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Caveolinopathies – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: Caveolin-3 Deficiency

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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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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

The caveolinopathies, a group of muscle diseases, can be classified into five phenotypes, which can be seen in different members of the same family:

- Limb-girdle muscular dystrophy 1C (LGMD1C), characterized by onset usually in the first decade, mild-to-moderate proximal muscle weakness, calf hypertrophy, positive Gower sign, and variable muscle cramps after exercise
- Isolated hyperCKemia (i.e., elevated serum concentration of creatine kinase (CK) in the absence of signs of muscle disease) (HCK)
- Rippling muscle disease (RMD), characterized by signs of increased muscle irritability, such as percussion-induced rapid contraction (PIRC), percussion-induced muscle mounding (PIMM), and/or electrically silent muscle contractions (rippling muscle)
- Distal myopathy (DM), observed in one individual only
- Hypertrophic cardiomyopathy (HCM), without skeletal muscle manifestations

Diagnosis/testing

CAV3, which encodes caveolin-3, a muscle-specific membrane protein and the principal component of caveolae membrane in muscle cells in vivo, is the only gene in which pathogenic variants are known to cause caveolinopathies. Sequence analysis identifies pathogenic variants in more than 99% of affected individuals.

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Management

Treatment of manifestations: Aggressive supportive care to preserve muscle function, maximize functional ability and treat complications, especially in those with the LGMD phenotype; weight control to avoid obesity; physical therapy and stretching exercises to promote mobility and prevent contractures; use of mechanical aids such as canes, walkers, orthotics, and wheelchairs as needed to help ambulation and mobility; social and emotional support.

Prevention of secondary complications: In individuals with isolated HCK, special precautions during surgical procedures and anesthesia because of possible risk for malignant hyperthermia (MH).

Surveillance: Periodic monitoring of spine, respiratory function, cardiac function, mobility, and muscle function based on individual needs.

Genetic counseling

Most caveolinopathies are inherited in an autosomal dominant manner; they may also be inherited in an autosomal recessive manner.

Autosomal dominant caveolinopathies: Most affected individuals have an affected parent; the proportion of cases caused by *de novo* pathogenic variants is unknown, but probably small. Each child of an individual with an autosomal dominant caveolinopathy has a 50% chance of inheriting the pathogenic variant.

Autosomal recessive caveolinopathies: The parents of an affected child are obligate heterozygotes (carriers) and therefore carry one mutated allele; heterozygotes can be asymptomatic or can display modest elevation of serum CK concentration and/or calf hypertrophy. At conception, each sib of an individual with autosomal recessive caveolinopathy 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. Carrier testing is possible if both pathogenic variants have been identified in the family.

Prenatal testing for a pregnancy at increased risk is possible if the pathogenic variant(s) have been identified in an affected family member.

GeneReview Scope

Caveolinopathies: Included Phenotypes [1]
• Limb-girdle muscular dystrophy 1C • Isolated hyperCKemia • Rippling muscle disease • Distal myopathy • Hypertrophic cardiomyopathy

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Clinical Diagnosis

Caveolinopathies have a wide spectrum of clinical presentations.

Clinical findings that may support the diagnosis of a caveolinopathy

- Onset usually in the first two decades
- Progressive, proximal, symmetric muscle weakness

- Calf hypertrophy
- Myalgia, cramps, and/or stiffness after exercise
- Muscle hyperirritability manifest as:
  - Percussion-induced rapid contraction (PIRC) in which tapping the muscle belly results in rapid contraction of the muscle;
  - Percussion-induced muscle mounding (PIMM) in which a visible localized swelling of the muscle is caused by contraction at the point of contact;
  - Muscle rippling - a silent (absence of action potentials) wave of muscle contractions that occurs on mechanical stretching of the muscle.
- Positive Gowers sign

Biochemical studies. Elevated serum creatine kinase (CK) concentration ranging from 450 to 5000 U/L (normal upper limit: 150 U/L)

Electrophysiologic studies. Electromyography (EMG) ranging from normal to a myopathic pattern. In some cases, muscle activity is electrically silent.

