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Calpainopathy

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Summary

Clinical characteristics

Calpainopathy is characterized by symmetric and progressive weakness of proximal limb-girdle muscles. Clinical findings of calpainopathy include the tendency to walk on tiptoe, difficulty in running, scapular winging, waddling gait, laxity of the abdominal muscles, Achilles tendon shortening, and scoliosis. Affected individuals typically do not have cardiac involvement or intellectual disability.

Three autosomal recessive calpainopathy phenotypes have been identified based on the distribution of muscle weakness and age at onset:

- Pelvifemoral limb-girdle muscular dystrophy (LGMD) (Leyden-Möbius LGMD) phenotype, the most frequently observed calpainopathy phenotype, in which muscle weakness is first evident in the pelvic girdle and later in the shoulder girdle, with onset that may occur as early as before age 12 years or as late as after age 30 years
- Scapulohumeral LGMD (Erb LGMD) phenotype, usually a milder phenotype with infrequent early onset, in which muscle weakness is first evident in the shoulder girdle and later in the pelvic girdle
- HyperCKemia, usually observed in children or young individuals, in which individuals are asymptomatic and have high serum creatine kinase (CK) concentrations

The autosomal dominant form of calpainopathy is clinically variable, ranging from almost asymptomatic to wheelchair dependence after age 60 years in a few individuals; phenotype is generally milder than the recessive form.

Diagnosis/testing

The diagnosis of calpainopathy is established by identification of biallelic pathogenic variants in *CAPN3* or a dominantly acting heterozygous *CAPN3* pathogenic variant by molecular genetic testing. Muscle biopsy showing absent or severely reduced calpain-3 on immunoblot analysis can confirm the diagnosis if molecular testing is inconclusive.

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Management

Treatment of manifestations: Physical therapy and stretching exercises to promote mobility and prevent contractures; supervised strengthening and gentle low-impact aerobic exercise; nutrition management as needed to maintain appropriate weight for height; mobility aids such as canes, walkers, orthotics, and wheelchairs to help maintain independence; knee-ankle-foot orthoses while sleeping to prevent contractures; positioning and seating devices to prevent scoliosis; surgery for foot deformities, scoliosis, and Achilles tendon contractures as needed; scapular fixation as needed for scapular winging; annual influenza vaccine; prompt treatment of chest and respiratory infections; nocturnal ventilator assistance as needed; respiratory aids to treat chronic respiratory insufficiency in late stages of the disease; social, emotional, and family support for care decisions.

Surveillance: Monitor muscle strength, joint range of motion, and orthopedic complications annually; assess for nocturnal hypoventilation annually; pulmonary evaluation as needed with forced vital capacity assessed in the sitting and supine position; examination of cardiac function in those with advanced disease as needed; assess need for social work support at each visit.

Agents/circumstances to avoid: Strenuous and excessive muscle exercise; obesity and excessive weight loss; physical trauma, bone fractures, and prolonged immobility. Avoid succinylcholine and halogenated anesthetic agents when possible; avoid cholesterol-lowering agents (e.g., statins) when possible.

Evaluation of relatives at risk: It is appropriate to clarify the status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of evaluation and subsequent surveillance.

Genetic counseling

Calpainopathy is typically inherited in an autosomal recessive manner. Less commonly, calpainopathy is inherited in an autosomal dominant manner.

- *Autosomal recessive inheritance:* If both parents are known to be heterozygous for a pathogenic variant associated with autosomal recessive calpainopathy, each sib of an affected individual has at conception 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 the *CAPN3* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives is possible.
- *Autosomal dominant inheritance:* Each child of an individual with autosomal dominant calpainopathy has a 50% chance of inheriting the *CAPN3* pathogenic variant.

Once the *CAPN3* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for calpainopathy are possible.

GeneReview Scope

Disorder	Phenotype(s) [1]
Autosomal recessive calpainopathy	• Pelvifemoral limb-girdle muscular dystrophy (Leyden-Möbius LGMD) • Scapulohumeral limb-girdle muscular dystrophy (Erb LGMD) • HyperCKemia
Autosomal dominant calpainopathy	Variable (generally milder than autosomal recessive calpainopathy)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Calpainopathy is a form of limb-girdle muscular dystrophy (LGMD).

Suggestive Findings

Calpainopathy **should be suspected** in individuals with the following clinical, laboratory, imaging, and electromyogram (EMG) findings.

Clinical findings

- Proximal muscle weakness (pelvic and/or shoulder girdle) with early onset (age <12 years), adult onset, or late onset (age >30 years)
- Symmetric atrophy and wasting of proximal limb and trunk muscles; calf hypertrophy is rarely and sometimes only transiently present [Fardeau et al 1996].
- Scapular winging, scoliosis, Achilles tendon contracture, and other joint contractures (including hip, knee, elbow, finger, and spine)
- Waddling gait; tiptoe walking; difficulty in running, climbing stairs, lifting weights, and getting up from the floor or from a chair
- Sparing of facial, ocular, tongue, and neck muscles
- Absence of cardiomyopathy and intellectual disability
- Back pain and myalgia; present in 50% of individuals with autosomal dominant calpainopathy [Vissing et al 2016]

Serum creatine kinase (CK) concentration is elevated (5-80 times normal) in autosomal recessive calpainopathy from early infancy, particularly during the active stage of the disease. Serum CK concentration decreases with disease progression, as muscles become progressively atrophic [Urtasun et al 1998]. In autosomal dominant calpainopathy, some individuals presented with normal CK levels [Vissing et al 2016].

