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SH3TC2-Related Hereditary Motor and Sensory Neuropathy

Synonyms: Charcot-Marie-Tooth Disease Type 4C, CMT4C, *SH3TC2*-HMSN, *SH3TC2*-Related Charcot-Marie-Tooth Neuropathy

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Summary

Clinical characteristics

SH3TC2-related hereditary motor and sensory neuropathy (*SH3TC2*-HMSN) is a demyelinating neuropathy characterized by severe spine deformities (scoliosis or kyphoscoliosis) and foot deformities (*pes cavus*, *pes planus*, or *pes valgus*) that typically present in the first decade of life or early adolescence. Other findings can include cranial nerve involvement (most commonly tongue involvement, facial weakness/paralysis, hearing impairment, dysarthria) and respiratory problems.

Diagnosis/testing

The diagnosis of *SH3TC2*-HMSN is established in a proband with suggestive findings and biallelic pathogenic variants in *SH3TC2* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic. Affected individuals are often managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, physical and occupational therapists, audiologists/otolaryngologists, speech and language therapists, and pulmonologists.

Surveillance: Routine follow up of motor and sensory manifestations, foot care, spine deformities, occupational and physical therapy needs, hearing, speech, and language therapy needs, and nutrition and growth.

Agents/circumstances to avoid: Obesity, which makes walking more difficult; medications that are toxic or potentially toxic to persons with hereditary motor and sensory neuropathy.

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Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual in order to identify as early as possible those who would benefit from early detection and treatment of scoliosis as well as awareness of agents/circumstances to avoid.

Genetic counseling

SH3TC2-HMSN is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SH3TC2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *SH3TC2* pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Because the carrier frequency for *SH3TC2*-HMSN in certain populations (e.g., individuals of Spanish Roma heritage) is relatively high and the onset of *SH3TC2*-HMSN may be late, some individuals who undergo carrier testing may be identified as being homozygous. Once the *SH3TC2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for *SH3TC2*-HMSN are possible.

Diagnosis

No consensus clinical diagnostic criteria for *SH3TC2*-related hereditary motor and sensory neuropathy (*SH3TC2*-HMSN) have been published.

Suggestive Findings

SH3TC2-HMSN **should be suspected** in individuals with the following clinical manifestations, nerve conduction velocities, neuropathology, and family history [Kessali et al 1997, Gabreëls-Festen et al 1999, Azzedine et al 2006].

Clinical manifestations

- Early and severe scoliosis, the presenting sign in most individuals
- Neuropathy, usually developing in the first decade or adolescence, but occasionally manifesting as delay in onset of independent ambulation in early childhood
- Slowly progressive neuropathy, with some individuals becoming wheelchair dependent because of involvement of the proximal lower limbs

Motor nerve conduction velocities (MNCV) are in the range observed in demyelinating disease:

- MNCV of the median nerve is typically 4-37 m/sec, with a mean of 22 m/sec.
- MNCV is not correlated with disease duration.
- In some cases, electroneuromyographic examination is incomplete or does not allow measurement of MNCVs because of the severity of the secondary axonal loss.

Neuropathology. Neuropathologic findings are no longer required to raise suspicion of *SH3TC2*-HMSN. If nerve biospy was performed in the past, see Clinical Description, Histopathology for characteristic findings.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *SH3TC2*-HMSN **is established** in a proband with Suggestive Findings and biallelic pathogenic (or likely pathogenic) variants in *SH3TC2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SH3TC2* variants of uncertain significance (or identification of one known *SH3TC2* pathogenic variant and one *SH3TC2* variant of uncertain significance) does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) (Option 1) and **comprehensive genomic testing** (exome sequencing, genome sequencing) (Option 2). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

Option 1

Single-gene testing can be considered (depending on the cost, compared to that of a multigene panel) before use of a multigene panel in the rare instance in which an affected individual has had a muscle biopsy that shows the distinctive histologic findings of *SH3TC2*-HMSN (see Clinical Description, Histopathology). Sequence analysis is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, if only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such *SH3TC2* variants have not been identified as a cause of this disorder.

