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Charcot-Marie-Tooth Neuropathy Type 4A

[*CMT4A, Charcot-Marie-Tooth Disease Type 4A*]

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Summary

Disease characteristics. Charcot-Marie-Tooth neuropathy type 4A (CMT4A), an aggressive form of hereditary motor and sensory neuropathy (HMSN), is confined to the peripheral nervous system, and typically affects the lower extremities earlier and more severely than the upper extremities. As the neuropathy progresses, the distal upper extremities also become severely affected. Even proximal muscles can become weak. The age at onset is from infancy to early childhood. In most cases, the disease progression causes disabilities within the first or second decade of life. At the end of the second decade, most individuals are wheelchair bound. Disease progression varies considerably even within the same family. The neuropathy can be either of the demyelinating type with reduced nerve conduction velocities or the axonal type with normal nerve conduction velocities. Vocal cord paresis is common. Intelligence is normal. Life expectancy is usually not affected, but on occasion may be reduced because of secondary complications.

Diagnosis/testing. Diagnosis of CMT4A is based on clinical findings and confirmed by molecular genetic testing of *GDAP1*, the only gene known to be associated with CMT4A. Such testing is clinically available.

Management. Treatment of CMT4A is symptomatic and involves evaluation and management by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment may include: ankle/foot orthoses, orthopedic surgery, forearm crutches or canes, wheelchairs, treatment of musculoskeletal pain with acetaminophen or nonsteroidal anti-inflammatory agents, and career and employment counseling. Surveillance includes regular evaluation by the multidisciplinary team to determine neurologic status and functional disability.

Genetic counseling. CMT4A is usually inherited in an autosomal recessive manner. The asymptomatic parents of an affected individual are obligate heterozygotes (carriers) and therefore carry one mutant allele. The sibs of an affected individual have 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. Carrier testing is available on a clinical basis once the mutations have

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been identified in the proband. Prenatal testing is available for families in which the disease-causing mutations have been identified.

Diagnosis

Clinical Diagnosis

The following findings suggest the clinical diagnosis of CMT4A, findings that overlap those in other CMT forms:

- Early onset of peripheral neuropathy, presenting especially with foot deformities, muscle wasting, and involvement of the sensory nerves
- Disability within the first and second decade of life
- Vocal cord paresis (hoarse voice)
- Diaphragm paralysis
- Facultative involvement of cranial and enteric nerves
- Proximal muscle involvement later in the disease course

Electrophysiology. Motor nerve conduction velocities (NCVs) are variable. Most affected individuals exhibit an axonal neuropathy with normal NCVs and reduced amplitudes [Sevilla et al 2003]. Some families have a demyelinating neuropathy with slowed NCVs [Baxter et al 2002, Nelis et al 2002, Ammar et al 2003, Sandre-Giovannoli et al 2003] and others have NCVs that fall in the intermediate range [Senderek et al 2003].

The axonal phenotype is probably more often associated with vocal cord paresis than the demyelinating phenotype [Cuesta et al 2002], but the converse has also been observed [Boerkoel et al 2003].

Sensory NCVs are moderately reduced.

Neuropathology. Both demyelinating and axonal peripheral nerve lesions have been observed. Prominent loss of medium-sized and large myelinated fibers has been described [Nelis et al 2002, Ammar et al 2003, Boerkoel et al 2003, Sevilla et al 2003]. Onion bulb formations as well as thinly myelinated and unmyelinated axons have been observed [Nelis et al 2002, Sandre-Giovannoli et al 2003]. In one study, findings were interpreted as an intermediate type of neuropathy [Senderek et al 2003]. Focally folded myelin is not a feature.

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. *GDAP1* is the only gene known to be associated with CMT4A [Baxter et al 2002, Cuesta et al 2002].

Clinical uses

- Diagnostic testing
- Carrier testing
- Prenatal diagnosis

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Clinical testing

- **Sequence analysis.** Mutations are identified in nearly 100% of individuals with autosomal recessive CMT whose disease has been mapped to 8q13-q21.1.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*GDAP1* sequence alterations	~100%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, and/or test method

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

Genetically Related (Allelic) Disorders

In addition to CMT4A, mutations in *GDAP1* cause autosomal dominant CMT2K [Claramunt et al 2005]. (See *GeneReview* on CMT2).