Muscle imaging findings

- CT reveals early and striking wasting of muscles predominantly from the posterior compartment of the thighs (but also hip adductors and quadriceps) [Fardeau et al 1996, Urtasun et al 1998], with sparing of the sartorius and gracilis muscles. The difference in distribution of muscle involvement between calpainopathy and other LGMDs (e.g., sarcoglycanopathies, dysferlinopathies) makes muscle imaging analysis an important element in clinical diagnosis [ten Dam et al 2012] (see Differential Diagnosis).
- MRI shows the selective muscle involvement and, in some instances, reveals edema-like changes on STIR sequences [Mercuri et al 2005, Borsato et al 2006, Stramare et al 2010, Kana et al 2014]. Muscle MRI is a useful tool in characterizing the degree of muscle atrophy and in some instances disease severity [Straub et al 2012, Díaz-Manera et al 2015].
- In the dominant form of calpainopathy, the paraspinal muscles are almost completely lost and replaced by fat [Prahm et al 2017].

Electromyogram (EMG) pattern is typically myopathic (showing small polyphasic potentials), although a normal EMG can also be observed in presymptomatic individuals. Myotonia and spontaneous discharges are not present.

Establishing the Diagnosis

The diagnosis of calpainopathy **is established** in a proband with suggestive findings and **one of the following** identified by molecular genetic testing (see Table 1):

- Biallelic pathogenic (or likely pathogenic) variants in *CAPN3*

- Heterozygous dominantly acting *CAPN3* pathogenic variant

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include use of a **multigene panel**, **comprehensive genomic testing** (exome sequencing, genome sequencing), and **single-gene testing** depending on the phenotype (see Table 1).

The clinical and laboratory findings in individuals with calpainopathy overlap with other forms of LGMD and other muscular dystrophies. Therefore, use of a multigene panel or comprehensive genomic testing is recommended [Thompson & Straub 2016]. If biallelic *CAPN3* pathogenic variants or a heterozygous dominantly acting *CAPN* pathogenic variant are not identified, other including muscle imaging and muscle biopsy with protein immunoanalysis (see Muscle Biopsy, **Calpain-3 immunoblot analysis**) testing should be considered.

Recommended Molecular Testing

A multigene panel that includes *CAPN3* 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 [Fattahi et al 2017, Magri et al 2017, Reddy et al 2017]. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Other Molecular Testing Options

Single-gene testing may be considered if a multigene panel and/or more comprehensive genomic testing is not available and calpainopathy appears to be a likely diagnosis based on clinical findings. Sequence analysis of *CAPN3* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

Note: Targeted analysis for pathogenic variants can be performed first in individuals of Amish ancestry or individuals from communities with an identified founder variant (e.g., Tlaxcala, Mexico; Mòcheni community, Italy; La Réunion Island; Chioggia, Italy; Guipúzcoa Province, Spain) (see Table 6).

Table 1. Molecular Genetic Testing Used in Calpainopathy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CAPN3	Sequence analysis [3]	80%-85% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	<5% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. In individuals showing absent or severely reduced calpain-3 protein on immunoblot testing, the probability of identifying *CAPN3* pathogenic variant(s) is about 84% [Fanin et al 2004].
5. In approximately 20%-30% of individuals with calpainopathy, only one *CAPN3* pathogenic variant was found, possibly because the second pathogenic variant is located in genomic regions outside the coding exons (e.g., introns or promoter) or is a large genomic rearrangement [Fanin & Angelini 2015].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Large genomic rearrangements involving *CAPN3* have been recognized as causative of calpainopathy [Richard et al 1999], including out-of-frame deletion of exons 2-8 [Joncourt et al 2003, Krahn et al 2007, Todorova et al 2007, Ginjaar et al 2008, Nascimbeni et al 2010], of exons 2-6 [Ginjaar et al 2008], or of the entire gene [Jaka et al 2014].

Muscle Biopsy

Muscle biopsy for histopathology and calpain-3 immunoblot analysis should be considered when results of molecular genetic testing are inconclusive.

Histopathology. A variety of qualitative and quantitative morphologic changes may be observed, irrespective of the age of the individual at the time of biopsy. Wide variability can be observed even among individuals who are homozygous for the same missense variant [Chae et al 2001, Fanin et al 2003].

- Most individuals have the typical features of an active dystrophic process: increased fiber size variability, increased fibrosis, regenerating fibers, degenerating and necrotic fibers. Others have mild and nonspecific myopathic features: increased central nuclei, fiber splitting, lobulated fibers (misaligned myofibrils that form a lobulated pattern), and type 1 fiber predominance [Vainzof et al 2003, Hermanová et al 2006, Keira et al 2007, Luo et al 2011].
- The extent of muscle regeneration is less than is typically observed in other LGMDs [Fanin et al 2007a, Sáenz et al 2008, Hauerslev et al 2012, Rosales et al 2013].
- Eosinophilic myositis can be an early and transient feature of calpainopathy and has been reported in individuals with increased CK levels; it is not typically present in muscle from older affected individuals with calpainopathy [Brown & Amato 2006, Krahn et al 2006b, Oflazer et al 2009, Krahn et al 2011].
- There is considerable muscle fiber atrophy, which correlates with the clinical-functional severity of the disease [Fanin et al 2013] and is significantly higher in affected males than affected females [Fanin et al 2014].
- Muscle biopsies from individuals with autosomal dominant calpainopathy show mild myopathic changes (increased internal nuclei, fiber size variability, occasional necrotic fibers, ring fibers, and fibrosis) that appear less severe than muscle biopsy findings in those with autosomal recessive calpainopathy [Vissing et al 2016].

