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Charcot-Marie-Tooth Neuropathy Type 4H – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Charcot-Marie-Tooth Disease Type 4H, CMT4H

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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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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 4H (CMT4H) is a demyelinating form of CMT that is characterized by early onset (usually before age 3 years; range: birth to age 10 years) and slow progression. The degree of distal muscle weakness and amyotrophy varies between affected individuals as does the presence or absence and severity of foot deformities, scoliosis, and sensory involvement. Neuropathic pain has not been reported. To date, findings in18 individuals with molecularly confirmed CMT4H from 13 families have been reported.

Diagnosis/testing

CMT4H is suspected in individuals with typical findings of CMT (distal amyotrophy, foot deformities), early onset, and slow progression. Motor nerve conduction velocities (MNCVs) and sensory nerve conduction velocities (SNCVs) are abnormal. The diagnosis is established by the presence of biallelic *FGD4* pathogenic variants.

Management

Treatment of manifestations: Often management is by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment is symptomatic and may include: ankle/foot orthoses (AFOs); physiotherapy (daily heel cord stretching exercises and physical activity to prevent contractures and help preserve flexibility); surgery to correct severe pes cavus deformity and/or spine deformities; and forearm crutches, canes, and/or wheelchairs for mobility. Musculoskeletal pain may be treated with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs).

Surveillance: Regular (annual) evaluation to determine neurologic status and functional disability.

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Agents/circumstances to avoid: Obesity because it makes walking more difficult; medications that are toxic or potentially toxic to persons with CMT.

Genetic counseling

CMT4H 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 diagnosis for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

Clinical Diagnosis

Formal diagnostic guidelines for Charcot-Marie-Tooth type 4H (CMT4H) do not exist.

Note: Although the CMT Neuropathy Score (CMTNS) and CMTNS version 2 (CMTNS2) are widely used in the diagnosis of CMT [Shy et al 2005, Murphy et al 2011], their limited ability to measure disability and severity of the disease in children under age ten years [Haberlová & Seeman 2010, Pagliano et al 2011] makes their use in the diagnosis of early childhood-onset disease like CMT4H problematic.

The diagnosis of Charcot-Marie-Tooth neuropathy type 4H (CMT4H) is suspected in individuals with findings typically observed in CMT (distal amyotrophy, foot deformities) and the following (see also Table 1):

- Early onset. The imprecise retrospective data available indicate that symptoms typically appear before age three years, with a range presumed to be birth to ten years.
- Slow progression. Despite early onset, the disease is stable with only very slow progression.
- Scoliosis; onset before age ten years (observed in some, but not all, affected individuals)
- Abnormal motor nerve conduction velocities (MNCVs) and sensory nerve conduction velocities (SNCVs). In the lower limbs, MNCVs were non-recordable in 8/9 individuals tested and severely reduced in one; SNCVs were non-recordable in 8/8 individuals tested. In the upper limbs, MNCVs were non-recordable in 3/16 and severely reduced in 13/16; SNCVs were non-recordable in 8/9 and reduced in one (for details see Table 2 [pdf]).
- Family history consistent with autosomal recessive inheritance. Parental consanguinity is common; parents are not affected unless multigenerational consanguinity exists. Note: Disease severity and disability vary even within the same family (i.e., among individuals with the same pathogenic variants).

The diagnosis of CMT4H is established in individuals with biallelic *FGD4* pathogenic variants [De Sandre-Giovannoli et al 2005, Delague et al 2007, Reddy et al 2008] (Table 1).

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

Gene [1]	Method	Pathogenic Variants Detected [2]	Variant Detection Frequency by Method [3]
FGD4	Sequence analysis [4]	Sequence variants [5]	13/13 [6]

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.
5. The test method does not allow detection or large genomic rearrangements within *FGD4*. However, except for deletions/duplications in CMT1A, large genomic rearrangements are not known as frequent molecular defects in CMT disease.
6. Individuals with CMT4H or autosomal recessive demyelinating CMT with clinical signs consistent with CMT4H [Delague et al 2007, Stendel et al 2007, Fabrizi et al 2009, Houlden et al 2009, Hayashi et al 2013]. Almost all pathogenic variants described to date were homozygous and in individuals born to consanguineous parents.

