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Myostatin-Related Muscle Hypertrophy – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Myostatin-related muscle hypertrophy is characterized by reduced subcutaneous fat pad thickness and increased muscle size in individuals with normal or increased muscle strength. Both heterozygotes and homozygotes for a causative variant in *MSTN* encoding the protein growth differentiation factor 8 (myostatin) can exhibit muscle hypertrophy. Clinical manifestations depend on the amount of myostatin protein present. An infant homozygous for an *MSTN* causative variant had muscle mass twice that of sex- and age-matched controls; intellect and cardiac function were normal. He displayed stimulus-induced myoclonus that subsided after two months. Heterozygotes may have increased muscle bulk and strength, but to a lesser degree.

Diagnosis/testing

Skeletal muscle size in an individual with myostatin-related muscle hypertrophy is measured by ultrasound examination, DEXA, or MRI. Subcutaneous fat pad thickness is measured by ultrasound or with a caliper. *MSTN* is the only gene in which mutation is known to cause myostatin-related muscle hypertrophy.

Management

Myostatin-related muscle hypertrophy is not known to cause medical complications.

Genetic counseling

The phenotypes associated with myostatin-related muscle hypertrophy are inherited in an incomplete autosomal dominant manner. At conception, the sibs of a child with homozygous myostatin-related muscle hypertrophy have a 25% chance of having homozygous myostatin-related muscle hypertrophy, a 50% chance of having one

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MSTN causative variant with or without increased muscle mass, and a 25% chance of having normal muscle mass and no *MSTN* causative variants. Heterozygotes may have increased muscle mass. Individuals diagnosed with heterozygous myostatin-related muscle hypertrophy may have a parent with the *MSTN* causative variant who may have increased muscle mass, or the proband may have the condition as the result of a *de novo* variant. The proportion of cases caused by a *de novo* variant is unknown. The chance that sibs of a proband with heterozygous myostatin-related muscle hypertrophy will inherit the *MSTN* variant is 50% if a parent has increased muscle mass or has an *MSTN* causative variant. Each child of an individual with heterozygous myostatin-related muscle hypertrophy has a 50% chance of inheriting the *MSTN* causative variant.

Diagnosis

Clinical Diagnosis

The diagnosis of myostatin-related muscle hypertrophy is established by clinical findings of reduced subcutaneous fat pad thickness and increased muscle size in individuals with normal or increased muscle strength and an *MSTN* causative variant identified on molecular genetic testing.

Testing

Skeletal muscle size can be measured by ultrasound, DEXA, or MRI. It is expected to be several deviations above normal for age- and sex-matched controls.

Subcutaneous fat pad thickness can be measured by ultrasound or with a caliper at various standard locations for which normal values exist.

Creatine kinase (CK) serum concentration is expected to be normal.

Molecular Genetic Testing

Gene. *MSTN,* which encodes the protein growth differentiation factor 8 (also known as myostatin) is the only gene in which variants are known to cause myostatin-related muscle hypertrophy.

Table 1. Molecular Genetic Testing Used in Myostatin-Related Muscle Hypertrophy

Gene [1]	Method	Variants Detected [2]	Variant Detection Frequency by Method [3]
MSTN	Sequence analysis [4]	Sequence variants including c.506+5G>A [5]	Unknown

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.. For issues to consider in interpretation of sequence analysis results, click here.
5. The only *MSTN* causative variant related to myostatin-related muscle hypertrophy that has been reported [Schuelke et al 2004]

Testing Strategy

To confirm/establish the diagnosis in a proband

- **Molecular genetic testing.** Targeted analysis of the causative variant c.506+5G>A should be performed first. If the variant is not detected and clinical suspicion is high, sequence analysis of the entire gene should be performed.

Clinical Characteristics

Clinical Description

Clinical manifestations of myostatin-related muscle hypertrophy appear to be dependent on the amount of myostatin protein present. Therefore both heterozygotes and homozygotes can exhibit muscle hypertrophy.

Homozygotes. A homozygous loss-of-function myostatin variant was identified in a hypermuscular infant with muscle mass approximately twice that of sex- and age-matched controls [Schuelke et al 2004]. At age 4.5 years, he continued to have increased muscle bulk and strength with normal intellect and normal cardiac function by echocardiography and electrocardiography.

He initially displayed stimulus-induced myoclonus that subsided after two months. The relationship between myoclonus and the *MSTN* causative variant is not clear.

Ultrasonography revealed normal muscle echogenicity and cross-sectional diameter of quadriceps muscle 7.2 SD above the mean.

Heterozygotes. Heterozygotes may have increased muscle bulk and strength. The mother of the child identified to be homozygous for the c.506+5G>A variant was a former professional athlete with large calf muscles [Schuelke et al 2004]. See also Genotype-Phenotype Correlations.

Genotype-Phenotype Correlations

No information is currently available as only one myostatin-related muscle hypertrophy-causing variant in *MSTN* has been identified.

In a multigenerational family segregating a 3.4-Mb deletion of chromosome 2q32.1q32.3 including *MSTN*, four of seven individuals with the deletion available for examination were reported to have increased muscle strength and increased size of the gastrocnemius and soleus muscles, whereas the other three individuals with the deletion did not have increased muscle strength or size [Meienberg et al 2010].

Penetrance

Penetrance is unknown.

Anticipation

Anticipation is not known to occur.

Prevalence

Prevalence is unknown.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are associated with variants in *MSTN*.

