GENEReviews

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Charcot-Marie-Tooth Neuropathy Type 2D/Distal Spinal Muscular Atrophy V

[*CMT2D, CMT2D/ dSMA-V, Distal Spinal Muscular Atrophy V, Hereditary Motor and Sensory Neuropathy Type 2D, dSMA-V*]

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Summary

Disease characteristics. Charcot-Marie-Tooth neuropathy type 2D/distal spinal muscular atrophy V (CMT2D/dSMA-V) is characterized by adolescent or early adult onset of bilateral weakness and atrophy of thenar and first dorsal interosseus muscles, sparing of the hypothenar eminence until later in the course of illness, and mild to moderate impairment of vibration sense in the hands and feet later in the disease course in a minority of individuals. The phenotype is considered the CMT2D subtype when sensory deficits — reduction of pinprick, temperature, touch, and vibration perception in a stocking and (less often) glove pattern — are present and dSMA-V when sensory deficits are absent. The lower limbs are involved in about half of affected individuals. The earliest elicited manifestations of illness in many individuals are transient cramping and pain in the hands on exposure to cold and cramping in calf muscles on exertion.

Diagnosis/testing. The diagnosis is based on clinical findings, electromyography (EMG), and sural nerve biopsy. The only gene known to be associated with CMT2D/dSMA-V is *GARS*. Molecular genetic testing is clinically available on a limited basis.

Management. Treatment of manifestations: ankle support, toe-up braces, ankle-foot orthotics as necessary. Surveillance: periodic assessment by a neurologist and/or neuromuscular disorders specialist.

Genetic counseling. CMT2D/dSMA-V is inherited in an autosomal dominant manner. Most individuals diagnosed with CMT2D/dSMA-V have an affected parent. The proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with CMT2D/dSMA-V has a 50% chance of inheriting the mutation. Prenatal testing may be available by custom prenatal diagnosis for families in which the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Charcot-Marie-Tooth neuropathy type 2D/distal spinal muscular atrophy V (CMT2D/dSMA-V) is characterized by the following:

- Adolescent or early adult onset of bilateral weakness and atrophy of thenar and first dorsal interosseus muscles. In most, but not all individuals, the disease progresses to involve hypothenar, foot, and peroneal muscles
- Mild to moderate impairment of vibration sense developing in advanced illness in a minority of individuals
- Chronic denervation on EMG in distal muscles with reduced compound motor action potentials at near-normal or normal motor conduction velocities and preserved sensory nerve action potentials, including the sural response
- Mild to moderate selective loss of small- and medium-size myelinated and small unmyelinated axons on sural nerve biopsy
- CMT2D phenotype only: presence of sensory deficits including reduction of pinprick, temperature, touch, and vibration perception in a stocking and (less often) glove pattern
- Family history consistent with autosomal dominant inheritance

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. Both the CMT2D subtype and the dSMA-V subtype are associated with mutations in *GARS*, the gene encoding glycyl-tRNA synthetase.

Clinical use

- Diagnostic testing

Clinical testing

- **Sequence analysis** is clinically available on a limited basis. The mutation detection rate is unknown**.**

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in CMT2D/dSMA-V

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	Point mutations in *GARS* coding sequence	Unknown	Clinical Testing

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *GARS*.

Clinical Description

Natural History

CMT2D (distal motor and sensory neuropathy) [Ionasescu et al 1996] and dSMA-V (exclusively motor distal involvement) [Christodoulou et al 1995] were originally thought to be distinct entities, but family studies [Sambuughin et al 1998, Ellsworth et al 1999] and later molecular genetic studies [Antonellis et al 2003, Del Bo et al 2006] determined that they are allelic.

Both disease subtypes, CMT2D and dSMA-V, are characterized by adolescent or early adult onset of unique patterns of motor and sensory manifestations. The hallmark is the onset of weakness and atrophy in the thenar and the first dorsal interosseus muscles and the sparing of the hypothenar eminence until later in the course of illness. The lower limbs are involved in about half of affected individuals; mild loss of vibration sense is observed in a third of individuals in advanced disease.

The presenting symptom is muscle weakness in the hands occurring between age eight and 36 years, with most individuals (75%) developing symptoms during the second decade of life [Sivakumar et al 2005]. The earliest elicited manifestations of illness in many individuals are transient cramping and pain in the hands on exposure to cold and cramping in calf muscles on exertion. Progressive weakness and atrophy of the thenar and first dorsal interossei muscles are the major complaints in affected individuals (Figure 1, Table 2)

Lower extremity involvement, when present, varies in severity from weakness and atrophy of the extensor digitorum brevis (EDB) and weakness of toe dorsiflexors to classic peroneal muscular atrophy with foot drop. Peroneal muscles are affected earlier and more severely than the calf muscles. If peroneal muscular atrophy develops, it is associated with *pes cavus* and moderate sensory abnormalities in stocking distribution and, less often, glove distribution. Individuals with lower leg involvement have a high steppage gait.

