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

Charcot-Marie-Tooth Type 2E/1F

[*CMT2E/1F*]

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Initial Posting: April 1, 2004.

Summary

Disease characteristics. Charcot-Marie-Tooth neuropathy type 2E/1F (CMT2E/1F) is characterized by a progressive peripheral motor and sensory neuropathy. The disease onset is within the first three decades of life. Some individuals have a very early onset within the first decade of life. Affected individuals have difficulty walking and running due to progressive distal weakness and wasting of the lower limbs. *Pes cavus*, hammer toes, and claw hands are frequently observed. Ambulation is generally preserved.

Diagnosis/testing. In most individuals, nerve eduction velocities (NCVs) are severely to moderately reduced and fall within the CMT1 range, i.e., less than 38 m/sec for motor median nerve, although near-normal NCVs have been described. *NEFL*, the gene encoding the protein neurofilament light chain, is the only gene known to be associated with CMT2E/1F. Sequence analysis of the *NEFL* gene is available on a clinical basis.

Genetic counseling. CMT2E/1F is inherited in an autosomal dominant manner. Most individuals with CMT2E/1F have an affected parent. Occasionally, family history may be negative due to a *de novo* mutation in the proband. Each child of an individual with CMT2E/1F has a 50% chance of inheriting the mutation. Prenatal testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

Charcot-Marie-Tooth neuropathy type 2E/1F (CMT2E/1F) is suspected in individuals with a progressive peripheral motor and sensory neuropathy.

- **Nerve conduction velocities (NCVs)** vary widely. In most individuals, NCVs are severely-to-moderately reduced and fall within the CMT1 range, i.e., less than 38 m/sec for motor median nerve, although near-normal NCVs have also been described. The lowest reported NCV in an individual with CMT2E/1F is 13 m/sec. The amplitudes of the compound action potentials are usually severely reduced. Sensory nerve action potentials are often unrecordable.
- **Electromyogram (EMG).** Concentric needle EMG shows chronic neurogenic alterations.

- **Peripheral nerve biopsy** is not obligatory for diagnosis. The one reported histopathological study of a sural nerve biopsy showed a mixed (demyelinating and axonal) pathology, characterized by thinly myelinated axons, axonal regeneration clusters, and onion bulb formations [Jordanova et al 2003].

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. *NEFL*, the gene encoding the protein neurofilament light chain, is the only gene known to be associated with CMT2E/1F.

Molecular genetic testing: Clinical uses

- Diagnosis
- Predictive testing
- Prenatal diagnosis

Molecular genetic testing: Clinical method

- **Sequencing.** Only point mutations in the *NEFL* gene have been identified so far. No reports of large *NEFL* rearrangements are available. One hundred percent of point mutations are identified by sequencing.

  Of note, Jordanova et al (2003) reported an individual who has two *NEFL* mutations c.23C↓G/ c.19G↓A (P8R/E7K). The individual transmitted the P8R mutation to her three affected children. Although the pathogenic nature of the E7K mutation was not proved, this finding illustrates that individuals with two different *NEFL* mutations either in trans configuration or cis configuration do exist. Molecular genetic testing should therefore include the complete coding sequence of the *NEFL* gene, especially in families seeking prenatal diagnosis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Charcot-Marie-Tooth Type 2E/1F

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	All reported *NEFL* mutations	100%	Clinical Testing

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

Genetically Related Disorders

CMT2E/1F is the only disorder associated with mutations in *NEFL*.

Vechio et al (1996) excluded disease-causing *NEFL* mutations in families with amyotrophic lateral sclerosis. A detailed mutation search and association study in German individuals with sporadic or familial Parkinson's disease also excluded *NEFL* as a pathogenic factor [Rahner et al 2002].

Clinical Description

CMT2E/1F is a progressive peripheral motor and sensory neuropathy with variable clinical and electrophysiological expression. The disease onset is within the first three decades of life and presents with a broad clinical phenotype - from an early onset and severe phenotype to milder forms.

Some affected individuals have a very early onset within the first decade of life. The presenting symptoms are difficulties in walking and running due to progressive distal weakness and wasting of the lower limbs. Paresis in the distal part of the lower limbs varies from mild weakness to a complete paralysis of the distal muscle groups. Tendon reflexes are diminished or absent. Sensory signs are not prominent but are present in all affected individuals. *Pes cavus* is the most frequently observed limb deformity, together with hammer toes and claw hands. Tremor is reported in some individuals. Ambulation is generally preserved during life. Only one individual is reported to be wheelchair bound.

In the first reported family, NCVs were within the CMT2 range; thus this CMT variant was initially described as CMT2E [Mersiyanova et al 2000]. The subsequent observation of slow NCVs in individuals belonging to similar families and in simplex cases (i.e., those with no family history of the disorder) created a nosological problem. OMIM classifies individuals with a CMT2 electrophysiological phenotype as CMT2E [Mersiyanova et al 2000], while those with a CMT1 electrophysiological phenotype are classified as CMT1F. Thus, CMT1F is characterized by slowly progressive distal muscle atrophy and weakness, absent deep tendon reflexes, hollow feet, and reduced nerve conduction velocities (<38 m per sec). Onset is in infancy or childhood and the course is usually more severe.