Calpain-3 immunoblot analysis of muscle tissue. Absent or severely reduced calpain-3 protein on immunoblot testing is highly specific for calpainopathy [Luo et al 2012]. Approximately 80% of individuals with *CAPN3* pathogenic variants show complete loss or severe reduction of calpain-3 protein; approximately 20% have a

normal amount of protein on immunoblot analysis due to *CAPN3* pathogenic variants associated with loss of protein function [Perez et al 2010].

Note: The results of calpain-3 immunoblot analysis need to be interpreted with caution, as the analysis is neither completely specific (i.e., it can yield false positive results) nor completely sensitive (i.e., it can yield false negative results). Furthermore, the results must be considered in the context of other muscle proteins [Anderson & Davison 1999] and optimal tissue preservation.

Issues with lack of specificity include the following:

- Calpain-3 protein levels can be partially reduced in other muscular dystrophies, such as dysferlinopathy and Udd muscular dystrophy (titinopathy) [Anderson et al 2000, Fanin et al 2001, Haravuori et al 2001, Hackman et al 2002].
- Although calpain-3 protein is extremely stable in muscle over time, protein quantity can be reduced by artificial degradation that occurs when muscle tissue is handled or stored under conditions that promote rapid calpain-3 autolysis (e.g., partial thawing and exposure to moisture) [Anderson et al 1998, Fanin et al 2003].

Issues with lack of sensitivity include the following:

- Approximately 20% of individuals with calpainopathy have normal quantitative protein expression [Groen et al 2007, Milic et al 2007, Fanin et al 2009b] but a loss of protein function.
- When calpain immunoblotting testing shows complete or severe calpain-3 deficiency, the probability that an individual has calpainopathy is very high (84%); the probability decreases as the amount of protein detected increases [Fanin et al 2004, Fanin et al 2009b].

Clinical Characteristics

Clinical Description

Calpainopathy is characterized by symmetric and progressive weakness of proximal limb-girdle muscles, symmetric muscle atrophy of the proximal limb and trunk muscles, scapular winging, scoliosis, and joint contractures. The age at onset of muscle weakness ranges from two to 40 years. Early motor milestones are usually normal. Significant intra- and interfamilial clinical variability is seen [Richard et al 1999, Fanin & Angelini 2015].

Three phenotypes of autosomal recessive calpainopathy have been identified based on the distribution of muscle weakness and age at onset:

- **Pelvifemoral limb-girdle muscular dystrophy (LGMD) (Leyden-Möbius LGMD) phenotype,** the most frequently observed calpainopathy phenotype. Muscle weakness is first evident in the pelvic girdle and later in the shoulder girdle. Onset can be early (age <12 years), adult (age 12-30 years), or late (age >30 years). Individuals with early onset and rapid disease course usually have pelvifemoral LGMD.
- **Scapulohumeral LGMD (Erb LGMD) phenotype.** Muscle weakness is first evident in the shoulder girdle and later in the pelvic girdle. Early onset is infrequent; the disease course is variable, but usually milder than that in the pelvifemoral phenotype.
- **HyperCKemia.** HyperCKemia may be considered a presymptomatic stage of calpainopathy, as it is usually observed in children or in young persons with recessive calpainopathy [Fanin et al 2009a, Kyriakides et al 2010]. Asymptomatic individuals may develop symptoms of muscle weakness later.

The first clinical findings of calpainopathy are usually:

- Tendency to walk on tiptoe;
- Difficulty in running;

- Scapular winging.

Early stage of the disorder. The following are frequently observed:

- Waddling gait and slight hyperlordosis
- Symmetric weakness [Matsubara et al 2007] of proximal more than distal limb muscles, trunk, and periscapular muscles. In particular, the gluteus maximus, thigh adductors, and posterior compartment of the limbs may be severely affected [Fardeau et al 1996, van der Kooi et al 1996, Dinçer et al 1997, Topaloğlu et al 1997, Urtasun et al 1998]; facial and neck muscles are usually spared.
- Scapular winging
- Marked laxity of the abdominal muscles [Bushby 1999, Pollitt et al 2001]
- Early Achilles tendon shortening and scoliosis

Variable findings include the following:

- Muscle pain, exercise intolerance, and elevated lactate levels in some individuals similar to that seen in a pseudometabolic myopathy [Pénisson-Besnier et al 1998, Pollitt et al 2001]
- Eosinophilic myositis with increased serum CK, an early and transient feature that is not present in older individuals [Brown & Amato 2006, Krahn et al 2006b, Krahn et al 2011]
- Significant atrophy of the calf muscle or more rarely calf hypertrophy
- Rhabdomyolysis (and/or myoglobinuria) triggered by physical exercise; occasionally observed in asymptomatic individuals or in individuals with mild muscle involvement [Lahoria & Milone 2016]

Advanced stage of the disorder. Commonly observed findings:

- The inability to climb stairs, rise up from a chair, lift weights, or get up from the floor
- Joint contractures (in the hips, knees, elbows, and fingers)

Occasionally observed findings:

- Rigid spine [Pollitt et al 2001]
- Foot drop [Burke et al 2010]
- Respiratory insufficiency with reduced lung vital capacity to 30%-50% due to deficiency in diaphragmatic function, weakness in thoracic and abdominal muscles, and scoliosis [Fardeau et al 1996, Urtasun et al 1998]. Compromised respiratory function was observed in 11% of individuals, showing forced vital capacity lower than 50% [Richard et al 2016]. Some of those with severe respiratory insufficiency required the use of respiratory aids [Mori-Yoshimura et al 2017].