Proximal limb muscle weakness is not observed in the upper or lower extremities.

Sensory examination is either normal or shows mild to moderate impairment of vibration sense in the hands and feet; in individuals with the CMT2D subtype, reduction of pinprick, temperature, touch, and vibration perception in a stocking and less often glove pattern is observed (Table 2).

Reflexes at the ankles are diminished or absent in individuals with leg muscle weakness and sensory deficits.

Table 2. Phenotypic Features of CMT2D/dSMA-V Disease Subtypes

Symptoms and Signs	Subtype	
	CMT2D (%)	dSMA-V (%)
Progressive bilateral weakness and wasting of thenar and FDI muscles [1]	100	100
Peroneal weakness with atrophy and *pes cavus*	100	57.5
Pyramidal dysfunction	0	12.5
Reduced sensation for touch, pain, and temperature	100	0
Reduced vibration sense	100	37.5

Sivakumar et al 2005

1. FDI = First dorsal interosseus

Electrophysiologic studies. Electrophysiologic studies are consistent with motor axonopathy and thus exclude a demyelinating neuropathy (Table 3). EMG shows denervation predominantly in the distal muscle groups at normal motor distal latencies and conduction velocities:

- Absent or markedly reduced (frequently <1 mV) compound muscle action potentials (CMAPs) are recorded from the abductor pollicis brevis (APB) by median nerve stimulation [Sivakumar et al 2005].
- Preserved CMAPs are recorded from the abductor digiti minimi (ADM) by ulnar nerve stimulation.
- CMAP amplitude recorded by stimulation of the peroneal nerve is below 2 mV in most individuals and below 1 mV in individuals having clinically evident leg atrophy.
- Normal median SNAP amplitudes and conduction velocities are seen in most individuals, even those with mildly prolonged distal motor latency.
- In individuals with advanced disease, needle EMG shows no voluntary motor activity in the abductor pollicis and first dorsal interossei because of marked atrophy. Spontaneous activity is often seen in these muscles.
- The elicited sural sensory nerve action potentials are preserved but with a reduced amplitude, despite sensory axonal loss identified histopathologically on examination of a sensory nerve from an individual with the CMT2D subtype; similar but milder changes were seen in individuals with dSMA-V.

Table 3. Results of Electrophysiologic Studies in CMT2D and dSMA-V Subtypes

Results of Electrophysiologic Studies		Subtype	
		CMT2D (%)	dSMA-V (%)
Motor Nerve Conduction	**Compound muscle action potential** [1]		
	Median-APB <4.5 mV	100	100
	Ulnar-ADM <3.5 mV	0	0
	Peroneal-EDB <2 mV	100	62.5
	Tibial-AH <2.5 mV	0	50
	Distal motor latency		
	Median <5.6 ms	0	0
	Ulnar <4.5 ms	0	11
	Peroneal & tibial <7.5 ms	0	0
	Nerve conduction velocity		
	Median & ulnar <39 m/s	0	0
	Peroneal & tibial <29 m/s	0	0
Sensory Nerve Conduction	**Sensory nerve action potential**		
	Median <10; ulnar <8 µV	0	12
	Sural <6 µV**	17	29

1. APB = Abductor pollicis brevis
ADM = Abductor digiti minimi

EDB = Extensor digitorum brevis
AH = Adductor hallucis

Nerve biopsy. The dSMA-V subtype shows clear signs of axonal pathology with two or more regenerative clusters per fascicle (Figure 2A). No evidence of active degeneration and no obvious signs of demyelination or typical onion bulb formation are present. Myelin structures appear normal. Overall myelinated fiber density is normal (Figure 2B). Fibers less than 7 mm in diameter represent 52% of the overall number of fibers in the affected individual compared to 65% in control specimens. Electron microscopy shows denervated Schwann cell subunits as indicated by an increased number of profiles, suggesting damage to small unmyelinated fibers (Figure 2C). The UMNF density is at the low normal level.

