GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Charcot-Marie-Tooth Neuropathy Type 4C

[*CMT4C, Charcot-Marie-Tooth Disease Type 4C*]

Hamid Azzedine, PhD
Department of Neurology - Charcot
National Center for Neurodegenerative Diseases
Centre Hospitalier Universitaire d'Angers
Angers, France
INSERM U679
Hôpital de la Pitié-Salpêtrière
Paris, France
azzedine@ccr.jussieu.fr, azzedine.hamid@yahoo.fr

Eric LeGuern, MD, PhD
INSERM U679
Département de génétique et cytogénétique
Hôpital de la Pitié-Salpêtrière
Paris, France
leguern@ccr.jussieu.fr

Initial Posting: March 31, 2008.

Summary

Disease characteristics. Charcot-Marie-Tooth neuropathy type 4C (CMT4C) is a demyelinating neuropathy characterized by early-onset severe spine deformities. The majority of affected children present with scoliosis or kyphoscoliosis between ages two and ten years, although earlier and later onset are observed. Slowly progressive neuropathy usually manifests in the first decade or adolescence, and occasionally earlier or later. Foot deformities (pes cavus, pes planus, or pes valgus) are common.

Diagnosis/testing. Diagnosis is based on clinical findings, the results of motor nerve conduction velocity testing, and molecular genetic testing of *SH3TC2(KIAA1985*), the only gene known to be associated with CMT4C. Because the diagnosis of CMT4C is defined by the presence of an *SH3TC2* mutation, all individuals with CMT4C have a mutation in this gene.

Management. *Treatment of manifestations:* Treatment of spinal deformities includes physiotherapy to preserve flexibility, bracing, and/or surgery, even at a young age. Treatment of foot deformities includes special shoes with good ankle support and/or ankle/foot orthoses (AFOs) to correct foot drop and aid walking, and in some cases surgery; associated pain and cramps may require medication. *Prevention of secondary complications:* Daily heel cord stretching exercises and physical activity may help prevent contractures. *Surveillance:* Monitor for onset and/or progression of scoliosis and changes in hand function and foot strength. *Agents/ circumstances to avoid:* obesity; drugs and medications known to cause nerve damage (e.g., vincristine, isoniazid, taxol, cisplatin, nitrofurantoin). *Other:* Career and employment may be influenced by hand and/or foot weakness.

Genetic counseling. CMT4C is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for at-risk pregnancies are possible if both disease-causing mutations have been identified in the family.

Diagnosis

Clinical Diagnosis

Charcot-Marie-Tooth neuropathy type 4C (CMT4C) is characterized by the following:

- Early and severe scoliosis, the presenting sign in most individuals [Kessali et al 1997, Gabreëls-Festen et al 1999, Azzedine et al 2006]
- Neuropathy that usually develops in the first decade or adolescence, but occasionally manifests as delay in onset of independent ambulation in early childhood
- Slowly progressive neuropathy; some individuals become wheelchair dependent because of involvement of the proximal lower limbs

Electrophysiology. The motor nerve conduction velocity (MNCV) of the median nerve is in the range observed in demyelinating disease: 4-37 m/sec, with a mean of 22 m/sec. MNCV is not correlated with disease duration.

Testing

Neuropathology. Nerve biopsies 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], including the following:

- Loss of myelinated fibers
- Relatively few and small classic onion bulbs, as observed in CMT1A (see CMT1)
- 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

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.

Molecular Genetic Testing—Gene. *SH3TC2(KIAA1985)* [Senderek et al 2003] is the only gene known to be associated with CMT4C.

Clinical testing

- **Sequence analysis.** Because this disorder is defined by the presence of a mutation in the causative gene, the mutation detection rate is 100%.