Uncommon findings include cardiomyopathy. In most individuals, cardiac symptoms that precede cardiac morbidity are not present (e.g., chest pain, lower limb edema, palpitations), and cardiac abnormalities may only be identified by echocardiography or electrocardiography. A systematic cardiac evaluation in affected individuals using cardiovascular MR showed no cardiac involvement, even in individuals of advanced age with severe disease [Quick et al 2015]. A few individuals have presented with non-life-threatening cardiac abnormalities [Richard et al 2016], atrial fibrillation, or variably impaired left ventricular function [Mori-Yoshimura et al 2017].

Note: Intellectual disability is not associated with this disorder. Macroglossia, described in affected individuals from a genetic isolate in the Alps [Fanin et al 2012], also does not to be associated with calpainopathy.

Progression and variability. The asymptomatic stage may be relatively long in some affected individuals, especially in females. In some individuals with calpainopathy, the onset of symptoms or the worsening of symptoms may be influenced by environmental factors, such as infectious disease, strenuous physical exercise, drug treatment, a traumatic event, or pregnancy [Sáenz et al 2005].

The disease is invariably progressive, and loss of ambulation occurs approximately ten to 30 years after the onset of symptoms (range: ages 10-48 years) [Richard et al 1999, Zatz et al 2003, Sáenz et al 2005, Angelini et al 2010, Gallardo et al 2011, Richard et al 2016]. In general, loss of independent ambulation occurs earlier in individuals with childhood onset [Gallardo et al 2011].

A more rapid progression was observed in males than in females [Richard et al 2016]. In a natural history study, a higher proportion of females remained ambulatory as compared to males (72% vs 48%) [Richard et al 2016]. Males are more susceptible to muscle fiber atrophy and have increased muscle weakness and clinical disability [Fanin et al 2014].

Intrafamilial variability in the clinical phenotype has been reported: in sibs with the same pathogenic variants the age at onset and the clinical course can vary considerably [Schessl et al 2008].

Autosomal dominant calpainopathy has a variable clinical phenotype, ranging from almost asymptomatic to wheelchair dependent after age 60 years in a small number of individuals [Vissing et al 2016]. A prominent feature of such individuals is back pain and myalgia (present in more than 50% of heterozygotes for *CAPN3* pathogenic variant c.643_663del21). The average age of onset of muscle weakness is 34 years, 16 years later than individuals with autosomal recessive calpainopathy. The clinical phenotype of autosomal dominant calpainopathy is generally milder than autosomal recessive calpainopathy.

Genotype-Phenotype Correlations

There are no consistent genotype-phenotype correlations in calpainopathy, although null homozygous variants are generally associated with a severe phenotype and absent calpain-3 protein in muscle [Richard et al 1999].

Individuals who are compound heterozygous for *CAPN3* variant c.1746-20C>G and another variant consistently present with a phenotype of mild-to-moderate severity. This variant is most frequently identified in individuals from northern and western regions of Russia and may originate from this region [Mroczek et al 2022].

CAPN3 variants in proximity to the calmodulin-binding site, which are predicted to interfere with proteolytic activation, are associated with autosomal dominant calpainopathy [González-Mera et al 2021].

Penetrance

Nearly full penetrance is observed by adulthood. Serum CK concentration is usually increased until the advanced stage of the disease.

Nomenclature

Calpainopathy was originally called LGMD2A because it was the first form of autosomal recessive LGMD to be mapped [Beckmann et al 1991]. The designation LGMDR1 has been proposed in revised nomenclature (LGMDR refers to genetic types of LGMD showing autosomal recessive inheritance).

Vissing et al [2016] proposed that autosomal dominant calpainopathy associated with *CAPN3* pathogenic variant c.643_663del21 be designated LGMD1I in the current nomenclature (LGMD1 refers to genetic types of LGMD showing dominant inheritance), and designated LGMDD4 in revised nomenclature [Straub et al 2018] (LGMDD refers to genetic types of LGMD showing autosomal dominant inheritance).

As both recessive and dominant forms are associated with *CAPN3* pathogenic variants, calpainopathy is the preferred term for this disorder.

Prevalence

Calpainopathy is the most common form of LGMD [Bushby & Beckmann 2003, Guglieri et al 2008], accounting for 30% of LGMD worldwide (range: 4%-80% depending on the geographic region) [Chou et al 1999, Zatz et al 2000].

A study in northeastern Italy estimated that calpainopathy has a prevalence of approximately 1:100,000 inhabitants (corresponding to a carrier frequency of ~1:160) [Fanin et al 2005]. Another study in southern Italy estimated the prevalence of calpainopathy at 1:42,700 inhabitants (corresponding to a carrier frequency of ~1:103) [Piluso et al 2005]. Three general population screening studies of the most common *CAPN3* pathogenic variant (c.550delA) in Lithuania, Croatia, and Poland identified carrier frequencies of 1:175, 1:133, and 1:124, respectively [Canki-Klain et al 2004, Dorobek et al 2015, Inashkina et al 2016].

Higher prevalence rates have been calculated in genetically isolated communities; the prevalence of the disease has been estimated at 48:1,000,000 in La Réunion Island [Fardeau et al 1996], 69:1,000,000 in Basque country [Urtasun et al 1998], 1,900:1,000,000 in the Mòcheni community in the Alps [Fanin et al 2012], 4,300:1,000,000 in the Tlaxcala village in central Mexico (with a carrier frequency of 1:11) (see Table 6) [Pantoja-Melendez et al 2017], and 13,000:1,000,000 among the Amish population of Indiana [Young et al 1992, Richard et al 1995].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are associated with germline pathogenic variants in *CAPN3*.