Muscle biopsy

- **Histology.** Typical findings in the five phenotypes caused by *CAV3* pathogenic variants may be normal or may include variability in fiber size, degenerating/regenerating muscle fibers with an increased number of central nuclei, and a mild increase in connective tissue. Phenotype-specific findings include the following:
  - **LGMD1C.** Muscle biopsy showed nonspecific myopathic changes with scattered necrotic fibers and increased connective tissue [Minetti et al 1998]. Other studies found variably sized, degenerating/regenerating muscle fibers with an increased number of central nuclei and a mild increase in connective tissue [Kunkel 1999, Herrmann et al 2000, Figarella-Branger et al 2003].
  - **Isolated hyperckemia (HCK).** Carbone et al [2000] found only mild fiber size variability in an Italian child. The expression of caveolin-3 was reduced both by immunohistochemistry and immunoblot analysis in muscle fibers.

    In a study of two members of an Italian family with HCK, muscle biopsy revealed a partial caveolin-3 deficiency [Merlini et al 2002].
  - **Rippling muscle disease (RMD).** In a study of five families with RMD, muscle biopsy showed increases in fiber size variability, centralized nuclei, and a mild type-1 fiber predominance [Betz et al 2001].
  - **Distal myopathy (DM).** Histologic analysis of the biceps brachii in an affected Japanese woman age 25 years showed mild variation in fiber size, an increased number of centralized nuclei, and a predominance of type 1 fibers. Caveolin-3 was markedly reduced using both immunohistochemistry and immunoblot analysis in muscle fibers [Tateyama et al 2002].

    Note: Individuals affected by hyperCKemia or hypertrophic cardiomyopathy often display normal muscle histology.
- **Ultrastructural analysis.** Loss of caveolae at the sarcolemma, large sub-sarcolemmal membrane vacuoles, and "honeycomb" membranous structures
- **Immunohistochemical** staining of skeletal muscle biopsy
  - Anti-caveolin-3 antibodies: reduced or nearly complete absence of caveolin-3 immuno-reactivity on the plasma membrane

- Dysferlin membrane staining: reduced or altered (Instead of a uniform immunostaining on the plasma membrane, dysferlin exhibits a "patchy-like" distribution, and accumulates in the cytoplasm.)

- **Western immunoblot analysis** of skeletal muscle biopsy. Quantitative caveolin-3 protein levels range from less than 5% to 35% of normal.

Molecular Genetic Testing

Gene. *CAV3*, which encodes caveolin-3, a muscle-specific membrane protein and the principal component of caveolae membrane in muscle cells in vivo, is the only gene in which pathogenic variants are known to cause caveolinopathies.

Table 1. Molecular Genetic Testing Used in Caveolinopathies

Gene [1]	Method	Pathogenic Variants Detected [2]	Variant Detection Frequency by Method [3]
CAV3	Sequence analysis [4]	Sequence variants	>99% [5]
	Deletion/duplication analysis [6]	Exon or whole-gene deletions [7]	Unknown

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
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. Woodman et al [2004]
6. 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.
7. Traverso et al [2008]

Testing Strategy

To confirm/establish the diagnosis in a proband whose clinical findings suggest the diagnosis of a caveolinopathy:

1. Obtain serum CK concentration.
2. Obtain muscle biopsy for histologic evaluation, ultrastructural analysis, and immunohistochemical staining.
3. In those with findings consistent with a caveolinopathy, perform molecular genetic testing of CAV.

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

Clinical Characteristics

Clinical Description

The caveolinopathies are a clinically heterogeneous group of muscle diseases that can be classified into the five following phenotypes [Cagliani et al 2003, Woodman et al 2004]:

- Limb-girdle muscular dystrophy 1C (LGMD1C)
- Isolated hyperCKemia (i.e., in the absence of any signs of muscle disease) (HCK)
- Rippling muscle disease (RMD)

- Distal myopathy (DM)
- Hypertrophic cardiomyopathy (HCM)

The five phenotypes are not family specific: families with overlapping phenotypes have been reported [Cagliani et al 2003, Woodman et al 2004].