A hereditary neuropathy multigene panel that includes *SH3TC2* 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 *SH3TC2*-HMSN has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *SH3TC2*-Related Hereditary Motor and Sensory Neuropathy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SH3TC2	Sequence analysis [3]	All variants reported to date [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

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. Azzedine et al [2006]
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No causative deletions or duplications involving *SH3TC2* have been reported.

Clinical Characteristics

Clinical Description

SH3TC2-related hereditary motor and sensory neuropathy (*SH3TC2*-HMSN) is a demyelinating neuropathy characterized by early-onset severe scoliosis. Scoliosis as well as foot deformities were the presenting findings in most individuals with *SH3TC2*-HMSN. Other findings include cranial nerve involvement, respiratory involvement, and sensory ataxia (Table 2).

Table 2. *SH3TC2*-Related Hereditary Motor and Sensory Neuropathy: Frequency of Select Features

Feature or Involved Organ/System		% of Persons w/Feature	Comment
Neuropathy		100	
Foot deformity [1]		>90	
Spine deformity [1]		>79	
Cranial nerve	Tongue	~37	Fasciculations, weakness/atrophy
	Facial weakness/ paralysis	~29	
	Hearing impairment	~26	Slightly ↓ auditory sensitivity
			Significant ↓ of auditory sensitivity
	Ophthalmologic	~14	Nystagmus (See Other Clinical Findings, **Ophthalmologic involvement**.), abnormal pupillary light reflexes, asymmetric pupil size
	Head tremor	~14	
	Vocal cord	~7	
Respiratory		~18	Hypoventilation / respiratory insufficiency
Sensory ataxia		>7	

Table 2. continued from previous page.

Feature or Involved Organ/System	% of Persons w/Feature	Comment
Cramps & pain	Rare	Facial pain / trigeminal neuralgia

Based on Senderek et al [2003], Gooding et al [2005], Azzedine et al [2006], Colomer et al [2006], Houlden et al [2009], Baets et al [2011], Laššuthová et al [2011], Fischer et al [2012], Yger et al [2012], Piscosquito et al [2016], Kontogeorgiou et al [2019], Skott et al [2019]
1. See Table 3.

Foot and Spine Deformities

See Table 3 for detailed data.

Foot deformities (*pes cavus*, *pes planus*, or *pes valgus*) were reported in 72% to 100% of affected individuals [Senderek et al 2003, Azzedine et al 2006, Colomer et al 2006, Kontogeorgiou et al 2019, Skott et al 2019]. Foot deformities were first observed between ages two and ten years, were moderately or severely disabling, and required surgery in 6% (1/18) to 11% (3/28) of individuals.

Spine deformities (scoliosis or kyphoscoliosis) were observed between ages two and ten years in most individuals [Kessali et al 1997, Gabreëls-Festen et al 1999], or more rarely, early in the second decade [Senderek et al 2003]. However, manifestations may be evident at birth or much later: onset at age 37 years was reported in one individual [Colomer et al 2006].

Cumulative data indicate that scoliosis occurs in 73% of persons with *SH3TC2*-HMSN. In some individuals the spine deformities are moderate; in others they are disabling. The curvature progressed three to five degrees annually and required surgery in 7% to 39% of reported individuals.

Table 3. *SH3TC2*-Related Hereditary Motor and Sensory Neuropathy: Occurrence of Foot and Spine Deformities by Study

Study Finding		Study (Total Persons)								
		Azzedine et al [2006] (28)	Colomer et al [2006] (14)	Senderek et al [2003] (18)	Houlden et al [2009] (6)	Baets et al [2011] (9)	Laššuthová et al [2011] (16)	Yger et al [2012] (14)	Fischer et al [2012] (6)	Cumulative Data
Age at onset (yrs)	1st symptoms	2-10	4-39	Infancy-12	1-16	<1	1-12	1-12	–	1-16
	Neuropathy	2-10	–	Infancy-12	1-16	<1	2-50	2-50	2-25	1-50
Age at (last) exam (yrs)		5-45	–	8-45	11-56	8-42	–	–	8-59	5-59
Foot deformity	*Pes cavus*	20/28	14/14 [1]	8/18	Yes	–	13/15	12/14	–	
	Pes planus	7/28		4/18	Yes	–	No	No	–	
	Pes valgus	1/28		–	–	–	No	3/14	–	
	Other	No	–	Hammer toes 8/18	Small feet	–	Hammer toes	No	–	
	Total	28/28	14/14	13/18 [2]	6/6 [1]	7/9	14/15	14/14	–	96/104 (92%)
	Age at onset (yrs)	2-10	–	2-12	–	–	–	1, 12 [3]	–	1-12
	Surgery	3/28	None	1/13	None	–	9/14	4/14	–	17/69 (24%)