Clinical Description

Natural History

CMT4A is an aggressive form of hereditary motor and sensory neuropathy (HMSN) with early onset, increased severity, and unusual symptoms. The disease is confined to the peripheral nervous system. Intelligence is normal. Variability in disease progression has been reported within one family [Azzedine et al 2003].

Onset is in infancy, often before two years of age. At birth, children might be hypotonic (the so-called "floppy infant").

Affected children can show delayed achievement of motor milestones, including walking. Typically, initial symptoms are in the distal lower extremities, including foot deformities such as high arch, hammertoe, and *pes cavus* or *equinovarus*; muscle wasting; areflexia; and sensory loss.

Most authors describe early involvement of the upper extremities with muscle wasting and finger contractions (claw hands), weakness of proximal muscles, and a hoarse voice caused by vocal cord paresis, which occurs during the disease progression [Sevilla et al 2003, Stojkovic et al 2004].

Progression leads to disability of the lower and upper extremities. At the end of the second decade, most individuals are wheelchair bound. Respiratory dysfunction has not been described in CMT4A.

Rare symptoms are spinal deformities [Birouk et al 2003, De Sandre-Giovannoli et al 2003, Sevilla et al 2003], facial weakness [Boerkoel et al 2003], and painless lower leg ulcers [Nelis et al 2002].

Life expectancy is usually not affected, but on occasion may be reduced because of secondary complications.

Genotype-Phenotype Correlations

Genotype-phenotype correlations have not been reported.

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Penetrance

All published pedigrees demonstrating CMT4A with the expected autosomal recessive inheritance show complete penetrance of the phenotype. In these families, heterozygotes for one disease-causing allele appeared to be free of symptoms.

Anticipation

Anticipation has not been observed.

Prevalence

Currently, CMT4A is considered the most frequent of all autosomal recessive forms of CMT.

Molecular genetic testing has shown that the following proportion of individuals with CMT have two disease-causing *GDAP1* alleles:

- Five of 33 (15%) individuals from Europe with autosomal recessive (AR) CMT [Nelis et al 2002]
- One of 153 (0.7%) individuals from North America with CMT
- Three of 14 (14%) Hispanics, caused by a founder effect [Boerkoel et al 2003]
- Four of 119 (3.3%) individuals from Europe with AR CMT [Ammar et al 2003]

Differential Diagnosis

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

(See Charcot-Marie-Tooth Hereditary Neuropathy Overview and Charcot-Marie-Tooth Type 4.)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Charcot-Marie-Tooth neuropathy type 4A (CMT4A):

- Physical examination to determine extent of weakness and atrophy, pes cavus, gait stability, and sensory loss
- NCV to help distinguish demyelinating, axonal, and mixed forms of neuropathy
- Detailed family history

Treatment of Manifestations

Individuals with CMT4A are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists [Carter et al 1995, Grandis & Shy 2005]. Treatment is symptomatic and may include the following:

- Ankle/foot orthoses (AFOs) to correct foot drop and aid walking [Carter et al 1995]
- Orthopedic surgery to correct severe pes cavus deformity [Guyton & Mann 2000]
- Forearm crutches or canes for gait stability
- Wheelchairs for mobility because of gait instability

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- Exercise within the affected individual's capability
- Treatment of musculoskeletal pain with acetaminophen or nonsteroidal anti-inflammatory agents [Carter et al 1998]
- Treatment of neuropathic pain with tricyclic antidepressants or drugs such as carbamazepine or gabapentin
- Career and employment counseling because of persistent weakness of hands and/or feet

Prevention of Primary Manifestations

No treatment for CMT or CMT4A that reverses or slows the natural disease process exists.

Prevention of Secondary Complications

Daily heel cord stretching exercises are recommended to prevent Achilles tendon shortening.