Myalgia is a common presenting symptom [Aboumousa et al 2008].

Limb-girdle muscular dystrophy 1C (LGMD1C). In the report of Minetti et al [1998] affected individuals in two unrelated Italian families had onset of symptoms at approximately age five years including mild-to-moderate proximal muscle weakness, calf hypertrophy, positive Gower sign, and serum CK concentrations approximately four- to 25-fold higher than normal. Two individuals from the same family had muscle cramps after exercise.

Subsequent reports included:

- A German girl age four years with myalgia and muscle cramps in the lower limbs but no muscle weakness [Kunkel 1999];
- A Japanese girl age 11 years with a history of floppiness at birth, marginally delayed motor milestones, progressive proximal muscle weakness, and exercise-induced myalgia [Herrmann et al 2000];
- A woman age 71 years without any previous neuromuscular symptoms, who had mild proximal muscle weakness, scapular winging, slight calf hypertrophy, and a positive Gower sign [Figarella-Branger et al 2003].

Two additional unrelated Japanese families with LGMD1C have been reported [Sugie et al 2004].

Isolated hyperckemia (HCK) (i.e., increased serum concentration of CK in the absence of any clinical findings of muscular disease) can be familial or can occur in simplex cases (i.e., a single occurrence in a family).

In two unrelated Italian children (age 4 and 6 years), the sole finding was variable but persistent hyperCKemia (~4- to 8-fold higher than normal) [Carbone et al 2000].

In two members of an Italian family (the proband and his mother), persistent hyperCKemia was associated with serum CK concentrations that were 17-fold and fourfold higher than normal, respectively, without any signs or symptoms of myopathy [Merlini et al 2002].

In three members of a Spanish family, persistent elevated serum CK concentrations (from 3- to 10-fold higher than normal) without any muscle weakness were reported. Calf hypertrophy was present in the proband [Alias et al 2004].

Rippling muscle disease (RMD) is characterized by signs of increased muscle irritability including percussion-induced rapid contraction (PIRC), percussion-induced muscle mounding (PIMM), and/or electrically silent muscle contractions (rippling muscle).

Betz et al [2001] identified *CAV3* pathogenic variants in five previously described families with autosomal dominant RMD. In one of the families reported by Betz et al [2001], five individuals from three generations had late-childhood or early-teen onset of proximal muscle stiffness and PIMM. All had muscle hypertrophy. Seven other relatives had PIMM, but apparently no other muscle symptoms.

Vorgerd et al [2001] described a man age 24 years, initially evaluated for possible myotonia, who had had painful muscle weakness and cramping since childhood. Family history was negative.

Schara et al [2002] described seven children with RMD and a history of myalgia, muscle cramping, stiffness, and rippling associated with movement starting in early childhood.

Recently, Van den Bergh et al [2004] described a Belgian family in which the proband (age 40 years) complained of fatigue, exercise-induced muscle pain, and muscle cramps from age 35 years. PIRCs were present; muscle rippling was not.

Kubisch et al [2003] reported two unrelated individuals with severe RMD. In addition, one individual had overlapping features consistent with LGMD1C.

Eight of ten patients in the UK with a caveolinopathy had rippling muscle movements [Aboumousa et al 2008].

Distal myopathy (DM). Tateyama et al [2002] reported one Japanese woman age 25 years with muscle atrophy in her hands and feet, decreased distal muscle function, and normal proximal muscle strength, in whom a *CAV3* pathogenic variant (p.Arg26Gln) was identified. Her serum CK concentration was 25 times increased. The distal myopathy may be preceded by hyperckemia and muscle hyperexcitability (percussion-induced rapid contractions) [González-Pérez et al 2009].

Hypertrophic cardiomyopathy (HCM). Hayashi et al [2004] described two sibs with hypertrophic cardiomyopathy (HCM). Neither had skeletal muscle manifestations; serum CK concentrations were normal. The caveolin-3 pathogenic variant was not found in their mother. Therefore, it was suggested that the pathogenic variant was inherited from the father, who had also been affected by HCM but had not been tested, had died at age 41, and had no sibs to be examined.

