or treatable medical conditions such as endocrine disorders, autoimmune disease, or nutritional deficiencies should be considered when appropriate. An example of a toxic exposure is a single case report of colchicine use causing isolated respiratory muscle weakness that resolved on discontinuation of treatment [Tanios et al 2004].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary myopathy with early respiratory failure (HMERF), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with HMERF

System/Concern	Evaluation	Comment
Neuromuscular	Neuromuscular assessment by neurologist w/expertise in inherited muscle disorders	
	PT	Assess lower limb function & general mobility.
	OT	Assess for need for home &/or office adaptations & mobility aids.
Respiratory	Assess pulmonary function & need for nocturnal ventilator support.	
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Social services consultation	Assist w/workplace adaptations &/or access to social/ disability benefits.

OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

At present no disease-modifying therapy exists. Management is supportive. Because of the rarity of this disorder, no formal treatment guidelines have been developed, although general recommendations based on clinical experience are provided in Table 4.

Table 4. Treatment of Manifestations in Individuals with HMERF

Manifestation/Concern	Treatment	Considerations/Other
Distal leg weakness	Ankle-foot orthoses	To optimize independent ambulation
	Other mobility aids such as canes, walkers, or wheelchairs	May be required later in disease course
Inactivity	Exercises & activities suggested by PT consultation	To prevent continued loss of physical function
Nocturnal hypoventilation	Noninvasive ventilation w/BiPAP or CPAP	
Respiratory failure	Mechanical ventilatory support as needed	
↑ susceptibility to respiratory tract infections	Influenza vaccination	
Gradually progressive nature of this disease	OT & social services support	

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; OT = occupational therapy; PT = physical therapy

Surveillance

No specific guidelines are in place for surveillance of this disorder; general recommendations are provided in Table 5.

Table 5. Recommended Surveillance for Individuals with HMERF

System/Concern	Evaluation	Frequency
Neuromuscular	Reassessment of muscle strength & clinical status w/neurologist who can coordinate any additional required services	Annually
Respiratory	Pulmonary function testing	Every 6-12 mos or guided by individual findings

Evaluation of Relatives at Risk

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

Pregnancy Management

Information is insufficient to determine if particular issues in HMERF relate to pregnancy. In general, onset of symptoms occurs after the age of childbearing. However, a pregnant woman with early manifestations of HMERF or at risk for HMERF should be considered at high risk because of the associated respiratory muscle weakness and the increased physiologic demands of pregnancy. Consultation with a high-risk maternal-fetal medicine specialist is recommended when possible.

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

Hereditary myopathy with early respiratory failure (HMERF) is inherited in an autosomal dominant manner with variable expressivity.

Note: The *TTN* pathogenic variant, p.Pro30091Leu, is associated with extremely variable expressivity. Individuals heterozygous for p.Pro30091Leu may have mild clinical manifestations or only subclinical manifestations (i.e., muscle abnormality demonstrable on imaging) while individuals homozygous for the variant are reported to have more severe (and earlier onset) disease manifestations [Palmio et al 2014]. For this reason, the terms "semirecessive" and "semidominant" have been proposed to describe the mode of inheritance associated with the p.Pro30091Leu pathogenic variant [Palmio et al 2014, Tasca & Udd 2018].

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with HMERF are heterozygous for a *TTN* pathogenic variant inherited from an affected parent.
- To date, *de novo* pathogenic variants have not been reported in any individuals with genetically confirmed HMERF.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Neither germline mosaicism nor *de novo* mutation has been reported; therefore, it is unknown whether germline mosaicism or *de novo* pathogenic variants occur in this disorder.

- The family history of some individuals diagnosed with HMERF may appear to the negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, a milder phenotype, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluation and/or molecular genetic testing has been performed on the parents of 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 *TTN* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Note: The HMERF phenotype may vary among individuals within the same family.
- If the proband has a known *TTN* pathogenic variant that 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 *TTN* 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 HMERF because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.
- If both parents are heterozygous for the p.Pro30091Leu *TTN* pathogenic variant, sibs have a 50% chance of inheriting one pathogenic variant and having mild or subclinical manifestations of HMERF and a 25% chance of inheriting two pathogenic variants and having severe disease manifestations.

