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NLM Citation: Penttilä S, Vihola A, Palmio J, et al. *ANO5* Muscle Disease. 2012 Nov 29 [Updated 2019 Aug 22]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

ANO5 Muscle Disease

Synonym: Anoctaminopathy

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Created: November 29, 2012; Updated: August 22, 2019.

Summary

Clinical characteristics

The spectrum of *ANO5* muscle disease is a continuum that ranges from asymptomatic hyperCKemia and exercise-induced myalgia to proximal and/or distal muscle weakness. The most typical presentation is limb-girdle muscular dystrophy type 2L (LGMD2L) with late-onset proximal lower-limb weakness in the fourth or fifth decade (range 15-70 years). Less common is Miyoshi-like disease (Miyoshi muscular dystrophy 3) with early-adult-onset calf distal myopathy (around age 20 years). Incidental hyperCKemia may be present even earlier. Initial symptoms are walking difficulties, reduced sports performance, and difficulties in standing on toes as well as nonspecific exercise myalgia and/or burning sensation in the calf muscles. Muscle weakness and atrophy are frequently asymmetric. Cardiac findings can include cardiomyopathy and arrhythmias and/or left ventricular dysfunction. Bulbar or respiratory symptoms have not been reported. Females have milder disease manifestations than males. Disease progression is slow in both the LGMD and distal forms; ambulation is preserved until very late in the disease course. Life span is normal.

Diagnosis/testing

The diagnosis of *ANO5* muscle disease is established in a proband with identification of biallelic pathogenic variants in *ANO5* on molecular genetic testing.

Management

Treatment of manifestations: No definitive treatments for the limb-girdle muscular dystrophies exist. Management is tailored to the individual. To assist with decreased mobility, the following are suggested: weight control to avoid obesity, physical therapy to promote mobility and prevent contractures, and use of mechanical aids to help ambulation and mobility.

Surveillance: Evaluate muscle strength and functional status every six to 12 months.

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Agents/circumstances to avoid: Heavy muscle force training of weak muscles. The use of statins, which can induce muscle pain and worsen muscle weakness should be avoided, but if absolutely necessary for the health of the individual, use requires extra monitoring of clinical status especially at the beginning of treatment.

Genetic counseling

ANO5 muscle disease is inherited in an autosomal recessive manner. 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. Carrier testing for at-risk family members, prenatal diagnosis for a pregnancy at increased risk and preimplantation testing are possible if the pathogenic variants in the family have been identified.

GeneReview Scope

ANO5 Muscle Disease: Included Phenotypes [1]
• Limb-girdle muscular dystrophy type 2L • Miyoshi muscular dystrophy 3

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

Diagnosis

Suggestive Findings

ANO5 muscle disease **should be suspected** in individuals with any of the following presentations:

- Late-adult-onset proximal lower-limb weakness (known as limb-girdle muscular dystrophy type 2L (LGMD2L)
  - Mean onset age 35 years; range 15-70 years
  - Asymmetric muscle weakness and atrophy, especially in thigh muscles
- Early-adult-onset (age 20-25 years) calf distal myopathy (known as Miyoshi muscular dystrophy 3)
- Asymptomatic hyperCKemia and exercise-induced myalgia

In all presentations:

- EMG shows myopathic changes with scattered necrotic fibers or may be normal in mildly affected individuals
- CT and MRI show fatty degeneration of the gastrocnemius medialis muscle in most affected individuals with involvement of the soleus and posterior thigh muscles with disease progression (see Figure 2).
- Serum CK concentration is markedly elevated (≥2-3x – and usually 10-50x – the upper limit of normal)
- Muscle biopsy shows scattered necrotic fibers or nonspecific myopathic or dystrophic findings

Establishing the Diagnosis

The diagnosis of *ANO5* muscle disease **is established** in a proband with biallelic pathogenic variants in *ANO5* identified on molecular genetic testing (see Table 1).

