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Udd Distal Myopathy – Tibial Muscular Dystrophy

Synonym: Udd Myopathy

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Summary

Clinical characteristics

Udd distal myopathy – tibial muscular dystrophy (UDM-TMD) is characterized by weakness of ankle dorsiflexion and inability to walk on the heels after age 30 years. Disease progression is slow and muscle weakness remains confined to the anterior compartment muscles for many years. The long toe extensors become clinically involved after ten to 20 years, leading to foot drop and clumsiness when walking. In the mildest form, UDM-TMD can remain unnoticed even in the elderly. EMG shows profound myopathic changes in the anterior tibial muscle, but preservation of the extensor brevis muscle. Muscle MRI shows selective fatty degeneration of the anterior tibial muscles and other anterior compartment muscles of the lower legs. Serum CK concentration may be normal or slightly elevated. Muscle biopsy shows progressive dystrophic changes in the tibialis anterior muscle with rimmed vacuoles at the early stages and replacement with adipose tissue at later stages of the disease.

Diagnosis/testing

The diagnosis of UDM-TMD is established in a proband with typical clinical findings and the identification of a heterozygous pathogenic variant in the last exon of *TTN* by molecular genetic testing.

Management

Treatment of manifestations: Orthotic devices for the foot drop; tibial posterior tendon transposition to replace lost ankle dorsiflexion function when foot drop is severe before age 55.

Surveillance: Neuromuscular examination every one to four years to evaluate disease progression and need for rehabilitation and orthotic treatment.

Agents/circumstances to avoid: Heavy muscle force training of weak muscles.

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Genetic counseling

UDM-TMD is inherited in an autosomal dominant manner. Most individuals diagnosed with UDM-TMD have an affected parent. Each child of an individual with UDM-TMD has a 50% risk of inheriting the *TTN* pathogenic variant. If the reproductive partner of a proband is also heterozygous for a UDM-TMD *TTN* pathogenic variant (a situation more likely to be seen in Finland and/or in reproductive partners of Finnish heritage – due to a founder effect), offspring are at risk for the early-onset severe limb-girdle muscular dystrophy phenotype associated with biallelic *TTN* pathogenic variants. Once the *TTN* pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Udd distal myopathy – tibial muscular dystrophy (UDM-TMD) **should be suspected** in individuals with the following:

- **Distal myopathy.** Ankle dorsiflexion weakness manifesting in the fourth to seventh decade
- **EMG abnormality.** Profound myopathic changes in the anterior tibial muscle but preservation of the extensor brevis muscle
- **Muscle MRI findings.** Selective fatty degeneration of anterior tibial muscles and other anterior compartment muscles of the lower legs
- **Serum CK concentration** that is normal or slightly elevated
- **Muscle biopsy** showing progressive dystrophic changes in the tibialis anterior muscle, with rimmed vacuoles at the early stages and end-stage replacement with adipose connective tissue at later stages of the disease

Establishing the Diagnosis

The diagnosis of UDM-TMD **is established** in a proband with typical clinical findings and a heterozygous pathogenic variant in the last exon of *TTN* identified by molecular genetic testing (see Table 1).

Note: The last six exons of *TTN* (359 to 364 in the LRG (NG_011618.3) reference, which numbers the exons sequentially along the chromosome; C-terminal domain) encode the part of titin that spans the sarcomere M-line; these exons are called Mex1-Mex6 (M-line encoding exons 1 through 6). For mapping of these exons to other transcripts, see Molecular Genetics.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of UDM-TMD is relatively distinct but overlaps with other adult-onset distal myopathies, individuals who exhibit the distinctive findings described in Suggestive Findings, or in whose family the diagnosis is known, are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Udd distal myopathy has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of UDM-TMD, molecular genetic testing approaches can include **single-gene testing of the last *TTN* exons** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TTN* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found gene-targeted deletion/duplication analysis be considered, although no intragenic deletions or duplications have been reported in this disorder.