Note: When molecular genetic testing is not available, sural nerve biopsy can be considered; however, histologic findings are not specific to CMT4H, and thus not confirmatory.

Histologic findings consistent with the diagnosis of CMT4H. Moderate to severe loss of myelinated fibers, mainly affecting large caliber fibers, probably secondary to a demyelination-remyelination process is observed in all individuals with CMT4H undergoing nerve biopsy reported to date (see Table 2 [pdf]). The remaining fibers usually have features of congenital hypomyelination (e.g., myelin thickening) and other signs of altered myelination (e.g., onion bulbs and myelin outfoldings). Although myelin outfoldings are not specific to CMT4H, they are observed in only a few CMT subtypes (CMT4B1, CMTB2, and CMT4F), and thus could support molecular genetic testing of *FGD4*.

Clinical Characteristics

Clinical Description

Charcot-Marie-Tooth neuropathy type 4H (CMT4H), an autosomal recessive demyelinating form of CMT, is characterized by early onset and slow progression. The most common findings observed in published reports of 18 affected individuals from 13 families with molecularly confirmed CMT4H are summarized in Table 3 (see Table 2 [pdf] for a comprehensive summary).

The degree of distal muscle weakness and amyotrophy varies between affected individuals as does the presence or absence and severity of foot deformities, scoliosis, and sensory involvement.

Although individuals with CMT do experience neuropathic pain that is usually moderate, preferentially located in the extremities, and symmetric [Ribiere et al 2012], neuropathic pain has not been documented in CMT4H.

Table 3. Clinical Characteristics of CMT4H in 18 Individuals from 13 Families

Patient [1]	Origin	Age in Yrs at First Symptoms / Last Exam	Age in Mos at Walking	Distal Muscles		Foot Deformity [4]	Scoliosis [5]	Distal Sensory Loss [6]	Functional Impairment	Reference
				Weakness [2]	Muscle Atrophy [3]					
Ia [7]	Lebanon	1-2 / 15	Delayed, 15-36	+++	++	++	+++	++	Moderate to severe: unsteady gait, walking w/out aid	Delague et al [2007]
Ib [7]	Lebanon	1-2 / 18	Delayed, 15-36	+++	++	++	-	++	Mild: unsteady gait, walking w/out aid	
Ic [7]	Lebanon	4 / 13	12	+++	++	+	++	++	Unknown	Stendel et al [2007]
II	Algeria	2 / unknown	Unknown	++	++	+	+	Unknown	Moderate: walking w/out aid, waddling gait	Delague et al [2007]
III	Turkey	<1 / 30	Delayed	+++	++	+	-	+	Unknown	Stendel et al [2007]
IV	Turkey	2 / unknown	Delayed, 26	++	+	-	-	-	Unknown	
V	Tamil	9 / unknown	16	+	+	-	-	-	Unknown	
VIa	Northern Ireland	Childhood [8] / 58	Unknown	+	+	+	-	++	Moderate: walking w/out aid at 58 yrs	Houlden et al [2009]
VIb	Northern Ireland	Childhood [9] / 50	Unknown	++	Unknown	+	-	++	Severe: at 50, walking w/2 crutches or wheelchair	
VII	Italy	<1 / 20	17	+	+	+	+	+	Moderate: unsteady gait w/ steppage	Fabrizi et al [2009]
VIII	Lebanon	5 / 21	14	+	+	+	-		Moderate: walking w/out aid	Baudot et al [2012]
IX	Algeria	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	

Table 3. continued from previous page.

Patient [1]	Origin	Age in Yrs at First Symptoms / Last Exam	Age in Mos at Walking	Distal Muscles		Foot Deformity [4]	Scoliosis [5]	Distal Sensory Loss [6]	Functional Impairment	Reference
				Weakness [2]	Muscle Atrophy [3]					
Xa	Tunisia	3 / 6	16	+++	++	+	+	-	Walking on tiptoes	Boubaker et al [2013]
Xb	Tunisia	3 / 18	Normal	+++	++	+	++	+		
Xc	Tunisia	3 / 22	Normal	+++	++	+	+++	+	Spine surgery at age 16	
XI	Japan	Childhood / unknown	Unknown	Unknown	Unknown	+	Unknown	Unknown	Walked w/out assistance until 65 years; severe gait disturbance from 68 yrs	Hayashi et al [2013]
XII	Japan	Birth / unknown	11	Unknown	Unknown	+	Unknown	Unknown	Abnormal gait from 3 yrs	
XIII	Japan	4 / unknown	14	Unknown	Unknown	Unknown	Unknown	Unknown	Frequent falls from age 4 years; walked w/ limp from 6 yrs	

For further information see Table 2 (pdf).

