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MFN2 Hereditary Motor and Sensory Neuropathy

Synonyms: *MFN2* Charcot-Marie-Tooth Neuropathy, *MFN2*-HMSN

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Summary

Clinical characteristics

MFN2 hereditary motor and sensory neuropathy (*MFN2*-HMSN) is a classic axonal peripheral sensorimotor neuropathy, inherited in either an autosomal dominant (AD) manner (~90%) or an autosomal recessive (AR) manner (~10%). *MFN2*-HMSN is characterized by more severe involvement of the lower extremities than the upper extremities, distal upper-extremity involvement as the neuropathy progresses, more prominent motor deficits than sensory deficits, and normal (>42 m/s) or only slightly decreased nerve conduction velocities (NCVs). Postural tremor is common. Median onset is age 12 years in the AD form and age eight years in the AR form. The prevalence of optic atrophy is approximately 7% in the AD form and approximately 20% in the AR form.

Diagnosis/testing

Molecular genetic testing establishes the diagnosis of *MFN2*-HMSN in 90% of probands with suggestive findings by identifying a heterozygous *MFN2* pathogenic variant and in 10% of probands with suggestive findings by identifying biallelic *MFN2* pathogenic variants.

Management

Treatment of manifestations: Neuropathy is often managed by a multidisciplinary team that includes a neurologist, a physiatrist, an orthopedic surgeon, and physical and occupational therapists. Symptomatic treatment relies on special shoes and/or ankle/foot orthoses to correct foot drop and aid walking; surgery as needed for severe *pes cavus*; forearm crutches, canes, wheelchairs as needed for mobility; exercise as tolerated; acetaminophen or nonsteroidal anti-inflammatory agents for musculoskeletal pain; treatment of neuropathic pain with tricyclic antidepressants or drugs such as carbamazepine or gabapentin. Optic atrophy is managed with low vision aids as per a low vision clinic, consultation with community vision services, and career/employment counseling.

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Surveillance: Routine evaluation by: a neurologist to assess disease progression; physical therapy to assess gross motor skills including gait and strength; occupational therapy to assess fine motor skills and coping strategies; and ophthalmologist and low vision clinic to assess visual acuity and need for modification of low vision aids, respectively.

Agents/circumstances to avoid: Obesity (which makes ambulation more difficult); medications (e.g., vincristine, isoniazid, nitrofurantoin) known to cause nerve damage; alcohol and malnutrition (which can cause or exacerbate neuropathy).

Genetic counseling

Approximately 90% of *MFN2*-HMSN is inherited an autosomal dominant (AD) manner, and approximately 10% is inherited in an autosomal recessive (AR) manner. Semi-dominant inheritance (i.e., an *MFN2* pathogenic variant is associated with mild disease in the heterozygous state and more severe disease in the homozygous or compound heterozygous state) has been reported in two families.

- **AD *MFN2*-HMSN.** Most affected individuals have an affected parent; the proportion of individuals with a *de novo MFN2* pathogenic variant is unknown. Each child of an affected individual has a 50% chance of inheriting the *MFN2* pathogenic variant.
- **AR *MFN2*-HMSN.** At conception, each sib of an individual with autosomal recessive *MFN2*-HMSN has a 25% chance of being affected, a 50% chance of being an asymptomatic heterozygote (i.e., carrier), and a 25% chance of being unaffected and not a carrier.

Once the *MFN2* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *MFN2*-HMSN are possible.

Diagnosis

Formal diagnostic criteria for *MFN2* hereditary motor and sensory neuropathy have not been established.

Suggestive Findings

MFN2 hereditary motor and sensory neuropathy (*MFN2*-HMSN) **should be considered** in individuals with the following clinical and neurophysiologic findings. Note: No specific findings distinguish *MFN2*-HMSN from other inherited hereditary motor and sensory neuropathies.