Overlapping muscle disease phenotypes. Fischer et al [2003] described family members with different, but overlapping, muscle disease phenotypes. RMD was evident in all 14 affected individuals, 12 of whom had evidence of LGMD or DM and two of whom had only RMD.

Overlapping phenotypes were also found within two Japanese families; four of six individuals with RMD also had DM [Yabe et al 2003].

An Italian family showed the LGMD1C, RMD, and HCK phenotypes [Cagliani et al 2003].

Other possible phenotypes. *CAV3* sequence analysis of 905 persons with long QT syndrome (LQTS) identified six heterozygous pathogenic missense variants (in 17 individuals) resulting in amino acid changes in highly conserved residues [Vatta et al 2006]. Caveolin-3 associates with the sodium channel in cardiomyocytes, thus suggesting that caveolin-3 could play a role in the regulation of cardiac excitability. Although the patients did not display any sign of cardiomyopathy or muscular disorder, CK measurement and assessment of additional family members are necessary to exclude muscular involvement. Three *CAV3* pathogenic variants (p.Val14Leu, p.Thr78Met, p.Leu79Arg) have been reported in three infants who died from sudden infant death syndrome (SIDS) [Cronk et al 2007].

Genotype-Phenotype Correlations

Genotype-phenotype correlations do not exist, as studies have shown that the same pathogenic variant can lead to heterogeneous clinical phenotypes and muscle histopathologic changes [Fulizio et al 2005]. For example, the *CAV3* pathogenic variant p.Thr63Ser found in an individual with HCM is analogous to pathogenic variants p.Thr63Pro and ΔTFT (deletion of amino acid residues 63-65) identified in association with LGMD1C. Similarly, the same p.Arg26Gln *CAV3* pathogenic variant was reported in a family with phenotypic variability. Of the 11 individuals with the confirmed pathogenic variant, three exhibited both RMD and LGMD1C features, two had predominantly LGMD1C features, two had muscle stiffness only, and one was asymptomatic.

This observed intrafamilial phenotypic variability suggests that other genetic modifiers may exist.

Penetrance

CAV3 pathogenic variants are characterized by high penetrance.

Fee et al [2004] described one family including one member with a confirmed p.Arg26Gln pathogenic variant and no clinical manifestations of disease at age 86 years.

Higher penetrance of isolated hyperCKemia (both familial and simplex [i.e., a single occurrence in a family]) has been reported in men [Capasso et al 2006].

Anticipation

Anticipation is not observed.

Prevalence

Fulizio et al [2005] and Fanin et al [2009] estimated that caveolinopathies account for 1%-2% of unclassified LGMD and other phenotypes including isolated HCK, RMD, and proximal and distal myopathy.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *CAV3*.

Differential Diagnosis

Dystrophinopathies are a group of disorders caused by pathogenic variants in *DMD*, which encodes the protein dystrophin. The clinical spectrum ranges from mild to severe. Mildly affected individuals can present with subclinical skeletal muscle involvement with hyperCKemia and calf hypertrophy, with or without muscle cramps or myalgia.

The severe end of the spectrum includes progressive muscle diseases that are classified as Duchenne/Becker muscular dystrophy when skeletal muscle is primarily affected and as *DMD*-related dilated cardiomyopathy when the heart is primarily affected. DMD is rapidly progressive, with affected children being wheelchair bound by age 12 years. Cardiomyopathy occurs in all affected individuals after age 18 years. Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness; individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement in BMD, heart failure from dilated cardiomyopathy (DCM) is common. *DMD*-related dilated cardiomyopathy is characterized by left-ventricular dilation and congestive heart failure. Female carriers of a *DMD* pathogenic variant are at increased risk for dilated cardiomyopathy.

Molecular genetic testing of *DMD* can establish the diagnosis of a dystrophinopathy without muscle biopsy in the majority of cases of DMD and BMD. The dystrophinopathies are inherited in an X-linked manner.