1. Roman numerals = family; letters = sibs

2. - = not affected; + = mild in the lower extremities; ++ = marked in the lower extremities; +++ = also affected the hands and forearms

3. - = affected; + = mild; ++ = severe

4. - = no deformities; + = pes cavus and hammer toes; ++ = pes equinus and toes retraction

5. - = none; + = mild; ++ = severe; +++ = surgery required

6. - = no deficit; + = decreased sensibility; +++ = no sensibility

7. Patients Ia, Ib, and Ic are from three different branches of the same Lebanese family. See also Table 5.

8. Difficulty running and poor balance

9. Clumsiness

Genotype-Phenotype Correlations

No genotype-phenotype correlations can be established in the 18 affected individuals from 13 families with molecularly confirmed CMT4H; remarkably, individuals homozygous for nonsense or frameshift variants do not have more severe manifestations than individuals with missense variants (summarized in detail in Table 2 [pdf]).

Prevalence

CMT4H is rare and it is difficult to estimate its prevalence. Only 13 families with molecularly confirmed CMT4H have been published to date.

Table 4 summarizes the proportion of individuals with CMT4H in published studies of CMT4. These studies have shown that *FGD4* pathogenic variants are most commonly homozygous variants identified in consanguineous families.

Table 4. Proportion of Individuals with CMT4H in Published Studies

# of Individuals w/CMT4H / Total # of Individuals w/CMT4	# of Individuals w/CMT4H / # of Individuals in the Study w/an Identified Pathogenic Variant	References
3/103 (~3%)	3/7 (43%)	Hayashi et al [2013]
2/45 (~4.5%) [1]	2/28 (7%)	Baets et al [2011]
4/63 (~6.3%)[2]	Unknown	Stendel et al [2007]
1/12 (~8.3%)	Unknown	Houlden et al [2009]
5/108 (~4.6%)	Unknown	Delague et al [2007]; Delague, personal communication

1. The proportion of CMT4H is probably higher than indicated, as a number of individuals in this series have autosomal dominant inheritance.
2. All affected individuals had (1) demyelinating sensorimotor neuropathy with onset in the first decade and (2) at least one of the following: (a) parental consanguinity or at least one other affected sib; (b) severely slowed NCVs (<15 m/s for the motor median nerve); (c) prominent scoliosis; and (d) myelin outfoldings on nerve biopsy. No parents of affected individuals had clinical or neurophysiologic findings of CMT.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *FGD4*.

Differential Diagnosis

See Charcot-Marie-Tooth Neuropathy.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Charcot-Marie-Tooth neuropathy type 4H (CMT4H), the following evaluations are recommended:

- Physical examination to determine extent of weakness and atrophy, pes cavus, gait stability, sensory loss, and skeletal deformities. In children with CMT, one should use the CMTPedS score defined by Burns et al [2012], a reliable, well-tolerated, valid, and sensitive global measure of disability for children with CMT from the age of 3 years [Burns et al 2012].

  Although the CMT Neuropathy Score (CMTNS) and CMTNS version 2 (CMTNS2) are widely used in the diagnosis of CMT [Shy et al 2005, Murphy et al 2011], they have shown limited potential in measuring disability and disease severity in children younger than age ten years [Haberlová & Seeman 2010, Pagliano et al 2011].

  The transition from the CMTPedS in childhood to the CMTNS2 in adulthood has been evaluated [Burns et al 2013]; together, the two measures provide a continuum for lifelong measurement of disability in patients with CMT.

