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Charcot-Marie-Tooth Neuropathy Type 4J – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Charcot-Marie-Tooth Disease Type 4J, CMT4J

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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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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 4J (CMT4J) is a peripheral neuropathy characterized by childhood onset (manifest as clumsy gait) with accelerated limb weakness and muscle atrophy during the teen or adult years that is typically asymmetric and can involve both distal and proximal limb muscles. Although sensory symptoms are minimal, examination may reveal decreased response to touch, pin prick, or vibration distally. Bulbar and cranial nerve functions are often spared; intellect is normal.

Diagnosis/testing

The diagnosis is established by neurologic findings, nerve conduction studies (NCS) that are decreased but not uniformly so and can vary within the same limb, electromyogram (EMG) that often shows diffuse denervation, and detection of biallelic pathogenic variants in *FIG4* (one of which is a missense variant and the other a truncating variant).

Management

Treatment of manifestations: Affected individuals are often managed by a multidisciplinary team that includes a neurologist, physiatrist, orthopedic surgeon, and physical and occupational therapists. Treatment is symptomatic and may include special shoes, ankle/foot orthoses to correct foot drop and aid walking, orthopedic surgery to correct severe *pes cavus* deformity, forearm crutches or canes for gait stability, wheelchair as needed, exercise within the individual's capability to remain physically active, and BIPAP for those with respiratory muscle weakness.

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Surveillance: Annual follow up with a neurologist for overall evaluation of neurologic deficits, with occupational therapy and physical therapy to assess fine motor and gross motor function, and with a pulmonologist for evaluation of respiratory function.

Agents/circumstances to avoid: Medications that are toxic or potentially toxic to persons with CMT, including those who are asymptomatic

Genetic counseling

CMT4J is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

No diagnostic criteria have been established for Charcot-Marie-Tooth neuropathy type 4J (CMT4J).

CMT4J is suspected in individuals with the following clinical and electrophysiologic findings, which differ from those of other CMT types:

- Mild motor symptoms during childhood, such as clumsy gait or difficulties with sports in school
- Accelerated limb weakness and muscle atrophy during the teen years or adulthood
- Asymmetric involvement that may include proximal muscles. Examination typically shows asymmetric muscle weakness and atrophy in both distal and proximal muscles.
- Usually minimal sensory complaints. Examination may reveal decreased response to touch, pin prick, or vibration in distal limbs [Zhang et al 2008, Nicholson et al 2011].
- Diminished or absent deep tendon reflexes
- Family history consistent with autosomal recessive inheritance
- Nerve conduction studies (NCS) that are decreased but not uniformly so. In contrast to the uniform slowing of conduction velocities observed in most individuals with CMT type I [Lewis et al 2000], conduction velocities in persons with CMT4J can vary within the same limb. For example, a median nerve may show a greater than 50% reduction of conduction velocity, while the ulnar nerve in the same limb may exhibit normal or near-normal conduction velocity. This decrease in nerve conduction velocity is often associated with temporal dispersion and prolonged distal latency and F-wave latency [Zhang et al 2008, Nicholson et al 2011], features reminiscent of acquired demyelinating neuropathies.
- Needle electromyogram (EMG). Despite clear evidence of sensory nerve conduction abnormalities, needle EMG often shows diffuse denervation, suggesting severe axonal loss or motor neuron degeneration [Zhang et al 2008, Nicholson et al 2011].

  Note: A high index of suspicion is necessary, particularly in individuals who manifest rapidly progressive and asymmetric limb weakness and evidence of sensory abnormalities on physical examination.

The diagnosis of CMT4J is confirmed by identification of biallelic pathogenic variants in *FIG4*, the only gene in which pathogenic variants are known to cause CMT4J [Chow et al 2007].

Thus far, all pathogenic variants are biallelic, and are usually compound heterozygous variants with one missense variant and one truncating variant. A common pathogenic missense variant occurs in individuals of European descent (see Molecular Genetics).

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

Gene [1]	Method	Variants Detected [2]	Variant Detection Frequency by Method [3]
FIG4	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 pathogenic 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.

Clinical Characteristics

Clinical Description

Findings of Charcot-Marie-Tooth neuropathy type 4J (CMT4J) during childhood include clumsy gait, tripping, and difficulties with sports in school. These findings are usually mild and typically not sufficient to bring affected children to medical attention.

Instances of early childhood onset are very rare.

A majority of affected individuals with biallelic pathogenic variants show accelerated limb weakness and atrophy during teenage years or adulthood with asymmetric involvement of both distal and proximal muscles. These findings are often rapidly progressive, resulting in severe paralysis.

Bulbar or cranial nerve functions are often spared clinically and on physical examination.

While readily detected on physical examination, sensory abnormalities are usually not included in the complaints of patients. Thus, this clinical constellation at presentation resembles amyotrophic lateral sclerosis.

No obvious cognitive dysfunction has been reported in CMT4J.

Severe weakness may prevent independent ambulation depending on the speed of progression. In some patients, respiratory functions may be compromised.

Thus far, no epidemiologic data document life expectancy in CMT4J.