Differential Diagnosis

Table 2. Genes of Interest in the Differential Diagnosis of Calpainopathy

	Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
Muscular dystrophies	*ANO5* *COL6A1* *COL6A2* *COL6A3* *CRPPA (ISPD)* *DAG1* *DYSF* *FKRP* *FKTN* *GMPPB* *LAMA2* *PLEC* *POGLUT1* *POMGNT1* *POMGNT2* *POMT1* *POMT2* *SGCA* *SGCB* *SGCD* *SGCG* *TCAP* *TRAPPC11* *TRIM32* *TTN*	Other forms of LGMDR [1]	AR	Other forms of LGMD2 cannot be distinguished from calpainopathy on clinical grounds, although calpainopathy generally has a later onset & is relatively mild, particularly by comparison w/sarcoglycanopathies. [2] Multigene panels or comprehensive genomic testing are increasingly used to diagnose a specific form of LGMD. If LGMD-related pathogenic variant(s) are not identified, other testing can be considered incl muscle imaging & muscle biopsy w/protein immunoanalysis.

Table 2. continued from previous page.

	Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
	DNAJB6 *HNRNPDL* *TNPO3*	Other forms of LGMDD [1]	AD	Other forms of LGMDD have a later disease onset (in adolescence or adulthood), ambulation is relatively well preserved, & there is less respiratory involvement.
	See footnote 3.	Facioscapulohumeral muscular dystrophy (FSHD)	AD Digenic [4]	FSHD shares some features w/Erb LGMD [5] in which muscle weakness w/onset in shoulder girdle, scapular winging, ↑ serum CK concentration, & nonspecific myopathic changes on muscle biopsy can be seen. However, facial muscle weakness & asymmetric scapular muscle involvement, which can be observed in FSHD, are uncommon in calpainopathy. In a few persons, both a contracted D4Z4 fragment (*DUX4*) & a heterozygous *CAPN3* pathogenic variant have been identified in assoc w/LGMD & FSHD-like phenotype. [6]
	DMD	Dystrophinopathies incl Becker muscular dystrophy (BMD)	XL	The dystrophinopathies incl a spectrum of muscle disease ranging from mild to severe that can overlap clinically w/LGMD. BMD muscle disease, at mild end of dystrophinopathy spectrum, should be considered in males w/ features that are in common w/calpainopathy: onset of weakness in lower girdle muscles in adolescence or adulthood & ↑ serum CK concentrations. Presence of heart involvement (mainly dilated cardiomyopathy) distinguishes BMD from calpainopathy.
Metabolic myopathies	*AGL*	Glycogen storage disease type III (GSD III)	AR	In metabolic myopathies muscle weakness can be either distal (e.g., GSD III) or proximal (e.g., GSD II) & may be transitory (e.g., CPT II deficiency) or permanent (e.g., GSD II, GSD V). Metabolic myopathies also differ from calpainopathy in terms of vacuolar muscle biopsy histopathologic features (e.g., glycogen storage).
	CPT2	Carnitine palmitoyltransferase II (CPT II) deficiency	AR	
	GAA	Pompe disease (Glycogen storage disease type II [GSD II])	AR	
	PYGM	Glycogen storage disease type V (GSD V)	AR	

Table 2. continued from previous page.

	Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
Myopathy w/ contractures	*EMD* *FHL1* *LMNA*	Emery-Dreifuss muscular dystrophy (EDMD)	XL AD AR [7]	The phenotype of calpainopathy may incl muscle weakness w/severe tendon contractures, [8] raising the possibility of EDMD.

AD = autosomal dominant; AR = autosomal recessive; LGMD = limb-girdle muscular dystrophy; LGMDD = autosomal dominant LGMD; LGMDR = autosomal recessive LGMD (LGMD2 in older nomenclature); MOI = mode of inheritance; XL = X-linked

1. Based on Table 1 in Straub et al [2018]

2. Nigro & Savarese [2014]

3. FSHD1 is associated with a heterozygous pathogenic contraction of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on a chromosome 4 permissive haplotype. FSHD2 is associated with 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 the result of a heterozygous pathogenic variant in *SMCHD1* or *DNMT3B*.

4. FSHD1 is inherited in an autosomal dominant manner. FSHD2 is inherited in a digenic manner.

5. Leidenroth et al [2012], Sacconi et al [2012]

6. Pastorello et al [2012], Simeoni et al [2015]

7. *EMD*- and *FHL1*-related EDMD are inherited in an X-linked manner. *LMNA*-related EDMD is inherited in an autosomal dominant or, rarely, autosomal recessive manner.

8. Pollitt et al [2001], Gallardo et al [2011], Richard et al 2016]

Note: (1) Calpainopathy has been reported in individuals with asthenia, myalgias, exercise intolerance, lower-limb proximal muscle weakness, and excessive lactate production after aerobic exercise [Pollitt et al 2001]. (2) The association between rhabdomyolysis and LGMD is less recognized than the association between rhabdomyolysis and metabolic myopathies (e.g., CPT II deficiency); this often leads to misdiagnosis or delayed diagnosis. Some individuals with calpainopathy present with rhabdomyolytic episodes, mild muscle weakness, and persistent CK elevation even long after a myoglobinuric episode (whereas in metabolic myopathies, CK levels between myoglobinuric episodes are usually normal) [Lahoria & Milone 2016].