  Note: Targeted analysis for pathogenic variants can be performed first in individuals of Finnish ancestry [See Table 1] or in other families with a known *TTN* pathogenic variant.

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

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

Option 2

When the diagnosis of UDM-TMD is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

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 Udd distal myopathy.

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 UDM-TMD

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TTN	Sequence analysis [3]	Close to 100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from Human Gene Mutation Database [Stenson et al 2020]
5. FINmaj is an 11-bp deletion/insertion observed in the last exon (364) of *TTN* **in all Finnish families** with UDM-TMD [Hackman et al 2002]. Note: The part of the TTN protein that spans the sarcomere M-line is encoded by six exons that have also been termed Mex1-Mex6 (M-line exons 1 through 6); in the gene, these correspond to exons 359 to 364 (reference sequence LRG NG_011618.3). Thus, Mex6 is the last exon of *TTN*.
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.

Clinical Characteristics

Clinical Description

To date, more than 500 individuals have been identified with a pathogenic variant in the last exon 364 of *TTN* causing Udd distal myopathy – tibial muscular dystrophy (UDM-TMD) [Udd et al 1993, Udd et al 2005, Hackman et al 2008, Pollazzon et al 2010, Evilä et al 2014]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Features of UDM-TMD

Feature	% of Persons w/Feature
Ankle dorsiflexion weakness	100%
Drop foot at age 60	60%
Knee flexion weakness at age 60	60%
Waddling gait at age 60	25%

Onset. The first symptoms of UDM-TMD are weakness of ankle dorsiflexion and inability to walk on the heels after age 30 years.

Progression. Disease progression is slow and muscle weakness remains confined to the anterior compartment muscles for many years. The long toe extensors become clinically involved after ten to 20 years, leading to foot drop and clumsiness when walking.

- After age 65 weakness of hamstring muscles is present on manual testing.
- At age 75 years, one third of affected individuals show moderate difficulty walking as a result of increasing proximal leg muscle weakness; some walking ability is otherwise preserved throughout life.
- In the mildest form, Udd distal myopathy can remain unnoticed even in elderly individuals. Disease severity is usually consistent within a family.

Atypical phenotypes. Nine percent of Finnish cases with the FINmaj pathogenic variant were reported with aberrant phenotypes including proximal lower-limb weakness and/or posterior calf muscle weakness even at

onset [Udd et al 2005]. Later, some of these individuals were identified as having recessive pathogenic variants on the second allele [Evilä et al 2014].

Life span is not reduced.

Genotype-Phenotype Correlations

Almost all individuals with UDM-TMD of Finnish heritage have the same pathogenic variant (FINmaj) in the last exon 364 (known as Mex6) of *TTN*. Other European families with single-nucleotide variants in the Mex6 exon of *TTN* have the common phenotype when compared to the Finnish phenotype. See Table 8.

Penetrance

Penetrance is close to 100% at age 65 years.

Prevalence

Prevalence in Finland is 15:100,000 individuals due to a founder effect. Outside of Finland UDM-TMD is rare but has been identified in other populations including descendants of immigrants from Finland.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *TTN* are summarized in Table 3.

Table 3. *TTN* Allelic Disorders

Disorder	Phenotype
Autosomal recessive limb-girdle muscular dystrophy LGMDR10, titin-related (OMIM 608807)	Early-onset severe limb-girdle muscular dystrophy phenotype
Hereditary myopathy with early respiratory failure	Presenting findings are gait disturbance due to distal &/or proximal leg weakness or nocturnal respiratory symptoms due to respiratory muscle weakness
Dilated cardiomyopathy	Increased risk of dilated cardiomyopathy
Hypertrophic cardiomyopathy	Rare cause of hypertrophic cardiomyopathy
Adult-onset proximal lower-limb rimmed vacuolar muscular dystrophy [1]	
Early- or juvenile-onset recessive distal titinopathy [2]	
Congenital titinopathy w/or w/out cardiomyopathy [3]	Multiple phenotypes, from fetal lethality w/arthrogryposis to nonprogressive myopathy incl Salih myopathy

1. Evilä et al [2014]
2. Evilä et al [2017]
3. Oates et al [2018]

Differential Diagnosis

Genes and disorders in the differential diagnosis of Udd distal myopathy – tibial muscular dystrophy (UDM-TMD) are listed in Table 4.