  Note: Because sequence analysis only detects sequence variants in the coding region of the gene, mutations such as exonic, multiexonic, and whole-gene deletions or gross genomic rearrangements would not be detected by this method.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Charcot-Marie-Tooth Neuropathy Type 4C

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
SH3TC2	Sequence analysis	Sequence variants	100% [1]	Clinical Testing

1. Because sequence analysis only detects sequence variants in the coding region of the gene, mutations such as exonic, multiexonic, and whole-gene deletions or gross genomic rearrangements would not be detected by this method.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To establish the diagnosis in a proband, the following findings are necessary:

- Clinical findings suggestive of CMT4C
- Family history consistent with autosomal recessive inheritance (includes simplex cases, i.e., a single occurrence in a family)
- MNCVs in the demyelinating range

  Note: In some cases, electroneuromyographic examination is incomplete or does not allow measurement of MNCVs because of the severity of the secondary axonal loss.
- For simplex cases, exclusion of 17p11.2 duplication and mutations in *PMP22* (CMT1A) (see CMT1), *MPZ* (CMT1B) (see CMT1), and *GJB1*, which encodes connexin 32 (CMTX1) (see CMTX)
- Molecular genetic testing of *SH3TC2*
- If molecular genetic testing does not reveal two *SH3TC2* mutations:
  - Another demyelinating neuropathy should be considered. Of note, two of ten (20%) individuals with various neuropathies associated with mutations in *EGR2* had scoliosis [Szigeti at al 2007] (see also Differential Diagnosis);

    or
  - A nerve biopsy may be needed to determine the nature of the neuropathy.

    Note: Nerve biopsy is of great diagnostic value in those with a demyelinating process.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *SH3TC2*.

Clinical Description

Natural History

Charcot-Marie-Tooth neuropathy type 4C (CMT4C) is a demyelinating neuropathy characterized by early-onset severe scoliosis. Scoliosis as well as foot deformities were the presenting findings in most individuals with CMT4C.

Spine deformities (scoliosis or kyphoscoliosis) were observed between ages two and ten years in most cases [Kessali et al 1997, Gabreëls-Festen et al 1999], or more rarely, early in the second decade [Senderek et al 2003]. However, the disease may start at birth or much later, as reported in a 37-year-old affected individual [Colomer et al 2006].

Cumulative data indicate that scoliosis occurs in 72% of persons with CMT4C (Table 2). Scoliosis or kyphoscoliosis was found in:

- 96% of affected individuals (27/28) in the largest series reported to date [Azzedine et al 2006].
- 47% (11/18) of individuals studied [Senderek et al 2003]
- 36% (5/14) of individuals studied [Colomer et al 2006]

In some cases 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 cases (Table 2) [Kessali et al 1997,Gabreëls-Festen et al 1999].

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]. 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 cases (Table 2).

Table 2. Occurrence of Manifestations of CMT4C by Study

Study Finding		Study (Total Patients)			Cumulative Data
		Azzedine et al 2006 (28)	Colomer et al 2006 (14)	Senderek et al 2003 (18)	
Age at Diagnosis		2-10 yrs	4-39 yrs	Birth-12 yrs	Birth-39 yrs
Foot deformities	**Pes cavus**	20/28	14/14 [1]	8/18	28/46
	Pes planus	7/28		4/18	11/46
	Pes vagus	1/28		--	1/28
	Total	28/28	14/14	13/18 [2]	55/60
	Age at Onset	2-10 yrs	No data	2-12 yrs	2-12 yrs
	Surgery	3/28	None	1/18	4/46
Spine deformities		27/28	5/14 [3]	11/18 [3]	43/60
	Age at Onset	2-10 yrs	4 yrs	4-12 [4] yrs	2-12 yrs
	Surgery	7 [5] + 6 [6] = 13/28	1/14	ND	14/42

1. Authors did not specify type of deformities.
2. Authors did not specify the foot deformity in the one patient who had surgery.
3. Authors did not indicate if they evaluated for kyphoscoliosis and/or lordosis.
4. Onset of scoliosis was in infancy, age not reported.
5. Kessali et al 1997
6. Gabreëls-Festen et al 1999

Other. No data are available on cramps and pain in individuals with CMT4C. In general, cramps and pain are common in all forms of CMT, occurring in 80% of affected individuals, according to a recent study from the French CMT association [O Dubourg, personal communication]. Cramps are usually present from the onset, whereas pain may develop as the disease progresses.

Hypoacousis (slightly diminished auditory sensitivity) was reported in 7/46 persons with CMT4C [Senderek et al 2003, Azzedine et al 2006] and deafness (significant reduction of auditory sensitivity) in 7/46 persons [Senderek et al 2003, Colomer et al 2006]. The cumulative data from the literature showed that hypoacousis and deafness were each present in 15% of individuals (Table 3). For more detailed discussion of hearing loss in general, see Deafness and Hereditary Hearing Loss Overview.