Limb-girdle muscular dystrophy (LGMD) is a purely descriptive term, generally reserved for childhood- or adult-onset muscular dystrophies that are distinct from the much more common X-linked dystrophinopathies. Individuals with LGMD generally show weakness and wasting restricted to the limb musculature, proximal greater than distal. Most individuals with LGMD show relative sparing of the heart and bulbar muscles, although exceptions occur, depending on the genetic subtype. The limb-girdle muscular dystrophies typically show degeneration/regeneration of muscle (dystrophic biopsy), which is usually associated with elevated serum creatine kinase concentration. Biochemical testing (i.e., protein testing by immunostaining) performed on a muscle biopsy can establish the diagnosis of the LGMD subtypes sarcoglycanopathy, calpainopathy, and dysferlinopathy. In some cases, demonstration of complete or partial deficiencies for any particular protein can then be followed by mutation studies of the corresponding gene.

Although LGMD previously referred to muscular dystrophies inherited in an autosomal recessive manner, it is now recognized that limb-girdle muscular dystrophy also includes rare dominantly inherited subtypes.

Isolated or familial hyperCKemia. Raised serum creatine kinase concentration (hyperCKemia) is a hallmark of several neuromuscular diseases. However, hyperCKemia is not specific to neuromuscular diseases and can be found in other diseases or conditions. Among the causes of isolated hyperCKemia that need to be considered are: metabolic and inflammatory disorders, hypothyroidism, malignant hyperthermia (see Malignant Hyperthermia Susceptibility), alcoholism, and drug use, as well as following intramuscular injections.

Myotonic disorders. Muscle stiffness and clinical signs of increased muscle irritability may be present in myotonic disorders:

- Myotonic dystrophy type 1
- Myotonic dystrophy type 2
- Myotonia congenita
- Hyperkalemic periodic paralysis type 1 (HyperPP1)

However, the percussion or rapid pressing of selective muscles (biceps, forearm extensor and flexor, anterior tibial) inducing rapid contraction can be suggestive of rippling muscle disease (RMD). In addition, EMG in persons with RMD does not show the typical myotonic runs of myotonia.

Distal myopathy. Dysferlinopathy, caused by pathogenic variants in *DYSF*, includes a spectrum of muscle disease characterized mainly by two phenotypes:

- Miyoshi myopathy, characterized in young adults by distal muscle weakness and atrophy, most marked in the gastrocnemius and soleus muscles. Over a period of years, weakness and atrophy spread to the thighs and gluteal muscles. The forearms may become mildly atrophic with decrease in grip strength, but the small muscles of the hands are spared.
- Limb-girdle muscular dystrophy syndrome (LGMD2B), characterized by early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood, with slow progression

Serum CK concentration is markedly elevated and the muscle biopsy demonstrates signs of a dystrophy with deficiency of dysferlin. Inheritance is autosomal recessive.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with caveolinopathies, initial evaluation includes the following:

- Orthopedic examination to assess the presence of scoliosis
- Analysis of respiratory function: spirometry (patients age >5 years), measurement of arterial pO_2 and pCO_2, measurement of transcutaneous O_2 saturation
- Cardiac examination: 24-hour electrocardiogram and echocardiogram
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No specific treatment is currently available for caveolinopathies.

Aggressive supportive care is essential to preserve muscle function, to maximize functional ability, and to treat complications, especially in cases with LGMD features. Management should include the following:

- Weight control to avoid obesity
- Physical therapy and stretching exercises to promote mobility and prevent contractures

- Use of mechanical aids such as canes, walkers, orthotics, and wheelchairs as needed to help ambulation and mobility
- Social and emotional support and stimulation to maximize a sense of social involvement and productivity and to reduce the sense of social isolation common in these disorders [Eggers & Zatz 1998]

Prevention of Secondary Complications

In individuals with isolated hyperCKemia, special precautions during surgical procedures and anesthesia should be considered, despite the fact that malignant hyperthermia (MH) has not been reported in association with *CAV3* pathogenic variants. (See Malignant Hyperthermia Susceptibility.)

