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Charcot-Marie-Tooth Neuropathy Type 2E/1F – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: CMT2E/1F

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Charcot-Marie-Tooth neuropathy type 2E/1F (CMT2E/1F) is characterized by a progressive peripheral motor and sensory neuropathy with variable clinical and electrophysiologic expression. Disease onset ranges from the first to the fifth decade of life; in some cases disease onset can be in infancy. Affected individuals have difficulty walking and running because of progressive distal weakness and wasting of the muscles 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*, hammer toes, and claw hands are frequently observed. Ambulation is generally preserved.

Diagnosis/testing

In most individuals, nerve conduction velocities (NCVs) are severely to moderately reduced and fall within the CMT1 range (i.e., <38 m/sec for the motor median nerve), although near-normal NCVs have been described. *NEFL,* encoding the protein neurofilament light chain, is the only gene known to be associated with CMT2E/1F.

Management

Treatment of manifestations: Affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment may include: special shoes with good ankle support, daily heel cord stretching exercises, ankle/foot orthoses, orthopedic surgery for severe *pes cavus* deformity, and crutches or canes for stability. Exercise is encouraged. Pain is treated symptomatically.

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Prevention of secondary complications: Daily heel cord stretching exercises to prevent Achilles' tendon shortening.

Surveillance: Monitoring gait and condition of feet to determine need for bracing, special shoes, surgery.

Agents/circumstances to avoid: Obesity because it makes walking more difficult; drugs and medications (e.g., vincristine, isoniazid, taxol, cisplatin, nitrofurantoin) that are known to cause nerve damage.

Genetic counseling

CMT2E/1F is usually inherited in an autosomal dominant manner; on rare occasion it can be inherited in an autosomal recessive manner.

Autosomal dominant CMT2E/1F: Most individuals with autosomal dominant CMT2E/1F have an affected parent. *De novo* pathogenic variants are more typical for individuals with a severe phenotype. The risk to sibs depends on the genetic status of the proband's parents. Each child of an individual with autosomal dominant CMT2E/1F has a 50% chance of inheriting the pathogenic variant.

Autosomal recessive CMT2E/1F: The risk to each sib of an affected individual at conception is 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Prenatal testing for pregnancies at increased risk for both autosomal dominant and autosomal recessive CMT2E/1F is possible if the pathogenic variant(s) in the family are known.

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 the motor median nerve, although near-normal NCVs have also been described. The lowest reported NCV in an individual with CMT2E/1F is 12 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. Histopathologic studies of sural nerve biopsies showed a mixed (demyelinating and axonal) pathology, characterized by reduction mainly of large nerve fibers, thinly myelinated axons, axonal regeneration clusters, and onion bulb formation [Jordanova et al 2003, Züchner et al 2004]. Giant axons with focal accumulation of disorganized neurofilaments are also described [Fabrizi et al 2004, Fabrizi et al 2007]. In an individual with autosomal recessive CMT2E/1F, a markedly reduced number of myelinated axons and only small diameter myelinated axons lacking intermediate filaments are observed [Yum et al 2009].

Molecular Genetic Testing

Gene. *NEFL*, encoding the protein neurofilament light chain, is the only gene in which pathogenic variants are known to cause CMT2E/1F.

Sequence analysis. Pathogenic variants identified to date are single-nucleotide variants, small deletions, insertions, or in/dels in *NEFL,* all of which are identifiable by sequence analysis.

To date, deletion or duplication of exons or of the entire gene has not been reported.

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

Gene [1]	Method	Variants Detected [2]	Variant Detection Frequency by Method [3]
NEFL	Sequence analysis [4]	Sequence variants	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.

Interpretation of test results. Because of the presence of recessive pathogenic variants, as well as normal variants in the coding region (see Table 2 for examples), segregation of the variants should be traced in the family (when possible) and normal controls should be tested. For example, Jordanova et al [2003] reported an individual with two *NEFL* variants p.Pro8Arg and p.Glu7Lys. Further studies demonstrated that these variants were in *trans* configuration and p.Pro8Arg was transmitted to the affected children while p.Glu7Lys was a normal variant [Pérez-Ollé et al 2004, Yamamoto et al 2004].

Testing Strategy

To confirm/establish the diagnosis in a proband with a progressive peripheral motor and sensory neuropathy requires sequence analysis of the complete *NEFL* coding sequence.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the pathogenic variant(s) in the family.

Prenatal diagnosis and preimplantation genetic testing for at-risk pregnancies require prior identification of the pathogenic variant(s) in the family.

Clinical Characteristics

Clinical Description

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

Some affected individuals have onset in infancy or early childhood and may display hypotonia and mildly delayed motor milestones. The presenting symptoms in most individuals are difficulties in walking and running as a result of 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. In the most severely affected people, mild-to-moderate proximal arm and shoulder girdle weakness can be observed.