Nystagmus was reported in 2/18 persons with CMT4C [Senderek et al 2003].

Pupillary light reflexes, facial paresis, hypoventilation/respiratory insufficiency, lingual fasciculation, head tremor, sensory ataxia, and diabetes mellitus were also reported (Table 3). The cumulative data from the literature showed that respiratory problems occurred in 20% of individuals with CMT4C. The other findings occur in 2% to 6% of individuals with CMT4C (Table 3).

Table 3. Additional Clinical Findings in CMT4C by study

Clinical Finding	Study (Total Patients)			Cumulative Data
	Azzedine et al 2006 (28)	Colomer et al 2006 (14)	Senderek et al 2003 (18)	
Hypoacusis	5/28	--	2/18	7/46
Deafness	--	5/14	2/18	7/46
Nystagmus	--	--	2/18	2/46
Pupillary light reflexes	--	3/14	--	3/46
Lingual fasciculation	--	3/14	--	3/46
Facial paresis	1/28	--	--	1/46
Head tremor	--	2/14	--	2/46
Sensory ataxia	--	2/14	--	>2/46 [1]
Respiratory insufficiency or hypoventilation	7/28 [2]	--	2/18	9/46
Diabetes mellitus	--	--	1/18	1/46
Romberg sign	--	2/14	--	2/46

1. Gabreëls-Festen et al (1999) reported mild sensory ataxia in some individuals, without indicating the number of cases.
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.

Pregnancy. 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.
- Exceptionally, 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].

Genotype-Phenotype Correlations

Significant intrafamilial variability in the disease course makes it difficult to identify phenotype-genotype correlations [Kessali et al 1997, Gabreëls-Festen et al 1999, Senderek et al 2003, Azzedine et al 2005].

- In 28 individuals with CMT4C, Azzedine et al (2006) showed the lack of correlation between the nature and the position of the mutation, disease duration, and the stage of disability. They also reported intrafamilial variability in age at onset, disease duration, and stage of disability.
- Colomer et al (2006) reported clinical variability in 14 affected individuals who had the same mutation.

Prevalence

CMT4C (caused by mutations in *SH3TC2*) is a relatively frequent cause of the autosomal recessive demyelinating neuropathy CMT4. On the basis of the cumulative data presented in Table 4, the prevalence of CMT4C among those with CMT4 is approximately 17%.

Table 4. Proportion of CMT4 Attributable to CMT4C by Study

	Study					Cumulative Data
	Azzedine et al 2006 [1]	Colomer et al 2006	Senderek et al 2003 [1]			
Individuals with CMT4C / all CMT4	10/38 [2] (26%)	--	4/14 [3]	6/55 [4]	2/21 [5]	22/128 (17%)
			Total: 12/90 (13%)			

1. Denominators represent the number of patients or families with CMT4 included in each study; numerators indicate the number with *SH3TC2* mutations.
2. Ten of 38 (26%) families with the CMT4 phenotype had *SH3TC2* mutations [Azzedine et al 2005, Azzedine et al 2006].
3. In 14 large and/or consanguineous families, five (36%) showed data consistent with but not significant for linkage to the CMT4C locus; however, *SH3TC2* mutations were identified in only four of the five [Senderek et al 2003]. Note: In the family with suggestive linkage to CMT4C but no mutation in *SH3TC2*, linkage may have been fortuitous or/and the mutation may not have been detectable by sequence analysis.
4. In 55 different families with CMT4, 15 showed data consistent with but not significant for linkage to CMT4C; only 6/15 (40%) had *SH3TC2* mutations. Note: In the nine families with suggestive linkage to CMT4C but no mutation in *SH3TC2*, linkage may have been fortuitous or/and the mutations may not have been detectable by sequence analysis.
5. In a group of 21 unrelated individuals with CMT4, two had mutations in *SH3TC2*.

Only one out of 19 (5%) Turkish families had an *SH3TC2* mutation [Parman et al 2004].