Genotype-Phenotype Correlations

CMT4J is usually caused by biallelic compound heterozygous pathogenic variants in *FIG4*, one of which is a missense variant and the other a truncating variant. The most common pathogenic missense variant reported to date is p.Ile41Thr, which has a 0.001 population frequency among individuals of northern European ancestry [Nicholson et al 2011].

Yunis-Varón syndrome (YVS) is caused by other biallelic pathogenic variants that cause complete loss of *FIG4* function, resulting in neural and non-neural lesions.

Prevalence

About 22 individuals with CMT4J have been reported. No other information regarding prevalence of CMT4J is available.

Genetically Related (Allelic) Disorders

In a subset of affected individuals, clinical presentation may include (in addition to severe neurologic deficits) severe skeletal abnormalities, such as cleidocranial dysplasia and digital anomalies. This constellation of findings has been called Yunis-Varón syndrome (YVS). YVS can also be caused by biallelic pathogenic variants in *FIG4* [Campeau et al 2013] (see Molecular Genetics).

To date, there is no evidence that heterozygous *FIG4* pathogenic variants cause disease. Although heterozygous pathogenic variants in *FIG4* have been suggested to be risk factors for amyotrophic lateral sclerosis, further substantiation is needed [Chow et al 2009].

Differential Diagnosis

See Charcot-Marie-Tooth Neuropathy Overview.

Two clinical scenarios in which CMT4J needs to be considered:

- Individuals presenting with an amyotrophic lateral sclerosis-like phenotype and abnormalities in sensory nerves
- Individuals presenting with a clinical and electrophysiologic phenotype of chronic inflammatory demyelination polyneuropathy (CIDP) in whom weakness is asymmetric and rapidly progressive

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Charcot-Marie-Tooth neuropathy type 4J (CMT4J), the following evaluations are recommended:

- Pulmonary function tests to determine whether respiratory functions are compromised
- Skeletal survey to determine if any of the skeletal abnormalities typically observed in Yunis-Varón syndrome (YVS) are evident. Non-neural deficits are often severe and overshadow neurologic symptoms. Thus far, no neuromuscular involvement has been identified in persons with YVS.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No specific treatment reverses the manifestations of CMT4J.

Affected individuals are often managed by a multidisciplinary team that includes a neurologist, physiatrist, orthopedic surgeon, and physical and occupational therapists [Carter et al 1995, Pareyson & Marchesi 2009, Reilly & Shy 2009].

Treatment is symptomatic and may include the following:

- Special shoes, including those with good ankle support
- Ankle/foot orthoses to correct foot drop and aid walking [Carter et al 1995]
- Orthopedic surgery to correct severe *pes cavus* deformity [Guyton & Mann 2000, Ward et al 2008]
- Forearm crutches or canes for gait stability; severely affected individuals need wheelchairs.
- Exercise within the individual's capability to remain physically active
- BIPAP for those with respiratory muscle weakness

Prevention of Secondary Complications

Ankle braces can help prevent tripping and falling or ankle injuries.

Surveillance

The following are appropriate:

- Annual follow up with a neurologist for overall evaluation of neurologic deficits
- Annual follow up with occupational therapy and physical therapy to assess fine motor and gross motor function
- Annual follow up with a pulmonologist for evaluation of respiratory function

Agents/Circumstances to Avoid

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.

Other

Because the segmental demyelination in patients with CMT4J is similar to that observed in acquired demyelinating neuropathies, a few patients have been treated with intravenous immunoglobin [Cottenie et al 2013]. No obvious effect has been observed.

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 4J (CMT4J) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of 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 risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- The offspring of an individual with CMT4J are obligate heterozygotes (carriers) for a pathogenic variant in *FIG4*.
- Unless an individual with CMT4J has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *FIG4*.

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 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 most centers would consider decisions regarding prenatal testing to be 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.

- **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
- **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 4J: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CMT4J	*FIG4*	6q21	Polyphosphoinositide phosphatase	IPN Mutations, FIG4 alsod/FIG4 genetic mutations FIG4 homepage - Leiden Muscular Dystrophy pages	FIG4	FIG4

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 4J (View All in OMIM)

609390	FIG4 PHOSPHOINOSITIDE 5-PHOSPHATASE; FIG4
611228	CHARCOT-MARIE-TOOTH DISEASE, TYPE 4J; CMT4J

Gene structure. The 23 coding exons in *FIG4* produce a 3,263-bp transcript and a protein of 907 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. No benign variants have been reported.

Pathogenic variants. The most common pathogenic missense variant is p.Ile41Thr, which is likely the result of a founder effect among persons of European ancestry.

Table 2. *FIG4* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.122T>C	p.Ile41Thr	NM_014845.5 NP_055660.1

Variants listed in the table have been provided by the author. *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.

Normal gene product. FIG4 has a molecular weight of 103 kd and comprises 907 amino acids. FIG4 (SAC3 in mammals) is a 5'-phosphoinositide phosphatase that coordinates the turnover of phosphatidylinositol-3,5-bisphosphate ($PI(3,5)P_2$), a very low abundance phosphoinositide.