Because the phenotype of *ANO5* muscle disease is indistinguishable from many other inherited muscle disorders, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *ANO5*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

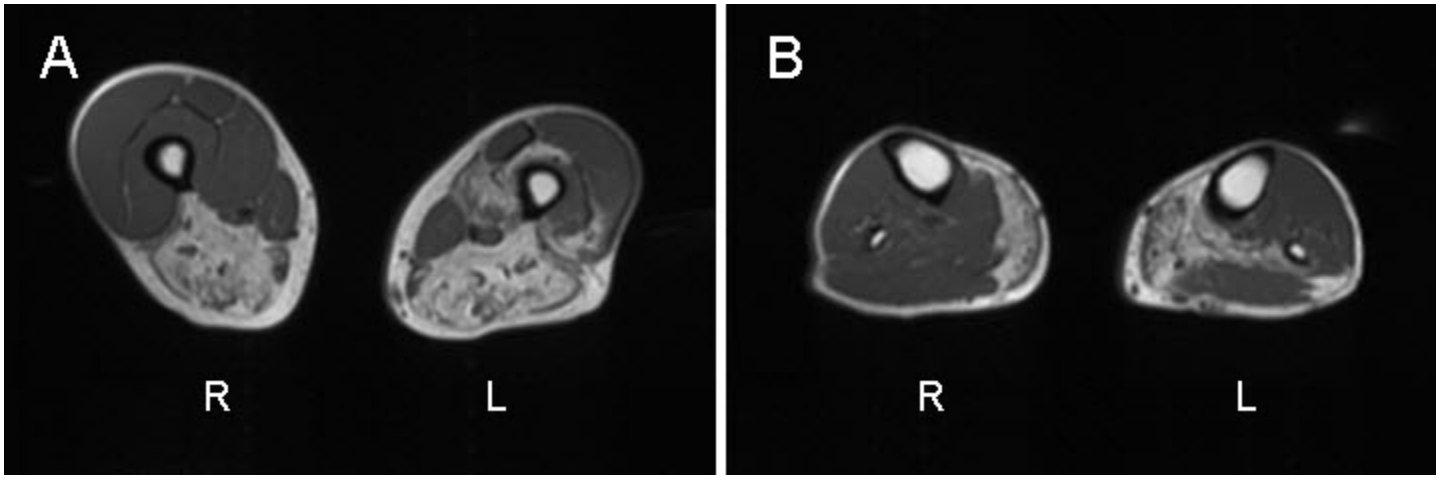

Figure 2. A. Fatty degenerative changes in posterior thigh muscles in the left vastus medialis and intermedius muscles

B. Fatty degenerative changes in the medial gastrocnemius (left greater than right) and in the left soleus muscle

- A muscle disease **multigene panel** that includes *ANO5* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1). Note: To date such variants have not been identified as a cause of *ANO5* muscle disease.

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

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of *ANO5* muscle disease.

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

Table 1. Molecular Genetic Testing Used in *ANO5* Muscle Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ANO5	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. The most common pathogenic variants in northern European populations are c.191dupA in exon 5 and c.2272C>T in exon 20.
5. Ten Dam et al [2019]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

The spectrum of *ANO5* muscle disease is a continuum ranging from asymptomatic hyperCKemia and exercise-induced myalgia to proximal and/or distal muscle weakness. The most typical presentation is late-onset proximal lower-limb weakness (also called limb-girdle muscular dystrophy type 2L or LGMD2) [Bolduc et al 2010, Hicks et al 2011, Penttilä et al 2012] (Table 2). Less common is early-adult-onset calf distal myopathy (also called Miyoshi muscular dystrophy 3) [Mahjneh et al 2010, Hicks et al 2011, Penttilä et al 2012].

Presentation. Onset of the proximal weakness in the limb-girdle muscular dystrophy (LGMD) form is in the fourth or fifth decade (age range 15-70 years); onset of calf weakness in the distal form is around age 20 years. Incidental hyperCKemia may be present even earlier. Initial symptoms are walking difficulties, reduced sports performance, and difficulties in standing on toes as well as nonspecific exercise myalgia and/or burning sensation in the calf muscles [Bolduc et al 2010, Hicks et al 2011, Penttilä et al 2012, Papadopoulos et al 2017, Ten Dam et al 2019].