Differential Diagnosis

The *MSTN* causative variant does not appear to be associated with myopathy or muscle weakness, thus allowing differentiation of myostatin-related muscle hypertrophy from muscular dystrophies with muscle hypertrophy, including:

- Duchenne and Becker muscular dystrophy (see Dystrophinopathies)
- Limb-girdle muscular dystrophy 1C (caveolinopathy)
- Limb-girdle muscular dystrophies 2C, 2D, 2E (sarcoglycanopthies)
- Channelopathies such as myotonia congenita, a chloride channelopathy resulting from pathogenic variants in *CLCN1*

The *MSTN* causative variant also causes decreased adipose tissue and needs to be distinguished from familial partial lipodystrophy, Dunnigan type (FPLD2), caused by pathogenic variants in *LMNA,* in which increased muscle mass is not seen [Schmidt et al 2001].

Management

Treatment of Manifestations

Myostatin-related muscle hypertrophy is not currently known to cause any medical complications.

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

The phenotypes associated with myostatin-related muscle hypertrophy are inherited in an incomplete autosomal dominant manner.

Risk to Family Members

Parents of a proband who is homozygous for myostatin-related muscle hypertrophy

- The parents of a child with homozygous myostatin-related muscle hypertrophy are obligate heterozygotes and therefore have one *MSTN* variant.
- Heterozygotes may have increased muscle mass.

Sibs of a proband

- At conception, each sib of a child with homozygous myostatin-related muscle hypertrophy has a 25% chance of having homozygous myostatin-related muscle hypertrophy, a 50% chance of having one *MSTN* causative variant with or without increased muscle mass, and a 25% chance of having normal muscle mass and no *MSTN* causative variants.

- Heterozygotes may have increased muscle mass.

Offspring of a proband. The offspring of an individual with homozygous myostatin-related muscle hypertrophy are obligate heterozygotes for a causative variant in *MSTN* and may have increased muscle mass.

Other family members of a proband. Each sib of the proband's parents has a 50% chance of having one *MSTN* causative variant and may have increased muscle mass.

Parents of a proband who is heterozygous for myostatin-related muscle hypertrophy

- Individuals diagnosed with heterozygous myostatin-related muscle hypertrophy may have a parent with an *MSTN* causative variant who may have increased muscle mass or may have the condition as the result of a *de novo* variant. The proportion of cases caused by a *de novo* variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* variant include clinical evaluation for evidence of muscle hypertrophy.

Note: Although individuals diagnosed with heterozygous myostatin-related muscle hypertrophy may have a parent with increased muscle mass, the family history may appear to be negative because of incomplete penetrance or failure to recognize the condition in family members.

Sibs of a proband

- The chance that the sibs of the proband will inherit the *MSTN* causative variant depends on the genetic status of the proband's parents.
- If a parent of the proband has increased muscle mass, the chance that the sibs will inherit the *MSTN* causative variant is 50%.

Offspring of a proband. Each child of an individual with heterozygous myostatin-related muscle hypertrophy has a 50% chance of inheriting the *MSTN* causative variant.

Other family members of a proband. The chance that other family members will be affected depends on the status of the proband's parents: if a parent has increased muscle mass, his or her family members may be affected.

Related Genetic Counseling Issues

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

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.

No specific resources for Myostatin-Related Muscle Hypertrophy have been identified by *GeneReviews* staff.

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. Myostatin-Related Muscle Hypertrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MSTN	2q32.2	Growth/differentiation factor 8	MSTN homepage - Leiden Muscular Dystrophy pages	MSTN	MSTN

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 Myostatin-Related Muscle Hypertrophy (View All in OMIM)

601788	MYOSTATIN; MSTN

Benign variants. Five missense substitutions in conserved amino acid residues have been identified [Ferrell et al 1999]. Two of these, p.Ala55Thr in exon 1 and p.Lys153Arg in exon 2, are polymorphic benign variants in the general population (see Table 2).

Pathogenic variants. Only one muscle hypertrophy-causing *MSTN* variant has been reported to date; c.506+5G>A results in misspliced mRNA [Schuelke et al 2004] (see Table 2; for more information, see Table A). In a multiplex family, a heterozygous contiguous gene deletion including the entire *MSTN* gene was reported. Some of the individuals in this family who had the heterozygous contiguous gene deletion had increased muscle strength and size [Meienberg et al 2010].

Table 2. Selected *MSTN* Variants

Variant Classification	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
Benign	c.163G>A	p.Ala55Thr	NM_005259.2 NP_005250.1
	c.458A>G	p.Lys153Arg	
Pathogenic	c.506+5G>A (IVS1+5G>A)	--	

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

Normal gene product. Myostatin, composed of 375 amino acids, is also known as growth differentiation factor 8 and belongs to the transforming growth factor β superfamily. Myostatin is a negative regulator of muscle growth expressed almost exclusively in developing and adult skeletal muscle [McPherron et al 1997].

Abnormal gene product. The only known causative variant results in no detectable myostatin production. Loss or inhibition of myostatin is associated with increased skeletal muscle growth by muscle fiber hyperplasia and hypertrophy [McPherron et al 1997].

- Mice heterozygous for an *Mstn* pathogenic variant have muscle mass intermediate between homozygous myostatin null mice and wild type mice.
- "Double-muscled" cattle previously linked to the muscular hypertrophy (mh) locus on chromosome 2 have also been found to have pathogenic variants in the gene for myostatin [Grobet et al 1997, Kambadur et al 1997].

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Chapter Notes

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