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.

Cerebellar dysfunction, tremor, and hearing loss are occasionally observed.

Ambulation is generally preserved during life. Only one individual is reported to be wheelchair bound.

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

Genotype-Phenotype Correlations

There are no obvious genotype/phenotype correlations, mainly because of the small number of reported individuals with *NEFL* pathogenic variants. However, Miltenberger-Miltenyi et al [2007] noted that pathogenic variants in the head domain of *NEFL* may cause more severe slowing of nerve conduction velocity than pathogenic variants in the coil 2B domain.

Individuals with autosomal recessive CMT2E/1F usually have more a severe phenotype, diagnosed as CMT1F.

Penetrance

Penetrance is most likely to be complete.

Anticipation

No clear evidence of anticipation is available in the literature.

Nomenclature

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 nosologic problem: OMIM classifies individuals with a CMT2 electrophysiologic phenotype as having CMT2E [Mersiyanova et al 2000], while those with a CMT1 electrophysiologic phenotype are classified as having CMT1F.

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 early infancy or childhood and the course is usually more severe. These individuals are often diagnosed as having Dejerine-Sottas syndrome (DSS), a term that refers to this phenotype and can be observed in individuals with pathogenic variants in a number of genes; thus, the term DSS has become more confusing than helpful when considering the nosology of CMT.

The reported autosomal dominant as well as autosomal recessive mode of inheritance of the disease further complicates the nosologic classification.

Prevalence

The true prevalence of CMT2E/1F is not known. Preliminary data indicate that *NEFL* pathogenic variants account for 2%-5% of individuals presenting with a CMT phenotype and for about 1% of the individuals with neuropathy onset within the first year of life [Baets et al 2011].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The clinical and electrophysiologic phenotype of CMT2E/1F 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

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Charcot-Marie-Tooth neuropathy type 2E/1F (CMT2E/1F), the following evaluations are recommended:

- Physical examination to determine extent of weakness and atrophy, *pes cavus*, gait stability, and sensory loss
- NCV to help distinguish demyelinating, axonal, and mixed neuropathies
- Complete family history
- Consultation with a cinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment is symptomatic and affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists [Grandis & Shy 2005].

- Special shoes, including those with good ankle support, may be needed.
- Daily heel cord stretching exercises to prevent Achilles' tendon shortening are desirable.
- Affected individuals often require ankle/foot orthoses (AFO) to correct foot drop and aid walking.
- Orthopedic surgery may be required to correct severe *pes cavus* deformity [Holmes & Hansen 1993, Guyton & Mann 2000].
- Some individuals require forearm crutches or canes for gait stability; fewer than 5% need wheelchairs.
- Exercise is encouraged within the individual's capability and many individuals remain physically active.
- Career and employment choices may be influenced by persistent weakness of hands and/or feet.
- Pain should be treated symptomatically [Gemignani et al 2004].

Prevention of Secondary Complications

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

Surveillance

Monitoring of gait and condition of feet to determine need for bracing, special shoes, surgery is appropriate.

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 CMT comprise a spectrum of risk ranging from definite high risk to negligible risk. See the Charcot-Marie-Tooth Association website (pdf) for an up-to-date list.

Evaluation of Relatives at Risk

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

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

Charcot-Marie-Tooth neuropathy type 2E/1F is typically inherited in an autosomal dominant manner.

To date, two families with autosomal recessive CMT2E/1F (caused by homozygous nonsense variants) have been reported [Abe et al 2009, Yum et al 2009].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals with autosomal dominant CMT2E/1F have an affected parent.
- Occasionally, family history may be negative because the proband has a *de novo* pathogenic variant or inheritance is autosomal recessive.
- Recommendations for the evaluation of parents of a simplex case (i.e., an individual with no family history of the disorder) include neurologic and electrophysiologic examination and, if the pathogenic variant in the proband has been identified, molecular genetic testing.

Note: Although most individuals diagnosed with autosomal dominant 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 on the genetic status of the proband's parents.
- If a parent has a autosomal dominant pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- The presence of a *NEFL* pathogenic variant in a sib does not predict the severity of symptoms, the age of onset, or the progression of the disorder.
- If the pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, it is most likely caused by a *de novo* pathogenic variant in the proband. Another remote possibility is germline mosaicism, which 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 pathogenic variant.

- The presence of a *NEFL* pathogenic variant 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 on the status of the proband's parents. If a parent is affected or known to have a pathogenic variant, his or her family members are at risk.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- Parents of a proband with CMT2E/1F inherited in an autosomal recessive manner are obligate heterozygotes and therefore carry one mutated 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 chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- The offspring of a proband with autosomal recessive CMT2E/1F are obligate heterozygotes (carriers).
- In the rare instance that an unrelated reproductive partner is a carrier, the offspring are at a 50% risk of being affected and a 50% risk of being carriers.