Mutations in *SH3TC2* have been found in individuals of diverse geographic origins (Algeria, Morocco, France, the Netherlands, Germany, Italy, Bosnia, Greece, Turkey, and Iran) and diverse ethnic origins (gypsies from Spain and Turkey) [LeGuern et al 1996, Gabreëls-Festen et al 1999, Guilbot et al 1999, Senderek et al 2003, Azzedine et al 2005, Azzedine et al 2006, Colomer 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 4C (CMT4C) accounts for an estimated 10% of demyelinating CMT in simplex cases (i.e., a single occurrence in a family) in which the following have been excluded:

- Duplication 17p11.2 that causes CMT1A
- Mutations in *PMP22* that cause CMT1E (see CMT1)
- Mutations in *MPZ* that cause CMT1B (see CMT1); and CMT2I and CMT2J (see CMT2)
- Mutations in *GJB1(CX32*) that cause CMTX1 (see CMTX)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Charcot-Marie-Tooth neuropathy type 4C (CMT4C), the following evaluations are recommended:

- Examination by a child neurologist to evaluate for weakness and atrophy, gait stability, sensory loss, and other associated signs. It is important to distinguish between neuropathic pain and mechanical pain.
- Examination by a pediatric orthopedist to assess the amount and progression of spinal curvature and to determine the extent of foot deformities
- Examination by an otolaryngologist and/or ophthalmologist if problems with hearing or vision are present

Treatment of Manifestations

Treatment is symptomatic. Affected individuals are often managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. See Grandis & Shy (2005) for a discussion of general treatment for CMT.

Treatment of spinal deformities

- Physiotherapy helps to preserve flexibility.
- If the curvature can be reduced with bracing, either a plaster or a thermo-molded plastic corset can be used.
- If bracing and physiotherapy together are not sufficient to correct the scoliosis, surgery can be performed at an early age, even before the end of linear growth (Table 2) [Kessali et al 1997,Gabreëls-Festen et al 1999]. Surgical intervention requires consensus among the family, child (if possible), and attending physicians.

Treatment of foot deformities

- Special shoes with good ankle support and/or ankle/foot orthoses (AFOs) to correct foot drop and aid walking
- Physiotherapy to preserve flexibility
- In approximately 9% of individuals, surgery to correct severe pes cavus deformity (Table 2) [Kessali et al 1997,Guyton & Mann 2000,Colomer et al 2006]

Treatment of pain and cramps

- Neuropathic pain can be treated with antiepileptic drugs (AEDs) (e.g., pregabalin, gabapentin).

- Mechanical pain can generally be managed with a combination of physiotherapy and orthopedic treatment.
- Cramps can be controlled with quinine.

Other

- Some individuals require forearm crutches or canes for gait stability; some need wheelchairs.
- Exercise to help the individual remain physically active according to his/her abilities is encouraged.

Prevention of Secondary Complications

Daily heel cord stretching exercises help prevent Achilles' tendon shortening.

Physical activity (e.g., swimming, bicycling, stretching) adapted to the abilities of each individual by a physiotherapist is useful to prevent contractures.

Individuals with diabetes mellitus need excellent foot care to avoid foot ulceration and necrosis.

Surveillance

Scoliosis needs to be closely followed. Monitoring four times a year is recommended.

Hand function and foot strength should be evaluated by an orthopedist every six months starting from the date of diagnosis.

Agents/Circumstances to Avoid

Obesity is to be avoided because it makes walking more difficult and increases risk factors for diabetes mellitus.

Drugs and medications known to cause nerve damage (e.g., vincristine, isoniazid, taxol, cisplatin, nitrofurantoin), should be avoided [Graf et al 1996, Chaudhry et al 2003]. See Weimer & Podwall 2005 for a more detailed review.

Testing of Relatives at Risk

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

Therapies Under Investigation

See Grandis & Shy 2005.

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

Other

Career and employment may be influenced by persistent weakness of hands and/or feet.

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.

- For general anesthesia, succinylcholine is usually contraindicated; however, it had no adverse effects in 41 persons with CMT [Antognini 1992].

- Blockers of the neuromuscular junction should be used with caution.
- Local-regional anesthesia, especially epidural analgesia at child birth, has been used without problems in CMT. This use of anesthesia should be discussed on a case-by-case basis with the anesthesiologist.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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 4C (CMT4C) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with CMT4C are obligate heterozygotes (carriers) for an *SH3TC2* disease-causing mutation.