- Orthopedic consultation to evaluate skeletal deformities such as foot deformities (pes cavus) and scoliosis and to determine the need for a surgery and/or ankle/foot orthoses
- Clinical genetics consultation and/or pediatric neurology consultation

Treatment of Manifestations

Individuals with CMT4H 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]
- Physiotherapy with daily heel cord stretching exercises to help prevent Achilles' tendon shortening and physical activity adapted to the abilities of each individual to prevent contractures and help preserve flexibility
- Orthopedic surgery to correct severe pes cavus deformity [Guyton & Mann 2000, Ward et al 2008]
- Surgery to correct spine deformities
- Forearm crutches or canes for gait stability
- Wheelchairs as needed because of gait instability
- Treatment of musculoskeletal pain with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) [Carter et al 1998]

Surveillance

Appropriate surveillance includes annual evaluation by a team comprising physiatrists, neurologists, and physical and occupational therapists to determine neurologic status and functional disability.

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 testing 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 4H (CMT4H) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of 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 CMT4H are obligate heterozygotes (carriers) for a pathogenic variant in *FGD4*.

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

Carrier (Heterozygote) Detection

Carrier testing for at-risk family members is possible if the pathogenic variants in the family have been identified.

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 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 variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CMT4H are possible.

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. While decisions regarding prenatal testing are the choice of the parents, discussion of these issues is appropriate.

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 4H: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CMT4H	*FGD4*	12p11.21	FYVE, RhoGEF and PH domain-containing protein 4	IPN Mutations, FGD4 FGD4 homepage - Leiden Muscular Dystrophy pages	FGD4	FGD4

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 4H (View All in OMIM)

609311	CHARCOT-MARIE-TOOTH DISEASE, TYPE 4H; CMT4H
611104	FYVE, RhoGEF, AND PH DOMAIN-CONTAINING PROTEIN 4; FGD4

Gene structure. *FGD4* comprises 17 exons, of which 14 are coding exons. The gene covers a genomic region of about 14 kb. There are several isoforms, but the major transcript (NM_139241.2) is 2931 bp long (2301 bp of coding sequence). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. 14 *FGD4* pathogenic variants have been described in 13 families. *FGD4* single-nucleotide variants have been described (occurring throughout the gene), including missense, nonsense, frameshift, splice site, and splicing variants.

See Table 5 for *FGD4* variants.

Table 5. *FGD4* Variants Identified in the 13 Reported Families

Family	Origin	Consanguinity	DNA Nucleotide Change (Alias [1])	Location in the Gene	Predicted Protein Change	Reference
Ia, Ib [2]	Lebanon	Yes	c.893T>G [3]	Exon 7	p.Met298ArgfsTer8 [3]	Delague et al [2007]
Ic [2]	Lebanon	Yes	c.893T>G [3]	Exon 7	p.Met298Arg [3]	Stendel et al [2007]
II	Algeria	Yes	c.893T>C	Exon 7	p.Met298Thr	Delague et al [2007]

Table 5. continued from previous page.

Family	Origin	Consanguinity	DNA Nucleotide Change (Alias [1])	Location in the Gene	Predicted Protein Change	Reference
III	Turkey	Yes	c.670C>T		p.Arg224Ter	Stendel et al [2007]
IV	Turkey	Yes	c.1628_1629delGA (1627_1628delGA or 1626_1627delAG)	Exon 13	p.Glu543GlyfsTer5	
V	Tamil	Sporadic	c.1756G>T	Exon 14	p.Gly586Ter	
VI	Northern Ireland	Yes	c.823C>T	Exon 6	p.Arg275Ter	Houlden et al [2009]
VII	Italy	Yes	c.1762-2A>G	Intron 14	p.Tyr587fsTer14	Fabrizi et al [2009]
VII	Lebanon	Yes	c.1698G>A	Exon 14	p.Met566Ile	Baudot et al [2012]
IX	Algeria	Yes	c.1325G>A	Exon 10	p.Arg442His	
X	Tunisia	Yes	c.514_515dupG (514_515insG)	Exon 4	p.Ala172GlyfsTer27	Boubaker et al [2013]
XI	Japan	Yes/no	c.1888_1892delAAAGG (1890_1894del)	Exon 15	p.Lys630AsnfsTer5	Hayashi et al [2013]
XII	Japan	Yes/no	c.[837-2A>G + 1132+1G>A]	Intron 6/ intron 8	p.[Trp279fsTer + Tyr355fsTer2]	
XIII	Japan	No/unknown	c.837-1G>A	Intron 6	p.Glu280LysfsTer23	