Table 3. continued from previous page.

Study Finding		Study (Total Persons)								
		Azzedine et al [2006] (28)	Colomer et al [2006] (14)	Senderek et al [2003] (18)	Houlden et al [2009] (6)	Baets et al [2011] (9)	Laššuthová et al [2011] (16)	Yger et al [2012] (14)	Fischer et al [2012] (6)	Cumulative Data
Spine deformity	Total	27/28	5/14 [4]	11/18 [4]	6/6	6/9	10/12	12/12	5/6	82/105 (78%)
	Age at onset (yrs)	2-10	4	4-12 [5]	–	2, 6, 7, 12 [6]	–	7-15	–	2-15
	Surgery	7 [7] + 6 [8] = 13/27	1/14	1/11	3/6	3/6	–	1/12	–	22/76 (29%)

– = not done or not documented
1. Authors did not specify type of deformities.
2. Authors did not specify the foot deformity in the one person who had surgery.
3. Unknown for 12 of 14 persons
4. Authors did not indicate whether they evaluated for kyphoscoliosis and/or lordosis.
5. Onset of scoliosis in infancy; age not reported
6. Age documented in four persons only
7. Kessali et al [1997]
8. Gabreëls-Festen et al [1999]

Other Clinical Findings

See Table 4 for detailed data.

Cranial nerve involvement is seen in 45% of individuals with *SH3TC2*-HMSN.

Hearing impairment. Hypoacusis (slightly diminished auditory sensitivity) was reported in 15/103 persons with *SH3TC2*-HMSN and deafness (significant reduction of auditory sensitivity) in 12/103 persons. The cumulative data from the literature showed that hypoacusis and deafness were each present in approximately 11.5% and 14.5% of individuals, respectively. For more detailed discussion of hearing loss in general, see Deafness and Hereditary Hearing Loss Overview.

Respiratory problems. The cumulative data from the literature showed that respiratory problems occurred in approximately 18%.

Ophthalmologic involvement. Nystagmus was reported in 2/18 persons [Senderek et al 2003] and in 4/5 persons, including one with cerebellar atrophy and vestibulopathy. The latter could be either causal or contributory (together with ataxia) to the nystagmus [Skott et al 2019].

Abnormal pupillary light reflexes, facial paresis, hypoventilation/respiratory insufficiency, lingual fasciculation, head tremor, sensory ataxia, and diabetes mellitus were also reported.

Cramps and pain. Little to no data are available on cramps and pain in *SH3TC2*-HMSN. In general, cramps and pain occur in 56%-96% of individuals with all forms of hereditary motor and sensory neuropathy (CMT) [Carter et al 1998, Abresch et al 2002, Tiffreau et al 2006, Padua et al 2008]. Cramps are usually present from the onset, whereas pain may develop as the disease progresses.

In individuals with *SH3TC2*-HMSN, the following have been reported:

- Facial pain in a woman age 80 years [Skott et al 2019]

- Trigeminal neuralgia in an affected person age 55 years [Piscosquito et al 2016], in a child of Greek heritage with onset before age five years [Kontogeorgiou et al 2019], and in a person of Spanish Roma heritage [Pérez-Garrigues et al 2014]

Table 4. *SH3TC2*-Related Hereditary Motor and Sensory Neuropathy: Additional Clinical Findings by Study