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

Carrier Detection

Carrier testing for at-risk family members is available once the disease-causing mutations have been identified in the family.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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.

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. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as CMT4C that do not affect intellect or life span are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. 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 4C

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CMT4C	*SH3TC2*	5q32	SH3 domain and tetratricopeptide repeats-containing protein 2

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 4C

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

Table C. Genomic Databases for Charcot-Marie-Tooth Neuropathy Type 4C

Gene Symbol	Locus Specific	Entrez Gene	HGMD
SH3TC2	SH3TC2	79628 (MIM No. 608206)	SH3TC2

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

Note: HGMD requires registration.

Normal allelic variants: The normal gene comprises 17 coding exons spanning 62 kb of genomic sequence.

Pathologic allelic variants: To date, 20 mutations have been reported [Senderek et al 2003, Azzedine et al 2005, Azzedine et al 2006, Colomer et al 2006]. See Table 5.

Table 5. *SH3TC2* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change (Alias [1])	Reference Sequence
c.28delG (26delG)	p.Glu10SerfsX4 (Arg9fs)	NM_024577.3 NP_078853.2
c.217_227delGCTGCTCGGAGinsCCAGTAA	p.Ala73ProfsX55	
c.530-2A>G	-- [2]	
c.920G>A	p. Trp307X	
c.1171-1G>A	-- [2]	
c.1586G>A	p.Arg529Gln	
c.1747_1748delAG	p.Arg583AlafsX4	
c.1969G>A	p.Glu657Lys	
c.1972C>T	p.Arg658Cys	
c.1982T>C	p.Leu662Pro	
c.2191delG	p.Glu731LysfsX20	
c.2491_2492delAG	p.Leu832HisfsX8	
c.2642A>T	p.Asn881Ser	
c.2710C>T	p. Arg904X	
c.2829T>G	p.Tyr943X	
c.2860C>T	p.Arg954X	
c.3325C>T	p.Arg1109X	
c.3326G>C	p.Arg1109Pro	
c.3341delC	p.Pro1114LeufsX2	
c.3601C>T	p.Gln1201X	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

For frameshift mutations, 'X#' indicates the codon position in the new reading frame that ends in a stop (X). The position of the stop in the new reading frame is calculated starting at the first changed amino acid that is created by the frameshift (e.g., p.Glu10Ser) and ending at the first stop codon (X#), e.g., p.Glu10SerfsX4). The shifted reading frame is thus open for '#-1' amino acids (thus in p.Glu10SerfsX4, the new reading frame is open for three more codons, therefore terminating at codon 13).

1. Variant designation that does not conform to current naming conventions
2. Because the splice donor or splice acceptor site is changed, the change is expected to affect splicing (the nomenclature designation is r.spl?).

Normal gene product: The protein, known as the SH3 domain and tetratricopeptide repeats containing protein 2 (SH3TC2), comprises 1,287 amino acids. It contains two Src homology-3 (SH3) domains and ten tetratricopeptide repeat (TPR) domains.

Proteins with TPR domains are involved in many cellular processes through protein-protein interactions: in mitosis and RNA synthesis by their association in multiprotein complexes controlling cell-cycle or transcription machinery, in protein transport, and in chaperon functions [Blatch & Lassle 1999]. SH3 domains are highly conserved in eukaryotes, prokaryotes, and viruses, and mediate interactions with enzymes (tyrosine kinases, phospholipases $c\gamma_1$ [$PLC\gamma_1$] and $PLC\gamma_2$, phosphoinositide 3-kinase and the NADPH-oxidase complex), cytoskeleton molecules (spectrin and nebulin), and myosins. They play important roles in cell-cell communication and signal transduction from the cell surface to the nucleus [Whisstock & Lesk 1999]. The spectrum of possible functions mediated by the TPR and SH3 domains is therefore large. The function of the molecule and the effect of the mutations will require further investigation in cellular and mouse models.

Abnormal gene product: Most mutations in *SH3TC2* lead to loss or truncation of the protein, compatible with loss of function in an autosomal recessive disease. Thirteen of the 19 mutations described in the authors' series [Azzedine et al 2005, Azzedine et al 2006] and previously reported [Senderek et al 2003] directly or indirectly affected the structure or the number of TPR domains. For example, the p.Arg904X mutation affected the TPR5 domain in exon 11 and reduced the number of TPR domains from ten to four. Furthermore, deletion of only the last TPR (TPR10) domain in the SH3TC2 protein caused by the p.Gln1201X mutation reported by Senderek et al (2003) was sufficient to induce the phenotype.