Surveillance

Periodic monitoring of the following is recommended:

- Spine: orthopedic consultation and, if needed, x-ray analysis
- Respiratory function: spirometry
- Cardiac function: 24-hour electrocardiography and echocardiography
- Mobility and muscle function: consultation with a physiatrist and physical therapist

The interval between visits is determined based on the symptoms and signs observed in the individual patient.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Most of the caveolinopathies are inherited in an autosomal dominant manner.

Caveolinopathies may also be inherited in an autosomal recessive manner.

- McNally et al [1998] found homozygosity for the *CAV3* pathogenic variant p.Gly55Ser in one of 82 individuals with muscular dystrophy screened for pathogenic variants in *CAV3*.
- Kubisch et al [2005] described a homozygous amino acid exchange (p.Leu86Pro) in one individual affected by RMD and displaying complete loss of caveolin-3 on muscle biopsy. Clinical and genetic analyses of additional family members were not performed.
- Müller et al [2006] reported a patient exhibiting a homozygous splice-site *CAV3* pathogenic variant resulting in aberrant splicing, in-frame deletion of 14 amino acids, and loss of caveolin-3 protein at muscle biopsy. The clinical phenotype is compatible with mild LGMD. Sequence analysis and family history

indicate an autosomal recessive inheritance. Additional family members were not available for genetic testing.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with a caveolinopathy have an affected parent.
- A proband with a caveolinopathy may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown, but probably small.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include measurement of serum CK concentration, neuromuscular evaluation, electrophysiologic studies, and molecular genetic testing if the pathogenic variant has been identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotype. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most individuals diagnosed with caveolinopathy have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, autosomal recessive inheritance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

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, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with a caveolinopathy has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. 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 are 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) can be asymptomatic or can display modest elevation of serum CK levels and/or calf hypertrophy.

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) can be asymptomatic or can display modest elevation of serum CK levels and/or calf hypertrophy.

Offspring of a proband. The offspring of an individual with an autosomal recessive caveolinopathy are obligate heterozygotes (carriers) for a pathogenic variant in *CAV3*.

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

Carrier (Heterozygote) Detection

Carrier testing for family members at risk for an autosomal recessive caveolinopathy is possible once the pathogenic variants have been identified in an affected family member.

Related Genetic Counseling Issues

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 or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

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

Prenatal Testing and Preimplantation Genetic Testing

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

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 - 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

- **My46 Trait Profile**
  Limb girdle muscular dystrophy

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. Caveolinopathies: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CAV3	3p25.3	Caveolin-3	Leiden Muscular Dystrophy pages (CAV3) CAV3 @ ZAC-GGM	CAV3	CAV3

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 Caveolinopathies (View All in OMIM)

123320	CREATINE PHOSPHOKINASE, ELEVATED SERUM
192600	CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC, 1; CMH1
601253	CAVEOLIN 3; CAV3
606072	RIPPLING MUSCLE DISEASE 2; RMD2
611818	LONG QT SYNDROME 9; LQT9
614321	MYOPATHY, DISTAL, TATEYAMA TYPE; MPDT

Molecular Pathogenesis

Caveolin-3 is essential for the biogenesis of caveolae, small invaginations of the muscle plasma membrane that play a critical role in the maintenance of muscle cell structural integrity and signaling.

The role of caveolae and caveolin-3 in muscle has become clinically relevant with the finding that pathogenic variants in *CAV3* are associated with several muscle pathologies including a rare form of LGMD1C, hereditary rippling muscle disease (RMD), distal myopathy (DM), hyperCKemia (HCK), and hypertrophic cardiomyopathy (HCM). Genotype-phenotype correlations do not exist, as studies have shown that the same pathogenic variant can lead to heterogeneous clinical phenotypes and muscle histopathologic changes [Fulizio et al 2005].