For further information see Table 2 (pdf).
Reference sequences: NM_139241.2 and NP_640334.2
1. Variant designation that does not conform to current naming conventions
2. Two individuals from different branches of the same Lebanese family
3. Stendel et al [2007] described c.893T>G as a missense variant leading to p.Met298Arg substitution, but Delague et al [2007] simultaneously described the same pathogenic variant in two other branches from the same Lebanese family and demonstrated that it is, in fact, a splicing variant predicted to result in a truncated protein of 305 amino acids instead of the full-length 766 residues (p.298MetfsTer8), or in total absence of the protein.

Normal gene product. *FGD4* encodes FRABIN (FGD1-related F-actin binding protein), a 766-amino acid protein (NP_640334.2) (105 kd), with five functional domains: a N-terminal F-actin binding domain, one DH (Dbl homology) domain, two PH (pleckstrin homology) domains, and one cysteine-rich FYVE domain [Delague et al 2007].

DH domains were first identified in the Dbl protein (and are present in many proteins where they play a key role in the catalysis of GDP to GTP exchange); while PH and FYVE domains are mainly involved in interactions with different forms of phosphoinositides.

FRABIN is a Rho GDP/GTP nucleotide exchange factor (RhoGEF), specific for Cdc42, a member of the Rho family of small GTP binding proteins (Rho GTPases) [Obaishi et al 1998, Umikawa et al 1999]. Rho GTPases play a key role in regulating signal transduction pathways in eukaryotes. In particular, they have a pivotal role in mediating actin cytoskeleton changes during cell migration, morphogenesis, polarization, and division [Etienne-Manneville & Hall 2002, Jaffe & Hall 2005].

The role of FRABIN in peripheral nerve is not well known; however, overexpression of Frabin in embryonic rat spinal motoneurons and rat RT4 schwannoma cells showed that Frabin colocalizes with F-actin in neurite tips and growth cones, and induces the formation of filopodia-like microspikes [Delague et al 2007, Stendel et al 2007].

Also, a recent study in a mouse model of CMT4H [Horn et al 2012] has shown that Frabin regulates the RhoGTPase Cdc42 and endocytosis in Schwann cells.

Abnormal gene product. Most *FGD4* pathogenic variants described to date are predicted to be loss-of-function variants. In particular, nonsense, frameshift, splice site and splicing variants are predicted to lead to either a truncated protein or to complete absence of FRABIN. No data describing the effect of the pathogenic variants at the protein level in individuals with CMT4H have been published to date.

References

Literature Cited

Baets J, Deconinck T, De Vriendt E, Zimoń M, Yperzeele L, Van Hoorenbeeck K, Peeters K, Spiegel R, Parman Y, Ceulemans B, Van Bogaert P, Pou-Serradell A, Bernert G, Dinopoulos A, Auer-Grumbach M, Sallinen SL, Fabrizi GM, Pauly F, Van den Bergh P, Bilir B, Battaloglu E, Madrid RE, Kabzińska D, Kochanski A, Topaloglu H, Miller G, Jordanova A, Timmerman V, De Jonghe P. Genetic spectrum of hereditary neuropathies with onset in the first year of life. Brain. 2011;134:2664–76. PubMed PMID: 21840889.

Baudot C, Esteve C, Castro C, Poitelon Y, Mas C, Hamadouche T, El-Rajab M, Lévy N, Megarbané A, Delague V. Two novel missense mutations in FGD4/FRABIN cause Charcot-Marie-Tooth type 4H (CMT4H). J Peripher Nerv Syst. 2012;17:141–6. PubMed PMID: 22734899.

Boubaker C, Hsairi-Guidara I, Castro C, Ayadi I, Boyer A, Kerkeni E, Courageot J, Abid I, Bernard R, Bonello-Palot N, Kamoun F, Cheikh HB, Lévy N, Triki C, Delague V. A novel mutation in FGD4/FRABIN causes Charcot Marie Tooth disease type 4H in patients from a consanguineous Tunisian family. Ann Hum Genet. 2013;77:336–43. PubMed PMID: 23550889.