It is still unclear whether the slowing of NCVs is progressive, with young individuals having normal or near-normal NCVs that decline with age and disease progression. If this turns out to be the case, it makes the distinction between CMT2E and CMT1F to a large extent artificial.

Affected individuals do not have palpably enlarged nerves, ulcerated feet, or paralysis of the vocal cords and/or diaphragm.

Genotype-Phenotype Correlations

Genotype-phenotype correlations are difficult to make because of the small number of reported individuals with *NEFL* mutations.

Penetrance

Penetrance is most likely to be full.

Anticipation

No clear evidence of anticipation is available in the literature.

Nomenclature

Individuals with onset of CMT in the first decade are often diagnosed as having Dejerine-Sottas syndrome (DSS), a term that refers to this phenotype and can be observed in individuals with mutations in a number of genes; thus, the term DSS has become more confusing than helpful when considering the nosology of CMT.

Prevalence

The true prevalence of CMT2E/1F is not known. Preliminary data indicate that *NEFL* mutations account for 2-5% of individuals presenting with a CMT or DSS phenotype.

Differential Diagnosis

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

The clinical and electrophysiological phenotype of CMT2E/CMT1F is undistinguishable from other forms of CMT/DSS (see Charcot-Marie-Tooth Hereditary Neuropathy Overview). In individuals with no family history of CMT, acquired neuropathy should also be considered.

Management

No effective treatment for CMT2E/1F exists. Care is symptomatic and supportive. Follow-up is performed by a multidisciplinary team of neurologist, orthopedic surgeon, psychiatrist, and ergotherapist. Some individuals require special shoes or foot/ankle orthoses, but occasionally need a wheelchair (only one individual reported).

Important social and employment implications may exist because of foot and hand weakness.

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 2E/1F is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals with CMT2E/1F have an affected parent.
- Occasionally, family history may be negative because the proband has a *de novo* mutation. Individuals with a severe phenotype typically have a *de novo* mutation.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include neurological and electrophysiological examinations.

Although most individuals diagnosed with CMT2E/1F have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to sibs depends upon the genetic status of the proband's parents.
- If a parent has a disease-causing mutation, the risk to the sibs of inheriting the mutation is 50%.
- The presence of a *NEFL* mutation in a sib does not predict the severity of symptoms, the age of onset, or the progression of the disorder.

- If the disease-causing mutation identified in the proband cannot be detected in the leukocytes of either parent, it is most likely caused by a *de novo* mutation in the proband. Another remote possibility is germline mosaicism, but this has not been reported to date.

Offspring of a proband

- Each child of an individual with CMT2E/1F has a 50% chance of inheriting the mutation.
- The presence of a *NEFL* mutation in the offspring does not predict the severity of symptoms, the age of onset, or the progression of the disorder.
- Individuals who are severely affected may not reproduce.

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

Related Genetic Counseling Issues

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

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

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of CMT2E/1F are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which a/the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, 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 Type 2E/1F

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CMT2E	*NEFL*	8p21	Neurofilament triplet L protein

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 Type 2E/1F

162280	NEUROFILAMENT PROTEIN, LIGHT POLYPEPTIDE; NEFL
607684	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2E

Table C. Genomic Databases for Charcot-Marie-Tooth Type 2E/1F

Gene Symbol	Locus Specific	Entrez Gene	HGMD
NEFL	NEFL	4747 (MIM No. 162280)	NEFL

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

Molecular Genetic Pathogenesis

The cytoskeleton of neuronal cells is mainly composed of three kinds of filaments: microtubules, neurofilaments, and actin filaments [Tokutake 1990]. Neurofilaments (NFs) belong to the family of intermediate filaments (IF) and are the most abundant component of the mature myelinated axon [Friede & Samorajski 1970]. They have a central 310 amino acid domain (rod-domain) shaped as a large coiled-coil α-helix flanked by two non-helical segments: the N-terminal head and C-terminal tail. Neurofilaments self-assemble into heteropolymers; this assembly is mediated by interactions among the rod domains of each subunit, whereas the specificity of the interactions is determined by the end domains [Carpenter & Ip 1996].

Neurofilaments in vertebrates are composed of three different protein subunits, referred to as neurofilament light chain (NEFL, 68 kDa), neurofilament medium chain (NEFM, 160 kDa), and neurofilament heavy chain (NEFH, 210 kDa), each of these encoded by different genes [Julien 1999]. NEFL is the most abundant unit of neurofilaments and plays a central role in their assembly. It is the only NF subunit capable of self-assembling into filaments in vitro [Carpenter & Ip 1996] and also able to regulate the assembly of the other NF subunits.