Clinical Finding	Study (Total Persons)							
	Azzedine et al [2006] (28)	Colomer et al [2006] (14)	Senderek et al [2003] (18)	Houlden et al [2009] (6)	Baets et al [2011] (9)	Laššuthová et al [2011] (16)	Yger et al [2012] (14)	Cumulative Data
Hypoacusis	5/28	0/14	2/18	0/6	0/9	0/15	8/13	15/103
Deafness	0/28	5/14	1/18	2/6	1/9	3/15	0/13	12/103
Nystagmus	0/28	0/14	2/18	0/6	2/9	0/15	0/13	4/103
Pupillary light reflexes	0/28	3/14	0/18	1/6	0/9	0/15	14/13	4/20
Other pupillary disturbances	–	–	–	Asymmetric size 1/6	–	–	–	1/6
Lingual fasciculation	–	3/14	–	–	–	–	–	3/14
Tongue atrophy &/or weakness	–	–	–	1/6	–	–	2/13	3/19
Facial paresis	1/28	–	–	1/6	1/9	–	4/13	7/56
Facial weakness	–	–	–	1/6	–	–	–	1/6
Head tremor	–	2/14	–	–	–	–	–	2/14
Vocal cord involvement	–	–	–	–	–	–	1/13	1/13
Total persons w/ cranial nerve involvement	5/28	9/14	5/14 [1]	4/6	–	–	10/13	33/73
Respiratory insufficiency / Hypoventilation	7/28 [2]	–	2/18	–	1/9	–	–	10/55
Sensory ataxia	1/28	2/14	–	–	–	–	–	>3/42 [3]
Diabetes mellitus	–	–	1/18	–	–	–	–	1/18
Romberg sign	–	2/14	–	–	–	–	–	2/14

– = not done or not documented

1. Only 14 of 18 ipersons were examined for cranial nerve involvement.

2. Kessali et al [1997] reported that 7/11 persons required spine surgery because the severity of their deformities caused difficulty in sitting and pulmonary restriction.

3. Gabreëls-Festen et al [1999] reported mild sensory ataxia in some persons, without specifying how many.

Additional findings include the following:

- Dropped head syndrome in one individual [de Oliveira et al 2019].
- Cerebellar atrophy together with mild cerebellar ataxia in 1/5 and thickening of cranial nerves in another 1/5 [Skott et al 2019].
- Vestibular areflexia in 7/10 Spanish individuals [Pérez-Garrigues et al 2014]

Histopathology

Nerve biopsies – no longer required to suspect the diagnosis of *SH3TC2*-HMSN – show a combination of morphologic features unique among the demyelinating forms of CMT [Kessali et al 1997, Gabreëls-Festen et al 1999, Gooding et al 2005]:

- Loss of myelinated fibers
- Relatively few and small classic onion bulbs, as observed in CMT1A, caused by heterozygous pathogenic variants in *PMP22*
- Basal membrane onion bulbs, consisting of concentric Schwann cell lamellae intermingled with single or double basal membranes or concentric basal membranes alone
- Schwann cells of unmyelinated axons, often with very thin processes and connecting links between axons

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified: to date, intra- and interfamilial variability is consistently observed [Azzedine et al 2006].

Nomenclature

Hereditary motor and sensory neuropathy is most commonly referred to by the eponymous name "Charcot-Marie-Tooth (CMT) neuropathy" or "Charcot-Marie-Tooth disease."

Based on an older classification system in which subtypes were defined by clinical findings, the mode of inheritance, neuropathy type (defined by electrophysiologic findings), pathologic finding (when available), and involved gene, *SH3TC2*-HMSN is also referred to as "Charcot-Marie-Tooth disease type 4C (CMT4C)."

For further review of nomenclature, see the Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Prevalence

SH3TC2-HMSN (caused by biallelic pathogenic variants in *SH3TC2*) is a relatively frequent cause of the autosomal recessive demyelinating neuropathy (also known as CMT4). On the basis of cumulative data available in 2013, the prevalence of *SH3TC2*-HMSN among those with CMT4 was approximately 18% (53/299) [Senderek et al 2003, Azzedine et al 2006, Houlden et al 2009, Fischer et al 2012, Iguchi et al 2013].