Management

Appropriate management, tailored to each individual, can improve quality of life and prolong survival. The general approach is based on the typical progression and complications of individuals with limb-girdle muscular dystrophy (LGMD) as described by McDonald et al [1995], Bushby [1999], and Norwood et al [2007], and revised by the Committee of the American Academy of Neurology [Narayanaswami et al 2014].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with calpainopathy, 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 Calpainopathy

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic eval incl: • Grading of muscle strength in single upper, lower, proximal, & distal muscles • Analysis of several functional performances (e.g., 6MWT, GSGC)	
	Orthopedics / physical medicine & rehab / PT eval	To incl assessment of: • Gross motor skills • Gait, mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills)
Pulmonary	Pulmonary function testing (incl forced vital capacity measurement)	
Cardiac	• Cardiac eval • Echocardiogram	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of calpainopathy to facilitate medical & personal decision making

6MWT = 6-minute walk test; ADL = activities of daily living; GSGC = gait, stairs, gower, chair; MOI = mode of inheritance; PT = physical therapy

1. Medical geneticist, certified

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Calpainopathy

Manifestation/Concern	Treatment	Considerations/Other
Neurologic	• Passive PT program & stretching exercises instituted early following diagnosis to promote mobility, prolong walking, & slow disease progression by maintaining joint flexibility [1] • Affected persons usually benefit from strengthening & gentle, [2] low-impact aerobic exercise (swimming, stationary bicycling) w/supervised submaximal effort to ↑ cardiovascular performance, ↑ muscle efficiency, & ↓ muscle fatigue. • Additional treatment per PT & OT [3] • Maintain appropriate weight for height w/nutrition mgmt as needed.	
Orthopedic	• Mobility aids for loss of certain motor abilities; canes, walkers, orthotics, & wheelchairs enable affected persons to regain independence. • Knee-ankle-foot orthoses while sleeping to prevent contractures • Consider need for positioning & seating devices, as scoliosis occurs mainly after wheelchair dependence. [4] • Surgical intervention as needed for orthopedic complications (foot deformities, scoliosis, Achilles tendon contractures) • Scapular fixation may be required for problematic scapular winging.	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Respiratory compromise	• Annual influenza vaccination • Prompt treatment for chest & respiratory infections w/ mechanical in-exsufflator when needed [5] • Nocturnal ventilator assistance (noninvasive ventilation by nasal masks) for those w/nocturnal hypoventilation &/or respiratory failure • Respiratory aids for those w/chronic respiratory insufficiency	• Wheelchair-bound persons may develop weak cough efforts, placing them at risk of atelectasis, pneumonia, progressive mismatch, & respiratory failure. • Nocturnal ventilator assistance may be lifesaving in severely affected persons. [6] • Respiratory aids may be indicated to prolong survival. [7]
Cardiac	Treatment per cardiology recommendations as needed	
Social & family support	Social & emotional support to ↑ quality of life, maximize sense of social involvement & productivity, & ↓ social isolation [8]	
	Anticipate & facilitate decision making for affected persons & their families as disease progresses incl: • Decisions regarding loss of mobility; • Need for assistance w/ADL, medical complications, & end-of-life care. [9]	

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy
1. Oygard et al [2011]
2. Sveen et al [2013]
3. Eagle [2002]
4. Norwood et al [2007]
5. Mori-Yoshimura et al [2017]
6. Dirik et al [2001], Hashiguchi et al [2014], Mori-Yoshimura et al [2017]
7. Pollitt et al [2001], Norwood et al [2007], D'Angelo et al [2011], Richard et al [2016], Mori-Yoshimura et al [2017]
8. Eggers & Zatz [1998]
9. Narayanaswami et al [2014]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Calpainopathy

System/Concern	Evaluation	Frequency
Neurologic	Assess muscle strength & joint range of motion.	Annually
Orthopedic	Monitor for orthopedic complications (foot deformities, scoliosis, & Achilles tendon contractures).	
Pulmonary	Assess for signs/symptoms of nocturnal hypoventilation (sleep disturbances, early morning headache, daytime drowsiness).	
	• Pulmonary eval (incl pulmonary function tests) in those w/nocturnal hypoventilation [1] • Noteorced vital capacity should be measured in sitting & supine position.	As needed
Cardiac	Exam of cardiac function in advanced stage of disease (although it is not frequently compromised) [2]	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Family/Community	Assess need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

1. Narayanaswami et al [2014]
2. Dirik et al [2001], Okere et al [2013]

Agents/Circumstances to Avoid

Strenuous and excessive muscle exercise should be discouraged as it exacerbates muscle necrosis and could precipitate the onset of weakness or accelerate muscle wasting. Although individuals with minimal muscle weakness and functional limitation may be able to perform strenuous exercise, in some instances this may result in rhabdomyolysis and myoglobinuria [Lahoria & Milone 2016], which may lead to severe complications such as acute kidney failure and compartment syndrome.

Body weight should be controlled to avoid obesity as well as excessive weight loss (atrophy of muscles can be accelerated by loss of muscle proteins).

Physical trauma, bone fractures, and prolonged immobility can induce disuse atrophy and thus should be avoided.

Although no association of the disease with malignant hyperthermia is reported, the use of succinylcholine and halogenated anesthetic agents should be avoided when possible (see Malignant Hyperthermia Susceptibility).

While the specific mechanism whereby cholesterol-lowering agents (e.g., statins) may produce muscle damage causing pain or weakness is unknown, such drugs should be avoided when possible.

Evaluation of Relatives at Risk

It is appropriate to clarify the status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of evaluation and subsequent surveillance. Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Neurologic examination for muscle weakness if the pathogenic variant(s) in the family are not known.

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

Pregnancy Management

Women with calpainopathy do not have impaired uterine smooth muscle strength or function and typically have uncomplicated pregnancies. A higher incidence of abnormal fetal presentation was reported in pregnant women with LGMD who were wheelchair bound [Awater et al 2012]. Epidural blockade can be difficult in those with severe spine deformities and appropriate general anesthesia may be necessary. About half of persons with LGMD reported deterioration of clinical symptoms in pregnancy [Awater et al 2012].