- In the limb-girdle muscular dystrophy form, muscle weakness is mainly proximal and more pronounced in the lower limbs; however, many affected individuals also have proximal upper-limb involvement.
- In the distal myopathy form, calf hypertrophy and exercise myalgia can occur before apparent weakness and later calf atrophy. Clinical manifestations can be mild or subjectively nonexistent even with clear changes observed on muscle imaging. Individuals with distal onset may have proximal lower-limb weakness in the later stages of the disease. Distal upper-limb weakness has not been reported.
- Muscle weakness and atrophy are frequently asymmetric (see Figure 1).

Table 2. The LGMD2L Phenotype of the Frst 20 Reported Individuals

Clinical Characteristic	# of Individuals
Increased creatine kinase value (>10x)	20/20
Proximal lower-limb weakness	20/20
Adult onset (>20 years)	19/20
Muscle atrophy	**19/20**
• Quadriceps/hamstrings	15/20

Table 2. continued from previous page.

Clinical Characteristic	# of Individuals
• Calf	14 (8 [1]) /20
• Quadriceps/hamstrings and calf	10/20
• Upper-limb (mainly biceps)	7/20
Asymmetry of muscle weakness or atrophy	18/20
Distal lower-limb weakness	**17/20**
• Mild	13/20
• Moderate to severe	5/20
Upper-limb proximal weakness	**13/20**
• Mild	11/20
• Moderate to severe	2/20
Good sports performance in presymptomatic period	8/20
Knee hyperextension	7/20
Scapular winging	6/20
Restriction/loss of ambulation	4/20
Contractures	4/20
Myoglobinuria	3/20

From Hicks et al [2011]
1. Medial part

Cardiac findings. In 19 individuals with *ANO5* muscle disease who underwent systematic cardiac investigations, two had dilated cardiomyopathy at age ≤42 years and three had left ventricular dilatation [Wahbi et al 2013]. Rarely, other individuals have been reported with arrhythmias [Witting et al 2013, Ten Dam et al 2019], hypertrophic cardiomyopathy [van der Kooi et al 2013], or left ventricular dysfunction [Ten Dam et al 2019].

Other. Bulbar or respiratory symptoms have not been reported.

Sex differences. Females tend to have milder disease manifestations than males [Bolduc et al 2010, Hicks et al 2011, Magri et al 2012, Penttilä et al 2012, Sarkozy et al 2013, van der Kooi et al 2013]. It is possible females are underrepresented in the reports due to milder disease course, which may be only hyperCKemia with or without myalgia or mild muscle weakness.

Progression and life span. Disease progression is slow in both the LGMD and distal form; ambulation is preserved until very late in the disease course. Most affected individuals remain ambulatory without assistance for decades. Life span appears to be normal.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *ANO5* have been identified [Penttilä et al 2012].

Nomenclature

Miyoshi muscular dystrophy 3 may also be referred to as non-dysferlin Miyoshi muscular dystrophy or MMD3.