Fig4/SAC3 is a SAC-domain phosphoinositide phosphatase with specificity toward the 5'-phosphate of $PI(3,5)P_2$. Structural studies of Fig4/SAC3 have not yet been performed, but have been inferred through its homologous protein in *S. cerevisiae* known as Sac1p. Sac1p has a catalytic domain containing the conserved catalytic motif $CX_5R(T/S)$ specific for phosphoinositide substrates. The catalytic core shares a similar topology with other phosphoinositide phosphatases like PTEN, but possesses a unique configuration in its P-loop domain which contains the catalytic $CX_5R(T/S)$ motif [Manford et al 2010].

In order for Fig4/Sac3 to exert its biologic function, it typically complexes with a scaffolding protein known as Vac14/ArPIKfyve and a 5'-kinase of PI3P known as Fab1/PIKfyve. This regulatory complex (PAS) is thought to localize on early endosomal membranes during the transition from early endosomes to late endosomes. Alongside the myriad of endosomal maturation processes that occur at this time, the PAS complex is thought to mediate the conversion of early endosomal PI3P to late endosomal $PI(3,5)P_2$ - a conversion that appears to be essential for protein sorting and the trafficking of late endosomes to the degradative lysosomal compartment.

Abnormal gene product. Deficiency of FIG4 severely affects the human and mouse nervous systems by causing two distinct forms of abnormal lysosomal storage. The first form occurs in spinal sensory neurons and fibroblasts, in which vacuolated endolysosomes accumulate in perinuclear regions. The second form occurs in cortical/spinal motor neurons and glia, in which enlarged endolysosomes become filled with electron-dense materials in a manner indistinguishable from other lysosomal storage disorders [Chow et al 2007, Zhang et al 2008, Katona et al 2011]. These findings reveal a signaling pathway involving FIG4 that appears to be important for lysosomal function. This notion is further supported by the observation that biallelic *FIG4* pathogenic variants cause the Yunis-Varón syndrome (YVS) [Campeau et al 2013].

Based on the current literature, the author proposes a hypothetic mechanism [Martyn & Li 2013]. Early in the endolysosomal pathway, FIG4 in complex with other proteins (PIKfyve/ArPIKfyve) is assembled and localized to the endosomes prior to their maturation to multivesicular bodies. $PI(3,5)P_2$ that begins to be synthesized on endosomal membranes is also required for the activation of lysosomal TRPML1/MCOLN1 channels. Thus, a deficiency of FIG4/$PI(3,5)P_2$ would impair TRPML1/MCOLN1 channel function, leading to the accumulation of calcium in the lysosomes. This would decrease calcium release from lysosomes as well, but would occur independent of $PI(3,5)P_2$. It is speculated that these alterations inhibit the fission of cytoplasmic membrane-targeted vesicles out of lysosomes, which would cause lysosomal storage.

The p.Ile41Thr pathogenic variant that underlies CMT4J is located in the SacN domain, which is thought (based on the structural study) to interact with other proteins. Interestingly, this pathogenic variant has been shown to affect the interaction between Fig4 and Vac14/ArPIKfyve, promoting $FIG4^{I41T}$ degradation [Jin et al 2008, Dove et al 2009]. Since FIG4 proteins with the common p.Ile41Thr pathogenic variant still have phosphatase activity, they are considered hypomorphic [Chow et al 2007, Zhang et al 2008, Nicholson et al 2011]. It has been proposed that this partial preservation of function protects non-neuronal tissues.

Once PI(3,5)P_2 has formed on late endolysosomal membranes, it interacts with a variety of proteins that may mediate endolysosomal acidification, endolysosomal membrane fusion and fission, and trafficking between the endolysosome and Golgi apparatus. Each component of the Fig4/Vac14/Fab1 complex is dependent on either direct or indirect interactions within the complex for proper function and stability. In this manner, Fig4/Sac3 can decrease PI(3,5)P_2 levels via its phosphatase function *and* also promote PI3,5P_2 synthesis by acting as a secondary scaffold for the Fab1/Vac14 interaction. However, the later function appears dominant. Loss of either component results in a similar outcome – a destabilization of the PAS complex and a reduction of PI(3,5)P_2 that gives rise to greatly dilated endolysosomes [Jin et al 2008, Dove et al 2009].

Given these findings, one could speculate that the deficiency of Fig4/SAC3 and PI(3,5)P_2 may impair endolysosomal membrane fusion/fission and protein sorting processes required to properly target proteins and lipids for lysosomal degradation [Martyn & Li 2013].

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Chapter Notes

Author Notes

The author specializes in neuromuscular diseases with particular research interest in inherited neuropathies (also called Charcot-Marie-Tooth disease or CMT) and myelin biology. Disabilities in many neurologic diseases, including inherited neuropathies, are usually caused by one of the two pathophysiologic processes: de-/dysmyelination and/or axonal degeneration. Our laboratory investigates the molecular mechanisms underlying the two pathologic processes at different levels of biologic system, including primary culture neurons/Schwann cells, genetically manipulated rodent models, and human subjects with inherited neuropathies.

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The author's website

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