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

Calpainopathy is typically caused by biallelic pathogenic variants and inherited in an autosomal recessive manner. Less commonly, calpainopathy is caused by a heterozygous, dominantly acting pathogenic variant and inherited in an autosomal dominant manner [Vissing et al 2016, González-Mera et al 2021].

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual with autosomal recessive calpainopathy are presumed to be heterozygous for a *CAPN3* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *CAPN3* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Individuals who are heterozygous for a pathogenic variant associated with autosomal recessive calpainopathy are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a pathogenic variant associated with autosomal recessive calpainopathy, each sib of an affected individual has at conception 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.
- Intrafamilial variability in the clinical phenotype has been reported: in sibs with the same pathogenic variants, the age at onset and the clinical course can vary considerably [Schessl et al 2008, Landires et al 2020].
- Individuals who are heterozygous for a pathogenic variant associated with autosomal recessive calpainopathy are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an affected individual's reproductive partner also has calpainopathy or is a carrier, offspring will be obligate heterozygotes for a pathogenic variant in *CAPN3*.

- Carrier testing for the reproductive partner of an affected individual should be considered, particularly if consanguinity is likely and/or if both partners are of the same ethnic background. Higher prevalence rates have been calculated in genetically isolated communities (see Prevalence).

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *CAPN3* pathogenic variant associated with autosomal recessive calpainopathy.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *CAPN3* pathogenic variants in the family.

Note: Carrier testing for the reproductive partner of a known carrier should be considered, particularly if consanguinity is likely and/or if both partners are of the same ethnic background. Higher prevalence rates have been calculated in genetically isolated communities (see Prevalence).

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- All individuals reported to date with autosomal dominant calpainopathy whose parents have undergone molecular genetic testing have inherited a *CAPN3* pathogenic variant from a heterozygous parent. Clinical variability has been reported within families [Vissing et al 2016] and a heterozygous parent may or may not have clinical features of calpainopathy.
- To date, *de novo* occurrence of the autosomal dominant form of calpainopathy has not been reported.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- If the proband has a known *CAPN3* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* variant in the proband or germline mosaicism in a parent (though theoretically possible, no instances of germline mosaicism have been reported).
- The family history of some individuals diagnosed with autosomal dominant calpainopathy may appear to be negative because of early death of the parent before the onset of symptoms, late onset of the disease in the affected parent (see Penetrance), or subclinical manifestations of calpainopathy in a heterozygous parent [Vissing et al 2016]. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to be heterozygous for the *CAPN3* pathogenic variant identified in the proband, the risk to sibs is 50%. Significant intrafamilial clinical variability has been observed between family members heterozygous for a pathogenic variant associated with autosomal dominant calpainopathy [Vissing et al 2016].
- If the proband has a known *CAPN3* 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 both parents are clinically unaffected but their genetic status is unknown, the sibs of a proband are still at increased risk for calpainopathy because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant calpainopathy has a 50% chance of inheriting the *CAPN3* 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/has the *CAPN3* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

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

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 is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *CAPN3* pathogenic variant(s) have been identified in an affected family member, prenatal 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 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. Calpainopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CAPN3	15q15.1	Calpain-3	CAPN3 homepage - Leiden Muscular Dystrophy pages	CAPN3	CAPN3

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 Calpainopathy (View All in OMIM)

114240	CALPAIN 3; CAPN3
253600	MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 1; LGMDR1
618129	MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL DOMINANT 4; LGMDD4

Molecular Pathogenesis

Calpain-3 is the muscle-specific member of a family of Ca^{++}-activated neutral proteases that cleave proteins into short polypeptides. Calpain-3 is expressed predominantly in skeletal muscle. Upon stimulation, calpain-3 both activates and inactivates itself rapidly through autocatalysis. In the sarcomeres, calpain-3 directly binds to titin [Keira et al 2003] and changes its localization from the M-lines to the NA2 regions as the sarcomeres extend. Calpain-3 is thought to process proteins involved in signaling pathways, transcription factors, calcium transport, and cytoskeletal proteins as part of a process called sarcomere remodeling, in which the synthesis of novel proteins is balanced by the degradation of misfolded proteins [Baghdiguian et al 1999, Baghdiguian et al 2001, Kramerova et al 2005, Duguez et al 2006, Kramerova et al 2007, Beckmann & Spencer 2008, Benayoun et al 2008, Kramerova et al 2008, Sáenz et al 2008, Fanin et al 2009c, Ono et al 2010, Ermolova et al 2011].

Most individuals with calpainopathy have complete or partial calpain-3 protein deficiency on muscle biopsy. In 10%-30% of individuals with calpainopathy, muscle biopsy shows a normal amount of protein [Talim et al 2001, de Paula et al 2002, Fanin et al 2004, Groen et al 2007, Milic et al 2007, Fanin et al 2009b] even though calpain-3 may have lost its autocatalytic activity and may be functionally inactive [Fanin et al 2003, Fanin et al 2007b].

The mobility of calpain-3 between the sarcomeric M-lines and the cytosol may have a key role in physical stress, and it is compromised in calpainopathy when its protease activity has been lost. An impairment of calpain proteolytic activity results in sarcomere remodeling by promoting ubiquitin-mediated degradation of sarcomeric proteins [Duguez et al 2006]. This degradation process may depend on ubiquitous calpains in the initial stage, and on the ubiquitin-proteasome system (UPS) in the later stages [Kramerova et al 2005, Beckmann & Spencer 2008, Rajakumar et al 2013]. Impaired sarcomere remodeling would also affect myoblast fusion and repair, as

well as the regenerative capacity of muscle in calpainopathy. The activation of the muscle atrophy process appears to depend mainly on the induction of the UPS [Fanin et al 2013].