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

Carrier (Heterozygote) Detection

Carrier testing for autosomal recessive CMT2E/1F is possible once the *NEFL* pathogenic variants have been identified in the family.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

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.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

- **Association CMT France**
  France
  Phone: 820 077 540; 2 47 27 96 41
  www.cmt-france.org
- **Charcot-Marie-Tooth Association (CMTA)**
  PO Box 105
  Glenolden PA 19036
  Phone: 800-606-2682 (toll-free); 610-499-9264
  Fax: 610-499-9267
  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, Inc.**
  432 Park Avenue South
  4th Floor
  New York NY 10016
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **My46 Trait Profile**
  Charcot Marie Tooth disease
- **National Library of Medicine Genetics Home Reference**

Charcot-Marie-Tooth disease

- **NCBI Genes and Disease**
  Charcot-Marie-Tooth syndrome
- **TREAT-NMD**
  Institute of Genetic Medicine
  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)**
  Lt Gen van Heutszlaan 6
  3743 JN Baarn
  Netherlands
  Phone: 31 35 5480481
  Fax: 31 35 5480499
  Email: enmc@enmc.org
  www.enmc.org
- **Muscular Dystrophy Association - USA (MDA)**
  222 South Riverside Plaza
  Suite 1500
  Chicago IL 60606
  Phone: 800-572-1717
  Email: mda@mdausa.org
  www.mda.org

- **Muscular Dystrophy UK**
  61A Great Suffolk Street
  London SE1 0BU
  United Kingdom
  Phone: 0800 652 6352 (toll-free); 020 7803 4800
  Email: info@musculardystrophyuk.org
  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. Charcot-Marie-Tooth Neuropathy Type 2E/1F: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CMT2E	*NEFL*	8p21.2	Neurofilament light polypeptide	Human Intermediate Filament Database NEFL IPN Mutations, NEFL NEFL homepage - Leiden Muscular Dystrophy pages	NEFL	NEFL

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 Charcot-Marie-Tooth Neuropathy Type 2E/1F (View All in OMIM)

162280	NEUROFILAMENT PROTEIN, LIGHT POLYPEPTIDE; NEFL
607684	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2E; CMT2E
607734	CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1F; CMT1F

Molecular 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 the 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 kd), neurofilament medium chain (NEFM, 160 kd), and neurofilament heavy chain (NEFH, 210 kd), 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. NEFL self-assembly is accelerated by binding to phosphatidylinositol phosphates [Kim et al 2011].

Disruption of axonal transport of NFs resulting in neurofilament accumulations is a major pathologic hallmark during the early stages of many human motor neuron diseases, 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 [Cifuentes-Diaz et al 2002].

Gene structure. *NEFL* is organized in four coding exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Allelic variants. Multiple benign and pathogenic sequence variants have been reported. See Table 2.

Table 2. Selected *NEFL* Variants

Variant Classification	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	References	Reference Sequences
Benign	c.-42delT	--	Yoshihara et al [2002]	NM_006158.3 NP_006149.2
	c.19G>A	p.Glu7Lys	Jordanova et al [2003]	
	c.123C>T (120A>T)	p.= (S40S)	Jordanova et al [2003]	
	c.192G>A (189G>A)	p.= (L63L)	Jordanova et al [2003]	
	c.227T>C (224T>C)	p.Val76Ala (Val75Ala)	Yoshihara et al [2002]	
	c.279G>A (276G>A)	p.= (Q92Q)	Yoshihara et al [2002]	
	c.423G>A (420G>A)	p.= (Q140Q)	Jordanova et al [2003]	
	c.667C>T (670C>T)	p.= (L224L)	Jordanova et al [2003]	
	c.720C>T (723C>T)	p.= (Y241Y)	Jordanova et al [2003]	
	c.1212C>T (1215C>T)	p.= (S405S)	Jordanova et al [2003]	
	c.1326C>T (1329C>T)	p.= (Y443Y)	Luo et al [2003]	
	c.1402G>A (1405G>A)	p.Asp468Asn (Asp469Asn)	Vechio et al [1996], Jordanova et al [2003]	
	c.1458C>T (1461G>T)	p.= (A487A)	Jordanova et al [2003]	
	c.1492G>A (1495G>A)	p.Ala498Thr (Ala499Thr)	Yoshihara et al [2002]	
	c.1579_1581del (1582-1584delGAG)	p.Glu527del (Glu528del)	Yoshihara et al [2002], Yamamoto et al [2004]	
	c.1573_1574insGAG (1576-1577insGAG)	p.Glu524_Glu525insGly (Glu526fs*532)	Andrigo et al [2005]	
Pathogenic	c.[22C>A; 23C>G]	p.Pro8Arg	De Jonghe et al [2001]	

Table 2. continued from previous page.