Three more recent studies revealed the following:

- Testing for 14 genes (*EGR2*, *FIG4*, *GARS*, *GDAP1*, *GJB1*, *HSPB1*, *LITAF*, *MFN2*, *MPZ*, *NEFL*, *PMP22*, *PRX*, *RAB7A*, and *SH3TC2*) in a large cohort of 17,880 individuals with neuropathy identified *SH3TC2* pathogenic variants in 0.8% [DiVincenzo et al 2014].
- Evaluation of 612 index cases with a Charcot-Marie-Tooth phenotype, hereditary sensory neuropathy, familial amyloid neuropathy, or small fiber neuropathy using a panel of 80 genes associated with autosomal recessive, autosomal dominant, and X-linked neuropathy identified *SH3TC2*-HMSN as the cause in 9.9% of all individuals (representing the third most involved gene of the cohort) and in 29.3% of individuals with neuropathy inherited in an autosomal recessive manner [Dohrn et al 2017].
- In a cohort of 50 Greek individuals with autosomal recessive demyelinating CMT, Kontogeorgiou et al [2019] identified *SH3TC2* pathogenic variants in 26%.
- Dohrn et al [2017] and Kontogeorgiou et al [2019] confirm the high prevalence of *SH3TC2*-HMSN among autosomal recessive demyelinating CMTs (CMT4).

SH3TC2-HMSN has been found in diverse geographic origins: Europe, Mediterranean Basin, Asia, North America; and diverse countries, including: Albania, Algeria, Austria, Belgium, Bosnia, Canada, China, Czech

Republic, England, France, Germany, Greece Hungary, Iran, Italy, Japan, Morocco, Spain, Sweden, the Netherlands, Turkey, and the United States.

SH3TC2-HMSN occurs in diverse ethnic groups:

- Romani from Spain and Turkey [LeGuern et al 1996, Gabreëls-Festen et al 1999, Guilbot et al 1999, Senderek et al 2003, Azzedine et al 2005a, Azzedine et al 2005b, Azzedine et al 2006, Colomer et al 2006, Houlden et al 2009, Baets et al 2011, Fischer et al 2012]
- The *SH3TC2* pathogenic variant p.Arg954Ter is recurrent in several populations, including people who originated from the Mediterranean basin, Europe, and America [Azzedine et al 2005a, Azzedine et al 2005b, Azzedine et al 2006]. This founder effect leads to an increase in the occurrence of the disease in those populations [Azzedine et al 2005a, Azzedine et al 2005b, Gosselin et al 2008].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SH3TC2*.

Differential Diagnosis

See Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Management

No clinical practice guidelines for *SH3TC2*-related hereditary motor and sensory neuropathy (*SH3TC2*-HMSN) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SH3TC2*-HMSN, 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 *SH3TC2*-Related Hereditary Motor and Sensory Neuropathy

System/Concern	Evaluation	Comment
Growth	Measure height, weight, head circumference.	
Neurologic	Neurologic exam by child neurologist	Assessment for: • Tone, weakness, atrophy, sensory loss, joint contractures • Foot &/or hand involvement • Spine involvement • Cranial nerve involvement • Ataxia • Gait stability using CMT Infant Scale [1] or CMT Pediatric Scale [2] • Pain w/attention to distinguishing between neuropathic & mechanical pain
Spine/foot deformities	By pediatric orthopedist to determine interventions needed	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Physical medicine & rehab / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills & need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Need for AFOs, specialized shoes • Mobility, ADL, & need for adaptive devices/durable equipment • Need for handicapped parking
	By pediatric orthopedist	Assess amount & progression of spinal curvature & extent of foot deformities.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Dysarthria	Speech/language assessment by speech therapist	To determine need for speech therapy
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/ dysphagia &/or aspiration risk.
Hearing	Audiologic eval	Assess for hearing loss.
Eyes	Ophthalmologic exam	Baseline exam
Respiratory	By pediatric pulmonologist	Baseline exam
Genetic counseling	By genetics professionals [3]	To inform affected persons & families re nature, MOI, & implications of *SH3TC2*-HMSN to facilitate medical & personal decision making
Family support/ resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; AFOs = ankle-foot orthotics; CMT = Charcot-Marie-Tooth; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Mandarakas et al [2018]

2. Burns et al [2012]

3. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Treatment is symptomatic. Affected individuals are often managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, physical and occupational therapists, audiologists/ otolaryngologists, speech and language therapists, and pulmonologists (Table 6).