Burns J, Ouvrier R, Estilow T, Shy R, Laurá M, Pallant JF, Lek M, Muntoni F, Reilly MM, Pareyson D, Acsadi G, Shy ME, Finkel RS. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol. 2012;71:642–52. PubMed PMID: 22522479.

Burns J, Menezes M, Finkel RS, Estilow T, Moroni I, Pagliano E, Laurá M, Muntoni F, Herrmann DN, Eichinger K, Shy R, Pareyson D, Reilly MM, Shy ME. Transitioning outcome measures: relationship between the CMTPedS and CMTNSv2 in children, adolescents, and young adults with Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2013;18:177–80. PubMed PMID: 23781965.

Carter GT, Abresch RT, Fowler WM Jr, Johnson ER, Kilmer DD, McDonald CM. Profiles of neuromuscular diseases. Hereditary motor and sensory neuropathy, types I and II. Am J Phys Med Rehabil. 1995;74:S140–9. PubMed PMID: 7576421.

Carter GT, Jensen MP, Galer BS, Kraft GH, Crabtree LD, Beardsley RM, Abresch RT, Bird TD. Neuropathic pain in Charcot-Marie-Tooth disease. Arch Phys Med Rehabil. 1998;79:1560–4. PubMed PMID: 9862301.

De Sandre-Giovannoli A, Delague V, Hamadouche T, Chaouch M, Krahn M, Boccaccio I, Maisonobe T, Chouery E, Jabbour R, Atweh S, Grid D, Mégarbané A, Lévy N. Homozygosity mapping of autosomal recessive demyelinating Charcot-Marie-Tooth neuropathy (CMT4H) to a novel locus on chromosome 12p11.21-q13.11. J Med Genet. 2005;42:260–5. PubMed PMID: 15744041.

Delague V, Jacquier A, Hamadouche T, Poitelon Y, Baudot C, Boccaccio I, Chouery E, Chaouch M, Kassouri N, Jabbour R, Grid D, Mégarbané A, Haase G, Lévy N. Mutations in FGD4 encoding the Rho GDP/GTP exchange factor FRABIN cause autosomal recessive Charcot-Marie-Tooth type 4H. Am J Hum Genet. 2007;81:1–16. PubMed PMID: 17564959.

Etienne-Manneville S, Hall A. Rho GTPases in cell biology. Nature. 2002;420:629–35. PubMed PMID: 12478284.

Fabrizi GM, Taioli F, Cavallaro T, Ferrari S, Bertolasi L, Casarotto M, Rizzuto N, Deconinck T, Timmerman V, De Jonghe P. Further evidence that mutations in FGD4/frabin cause Charcot-Marie-Tooth disease type 4H. Neurology. 2009;72:1160–4. PubMed PMID: 19332693.

Grandis M, Shy ME. Current therapy for Charcot-Marie-Tooth disease. Curr Treat Options Neurol. 2005;7:23–31. PubMed PMID: 15610704.

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 PMID: 11232233.

Haberlová J, Seeman P. Utility of Charcot-Marie-Tooth Neuropathy Score in children with type 1A disease. Pediatr Neurol. 2010;43:407–10. PubMed PMID: 21093731.

Hayashi M, Abe A, Murakami T, Yamao S, Arai H, Hattori H, Iai M, Watanabe K, Oka N, Chida K, Kishikawa Y, Hayasaka K. Molecular analysis of the genes causing recessive demyelinating Charcot-Marie-Tooth disease in Japan. J Hum Genet. 2013;58:273–8. PubMed PMID: 23466821.

Horn M, Baumann R, Pereira JA, Sidiropoulos PN, Somandin C, Welzl H, Stendel C, Lühmann T, Wessig C, Toyka KV, Relvas JB, Senderek J, Suter U. Myelin is dependent on the Charcot-Marie-Tooth Type 4H disease culprit protein FRABIN/FGD4 in Schwann cells. Brain. 2012;135:3567–83. PubMed PMID: 23171661.

Houlden H, Hammans S, Katifi H, Reilly MM. A novel Frabin (FGD4) nonsense mutation p.R275X associated with phenotypic variability in CMT4H. Neurology. 2009;72:617–20. PubMed PMID: 19221294.