Table 4. Genes of Interest in the Differential Diagnosis of UDM-TMD

Gene(s)	Disorder	MOI	Mean Age at Onset	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Muscle Biopsy	Comment
TTN	**Udd distal myopathy [1]**	**AD**	**>35 yrs**	**Anterior compartment in legs**	**Normal or slightly ↑**	**± rimmed vacuoles**	
ACTN2	Distal actininopathy [2] (OMIM 618655)	AD	15-35	Lower legs; later, also proximal limbs	3-8x	± rimmed vacuoles	
ANO5	*ANO5* muscle disease (distal anoctaminopathy)	AR	15-55	Asymmetric calf involvement	>10x	Nonspecific dystrophic myopathology	• May present w/ similarities to Miyoshi myopathy • Calf involvement starting w/pain & hypertrophy & → weakness & atrophy • Nonspecific dystrophic myopathology w/ scattered fiber necrosis • Evolves slowly; persons remain ambulant into late adulthood.
CRYAB	Alpha-B crystallinopathy (OMIM 608810)	AD	32-68	Distal limbs	1.5-2.5x	Rimmed vacuolar pathology	
DES	Desminopathy (OMIM 601419)	AD AR	Juvenile / early adulthood	Distal limbs	Moderately ↑	Consistent w/ myofibrillar myopathy	
DUX4 [3] *SMCHD1*	Facioscapulo-humeral muscular dystrophy	AD Digenic	<20	Some may present w/ ankle dorsiflexion weakness	1-4x	Nonspecific	
DYSF	Miyoshi myopathy (See Dysferlinopathy.)	AR	Early adult	Posterior compartment in legs	>50x	Myopathic changes	Manifests as difficulty climbing stairs & toe-walking; progresses to other distal & proximal muscles (as in LGMD2B)
FLNC	Distal actin binding domain (ABD)-filaminopathy (OMIM 609524)	AD	Early adulthood	Distal upper limbs & calves	Normal or slightly ↑	Scattered, grouped atrophic fibers	

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Mean Age at Onset	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Muscle Biopsy	Comment
GNE	*GNE*-related myopathy (Nonaka distal myopathy)	AR	15-20	Anterior compartment in legs & in toe extensors	<10x	Rimmed vacuoles	Foot drop & steppage gait w/progression to loss of ambulation after 12-15 yrs
LDB3	Zaspopathy [4] (OMIM 609452)	AD	>40	Anterior compartment in legs	Normal or slightly ↑	Vacuolar & myofibrillar myopathy	• Weakness of ankle dorsiflexion followed by slow progression to calf muscles, finger & wrist extensor muscles, & intrinsic muscles of the hand • Proximal leg muscles eventually become involved. • Cardiomyopathy may occur at late stages.
MATR3	Vocal cord & pharyngeal distal myopathy [5] (See ALS Overview.)	AD	35-60	Lower legs & hands; dysphonia, respiratory	1-8x	Rimmed vacuoles	
MYH7	Laing distal myopathy	AD	<20	Anterior compartment in legs & neck flexors	Moderately ↑	Type 1 fiber atrophy in tibial anterior muscles; disproportion in proximal muscles	• Early-onset (usually age <5 yrs) weakness, 1st of dorsiflexors of the ankles & great toes & then of finger extensors • Weakness of neck flexors • After >10 yrs of distal weakness, mild proximal weakness • Life expectancy normal [6]