Surveillance

Individuals should be evaluated regularly by a team comprising physiatrists, neurologists, and physical and occupational therapists to determine neurologic status and functional disability.

Agents/Circumstances to Avoid

Drugs and medications that are known to cause nerve damage should be avoided [Graf et al 1996, Chaudhry et al 2003, Weimer & Podwall 2006]. These include:

- Vincristine
- Taxol
- Cisplatin
- Isoniazid
- Nitrofurantoin

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

Therapies Under Investigation

Donaghy et al (2000), and Ginsberg et al (2004) have described a few individuals with CMT1 and sudden deterioration in whom treatment with steroids (prednisone) or IVIg has produced variable levels of improvement. There is no similar report for individuals with CMT4A.

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

Other

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.

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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 4A is inherited in an autosomal recessive manner.

Risk to Family Members — Autosomal Recessive CMT4A

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 have 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 CMT4A are obligate heterozygotes (carriers) for a disease-causing mutation in the *GDAP1* gene.

Other family members of a proband. Sibs of the proband's parents are at 50% risk of being carriers.

Carrier Detection

Carrier testing is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and clarification of carrier status 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

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation

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or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles 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.

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 4A

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CMT4A	*GDAP1*	8q13-q21.1	Ganglioside-induced differentiation-associated protein 1

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 4A

214400	CHARCOT-MARIE-TOOTH DISEASE, TYPE 4A; CMT4A
606598	GANGLIOSIDE-INDUCED DIFFERENTIATION-ASSOCIATED PROTEIN 1; GDAP1

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

Gene Symbol	Locus Specific	Entrez Gene	HGMD
GDAP1	GDAP1	54332 (MIM No. 606598)	GDAP1

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

Normal allelic variants: The normal gene comprises six exons spanning about 14 kb.

Pathologic allelic variants: To date, 17 pathologic mutations have been identified. Known mutations include nonsense exonic, missense, splice site, deletion, and insertion mutations throughout the gene. A founder effect has been shown in the Hispanic population (Q163X) [Boerkoel et al 2003].

- A case with a missense mutation and 3' splice site mutation has been reported from Poland [Kabzinska et al 2005].
- In a Spanish population, Claramunt et al (2005) reported 12 mutations in 125 index cases in which more common CMT genes had been excluded. Three of these cases were heterozygous mutations compatible with autosomal dominant inheritance.
- In Italy, four of 76 persons with normal parents and negative for mutations in four other CMT genes had the same homozygous mutation (M116R) in *GDAP1* [Di Maria et al 2004]. A founder effect was suggested.

Normal gene product: The protein ganglioside-induced differentiation-associated protein-1 comprises 358 amino acids. It contains a glutathione-S-transferase (GST) domain and belongs to a new class of GST-like proteins, which have a transmembrane domain in the C-terminal extension [Marco et al 2004]. Pedrola et al (2005) investigated a human neuroblastoma cell line that transiently over-expressed GDAP1 and found co-localization with mitochondrial marker proteins. Western blots of subcellular fractions confirmed this finding. They also showed that C-terminal transmembrane domains are necessary for the correct localization in

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mitochondria; however, missense mutations did not change the mitochondrial pattern of the wild-type protein [Pedrola et al 2005].

Niemann et al (2005) showed that GDAP1 is located in the mitochondrial outer membrane and regulates the mitochondrial network. GDAP1 induces fragmentation of mitochondria, the opposite function of mitofusin 2, the gene causing CMT2A.

Abnormal gene product: Truncating *GDAP1* mutations have lost mitochondrial fragmentation activity. The latter activity also is reduced strongly for disease-associated *GDAP1* point mutations [Niemann et al 2005]. Different mutations affect all portions of the protein. Either demyelinating or axonal phenotypes can result.

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.

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

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
B-2610 Antwerp
Belgium
Fax: 32-3-2651002
Email: gisele.smeyers@ua.ac.be

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
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Phone: (+44) 0 020 7720 8055
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Email: info@muscular-dystrophy.org
www.muscular-dystrophy.org

NCBI Genes and Disease
Charcot-Marie-Tooth syndrome

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

Revision History

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