Phenotypic characterization of the first two *CAV3* pathogenic variants identified in individuals with LGMD1C (p.Pro104Leu and ΔTFT [deletion of amino acid residues 63-65]) indicated that these mutated variants form unstable high-molecular-mass aggregates that are retained in the Golgi complex and are not correctly targeted to the plasma membrane [Minetti et al 1998, Galbiati et al 1999b]. Consistent with their autosomal dominant inheritance, these pathogenic variants cause retention of wild-type caveolin-3 in the Golgi compartment, thus inducing the proteolysis of wild-type caveolin-3 by ubiquitination and proteasomal degradation [Galbiati et al 1999b, Galbiati et al 2000]. Moreover, Smythe et al [2003] determined that ΔTFT in post-mitotic skeletal myotubes severely reduces the binding of the signal molecule Src to caveolin-3, diminishes targeting of Src to lipid rafts, and causes abnormal perinuclear accumulation of Src. Along with these alterations of Src localization and targeting, Src activation is elevated in myotubes expressing the ΔTFT pathogenic variant, and an increased incidence of apoptosis in those cells compared with control myotubes is observed. These results indicate that *CAV3* pathogenic variants, by impairing the formation of caveolae at muscle sarcolemma, disrupt normal cellular signal transduction pathways, alter muscle cell structural integrity, and cause apoptosis.

A similar experimental approach was utilized to complete a functional characterization of the *CAV3* pathogenic variant p.Arg26Gln, which was identified in individuals with LGMD1C, RMD, DM, and HCK. The p.Arg26Gln amino acid change decreases the steady-state expression levels of caveolin-3, leads to intracellular retention of the protein in a perinuclear Golgi compartment, and causes caveolin-3 to be partially excluded from lipid rafts/caveolae-enriched membrane domains. However, this pathogenic variant does not behave in a dominant-negative fashion because it does not affect the subcellular localization of wild-type caveolin-3 [Sotgia et al 2003b]. These data provide a likely explanation for the observed differences in detectable levels of the caveolin-3 protein in human muscle tissue biopsies taken from patients with ΔTFT/p.Pro104Leu pathogenic variants (90%-95% reduction in caveolin-3 levels [Minetti et al 1998]) vs. the p.Arg26Gln pathogenic variant (60%-80% reduction in caveolin-3 levels [Cagliani et al 2003]). These differences in the levels and functionality of the remaining wild-type caveolin-3 protein may explain the varied clinical presentations as well.

It is important to note that individuals with LGMD1C and experimental models of p.Pro104Leu and ΔTFT *CAV3* pathogenic variants also manifest mislocalization of dysferlin, a muscle membrane protein that is decreased in Miyoshi myopathy and LGMD2B. In physiologic conditions, dysferlin interacts with caveolin-3 on the muscle sarcolemmma, whereas in the presence of caveolin-3 deficiency it accumulates in the cytoplasm or it displays an irregular "patchy" distribution on the membrane [Matsuda et al 2001, Hernández-Deviez et al 2006]. Selcen et al [2001] indicated striking disruptions of the structure of the sarcolemma in muscle biopsy from individuals with Myoshi myopathy, thus suggesting an important role for dysferlin in muscle cell structure. It is possible that changes in dysferlin cellular localization may contribute to the pathogenesis of caveolin-3 associated disorders. The functional relevance and the mechanisms of action of caveolin-3 in skeletal muscle cells has been further demonstrated by the analysis of the consequences of *CAV3* inactivation both in vitro and in vivo. Antisense inhibition of caveolin-3 expression in cultured skeletal myoblasts precludes myoblast fusion and myotube formation, normal processes of skeletal muscle development [Galbiati et al 1999a, Volonte et al 2003].

Cav3 knockout mice lack muscle cell caveolae and display a number of myopathic changes consistent with mild muscular dystrophy. Soleus muscle degenerates in the knockout animals by age eight weeks, as does the diaphragm at eight to thirty weeks, but there is otherwise no effect on growth and motor movement relative to wild-type mice. Cav3 +/- hemizygotes have no muscle myopathy, indicating an autosomal recessive transmission of the myopathic phenotype, which contrasts with the dominant-negative Cav3 pathogenic missense variants associated with LGMD1C [Hagiwara et al 2000]. Cav3 -/- mice develop cardiomyopathy characterized by cardiac hypertrophy, dilation, and reduced fractional shortening by age four months. Histologically, the cardiac muscle shows increased cellular infiltration with accompanying perivascular fibrosis [Hnasko & Lisanti 2003].