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.

Charcot-Marie-Tooth Association
2700 Chestnut Street
Chester PA 19013-4867
Phone: 800-606-CMTA (800-606-2682); 610-499-9264; 610-499-9265
Fax: 610-499-9267
Email: info@charcot-marie-tooth.org
www.charcot-marie-tooth.org

European Charcot-Marie-Tooth Consortium
Department of Molecular Genetics
University of Antwerp
Antwerp B-2610
Belgium
Fax: 03 2651002
Email: gisele.smeyers@ua.ac.be

The Hereditary Neuropathy Foundation
1751 2nd Avenue Suite 103
New York NY 10128
Phone: 877-463-1287; 212-722-8396
Email: email: info@hnf-cure.org
www.hnf-cure.org

NCBI Genes and Disease
Charcot-Marie-Tooth syndrome

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-572-1717
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.

Literature Cited

Antognini JF. Anaesthesia for Charcot-Marie-Tooth disease: a review of 86 cases. Can J Anaesth. 1992;39:398–400. [PubMed: 1563065]

Azzedine H, Ravise N, Verny C, Gabreels-Festen A, Lammens M, Grid D, Vallat JM, Durosier G, Senderek J, Nouioua S, Hamadouche T, Bouhouche A, Guilbot A, Stendel C, Ruberg M, Brice A, Birouk N, Dubourg O, Tazir M, LeGuern E. Spine deformities in Charcot-Marie-Tooth 4C caused by SH3TC2 gene mutations. Neurology. 2006;67:602–6. [PubMed: 16924012]

Azzedine H, Verny C, Tazir M, Gabreels-Festens A, Birouk N, Dubourg O, Senderek J, Ravise N, Grid D, Brice A, LeGuern E. Eight new Mutations of KIAA1985 gene associated with severe form of demyelinating autosomal recessive Charcot-Marie-Tooth disease (CMT4C) in 11 families and a founder effect occurs in families originated from North Africa and Europe. 57th annual meeting of the American Academy of Neurology, Miami, April 9th-16th 2005. 2005

Blatch GL, Lassle M. The tetratricopeptide repeat: a structural motif mediating protein-protein interactions. Bioessays. 1999;21:932–9. [PubMed: 10517866]

Chaudhry V, Chaudhry M, Crawford TO, Simmons-O'Brien E, Griffin JW. Toxic neuropathy in patients with pre-existing neuropathy. Neurology. 2003;60:337–40. [PubMed: 12552058]

Colomer J, Gooding R, Angelicheva D, King RH, Guillen-Navarro E, Parman Y, Nascimento A, Conill J, Kalaydjieva L. Clinical spectrum of CMT4C disease in patients homozygous for the p.Arg1109X mutation in SH3TC2. Neuromuscul Disord. 2006;16:449–53. [PubMed: 16806930]

Gabreels-Festen A, van Beersum S, Eshuis L, LeGuern E, Gabreels F, van Engelen B, Mariman E. Study on the gene and phenotypic characterisation of autosomal recessive demyelinating motor and sensory neuropathy (Charcot-Marie-Tooth disease) with a gene locus on chromosome 5q23-q33. J Neurol Neurosurg Psychiatry. 1999;66:569–74. [PubMed: 10209165]

Gooding R, Colomer J, King R, Angelicheva D, Marns L, Parman Y, Chandler D, Bertranpetit J, Kalaydjieva L. A novel Gypsy founder mutation, p.Arg1109X in the CMT4C gene, causes variable peripheral neuropathy phenotypes. J Med Genet. 2005;42:e69. [PubMed: 16326826]

Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP, Bird TD. Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. Cancer. 1996;77:1356–62. [PubMed: 8608515]

Grandis M, Shy ME. Current Therapy for Charcot-Marie-Tooth Disease. Curr Treat Options Neurol. 2005;7:23–31. [PubMed: 15610704]