Table 6. Treatment of Manifestations in Individuals with *SH3TC2*-Related Hereditary Motor and Sensory Neuropathy

Manifestation/ Concern	Treatment	Considerations/Other
Neuropathy	Foot care	Those w/sensory loss need excellent foot care to avoid foot ulceration & necrosis.

Table 6. continued from previous page.

Manifestation/ Concern		Treatment	Considerations/Other
Foot deformity		Special shoes w/good ankle support &/or AFOs to correct foot drop & aid walking	When necessary, surgery to correct severe *pes cavus* deformity [2]
		PT to preserve flexibility	
Spine deformities		• PT to preserve flexibility • Bracing when possible	If these are not successful, surgery can be performed even before cessation of linear growth. [1]
Musculoskeletal		PT	• Daily heel cord stretching to help w/flexibility & prevent contractures • Other activities to help person remain as physically active as possible
		Durable medical equipment	Such as forearm crutches or canes for gait stability; wheelchairs for mobility
Development		See Developmental Delay / Intellectual Disability Management Issues.	
Dysarthria		Speech/language intervention	Per speech/language therapist
Gastrointestinal/ Feeding		Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Hearing		Intervention per audiologist & otolaryngologist	
Eyes		Intervention per ophthalmologist	
Respiratory		Intervention per pulmonologist	
Pain	**Neuropathic**	ASM	Such as pregabalin, gabapentin
	Mechanical	Combination of PT & orthopedic treatment	
Cramps		Quinine	Quinine is known to induce tinnitus & reversible high-tone hearing loss.
Career/Employment		Career counseling	May be influenced by persistent weakness of hands &/or feet

ASM = anti-seizure medication; AFOs = ankle-foot orthotics; PT = physical therapy
1. Kessali et al [1997], Gabreëls-Festen et al [1999]
2. Kessali et al [1997], Guyton & Mann [2000], Colomer et al [2006]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 7. Recommended Surveillance for Individuals with *SH3TC2*-Related Hereditary Motor and Sensory Neuropathy

System/Concern	Evaluation	Frequency
Neuropathy	Assess for motor & sensory changes.	Every 6 mos
Foot deformity	Assess foot deformities & compliance w/daily heel cord stretching exercises to prevent Achilles' tendon shortening.	
	Assess feet for sores, ill-fitting shoes.	Daily monitoring by patient
Spine deformity	Orthopedist: monitor type & degree of spinal deformities.	4x/yr recommended
Musculoskeletal	• OT: Monitor hand function. • PT: Monitor strength, mobility. • Both: Monitor ADL.	Every 6 mos
Development	Monitor developmental progress & educational needs.	Annually
Dysarthria		Per speech/language therapist
Gastrointestinal/ Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	Per gastroenterologist
Hearing	Assess & monitor hearing impairment.	Per audiologist & otolaryngologist
Eyes	Assess & monitor ophthalmologic involvement.	Per ophthalmologist

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Respiratory	Monitor for development of respiratory insufficiency / hypoventilation.	Per pulmonologist
Pain	Intensity, frequency, response to medications	As dictated by clinical evolution
Cramps		
Career/Employment	Highlight importance of investing in education to assure independent living.	At each visit to neurology clinic
Family support/ resources	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Obesity is to be avoided because it makes walking more difficult.

Medications that are toxic or potentially toxic to persons with Charcot-Marie-Tooth (CMT) disease comprise a range of risks ranging from definite high risk to negligible risk [Salih & Azzedine 2020]. See www.cmtausa.org for an up-to-date list.

Anesthesia. Relatively few studies reported in the literature address risks of anesthesia in patients with CMT. No complications were observed after anesthesia in a large cohort followed in specialized consultation, but the advice of the anesthesiologist should be followed. See also CMT Overview.