Benign variants. See Table 2 (pdf) for a list of *CAV3* variants reported to have no noticeable phenotypic effect.

Pathogenic variants. To date, 30 single-nucleotide variants and two microdeletions have been described in *CAV3*. Although the first two pathogenic variants discovered, i.e. p.Pro104Leu and ΔTFT, involve two of the 12 residues conserved among all the members of the caveolin protein family, other pathogenic variants are not in conserved residues [Gazzerro et al 2010].

See Table 3 (pdf) for a list of *CAV3* pathogenic variants and associated phenotypes.

Normal gene product. Caveolae are vesicular invaginations of the plasma membrane that regulate vesicular trafficking events and signal transduction processes. Caveolins function as scaffolding proteins to organize specific lipids (cholesterol and glycosphingolipids) and signaling molecules (Src-like kinase, Ha-Ras, nitric oxide synthase, and G proteins) within caveolae membranes.

Caveolin-3 is a muscle-specific membrane protein and the principal component of caveolae membrane in muscle cells in vivo [Tang et al 1996, Way & Parton 1996]. Caveolin-3 contains a 20-amino acid scaffolding domain that is critical for homo-oligomerization and for interaction with several caveolin-associated molecules,

and a 33-amino acid hydrophobic domain that spans the cell membrane [Williams & Lisanti 2004]. During the process of caveolae formation, caveolin-3 undergoes two stages of self-association or oligomerization in the endoplasmic reticulum. Each homo-oligomer contains approximately 14-16 caveolin monomers. At a later stage, the caveolin homo-oligomers interact with each other to form clusters that are approximately 25-50 nm in diameter.

The expression of caveolin-3 is induced during the differentiation of skeletal myoblast, and caveolin-3 displays several functions in muscle cells. On the muscle sarcolemma it forms a complex with dystrophin and its associated glycoproteins, thus contributing to the structural stability of the plasma membrane [Song et al 1996]. A direct interaction between β-dystroglycan and caveolin-3 has been demonstrated [Sotgia et al 2000]. However, under certain conditions caveolin-3 can be physically separated from the dystrophin complex [Crosbie et al 1998]. This indicates that although caveolin-3 is dystrophin associated, it is not absolutely required for the biogenesis of the dystrophin complex. Electron microscopy studies have demonstrated a transient association of caveolin-3 with transverse tubules (T tubules) during differentiation of mouse skeletal fibers. Moreover, on the plasma membrane caveolin-3 interacts with nitric oxide synthase, a molecule that is important for the regulation of muscle contractility and exercise-induced glucose uptake [García-Cardeña et al 1997, Williams & Lisanti 2004].

In addition to its structural functions, caveolin-3 is required for the insulin receptor-mediated activation of glucose uptake and it regulates the subcellular distribution of phosphofructokinase (PFK), a key enzyme of carbohydrate metabolism [Sotgia et al 2003a, Fecchi et al 2006]. These data indicate that caveolae play a critical role also in the control of energy metabolism of skeletal muscle fibers.

Abnormal gene product. Most *CAV3* pathogenic variants result in a severe reduction of the caveolin-3 protein in muscle and a loss of caveolae at the sarcolemma.

Functional studies utilizing overexpression of p.Pro104Leu, ΔTFT, and p.Arg26Gln pathogenic variants in a heterologous cell system (NIH3T3) have indicated that these mutated forms of caveolin-3 display an impaired homo-oligomerization, are retained within the Golgi complex, and do not localize at the plasma membrane. In addition, misfolded caveolin-3 oligomers are targeted to proteasomal degradation and can exert a dominant-negative effect on wild-type protein [Gazzerro et al 2010].

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