Guilbot A, Kessali M, Ravise N, Hammadouche T, Bouhouche A, Maisonobe T, Grid D, Brice A, LeGuern E. The autosomal recessive form of CMT disease linked to 5q31-q33. Ann N Y Acad Sci. 1999;883:453–6. [PubMed: 10586271]

Guyton GP, Mann RA. The pathogenesis and surgical management of foot deformity in Charcot-Marie-Tooth disease. Foot Ankle Clin. 2000;5:317–26. [PubMed: 11232233]

Hoff JM, Gilhus NE, Daltveit AK. Pregnancies and deliveries in patients with Charcot-Marie-Tooth disease. Neurology. 2005;64:459–62. [PubMed: 15699375]

Kessali M, Zemmouri R, Guilbot A, Maisonobe T, Brice A, LeGuern E, Grid D. A clinical, electrophysiologic, neuropathologic, and genetic study of two large Algerian families with an autosomal recessive demyelinating form of Charcot-Marie-Tooth disease. Neurology. 1997;48:867–73. [PubMed: 9109869]

LeGuern E, Guilbot A, Kessali M, Ravise N, Tassin J, Maisonobe T, Grid D, Brice A. Homozygosity mapping of an autosomal recessive form of demyelinating Charcot-Marie-Tooth disease to chromosome 5q23-q33. Hum Mol Genet. 1996;5:1685–8. [PubMed: 8894708]

Parman Y, Battaloglu E, Baris I, Bilir B, Poyraz M, Bissar-Tadmouri N, Williams A, Ammar N, Nelis E, Timmerman V, De Jonghe P, Najafov A, Deymeer F, Serdaroglu P, Brophy PJ, Said G. Clinicopathological and genetic study of early-onset demyelinating neuropathy. Brain. 2004;127:2540–50. [PubMed: 15469949]

Rayl J, Gibson PJ, Hickok DE. A population-based case-control study of risk factors for breech presentation. Am J Obstet Gynecol. 1996;174:28–32. [PubMed: 8572022]

Senderek J, Bergmann C, Stendel C, Kirfel J, Verpoorten N, De Jonghe P, Timmerman V, Chrast R, Verheijen MH, Lemke G, Battaloglu E, Parman Y, Erdem S, Tan E, Topaloglu H, Hahn A, Muller-Felber W, Rizzuto N, Fabrizi GM, Stuhrmann M, Rudnik-Schoneborn S, Zuchner S, Michael Schroder J, Buchheim E, Straub V, Klepper J, Huehne K, Rautenstrauss B, Buttner R, Nelis E, Zerres K. Mutations in a gene encoding a novel SH3/TPR domain protein cause autosomal recessive Charcot-Marie-Tooth type 4C neuropathy. Am J Hum Genet. 2003;73:1106–19. [PubMed: 14574644]

Szigeti K, Wiszniewski W, Saifi GM, Sherman DL, Sule N, Adesina AM, Mancias P, Papasozomenos SCh, Miller G, Keppen L, Daentl D, Brophy PJ, Lupski JR. Functional, histopathologic and natural history study of neuropathy associated with EGR2 mutations. Neurogenetics. 2007;8:257–62. [PubMed: 17717711]

Weimer LH, Podwall D. Medication-induced exacerbation of neuropathy in Charcot Marie Tooth disease. J Neurol Sci. 2006;242:47–54. [PubMed: 16386273]

Whisstock JC, Lesk AM. SH3 domains in prokaryotes. Trends Biochem Sci. 1999;24:132–3. [PubMed: 10322416]

Chapter Notes

Acknowledgments

We would like to thank Dr Merle Ruberg for critical review of the manuscript and Drs M Tazir, A Gabreëls-Festen, M Lammens, N Birouk, and O Dubourg for referral of affected individuals. This work was supported by the Association Française contre les Myopathies (AFM); The National center for neurodegenerative diseases, Department of Neurology, Section Charcot, CHU Angers; the Assistance Publique des Hôpitaux de Paris (AP-HP); the Institut National

de la Santé et de la Recherche Médicale (INSERM) and GIS-Maladies rares. Hamid Azzedine and Eric LeGuern are members of the **French GIS-maladies rares research network on autosomal recessive forms of CMT**.

Revision History

- 31 March 2008 (me) Review posted to live Web site
- 10 February 2006 (ha) Original submission