- Although it had no adverse effects in 41 persons with CMT [Antognini 1992], use of succinylcholine for general anesthesia is usually contraindicated.
- Blockers of the neuromuscular junction should be used with caution.
- Local/regional anesthesia, especially epidural analgesia at childbirth, has been used without problems in CMT. This use of anesthesia should be discussed on a case-by-case basis with the anesthesiologist.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual in order to identify as early as possible those who would benefit from awareness of agents/ circumstances to avoid and early detection and treatment of scoliosis.

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

Pregnancy Management

There are no guidelines for pregnancy management in CMT of any type; the following general statements are offered as possible considerations.

CMT appears to be an independent risk factor for complications during pregnancy and delivery.

- The symptoms of CMT can worsen during pregnancy; in particular: cramps, subjective sensitivity (e.g., paresthesias), difficulty walking, and fatigue.
- In rare instances, crises occurring during pregnancy do not subside post partum.
- A retrospective study in Norway between 1967 and 2002 comparing 108 births to mothers with CMT with 2.1 million births to mothers without CMT determined that mothers with CMT more frequently needed interventions during delivery [Hoff et al 2005]. Bleeding post partum was also more common in mothers with CMT.

- It has been postulated that fetal presentation tends to be abnormal because of the combination of CMT in the mother and fetus [Rayl et al 1996, Hoff et al 2005].

Note: Because *SH3TC2*-HMSN is an autosomal recessive type of CMT typically associated with early onset and severe manifestations, management of pregnancy in affected females is rarely an issue; however, an affected mother with late-onset disease who gave birth before becoming symptomatic has been reported [Gooding et al 2005].

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

SH3TC2-related hereditary motor and sensory neuropathy (*SH3TC2*-HMSN) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are typically heterozygotes (i.e., carriers of one *SH3TC2* pathogenic variant).
- In families in which the parents are of the same ethnic origin, where endogamy is frequent, a parent of the proband may have signs of *SH3TC2*-HMSN and be found to have homozygous *SH3TC2* pathogenic variants.
  - The carrier frequency of *SH3TC2*-HMSN is relatively high in certain populations. For example, the carrier frequency in individuals of Spanish Roma heritage is approximately 4% (see Prevalence).
  - Because a parent with biallelic *SH3TC2* pathogenic variants may have a late age of onset [Gooding et al 2005, Colomer et al 2006], their clinical status may not be apparent or recognized until their child is diagnosed with *SH3TC2*-HMSN.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SH3TC2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent of a proband with *SH3TC2*-HMSN, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband.
  - One of the pathogenic variants identified in the proband was inherited from a mosaic parent [Jónsson et al 2017].
  - The proband inherited a chromosome or a particular chromosomal region from only one of the proband's parents (if the chromosome or the chromosomal region encompasses an *SH3TC2* pathogenic variant, the child will be homozygous for this pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *SH3TC2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *SH3TC2* pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Intrafamilial clinical variability may be observed in sibs who inherit biallelic *SH3TC2* pathogenic variants [Azzedine et al 2006].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing *SH3TC2*-HMSN.

Offspring of a proband. Unless an affected individual's reproductive partner also has *SH3TC2*-HMSN or is a carrier (e.g., in a consanguineous union and/or in a union between two individuals of the same ethnic origin), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SH3TC2* (see Prevalence).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SH3TC2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SH3TC2* pathogenic variants in the family.

Related Genetic Counseling Issues

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

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *SH3TC2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *SH3TC2*-HMSN 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.

- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682 (toll-free); 610-427-2971
  Email: info@cmtausa.org
  www.cmtausa.org
- **European Charcot-Marie-Tooth Consortium**

Department of Molecular Genetics
University of Antwerp
Antwerp Antwerpen B-2610
Belgium
Fax: 03 2651002
Email: gisele.smeyers@ua.ac.be

- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **Medical Home Portal**
  Charcot-Marie-Tooth Disease (Hereditary Motor Sensory Neuropathy)
- **NCBI Genes and Disease**
  Charcot-Marie-Tooth syndrome
- **TREAT-NMD**
  Institute of Translational and Clinical Research
  University of Newcastle upon Tyne
  International Centre for Life
  Newcastle upon Tyne NE1 3BZ
  United Kingdom
  Phone: 44 (0)191 241 8617
  Fax: 44 (0)191 241 8770
  Email: info@treat-nmd.eu
  Charcot-Marie-Tooth Disease
- **Association Francaise contre les Myopathies (AFM)**
  1 Rue de l'International
  BP59
  Evry cedex 91002
  France
  Phone: +33 01 69 47 28 28
  Email: dmc@afm.genethon.fr
  www.afm-telethon.fr
- **European Neuromuscular Centre (ENMC)**
  Netherlands
  Phone: 31 35 5480481
  Email: enmc@enmc.org
  www.enmc.org
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352

www.musculardystrophyuk.org

- **RDCRN Patient Contact Registry: Inherited Neuropathies Consortium**
  Patient Contact Registry

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. SH3TC2-Related Hereditary Motor and Sensory Neuropathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SH3TC2	5q32	SH3 domain and tetratricopeptide repeat-containing protein 2	SH3TC2 homepage - Leiden Muscular Dystrophy pages	SH3TC2	SH3TC2

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 SH3TC2-Related Hereditary Motor and Sensory Neuropathy (View All in OMIM)

601596	CHARCOT-MARIE-TOOTH DISEASE, TYPE 4C; CMT4C
608206	SH3 DOMAIN AND TETRATRICOPEPTIDE REPEAT DOMAIN 2; SH3TC2

Molecular Pathogenesis

The SH3TC2 protein has been reported to contain Src homology-3 (SH3) domains and tetratricopeptide repeat (TPR) domains (see Roberts et al [2010] for more information about possible pathogenic mechanisms). The spectrum of possible functions mediated by the TPR and SH3 domains is large.

- SH3 domains are highly conserved in eukaryotes, prokaryotes, and viruses, and mediate interactions with enzymes (tyrosine kinases, phospholipases cγ [PLCγ], and PLCγ, phosphoinositide 3-kinase, and the NADPH-oxidase complex), cytoskeleton molecules (spectrin and nebulin), and myosins. They play important roles in cell-to-cell communication and signal transduction from the cell surface to the nucleus [Whisstock & Lesk 1999].
- Proteins with TPR domains are involved in many cellular processes through protein-protein interactions: in mitosis and RNA synthesis by their association in multi-protein complexes controlling cell-cycle or transcription machinery, in protein transport, and in chaperone functions [Blatch & Lassle 1999].

Mechanism of disease causation. Most pathogenic variants in *SH3TC2* lead to loss or truncation of the protein, compatible with loss of function in an autosomal recessive disorder.

Table 8. Notable *SH3TC2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_024577.3 NP_078853.2	c.2860C>T	p.Arg954Ter	Founder variant identified in persons from Algeria, Albania, Austria, Belgium, Bosnia, Canada, Czech, England, France, Germany, Greece, Hungary, Italy, Iran, Japan, Morocco, Sweden, the Netherlands, & Turkey [1]
	c.3325C>T	p.Arg1109Ter	Founder effect identified in Spanish Roma & Turkish Roma families [2] & in non-Roma families from Albania, Italy, & Greece [3]

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. Azzedine et al [2005a], Azzedine et al [2005b], Azzedine et al [2006], Colomer et al [2006], Houlden et al [2009], Baets et al [2011], Laššuthová et al [2011], Fischer et al [2012], Piscosquito et al [2016], Kontogeorgiou et al [2019], Skott et al [2019]
2. Gooding et al [2005], Colomer et al [2006], Claramunt et al [2007]
3. Piscosquito et al [2016], Kontogeorgiou et al [2019]

Chapter Notes

Author Notes

For more than two decades, our work has been mainly devoted to peripheral neuropathies and related disorders, especially the autosomal recessive forms. We intended to identify the genetic basis of these disorders, to establish genotype-phenotype correlations, if any, and to better characterize each clinical phenotype. We are also interested in the pathophysiology underlying the different phenotypes encountered in this highly variable genetic disorder. This work leads to a better knowledge of the disease and paves the way for therapeutic research.

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