Variant Classification	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	References	Reference Sequences
	c.23C>G	p.Pro8Arg	Jordanova et al [2003]	
	c.23C>A	p.Pro8Gln	Jordanova et al [2003]	
	c.23C>T	p.Pro8Leu	Jordanova et al [2003]	
	c.64C>A	p.Pro22Thr	Yoshihara et al [2002]	
	c.64C>T	p.Pro22Ser	Georgiou et al [2002]	
	c.268G>A (265G>A)	p.Glu90Lys (Glu89Lys)	Jordanova et al [2003]	
	c.293A>G (290A>G)	p.Asn98Ser (Asn97Ser)	Yoshihara et al [2002], Jordanova et al [2003]	
	c.418G>T [2]	p.Glu140Ter	Abe et al [2009]	
	c.446C>T (443C>T)	p.Ala149Val (Ala148Val)	Yoshihara et al [2002]	
	c.628G>T [2]	p.Glu210Ter	Yum et al [2009]	
	c.995A>C (998A>C)	p.Gln332Pro (Gln333Pro)	Mersiyanova et al [2000]	
	c.998T>C (1001T>C)	p.Leu333Pro (Leu334Pro)	Choi et al [2004]	
	c.1186G>A (1189G>A)	p.Glu396Lys (Glu397Lys)	Choi et al [2004], Züchner et al [2004]	

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.
p. = designates that protein has not been analyzed, but no change is expected.
1. Variant designation that does not conform to current naming conventions
2. Pathogenic variants that result in autosomal recessive inheritance

Normal gene product. *NEFL* codes for a structural protein of 543 amino acids that has head, rod, and tail domains. NEFL is a structural protein, exclusively and abundantly expressed in neurons and localized principally in axons, with higher levels in large myelinated 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. NEFL interacts in peripheral nerve with myotubularin-related 2 protein phosphatase (MTMR2), another CMT-associated protein mutated in CMT4B1 [Previtali et al 2003]. Neurofilaments are involved in radial growth and caliber maintenance of large myelinated axons and thereby play a role in their conduction velocity.

Abnormal gene product. In the absence of NEFL, NEFM and NEFH subunits are unable to assemble into 10-nm filaments. As a result, mice lacking NEFL protein have normal development but reduced axonal caliber and delayed maturation of regenerating myelinated axons after nerve injury. They develop mild sensorimotor dysfunction and spatial deficit without overt signs of paresis [Dubois et al 2005]. In Japanese quail natural mutants lacking NEFL, the normal radial growth of myelinated axons is severely attenuated.

The effect of dominant *NEFL* pathogenic variants described in individuals with CMT has been investigated in transgenic mammalian cells and neurons [Brownlees et al 2002, Pérez-Ollé et al 2002, Pérez-Ollé et al 2004, Pérez-Ollé et al 2005, Sasaki et al 2006, Zhai et al 2007]. In transfected cells, dominant *NEFL* mutants disrupt

both neurofilament self-assembly and co-assembly. In transfected neurons, at least some of them cause aberrant axonal transport of neurofilaments, affect the anterograde and retrograde transport of other cell components, and perturb the localization of mitochondria. This leads to progressive degeneration and loss of neuronal viability. In contrast, the recessive p.Glu210Ter variant causes loss of NEFL protein. In affected persons homozygous for this pathogenic variant, this leads to lack of neurofilaments and progressive axonal loss [Yum et al 2009].

Two transgenic mouse CMT2E models have been generated to date, expressing p.Pro22Ser and p.Glu396Lys pathogenic variants respectively [Dequen et al 2010, Shen et al 2011]. Transgenic mice recapitulate the hallmark features of human pathology, including abnormal hindlimb posture, motor performance deficit, and loss of muscle innervation. Importantly, suppression of the mutated $NEFL^{Pro22Ser}$ product after disease onset reverses the neurologic phenotype in mice. These experiments indicate that therapeutic approaches aimed at abolishing or neutralizing the mutated *NEFL* allele could potentially halt disease progression and reverse the associated disabilities [Dequen et al 2010].

References

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Chapter Notes

Revision History

- 15 August 2019 (ma) Chapter retired: covered in Charcot-Marie-Tooth Hereditary Neuropathy Overview
- 27 October 2011 (me) Comprehensive update posted live
- 15 June 2006 (ca) Comprehensive update posted live
- 1 April 2004 (me) Review posted live
- 6 October 2003 (pdj) Original submission

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