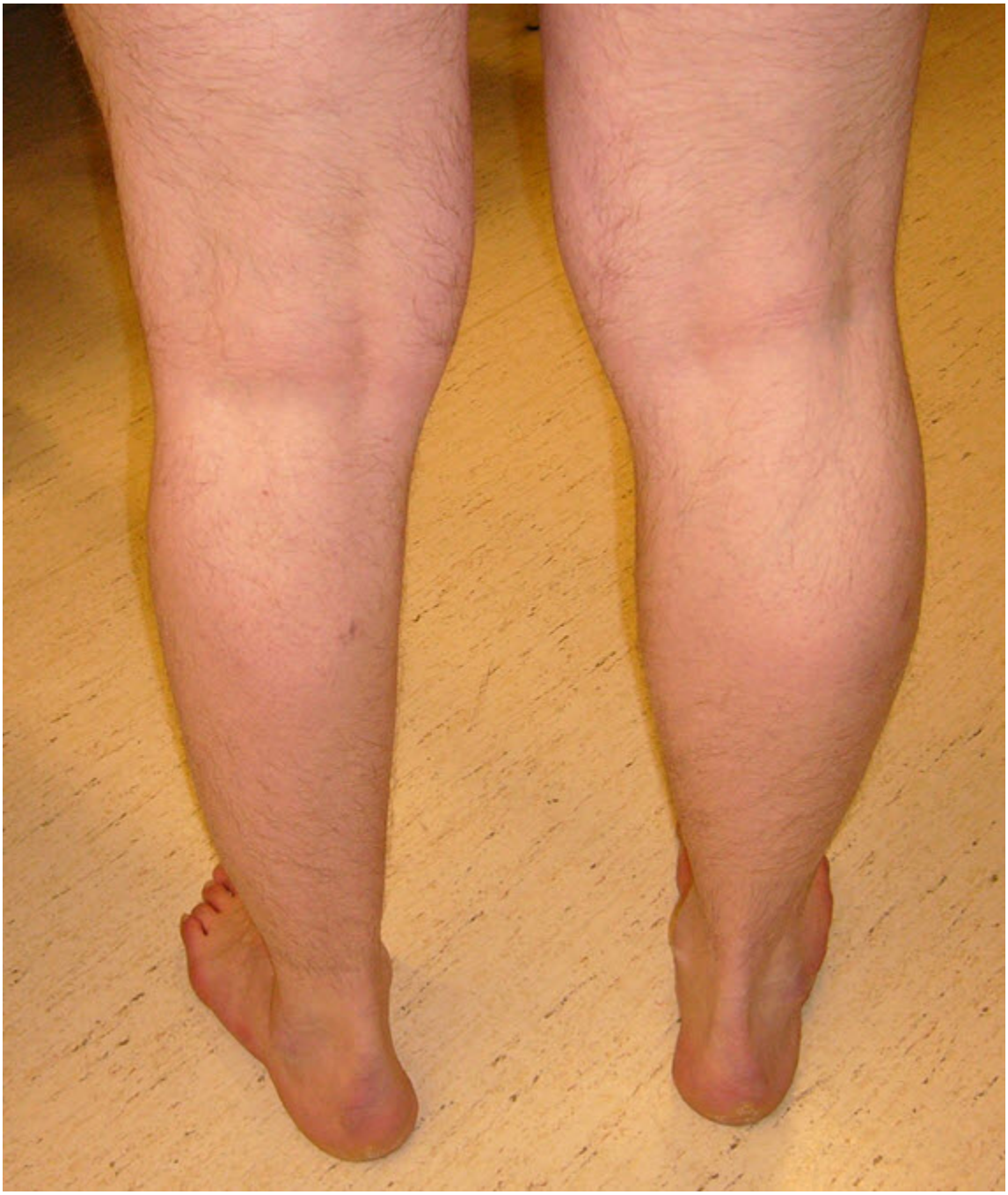

Figure 1. Asymmetric atrophy of the muscles of the left calf in an individual with an ANO5 pathogenic variant

Prevalence

ANO5 muscle disease has been estimated to be one of the most common causes of limb-girdle muscular dystrophy. Prevalence in Finland is as high as 2:100,000 [Penttilä et al 2012]; in the North of England it has been estimated at 0.26:100,000 [Hicks et al 2011]. In Europe, *ANO5* muscle disease has been estimated to be the third most prevalent LGMD subtype (26%) although this may be an underestimation due to the less severe phenotype [Ten Dam et al 2019]. In a large cohort study of 4656 individuals with clinically suspected LGMD across the US, *ANO5* was the fourth most prevalent LGMD subtype (7%) [Nallamilli et al 2018].