Clinical findings

- Onset before age ten years (although a wide range has been reported)
- Involvement of the lower extremities earlier and more severely than the upper extremities
- Involvement of the distal upper extremities as the neuropathy progresses
- Motor deficits more prominent than sensory deficits
- Optic atrophy (~7% in the autosomal dominant form, and ~20% in the autosomal recessive form)

Neurophysiologic findings

- Nerve conduction velocities (NCVs) are normal (>42 m/s) or only slightly decreased [Saito et al 1997, Züchner et al 2004].
- Electromyogram (EMG) reveals signs of chronic denervation.

Establishing the Diagnosis

The diagnosis of *MFN2*-HMSN **is established** in a proband who has **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous pathogenic variant involving *MFN2* (~90% of affected individuals) [Pipis et al 2020]
- Biallelic *MFN2* pathogenic variants (~10% of affected individuals) [Pipis et al 2020]

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) (see Option 1) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) (see Option 2) depending on the phenotype.

Option 1

A peripheral neuropathy or axonal neuropathy multigene panel that includes *MFN2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of *MFN2*-HMSN is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *MFN2* Hereditary Motor and Sensory Neuropathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MFN2	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. One in 360 individuals with *MFN2*-HMSN had a deletion of exons 7 and 8 [Polke et al 2011].

Clinical Characteristics

Clinical Description

MFN2 hereditary motor and sensory neuropathy (*MFN2*-HMSN) is a classic axonal peripheral sensorimotor neuropathy characterized by earlier and more severe involvement of the lower extremities than the upper extremities, distal upper-extremity involvement as the neuropathy progresses, and more prominent motor deficits than sensory deficits.

MFN2-HMSN can be caused by a heterozygous pathogenic variant (autosomal dominant inheritance) or biallelic pathogenic variants (semi-dominant inheritance or autosomal recessive inheritance). The phenotypes associated with the different modes of inheritance do not differ significantly [Pipis et al 2020].

Autosomal Dominant *MFN2*-HMSN

The age at onset and disease progression of *MFN2*-HMSN vary within and among families; onset ranges from age one year to the sixth decade. Most individuals develop manifestations in the first and second decade. The initial finding is often foot drop or foot weakness. *Pes cavus* foot deformity may occur.

Motor signs (weakness and atrophy) predominate, but mild sensory loss in the feet is common. Tendon reflexes are usually absent, but occasionally intact or increased. Mild pyramidal signs including extensor plantar responses, mild increase in tone, and preserved or increased reflexes but without spastic gait have been observed [Vucic et al 2003, Zhu et al 2005].

Some individuals with *MFN2* pathogenic variants are asymptomatic and have only mild findings on examination; however, the phenotype in those individuals could eventually convert to late-onset *MFN2*-HMSN [Lawson et al 2005, Dankwa et al 2019, Lin et al 2019].

Postural tremor is common [Muglia et al 2001, Bissar-Tadmouri et al 2004].

Affected individuals with early onset (age <10 years) tend to have more severe disability than those with later onset [Chung et al 2006, Pipis et al 2020]. Those with early onset may show optic atrophy, hoarse voice, and proximal weakness.

Subacute onset of optic atrophy with subsequent slow recovery in 60% of individuals with early onset has been reported [Chung et al 2006, Verhoeven et al 2006, Züchner et al 2006]. The majority of reported instances of optic atrophy associated with *MFN2*-HMSN resulted from *de novo MFN2* pathogenic variants.

To date, a single individual with early-onset stroke has been reported [Chung et al 2008].

MFN2-HMSN is progressive. Nearly 27% of individuals become dependent on a wheelchair [Muglia et al 2001, Pipis et al 2020]. Life span is usually not reduced.

Semi-Dominant and Autosomal Recessive *MFN2*-HMSN

Approximately 10% of families have biallelic compound heterozygous variants in *MFN2*. Most of these have been reported in individuals who showed early onset of disease [Polke et al 2011, Pipis et al 2020]. However, Hikiami et al [2018] reported an adult-onset mild phenotype in sisters with homozygous *MFN2* variants.

All *MFN2*-HMSN

Neuroimaging. Periventricular, subcortical, and cerebellar peduncular white matter lesions on brain MRI have been reported in a few individuals [Chung et al 2006, Züchner et al 2006, Klein et al 2011, Oh et al 2014].