Mechanism of disease causation

- The majority of *CAPN3* pathogenic variants are loss-of-function variants and result in recessive disease.
- The mechanism by which *CAPN3* pathogenic variant c.643_663del21 results in autosomal dominant calpainopathy has been proposed to be a dominant-negative effect [Vissing et al 2016]. Since the active calpain-3 is a homodimer, the aberrant protein could polymerize with the wild type protein and render the complex inactive.

***CAPN3*-specific laboratory technical considerations.** Alternate *CAPN3* promoters and alternative splicing result in multiple transcript variants encoding different isoforms [De Tullio et al 2003, Kawabata et al 2003]. Muscle tissue expresses only one isoform (the full-length transcript), whereas leukocytes express four different transcripts (produced by alternative splicing of exons 6, 15, and 16), all of which lack exon 15. Since peripheral blood instead of muscle tissue has increasingly been used to obtain mRNA for cDNA sequencing, the results of the two analyses could be discordant in some instances [Blázquez et al 2008].

Many deep intronic pathogenic variants that disrupt the correct splicing can be overlooked by sequencing of genomic DNA [Krahn et al 2007]; their identification may require the sequencing of cDNA obtained from muscle or blood tissues [Krahn et al 2006a, Blázquez et al 2008, Nascimbeni et al 2010]. Deep intronic variants causing a pseudoexonization of an intronic sequence have been reported [Blázquez et al 2008, Blázquez et al 2013].

A small number of *CAPN3* pathogenic variants are associated with autosomal dominant calpainopathy [Vissing et al 2016, González-Mera et al 2021]. Of note, one of these variants (c.643_663del21) has been identified in compound heterozygosity with other pathogenic *CAPN3* variants [Richard et al 1997, Groen et al 2007, Sáenz & López de Munain 2017].

Table 6. Notable *CAPN3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000070.3 NP_000061.1	c.347C>A [2]	p.Ala116Asp	Founder variant in persons from Tlaxcala village in central Mexico [Pantoja-Melendez et al 2017]
	c.550delA	p.Thr184ArgfsTer36	Most common variant accounting for up to 75% of pathogenic variants among persons from several countries (Russia, Croatia, Turkey, Czech Republic, Bulgaria, Germany, Italy, Poland); [3] may have originated in eastern Mediterranean region [Hermanová et al 2006]
	c.598_612del15	p.Phe200_Leu204del	Pathogenic variant assoc w/AD calpainopathy [González-Mera et al 2021]
	c.643_663del21	p.Ser215_Gly221del	Pathogenic variant assoc w/AD calpainopathy; common variant in persons of northern European ancestry (incl UK, Norway, Sweden, Denmark) [Vissing et al 2016]
	c.700G>A	p.Gly234Arg	Pathogenic variant associ w/AD calpainopathy [González-Mera et al 2021]
	c.1327T>C	p.Ser443Pro	
	c.1333G>A	p.Gly445Arg	
	c.1466G>A	p.Arg489Gln	Founder variant in persons from Chioggia village in Venetian lagoon of Italy [Fanin et al 2005]

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
	c.1661A>C	p.Tyr554Ser	Pathogenic variant assoc w/AD calpainopathy [González-Mera et al 2021]
	c.1706T>C	p.Phe569Ser	
	c.1795dupA	p.Thr599AsnfsTer33	Founder variant in persons of Japanese ancestry [Kawai et al 1998, Chae et al 2001]
	c.2306G>A	p.Arg769Gln	Founder variant in Amish persons from northern Indiana, US [Young et al 1992, Richard et al 1995]
	c.2338G>C	p.Asp780His	Founder variant in Agarwal community in northern India [Ankala et al 2013, Khadilkar et al 2016]
	c.2362_2363delAGinsTCATCT (2362AG>TCATCT)	p.Arg788SerfsTer14	Founder variant in persons from Guipúzcoa Province in Basque country of Spain & persons of Brazilian ancestry [Urtasun et al 1998, de Paula et al 2002]
NM_000070.3	c.946-1G>A (IVS6-1G>A)	--	Founder variant in La Réunion Islanders [Fardeau et al 1996]
	c.1193+6T>A	--	Founder variant in Mòcheni community in Fersina River Valley in Italian Alps [Fanin et al 2012]
	c.2051-1G>T	--	Founder variant in Agarwal community in northern India [Ankala et al 2013, Khadilkar et al 2016]

AD = autosomal dominant

Variants listed in the table have been provided by the author. *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. This variant was reported as c.348C>A; however, based on the sequencing trace in Pantoja-Melendez et al [2017], the correct naming of this variant is c.347C>A.

3. Dinçer et al [1997], Pogoda et al [2000], Canki-Klain et al [2004], Chrobáková et al [2004], Fanin et al [2005], Milic & Canki-Klain [2005], Balci et al [2006], Hanisch et al [2007], Todorova et al [2007], Stehlíková et al [2014], Dorobek et al [2015]

Chapter Notes

Author Notes

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Email: info@curecalpain3.org

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Marina Fanin, PhD; University of Padova (2005-2022)

Revision History

- 1 December 2022 (sw) Comprehensive update posted live
- 3 August 2017 (ha) Comprehensive update posted live
- 5 July 2012 (me) Comprehensive update posted live
- 8 July 2010 (cd) Revision: deletion/duplication analysis available clinically
- 3 December 2007 (me) Comprehensive update posted live
- 15 December 2005 (ca) Revision: prenatal diagnosis available
- 10 May 2005 (me) Review posted live
- 29 November 2004 (ca) Original submission

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