Offspring of a proband

- Each child of an individual with heterozygous HMERF-associated pathogenic variants has a 50% chance of inheriting the *TTN* pathogenic variant.
- All offspring of an individual with biallelic p.Pro30091Leu pathogenic variants will be heterozygous for the *TTN* pathogenic variant.

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

Related Genetic Counseling Issues

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

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

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

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

College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of HMERF it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

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

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism in unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *TTN* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association Francaise contre les Myopathies (AFM)**
  1 Rue de l'International
  BP59
  Evry cedex 91002
  France
  Phone: +33 01 69 47 28 28
  Email: dmc@afm.genethon.fr
  www.afm-telethon.fr
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **Muscular Dystrophy Canada**
  Canada

Phone: 800-567-2873
Email: info@muscle.ca
www.muscle.ca

- **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. Hereditary Myopathy with Early Respiratory Failure: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TTN	2q31.2	Titin	TTN homepage - Leiden Muscular Dystrophy pages	TTN	TTN

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 Hereditary Myopathy with Early Respiratory Failure (View All in OMIM)

188840	TITIN; TTN
603689	MYOPATHY, MYOFIBRILLAR, 9, WITH EARLY RESPIRATORY FAILURE; MFM9

Molecular Pathogenesis

Titin is the molecular scaffold protein that spans half of the sarcomere. Pathogenic variants in different domains of titin can result in different disorders affecting muscle tissue, with combinations of cardiomyopathy, proximal myopathy, distal myopathy, and respiratory failure, the presentation of which can range from congenital to very late onset.

Pathogenic variants causing HMERF are all located within the 119th fibronectin-3 domain of titin (see exon designations below). The function of this domain and disease mechanism of HMERF are unknown. Genetic constructs expressing the FN119 domain with HMERF-associated variants demonstrated reduced solubility compared to normal [Hedberg et al 2014], suggesting that myofibrillar aggregates may cause disease pathogenesis and the myopathologic resemblance to myofibrillar myopathy.

Mechanism of disease causation. The mechanism of disease causation is presumably gain of function, similar to the mechanism causing other myofibrillar myopathies; however, this has not to date been formally studied or proven for HMERF.

***TTN*-specific laboratory technical considerations.** All HMERF-associated pathogenic variants reside in a single *TTN* exon, which contains non-repetitive sequence.

The FN119 domain exon corresponds to the following:

- NM_001267550.2: exon 343
- NM_001256850.1: exon 293
- NM_133378.4: exon 292

Table 6. Notable *TTN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_001256850.1 NP_001243779.1 [2]	c.95134T>C (g.178546102A>G)	p.Cys31712Arg	The most common pathogenic variant assoc w/ HMERF; identified in majority of cases. There appears to have been an ancient founder effect linking families in England, Scandinavia, Europe, & Canada [Ohlsson et al 2012, Pfeffer et al 2012, Palmio et al 2014, Pfeffer et al 2014a, Pfeffer et al 2014b].
	c.95195C>T (g.178546041G>A)	p.Pro31732Leu	Variant known to be assoc w/either dominant or recessive inheritance, w/highly variable expressivity [Palmio et al 2014, Pfeffer et al 2014a]

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. Previously used reference sequences: AJ277892.2, Q8WZ42.4

Chapter Notes

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Revision History

- 14 April 2022 (gm) Revision: correction of nomenclature for 119th fibronectin-3 domain of titin (see Establishing the Diagnosis and Molecular Genetics) [Chauveau et al 2014]
- 19 March 2020 (ha) Comprehensive update posted live
- 27 February 2014 (me) Review posted live
- 5 December 2013 (gp) Original submission

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