Genetically Related (Allelic) Disorders

Dominant pathogenic variants in *ANO5* are known to cause gnathodiaphyseal dysplasia (OMIM 166260), a generalized skeletal syndrome characterized by cemento-osseus lesions of the jawbones, in conjunction with bone fragility, bowing/cortical thickening of tubular bones, and diaphyseal sclerosis of long bones. The functional difference between dominant and recessive ANO5 pathogenic variants is not understood. However, dominant *ANO5* variants appear to locate in an extracellular domain following the first transmembrane domain or in the fourth putative transmembrane domain [Jin et al 2017]. Recessive *ANO5* variants have been shown to decrease the ANO5 protein expression [Vihola et al 2018].

Differential Diagnosis

Limb-girdle muscular dystrophy (LGMD). The differential diagnosis of *ANO5* muscle disease includes all the LGMDs (see OMIM phenotypic series: LGMD, autosomal recessive and LGMD, autosomal dominant). Of particular note is LGMD2B with primarily proximal weakness. LGMD2B is a dysferlinopathy characterized by early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood, with slow progression.

Distal myopathy. Muscle MRI, muscle pathology, and mode of inheritance may be useful in distinguishing between distal myopathies in the differential diagnosis of *ANO5* muscle disease (see Table 3).

Table 3. Genes Associated with Distal Myopathies of Interest in the Differential Diagnosis of *ANO5* Muscle Disease

Gene	Disorder	MOI	Mean Onset Age (yrs)	Initial Muscle Group Involved	Serum CK Concentration	Muscle Biopsy
ANO5 [1]	**Miyoshi muscular dystrophy 3**	**AR**	**20-25**	**Asymmetric posterior compartment in legs**	**>10x**	**Myopathic changes; scattered necrotic fibers**
DYSF	Miyoshi myopathy [2] (See Dysferlinopathy.)	AR	19 (median age at onset)	Posterior compartment in legs	>10x	Myopathic changes
GNE	Nonaka distal myopathy	AR	15-20	Anterior compartment in legs	<10x	Rimmed vacuoles
LDB3	Zaspopathy [3] (OMIM 609452)	AD	>40	Anterior compartment in legs	Normal or slightly ↑	Vacuolar & myofibrillar myopathy
MYH7	Laing distal myopathy	AD	<5	Anterior compartment in legs & neck flexors	Normal to (rarely) moderately ↑	Type 1 fiber atrophy in tibial anterior muscles; disproportion in proximal muscles
MYOT	Distal myotilinopathy (OMIM 609200)	AD	>40	Posterior > anterior in legs	Slightly ↑	Vacuolar & myofibrillar
TIA1	Welander distal myopathy (OMIM 604454)	AR AD	>40	Distal upper limbs (finger & wrist extensors)	Normal or slightly ↑	Rimmed vacuoles

Table 3. continued from previous page.

Gene	Disorder	MOI	Mean Onset Age (yrs)	Initial Muscle Group Involved	Serum CK Concentration	Muscle Biopsy
TTN	Udd distal myopathy	AD	>35	Anterior compartment in legs	Normal or slightly ↑	± rimmed vacuoles

AD = autosomal dominant; AR = autosomal recessive; CK = creatine kinase; MOI = mode of inheritance
1. Topic of this *GeneReview*; included to facilitate quick comparison of disorders
2. Miyoshi myopathy is characterized by muscle weakness and atrophy, most marked in the distal parts of the legs, especially the gastrocnemius and soleus muscles. Over a period of years, the weakness and atrophy spread to the thighs and gluteal muscles (see Figure 2). The forearms may become mildly atrophic with decrease in grip strength; the small muscles of the hands are spared.
3. Zaspopathy may also be referred to as Markesbery-Griggs late-onset distal myopathy.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *ANO5* muscle disease, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *ANO5* Muscle Disease

System/Concern	Evaluation	Comment
Neuromuscular	Neurologic eval & manual muscle force measurement	To establish a baseline for future assessment of disease progression & possible need for assistive devices
	Muscle imaging (CT or MRI)	To identify the pattern of affected muscles in detail
Cardiac	Baseline cardiac eval	
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

No definitive treatments for the limb-girdle muscular dystrophies exist. Management is tailored to each individual and each specific subtype.