Jaffe AB, Hall A. Rho GTPases: biochemistry and biology. Annu Rev Cell Dev Biol. 2005;21:247–69. PubMed PMID: 16212495.

Obaishi H, Nakanishi H, Mandai K, Satoh K, Satoh A, Takahashi K, Miyahara M, Nishioka H, Takaishi K, Takai Y. Frabin, a novel FGD1-related actin filament-binding protein capable of changing cell shape and activating c-Jun N-terminal kinase. J Biol Chem. 1998;273:18697–700. PubMed PMID: 9668039.

Murphy SM, Herrmann DN, McDermott MP, Scherer SS, Shy ME, Reilly MM, Pareyson D. Reliability of the CMT neuropathy score (second version) in Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2011;16:191–8. PubMed PMID: 22003934.

Pagliano E, Moroni I, Baranello G, Magro A, Marchi A, Bulgheroni S, Ferrarin M, Pareyson D. Outcome measures for Charcot-Marie-Tooth disease: clinical and neurofunctional assessment in children. J Peripher Nerv Syst. 2011;16:237–42. PubMed PMID: 22003938.

Reddy KL, Zullo JM, Bertolino E, Singh H. Transcriptional repression mediated by repositioning of genes to the nuclear lamina. Nature. 2008;452:243–7. PubMed PMID: 18272965.

Ribiere C, Bernardin M, Sacconi S, Delmont E, Fournier-Mehouas M, Rauscent H, Benchortane M, Staccini P, Lantéri-Minet M, Desnuelle C. Pain assessment in Charcot-Marie-Tooth (CMT) disease. Ann Phys Rehabil Med. 2012;55:160–73. PubMed PMID: 22475878.

Stendel C, Roos A, Deconinck T, Pereira J, Castagner F, Niemann A, Kirschner J, Korinthenberg R, Ketelsen UP, Battaloglu E, Parman Y, Nicholson G, Ouvrier R, Seeger J, De Jonghe P, Weis J, Krüttgen A, Rudnik-Schöneborn S, Bergmann C, Suter U, Zerres K, Timmerman V, Relvas JB, Senderek J. Peripheral nerve demyelination caused by a mutant Rho GTPase guanine nucleotide exchange factor, frabin/FGD4. Am J Hum Genet. 2007;81:158–64. PubMed PMID: 17564972.

Shy ME, Blake J, Krajewski K, Fuerst DR, Laura M, Hahn AF, Li J, Lewis RA, Reilly M. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology. 2005;64:1209–14. PubMed PMID: 15824348.

Umikawa M, Obaishi H, Nakanishi H, Satoh-Horikawa K, Takahashi K, Hotta I, Matsuura Y, Takai Y. Association of frabin with the actin cytoskeleton is essential for microspike formation through activation of Cdc42 small G protein. J Biol Chem. 1999;274:25197–200. PubMed PMID: 10464238.

Ward CM, Dolan LA, Bennett DL, Morcuende JA, Cooper RR. Long-term results of reconstruction for treatment of a flexible cavovarus foot in Charcot-Marie-Tooth disease. J Bone Joint Surg Am. 2008;90:2631–42. PubMed PMID: 19047708.

Chapter Notes

Author Notes

Author's Team

My team leads translational research in the field of Inherited Peripheral Neuropathies (mostly Charcot-Marie-Tooth disease), a group of neuromuscular disorders affecting peripheral nerve. Our aim is to better understand the genetics and physiopathology of this group of diseases. We focus our research on autosomal recessive forms of these diseases, by studying large consanguineous families. By using traditional positional cloning strategies, combined to high-throughput Next Generation Sequencing strategies, we identify new defective genes in Inherited Peripheral Neuropathies. We further study the physiopathology of these diseases, by developing different models, in order to identify potential therapeutic strategies for these diseases. We study in particular two CMT subtypes: CMT4H, caused by pathogenic variants in *FGD4/FRABIN* and *AR-CMT2A*, caused by pathogenic variants in *LMNA*.

In close relationship with the Molecular Genetics Department of The Children's Hospital "La Timone," we develop innovative diagnosis strategies.

Revision History

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- 8 August 2013 (me) Review posted live
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