Neuropathology. Neuropathologic findings include loss of myelinated nerve fibers (especially large fibers), mitochondrial abnormalities, and (rarely) onion bulb formation [Saito et al 1997, Muglia et al 2001, Verhoeven et al 2006].

Genotype-Phenotype Correlations

Autosomal dominant *MFN2*-HMSN. Variants in certain amino acid residues are always pathogenic, with no evidence of reduced penetrance or variable expressivity (range of phenotypic expression) despite different amino acid substitutions. Examples of different missense changes observed at the same conserved amino acid residue include p.Arg94Trp/Gln, p.Arg104Glu/Trp, p.Ser249Thr/Cys, p.Trp740Ser/Arg [Pipis et al 2020].

In contrast, variants in other amino acid residues are associated with variable expressivity (early vs later onset of disease) dependent on the amino acid substitution at the same residue.

Autosomal dominant vs autosomal recessive variants. No significant genotype-phenotype correlations can be made.

Penetrance

The penetrance for AD *MFN2*-HMSN is considered to be complete. While some individuals with a heterozygous *MFN2* pathogenic variant are asymptomatic and have only mild findings on examination at the time of diagnosis, the disease may prove to be late onset in these instances [Lawson et al 2005].

Nomenclature

Hereditary motor and sensory neuropathy is most commonly referred to by the eponymous name "Charcot-Marie-Tooth (CMT) neuropathy" or "Charcot-Marie-Tooth disease."

Based on an older classification system in which subtypes were defined by clinical parameters such as mode of inheritance, clinical findings, neuropathy type (defined by electrophysiologic findings), and involved gene, *MFN2*-HMSN has been referred to in the past by multiple designations (see Table 2).

Table 2. Clinical Designations Used to Refer to *MFN2* Hereditary Motor and Sensory Neuropathy

Designation	MOI	Clinical Findings
CMT2A [1]	AD AR	Axonal peripheral sensorimotor neuropathy
HMSN V	AD	Axonal peripheral sensorimotor neuropathy w/brisk reflexes
CMT6 CMT6A HMSN VI	AD	Optic atrophy assoc w/*MFN2*-HMSN phenotype
HMSN VII	AD	Axonal CMT phenotype w/mild pyramidal signs incl extensor plantar responses, mild ↑ in tone, & preserved or ↑ reflexes, but no spastic gait [2]

AD = autosomal dominant; AR = autosomal recessive; HMSN = hereditary motor and sensory neuropathy; MOI = mode of inheritance

1. Older classification systems may further divide this designation into CMT2A2A (to refer to AD inheritance) and CMT2A2B (to refer to AR inheritance).

2. Vucic et al [2003], Zhu et al [2005]

Classification using these clinically defined parameters becomes difficult when pathogenic variants in a single gene (e.g., *MFN2*) are associated with more than one mode of inheritance (i.e., both autosomal dominant and autosomal recessive) and a range of clinical features (i.e., a pure *MFN2*-HMSN phenotype and *MFN2*-HMSN with optic atrophy).

To disambiguate, the general term *MFN2* hereditary motor and sensory neuropathy (*MFN2*-HMSN) is used in this *GeneReview*. For further review of nomenclature, see the Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Prevalence

The proportion of CMT caused by pathogenic variants in *MFN2* varies by study:

- Züchner et al [2004] reported seven *MFN2* pathogenic variants in 36 families with CMT2, indicating that 19.5% of CMT2 could be caused by *MFN2* pathogenic variants.
- Chung et al [2006] reported that 24% of 62 families with CMT2 in South Korea had pathogenic variants in *MFN2*.
- Verhoeven et al [2006] reported that 33% of families with CMT2 in a European/USA study had pathogenic variants in *MFN2*.
- Engelfried et al [2006] reported that 8% (6/73) of persons with CMT2, including simplex cases (i.e., a single occurrence in a family), had *MFN2* pathogenic variants.
- Feely et al [2011] reported that *MFN2*-HMSN accounted for 91% of severely impaired individuals with CMT2 but only 11% of mildly or moderately impaired people.
- Subsequent publications confirm the frequencies in these early reports both in families/populations largely of Western European ancestry (i.e., in Italy [Gentile et al 2020] and Hungary [Milley et al 2018]), as well as in other populations (i.e., Han Chinese [Sun et al 2017], Han Chinese in Taiwan [Hsu et al 2019], and Japanese [Ando et al 2017]).