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Mean Age at Onset	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Muscle Biopsy	Comment
MYOT	Distal myotilinopathy (OMIM 609200)	AD	>40	Posterior >/= anterior in legs	Slightly ↑	Vacuolar & myofibrillar	• Onset of ankle weakness may occur very late in 7th decade. • In contrast to the late onset, progression is not very slow & can → wheelchair dependence even 10-15 yrs after onset, incl weakness & atrophy of proximal & upper limb muscles. [7]
NEB	Distal nebulin / nemaline myopathy (OMIM 256030)	AR AD [8]	Childhood	Ankle dorsiflexion, weakness of hand & finger extensors	Normal or slightly ↑	Scattered, grouped atrophic fibers w/out nemaline rods	
SQSTM1 + *TIA1*	WDM-like distal myopathy [9]	Digenic	>40	Distal upper limbs (index finger & wrist extensors), some w/onset in anterior lower legs	Normal or slightly ↑	Rimmed vacuoles	• May have onset in anterior compartment muscles of lower legs (rather than usual onset in index finger & wrist extensors) • Typically, weakness of extensor of index finger followed by slow progression to other finger extensors & to anterior & posterior leg muscles
TIA1	Welander distal myopathy (OMIM 604454)	AD AR	>40	Distal upper limbs (index finger & wrist extensors), some w/onset in anterior lower legs	Normal or slightly ↑	Rimmed vacuoles	

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Mean Age at Onset	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Muscle Biopsy	Comment
VCP	*VCP* distal myopathy (allelic w/IBMPFD)	AD	20-25	Distal limbs (FTD common)	Slightly ↑	Rimmed vacuoles	

AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; FTD = frontotemporal dementia; IBMPFD = inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia; LGMD = limb-girdle muscular dystrophy; MOI = mode of inheritance; WDM = Welander distal myopathy

1. Topic of this GeneReview; included for comparison for quick reference.

2. Savarese et al [2019]

3. Derepression and dysregulation of *DUX4* (within the macrosatellite repeat D4Z4) underlie both FSHD1 and FSHD2. For FSHD1 the derepression is a consequence of the contraction of the D4Z4 repeat and for FSHD2 this is caused by pathogenic variants in *SMCHD1*. In FSHD and some congenital myopathies, the initial symptom can be a selective defect in the tibialis anterior muscle as with Udd distal myopathy. FSHD typically presents before age 20 years with weakness of the facial muscles and the stabilizers of the scapula or the dorsiflexors of the foot. Severity is highly variable. Weakness is slowly progressive and about 20% of affected individuals eventually require a wheelchair. Life expectancy is not shortened.

4. Zaspopathy is also referred to as Markesbery-Griggs late-onset distal myopathy.

5. Palmio et al [2016]

6. A cohort of more than 60 affected individuals was reported in Spain [Muelas et al 2010, Muelas et al 2012].

7. Pénisson-Besnier et al [2006]

8. Kiiski et al [2019]

9. Lee et al [2018]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Udd distal myopathy – tibial muscular dystrophy (UDM-TMD), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with UDM-TMD

System/Concern	Evaluation	Comment
Neuromuscular	Muscle MRI	Can identify affected muscles w/high specificity
	EMG	Can help identify involved muscles but is much less accurate & less convenient for patient
	Manual muscle force measurement	Can be used to help identify involved muscles but is even less specific than EMG
	Assessment for foot drop	To determine the need for ankle orthoses
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with UDM-TMD

Manifestation/ Concern	Treatment	Considerations/Other
Foot drop (typical)	Orthotic devices	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Foot drop (severe)	Tibial posterior tendon transposition	Can be performed in patients in their 40s & 50s to replace lost function of anterior tibial muscle & long toe extensor muscles

Surveillance

Table 7. Recommended Surveillance for Individuals with UDM-TMD

System/Concern	Evaluation	Frequency
Neuromuscular	Evaluate disease progression & need for rehabilitation & orthotic treatment.	Every 1-4 yrs

Agents/Circumstances to Avoid

Heavy muscle force training of weak muscles should be avoided.

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

Udd distal myopathy – tibial muscular dystrophy (UDM-TMD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, all reported individuals diagnosed with UDM-TMD inherited a *TTN* pathogenic variant from a parent; typically the heterozygous parent is affected.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant (i.e., neither parent is known to be affected).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (see Note). Though theoretically possible, no instances of a *de novo* pathogenic variant in the proband or germline mosaicism in a parent have been reported.