Disruption of axonal transport of NFs resulting in neurofilament accumulations is a major pathological hallmark during the early stages of many human motor neuron diseases [Xu et al 1993], including giant axonal neuronopathy [Flanigan et al 1998], amyotrophic lateral sclerosis [Julien 1995], Parkinson disease [Goldman et al 1983], Lewy-body-type dementia [Shepherd et al 2002], Alzheimer disease [Figlewicz et al 1994, Tomkins et al 1998, Al-Chalabi et al 1999], and spinal muscular atrophy [Cifuente-Diaz et al 2002].

Normal allelic variants: The *NEFL* gene is organized in four coding exons. So far, 13 normal sequence variants are reported.

Table 2. Published Polymorphic Variants in the *NEFL* Gene Sequence

Exon	Nucleotide Change [1]	Amino Acid Change	Approximate Frequency [2]	Reference
5'-UTR	c.-42delT	—	2/248	Yoshihara et al 2002
1	c.120A↓T	S40S		Jordanova et al 2003
	c.189G↓A	L63L		Jordanova et al 2003
	c.224T↓C	V75A	5/248	Yoshihara et al 2002
	c.276G↓A	Q92Q	6/248	Yoshihara et al 2002
	c.420G↓A	Q140Q		Jordanova et al 2003
	c.670C↓T	L224L		Jordanova et al 2003
	c.723C↓T	Y241Y		Jordanova et al 2003
3	c.1215C↓T	S405S		Jordanova et al 2003
	c.1329C↓T	Y443Y	1/32	Luo et al 2003
	c.1405G↓A	D469N	0/165	Vechio et al 1996, Jordanova et al 2003
	c.1461G↓T	A487A		Jordanova et al 2003
4	c.1495G↓A	A499T	3/248	Yoshihara et al 2002
	c.1582-1584delGAG	E528del	9/248	Yoshihara et al 2002

1. With reference to the cDNA sequence GenBank Accession number X05608
2. Screening in normal individuals

Pathologic allelic variants: The first disease-causing *NEFL* mutation was reported by Mersiyanova et al (2000). All currently known *NEFL* mutations are listed in the Mutation Database of Inherited Peripheral Neuropathies [Nelis et al 1999].

Table 3. Published Disease-Causing Mutations in the *NEFL* Gene

Exon	Nucleotide Change [1]	Amino Acid Change	Protein Domain	Reference
1	c.19G↓A	E7K	Head	Jordanova et al 2003
1	c.22C↓A+c.23C↓G	P8R	Head	De Jonghe et al 2001
1	c.23C↓G	P8R	Head	Jordanova et al 2003
1	c.23C↓A	P8Q	Head	Jordanova et al 2003
1	c.23C↓T	P8L	Head	Jordanova et al 2003
1	c.64C↓A	P22T	Head	Yoshihara et al 2002
1	c.64C↓T	P22S	Head	Georgiou et al 2002
1	c.265G↓A	E89K	Head	Jordanova et al 2003
1	c.290A↓G	N97S	Rod	Yoshihara et al 2002, Jordanova et al 2003
1	c.998A↓C	Q333P	Rod	Mersiyanova et al 2000
1	c.443C↓T	A148V	Rod	Yoshihara et al 2002
1	c.1189G↓A	E97K	Rod	Zuchner et al 2004

1. With reference to the cDNA sequence GenBank Accession number X05608

Normal gene product: The *NEFL* gene codes for a structural protein of 544 amino acids, with a head, rod, and tail domain. NEFL is a structural protein, exclusively and abundantly expressed

in neurons and localized principally in axons. It assembles with neurofilaments of higher molecular mass, medium (NEFM) and heavy (NEFH), into intermediate filaments type IV, and forms the cytoskeleton of the neuronal cell. Neurofilaments are involved in radial growth and caliber maintenance of large myelinated axons and thereby play a role in their conduction velocity [Hoffman et al 1987].

Abnormal gene product: In the absence of NEFL, NEFM and NEFH subunits are unable to assemble into 10nm filaments. As a result, mice lacking NEFL have normal development, but reduced axonal caliber and delayed maturation of regenerating myelinated axons after nerve injury [Zhu et al 1997]. In Japanese quail natural mutants lacking NEFL, the normal radial growth of myelinated axons is severely attenuated [Yamasaki et al 1992, Ohara et al 1993]. The more severe CMT-like phenotypes resemble mice with NEFL overexpression or knock-in mutant mice (L394P). They have massive selective degeneration of spinal motor neurons, accompanied by abnormal accumulations of NFs and severe neurogenic atrophy of skeletal muscles [Xu et al 1993, Lee et al 1994].

So far, two groups have investigated the effect of *NEFL* mutations, described in individuals with CMT, in transgenic mammalian cells and neurons [Brownlees et al 2002, Perez-Olle et al 2002]. CMT mutant neurofilaments disrupt both neurofilament assembly and axonal transport and perturb the localization of mitochondria in neurons.

Resources

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

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CMT News
www.cmtnews.com

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NCBI Genes and Disease Webpage
Charcot-Marie-Tooth syndrome

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References

Medical Genetics 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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