Genetically Related (Allelic) Disorders

A rare complex phenotype caused by pathogenic variants in *MFN2* is lipomatosis or lipodystrophic syndrome involving both lipomatous masses and lipoatrophy [Sawyer et al 2015, Capel et al 2018].

Differential Diagnosis

All hereditary motor and sensory neuropathy (HMSN) forms in which axonal phenotypes have been reported, including *PMP22*-HMSN, *MPZ*-HMSN, and *GJB1*-HMSN (see *GJB1* Disorders) need to be considered in the differential diagnosis of *MFN2*-HMSN. See Charcot-Marie-Tooth Hereditary Neuropathy Overview.

MFN2 pathogenic variants are by far the most common cause of autosomal dominant Charcot-Marie-Tooth disease type 2 (CMT2). As many as one third of all individuals with CMT2 with a positive family history have a pathogenic variant in *MFN2* [Verhoeven et al 2006]. Thus, testing of *MFN2* is probably the first genetic test to consider in families with an axonal neuropathy demonstrating male-to-male transmission.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *MFN2* hereditary motor and sensory neuropathy (*MFN2*-HMSN), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *MFN2* Hereditary Motor and Sensory Neuropathy

System/Concern	Evaluation	Comment
Peripheral neuropathy	Neurologic exam	To determine extent of weakness & atrophy, *pes cavus*, gait stability, & sensory loss
	EMG w/NCV	To determine axonal form of neuropathy, severity, & involvement of sensory system
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills & need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Feet for evidence of *pes cavus*, need for AFOs, specialized shoes • Mobility, ADL, & need for adaptive devices • Need for handicapped parking
Optic atrophy	Ophthalmologic exam incl VEP	To incl visual acuity, color vision testing, visual field testing for evidence of central scotomas
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *MFN2*-HMSN to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; AFOs = ankle/foot orthoses; EMG = electromyogram; MOI = mode of inheritance; NCV = nerve conduction velocity; OT = occupational therapy; PT = physical therapy; VEP = visual evoked potentials
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Neuropathy is often managed by a multidisciplinary team that includes a neurologist, physiatrist, orthopedic surgeon, and physical and occupational therapists [Carter et al 1995]. Treatment is symptomatic and may include the following:

- Exercise within the individual's capability
- Daily heel cord stretching exercises to prevent Achilles tendon shortening
- 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 [Holmes & Hansen 1993, Guyton & Mann 2000]
- Forearm crutches or canes for gait stability
- Wheelchairs for mobility because of gait instability
- Exercising and developing coping strategies for fine motor deficits (e.g., buttoning shirts, sliding credit cards)
- Treatment of musculoskeletal pain with acetaminophen or nonsteroidal anti-inflammatory agents [Carter et al 1998]
- Treatment of neuropathic pain with tricyclic antidepressants or drugs such as carbamazepine or gabapentin
- Career and employment counseling because of persistent weakness of hands and/or feet

Optic atrophy

- **For individuals of all ages.** Low vision aids as prescribed by a low vision clinic, and consultation with community vision services
- **For school-age children**
  - Individualized education plan (IEP) services that provides specially designed instruction and related services to children who qualify. Vision consultants should be a part of the child's IEP team to support access to academic material.
  - A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

Surveillance

Table 4. Recommended Surveillance for Individuals with *MFN2* Hereditary Motor and Sensory Neuropathy

System/Concern		Evaluation	Frequency
Neurologic		• Neurologic exam • Electroneurography of peripheral nerves • EMG/ENG	Annually
Musculoskeletal		• PT assessment (gross motor skills incl gait & strength) • OT assessment (fine motor skills)	Annually
Imaging		MRI of legs to assess amount & location of fat replacing muscles [1]	Specialized centers only, every few yrs
Foot exam		For pressure sores or poorly fitting footwear	Annually
Vision	Those w/o visual manifestations	Routine ophthalmologic exam	When visual changes occur
	Those w/optic atrophy	Assessment of visual acuity, visual fields	Per treating ophthalmologist
		Assessment of low vision aids	Per treating low vision clinic
		For children: assessment of educational needs	Annually
Family support/resources			At each visit

EMG = electromyogram; ENG = electronystagmography; OT = occupational therapy; PT = physical therapy
1. Morrow et al [2018]

Agents/Circumstances to Avoid

Obesity, which makes walking more difficult, should be avoided.