The CMT2D subtype shows clear evidence of axonal pathology in nerve biopsy in one individual. Axonal swelling with filamentous accumulations (Figure 2D) and four to eight regenerative clusters per fascicle are observed (Figure 2E). Pseudo onion bulb formations and a few thinly myelinated fibers are seen. Myelin structures appear intact. Overall myelinated fiber density is reduced. The proportion of fibers less than 7 mm in diameter is only 46%. Denervation of Schwann cell subunits as indicated by an increased number of profiles is seen on EM.

Genotype-Phenotype Correlations

At this point, no genotype-phenotype correlations can be made as the same mutations in *GARS* can cause both the dSMA-V and CMT2D subtypes even in the same family.

Penetrance

Penetrance is estimated to be about 80%.

Anticipation

Anticipation is not observed.

Prevalence

Disease prevalence is unknown. Eight families manifesting CMT2D/dSMA-V have been identified worldwide [Antonellis et al 2003, Sivakumar et al 2005, Del Bo et al 2006].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Charcot-Marie-Tooth neuropathy type 2D/distal spinal muscular atrophy V (CMT2D/dSMA-V) needs to be distinguished from other forms of CMT, spinal muscular atrophy (SMA), and unrelated but similar neurologic conditions.

Charcot-Marie-Tooth disease type 2 (CMT2) has a wide range of onset age and diverse manifestations. Several genes are known to be associated with some of the CMT2 subtypes [Zuchner & Vance 2006]. Generally, individuals with CMT2 present with distal muscular atrophy, loss of reflexes, sensory deficits, reduced sensory nerve action potentials, and normal or mildly slowed motor nerve conduction velocity. The unique pattern of hand involvement before leg involvement and preserved sensory nerve action potentials helps distinguish CMT2D from other CMT2 subtypes.

Distal spinal muscular atrophy (dSMA), a genetically heterogeneous group of disorders caused by progressive degeneration of anterior horn neurons, is characterized by slowly progressive muscle weakness and atrophy in the distal limbs without sensory deficits. Sensory nerve action potentials are preserved and motor conduction velocities are nearly normal. A separate set of disease-causing genes have been associated with dSMA subtypes [Irobi, De Jonghe et al 2004; Irobi, Van Impe et al 2004]. The pattern of hand involvement before leg involvement distinguishes dSMA-V from other dSMA subtypes. A dSMA-V variant associated with spasticity in the legs and amyotrophy in the hands is known as Silver syndrome [Silver 1966]. Caused by mutations in *BSCL2*, encoding seipin [Irobi, Van den Bergh et al 2004; Windpassinger et al 2004], Silver syndrome is now known to be part of the spectrum of the *BSCL2*-related neurologic disorders. In contrast to Silver syndrome, in which most individuals have spasticity, only a minority of individuals with *GARS*-related dSMA-V subtype show mild pyramidal signs and spasticity (Table 2) [Christodoulou et al 1995, Sivakumar et al 2005, Dubourg et al 2006].

Other neurologic disorders. The clinical pattern of disease onset with hand weakness and atrophy rather than foot involvement and absent sensory deficits in the early stages of the illness should raise a suspicion of carpal tunnel syndrome, neurogenic thoracic outlet syndrome, or multifocal motor neuropathy:

- When there is no family history, paresthesia, or pain, the clinical pattern of median nerve dysfunction at the wrist in individuals with carpal tunnel syndrome may be similar to that seen in the early stages of CMT2D/dSMA-V. Carpal tunnel syndrome is usually asymmetric and limited to median nerve.
- Compression of the lower cervical and T1 roots caused by a cervical rib may result in neurogenic thoracic outlet syndrome. In this condition, thenar, hypothenar and interossei weakness/atrophy is associated with ulnar and medial antebrachial cutaneous hypesthesia that could be validated by EMG findings of reduced sensory nerve action potential amplitudes in the ulnar nerve.
- Multifocal motor neuropathy is an autoimmune demyelinating disease causing slowly progressing motor disturbances in peripheral nerve distributions, predominantly in the distal upper extremities. It is often asymmetric and eventually involves hand muscles innervated by two or more nerves. Electrophysiologic conduction block can be demonstrated in the motor nerves and anti GM1 antibody titers are often elevated.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Charcot-Marie-Tooth neuropathy type 2D/distal spinal muscular atrophy V (CMT2D/dSMA-V):

- Clinical examination for evidence of myopathy affecting distal muscles of the upper limbs
- Nerve conduction studies

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- Clinical examination for evidence of myopathy affecting distal muscles of the upper limbs
- Nerve conduction studies

Treatment of Manifestations

- Ankle support, toe-up braces, and ankle-foot orthotics, as necessary

Surveillance

- Periodic assessment by a neurologist and/or a neuromuscular disorders specialist

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Charcot-Marie-Tooth neuropathy type 2D/distal spinal muscular atrophy V (CMT2D/dSMA-V) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with CMT2D/dSMA-V have an affected parent. The family history may appear to be negative because of failure to recognize the disorder in family members, early death of a parent before the onset of symptoms, or late onset of the disease.
- A proband with CMT2D/dSMA-V may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include neurologic exam; a nerve conduction study, and molecular genetic testing if a mutation has been identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low but is greater than that of the general population because of the possibility of germline mosaicism.

- Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with CMT2D/dSMA-V has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has a disease-causing mutation and/or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis for CMT2D/dSMA-V are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Charcot-Marie-Tooth Neuropathy Type 2D/Distal Spinal Muscular Atrophy V

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CMT2D	*GARS*	7p15	Glycyl-tRNA synthetase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Charcot-Marie-Tooth Neuropathy Type 2D/Distal Spinal Muscular Atrophy V

600287	GLYCYL-tRNA SYNTHETASE; GARS
600794	SPINAL MUSCULAR ATROPHY, DISTAL, TYPE V; DSMAV
600794	SPINAL MUSCULAR ATROPHY, DISTAL, TYPE V; DSMAV
601472	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2D; CMT2D

Table C. Genomic Databases for Charcot-Marie-Tooth Neuropathy Type 2D/Distal Spinal Muscular Atrophy V

Gene Symbol	Locus Specific	Entrez Gene	HGMD
GARS	GARS	2617 (MIM No. 600287)	GARS

For a description of the genomic databases listed, click here.

Normal allelic variants: The *GARS* gene spans 40 kb and contains 17 exons. The 2.7-kb *GARS* transcript is ubiquitously expressed. There are six known sequence variants: two (p.S252L, p.Q334R) are non-synonymous and four are synonymous.

Pathologic allelic variants: p.E71G, p.L129P, p.G240R, p.H418R, p.D500N, p.G526R [Antonellis et al 2003, Sivakumar et al 2005, Del Bo et al 2006].

Normal gene product: Glycyl-tRNA synthetase, a class II aminoacyl-tRNA synthetase, performs an essential function in protein synthesis by catalyzing aminoacylation of glycyl-tRNA, which is required for charging tRNA with cognate amino acids [Ge et al 1994]. The enzyme must properly recognize the tRNA species and the amino acid in order to maintain fidelity of translation. In accordance with its function, glycyl-tRNA synthetase contains three domains: a catalytic core, a C-terminal anticodon recognition domain, and a domain that interacts with the acceptor stem of glycyl-tRNA [Freist et al 1996].

Abnormal gene product: Three of the five known *GARS* mutations occurred within or next to the catalytic core, indicating that the mutations may interfere with the ability of glycyl-tRNA to interact with the receptor of the cognate tRNA [Antonellis et al 2003]. Modeling in yeast demonstrated granular deposits in neurite projections and loss-of-function features in experiments with at least four mutations, suggesting that tRNA-charging enzymes play a key role in maintaining peripheral axons [Antonellis et al 2006]. In contrast, phenotypes observed in transgenic mice were not caused by insufficiencies in protein synthesis [Seburn et al 2006]. Further research efforts are needed for identification of specific disease mechanisms affecting peripheral axons.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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Chester PA 19013-4867
Phone: 800-606-CMTA (800-606-2682); 610-499-9264; 610-499-9265
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Email: info@charcot-marie-tooth.org
www.charcot-marie-tooth.org

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Department of Molecular Genetics
University of Antwerp
B-2610 Antwerp
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The Hereditary Neuropathy Foundation
P.O. Box 287103
New York NY 10128
Phone: 917-648-6971
Email: email: info@hnf-cure.org
www.hnf-cure.org

National Library of Medicine Genetics Home Reference
Charcot-Marie-Tooth disease

NCBI Genes and Disease
Charcot-Marie-Tooth syndrome

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

Muscular Dystrophy Campaign
7-11 Prescott Place
London SW4 6BS
United Kingdom
Phone: (+44) 0 020 7720 8055
Fax: (+44) 0 020 7498 0670
Email: info@muscular-dystrophy.org
www.muscular-dystrophy.org

Teaching Case-Genetic Tools
Cases designed for teaching genetics in the primary care setting.
Case 7. Resident Receives a Troubling Phone Call about Peripheral Neuropathy from a Patient's Relative

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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Revision History

- 30 January 2007 (lgg) Revision: sequence analysis clinically available for mutations in *GARS*
- 8 November 2006 (me) Review posted to live Web site
- 24 February 2006 (lgg) Original submission