Table 5. Treatment of Manifestations in Individuals with *ANO5* Muscle Disease

Manifestation/ Concern	Treatment	Considerations/ Other
Decreased mobility	• Weight control to avoid obesity • Physical therapy to promote mobility & prevent contractures • Mechanical aids to help ambulation & mobility	

Surveillance

Table 6. Recommended Surveillance for Individuals with *ANO5* Muscle Disease

System/Concern	Evaluation	Frequency
Neuromuscular	Evaluate muscle strength &functional status.	Every 6-12 mos

Agents/Circumstances to Avoid

Heavy muscle force training of weak muscles should be avoided as very high levels of CK have been measured after strenuous exercise [Milone et al 2012, Penttilä et al 2012].

The use of statins, which can induce muscle pain and worsen muscle weakness should be avoided. If absolutely necessary for the health of the individual, statin use requires extra monitoring of clinical status especially at the beginning of treatment.

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

ANO5 muscle disease is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *ANO5* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing an *ANO5* muscle disease.

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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing an *ANO5* muscle disease.

Offspring of a proband. The offspring of an individual with an *ANO5* muscle disease are obligate heterozygotes (carriers) for a pathogenic variant in *ANO5*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ANO5* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *ANO5* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis 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.

- **Genetic and Rare Diseases Information Center (GARD)**
  PO Box 8126
  Gaithersburg MD 20898-8126
  Phone: 888-205-2311 (toll-free); 888-205-3223 (toll-free TTY)
  Fax: 301-251-4911
  Email: GARDinfo@nih.gov
  Limb-Girdle Muscular Dystrophy

- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org

- **Muscular Dystrophy Canada**
  Canada
  Phone: 800-567-2873
  Email: info@muscle.ca
  muscle.ca

- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  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. ANO5 Muscle Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ANO5	11p14.3	Anoctamin-5	ANO5 @LOVD	ANO5	ANO5

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 ANO5 Muscle Disease (View All in OMIM)

608662	ANOCTAMIN 5; ANO5
611307	MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 12; LGMDR12
613319	MIYOSHI MUSCULAR DYSTROPHY 3; MMD3

Molecular Pathogenesis

ANO5 (anoctamin 5) belongs to a protein family of Ca^{2+} activated ion channels and phospholipid scramblases. However, not much is known about its normal function and also the molecular pathogenesis is so far not understood. According to a recent study, it appears that ANO5 deficiency compromises the plasma membrane repair ability of myoblasts [Chandra et al 2019].

Mechanism of disease causation. It seems likely that the main disease mechanism in anoctaminopathy is loss of function. This is based on the observation that in most cases, regardless of the pathogenic variant (truncating or missense), the ANO5 protein is clearly reduced in biopsies of affected individuals.

***ANO5*-specific laboratory technical considerations.** A western blotting method has been developed to detect endogenous ANO5 protein in membrane fractions extracted from human muscle biopsies. This method can be used to quantify the ANO5 protein and evaluate the pathogenicity of novel *ANO5* variants of uncertain significance.

Table 7. Notable *ANO5* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_213599.2 NP_998764.1	c.191dupA	p.Asn64LysfsTer15	Common in northern European populations [Hicks et al 2011, Nallamilli et al 2018]
	c.2272C>T	p.Arg758Cys	Common in northern European populations [Penttilä et al 2012]
	c.1898+1G>A	p.Met470LeufsTer16	Founder variant in the Netherlands [Nallamilli et al 2018]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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Chapter Notes

Revision History

- 22 August 2019 (ha) Comprehensive update posted live
- 29 November 2012 (me) Review posted live
- 19 July 2012 (sp) Original submission

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