Note: Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.

- The family history may appear to be negative because of failure to recognize the disorder in a family member(s) because of a milder phenotypic presentation, death of a parent before the onset of symptoms, or very late onset of mild disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *TTN* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband

- Each child of an individual with UDM-TMD has a 50% risk of inheriting the *TTN* pathogenic variant.
- If the reproductive partner of a proband is also heterozygous for a UDM-TMD *TTN* pathogenic variant – a situation more likely to be seen in Finland and/or in reproductive partners of Finnish heritage, due to a founder effect – offspring are at risk for the early-onset severe limb-girdle muscular dystrophy phenotype associated with biallelic FINmaj variants (or compound heterozygosity for the FINmaj variant and another deleterious nonsense/frameshift *TTN* pathogenic variant).

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *TTN* pathogenic variant, members of the parent's family may be at risk.

Related Genetic Counseling Issues

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

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

- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321

Email: ResourceCenter@mdausa.org
mda.org

- **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. Udd Distal Myopathy - Tibial Muscular Dystrophy: Genes and Databases

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

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Udd Distal Myopathy - Tibial Muscular Dystrophy (View All in OMIM)

188840	TITIN; TTN
600334	TIBIAL MUSCULAR DYSTROPHY, TARDIVE; TMD

Molecular Pathogenesis

Titin, a myofilament in the sarcomere, is expressed as several different isoforms, caused by alternative splicing, in skeletal and cardiac muscle. Titin spans more than one half the length of a sarcomere in heart and skeletal muscle. Structurally different parts of the protein perform distinct functions (mechanical, developmental, and regulatory). Titin binds and interacts with a large number of other sarcomeric proteins.

The molecular pathomechanism of UDM-TMD is not fully clarified but the normal C terminus of the protein undergoes proteolytic fragmentation, the fragments from which maintain a steady state level in the muscle fibers and are not immediately degraded. These normal fragments are lost in the FINmaj protein (see Table 8) because this indel induces an abnormal cleavage of the C terminus, the product which is degraded [Charton et al 2015].

Mechanism of disease causation. Mex6 variants may cause conformational changes in titin and alter the interactions with other sarcomeric proteins and/or may cause proteolysis of C-terminal titin domains. Because of the rimmed vacuolar pathology in the affected muscles and the fact that heterozugous null allele carriers are healthy, a dominant-negative effect is postulated.

***TTN*-specific laboratory technical considerations.** The Mex1-Mex6 domain exons correspond to the following exons:

- LRG_391 (NG_011618.3): exons 359-364
- NM_133378.4: exons 307-312
- NM_001267550.2: exons 358-363
- NM_001256850.1: exons 307-312

All variants associated with UMD-TMD are located in the Mex6 (last) domain exon.

Table 8. Notable *TTN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_001267550.2 NP_001254479.2	c.107780_107790 (delinsTGAAAGAAAAA) [FINmaj]	p.Glu35927_Trp35930 (delinsValLysGluLys)	Finnish founder variant [Hackman et al 2002]
	c.107837A>C	p.His35946Pro	Italian founder variant [Pollazzon et al 2010]
	c.107840T>A	p.Ile35947Asn	Founder variant in Belgians & in Normandy [Van den Bergh et al 2003]
	c.107867T>C	p.Leu35956Pro	French founder variant [Hackman et al 2002]

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

Chapter Notes

Author History

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Revision History

- 2 January 2020 (ha) Comprehensive update posted live
- 8 August 2013 (cd/bu) Revision: pathogenic variants in *TIA1* reported to cause Welander distal myopathy; distal anoctaminopathy added to differential diagnosis
- 23 August 2012 (me) Comprehensive update posted live
- 4 March 2010 (me) Comprehensive update posted live
- 3 April 2007 (me) Comprehensive update posted live
- 17 February 2005 (me) Review posted live
- 27 July 2004 (bu) Original submission

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