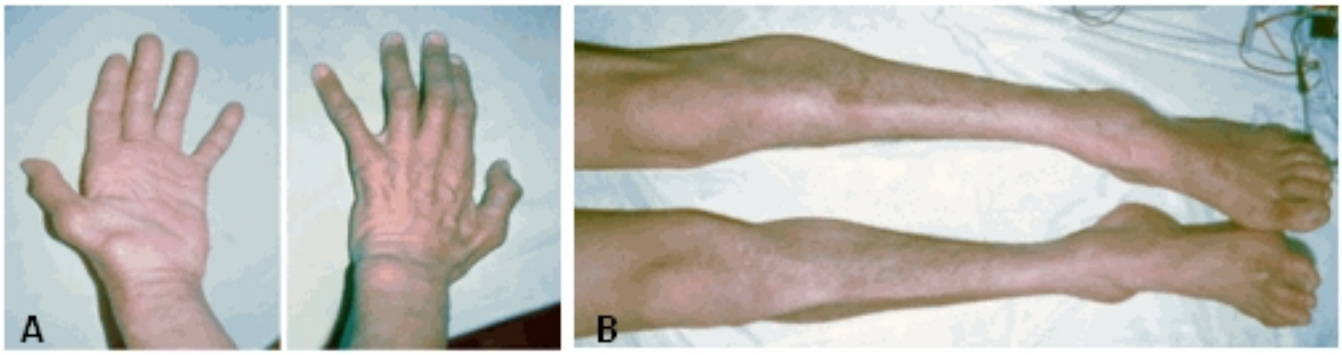

Figure 1. Distribution of muscle weakness and atrophy in individuals with two major clinical subtypes of *GARS* mutation associated disease:
A. Thenar and first dorsal interosseus muscle wasting with relatively preserved hypothenar in an individual with dSMA-V phenotype
B. Peroneal atrophy, *pes cavus*, and hammerhead toes in an individual with the CMT2D clinical variant; this individual also has a reduction of pinprick, temperature, touch, and vibration sense in stocking distribution.
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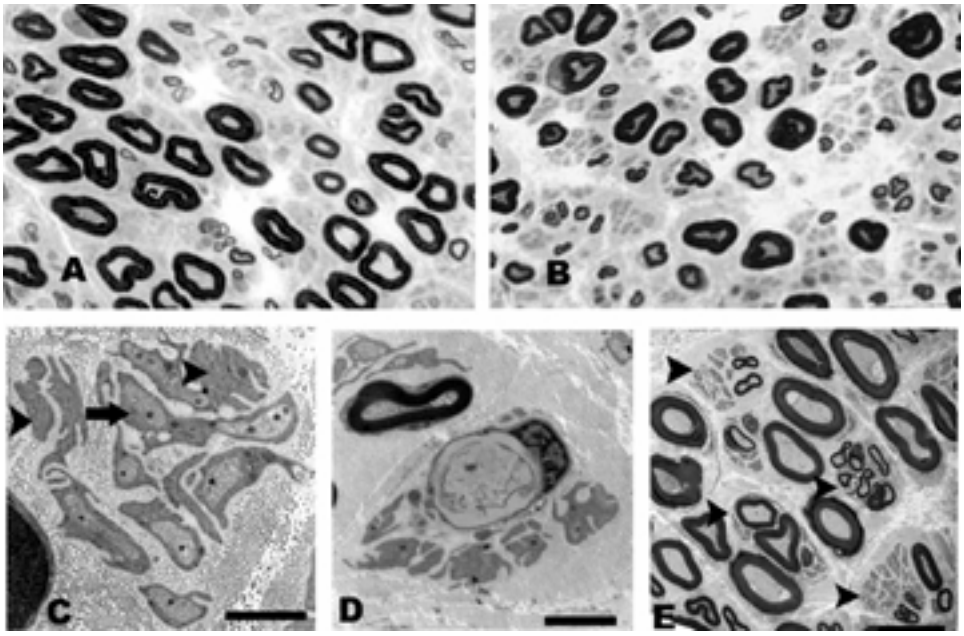

Figure 2. Sural nerve morphology in *GARS* mutation-related dSMA-V and CMT2D phenotypes:
A. dSMA-V. Pathologic changes are minimal with a near-normal myelinated nerve fiber density.
B. CMT2D. Myelinated nerve fiber density is moderately reduced.
C. CMT2D. Unmyelinated fiber cluster
D. CMT2D. Active axonal degeneration of myelinated nerve fiber
E. CMT2D. Multiple regenerative clusters (arrowheads)
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