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 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.

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

MFN2 hereditary motor and sensory neuropathy (*MFN2*-HMSN) is inherited an autosomal dominant manner in about 90% of affected individuals, and in autosomal recessive manner in about 10% of affected individuals.

Semi-dominant inheritance (i.e., a pathogenic variant is associated with mild disease in the heterozygous state and more severe disease in the homozygous or compound heterozygous state) of *MFN2*-HMSN has been reported in two families [Piscosquito et al 2015, Tomaselli et al 2016].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant *MFN2*-HMSN have an affected parent.
- A proband with *MFN2*-HMSN may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with *MFN2*-HMSN caused by a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (somatic and germline mosaicism have been reported [Schon et al 2017]).
- The family history of some individuals diagnosed with *MFN2*-HMSN may appear to be negative because of failure to recognize the disorder in family members (a heterozygous family member may be asymptomatic and have only mild findings on examination; see discussion of the CMT neuropathy score in Murphy et al [2011]), early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected [Schon et al 2017].

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. Intrafamilial clinical variability has been observed in *MFN2*-HMSN; a sib who inherits an *MFN2* may be more or less severely affected than the proband [Dankwa et al 2019].
- If the proband has a known *MFN2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Schon et al 2017].
- When the parents are clinically unaffected, the risk to sibs of the proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *MFN2*-HMSN because of the possibility of age-related penetrance in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant *MFN2*-HMSN has a 50% chance of inheriting the *MFN2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *MFN2* pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *MFN2* pathogenic variant based one family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *MFN2* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Individuals who are heterozygous for one autosomal recessive *MFN2* pathogenic variant are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *MFN2* pathogenic variant, each sib of an individual with autosomal recessive *MFN2*-HMSN has at conception 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.
- Individuals who are heterozygous for one autosomal recessive *MFN2* pathogenic variant are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with autosomal recessive *MFN2*-HMSN has children with an affected individual or a carrier, the proband's offspring will be obligate heterozygotes (carriers) for a pathogenic variant *MFN2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *MFN2* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *MFN2* pathogenic variants 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 identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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, at risk of being affected, or at risk of being a carrier of autosomal recessive *MFN2*-HMSN.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MFN2* 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.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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)**
  Phone: 800-606-2682 (toll-free); 610-427-2971
  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**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **Medical Home Portal**
  Charcot-Marie-Tooth Disease (Hereditary Motor Sensory Neuropathy)
- **National Library of Medicine Genetics Home Reference**
  Charcot-Marie-Tooth disease
- **NCBI Genes and Disease**
  Charcot-Marie-Tooth syndrome
- **TREAT-NMD**
  Institute of Translational and Clinical Research
  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)**
  Netherlands
  Phone: 31 35 5480481
  Email: enmc@enmc.org
  www.enmc.org
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  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. MFN2 Hereditary Motor and Sensory Neuropathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MFN2	1p36.22	Mitofusin-2	MFN2 homepage - Leiden Muscular Dystrophy pages	MFN2	MFN2

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 MFN2 Hereditary Motor and Sensory Neuropathy (View All in OMIM)

601152	NEUROPATHY, HEREDITARY MOTOR AND SENSORY, TYPE VIA, WITH OPTIC ATROPHY; HMSN6A
608507	MITOFUSIN 2; MFN2
609260	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, AUTOSOMAL DOMINANT, TYPE 2A2A; CMT2A2A

Table B. continued from previous page.

617087	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, AUTOSOMAL RECESSIVE, TYPE 2A2B; CMT2A2B

Molecular Pathogenesis

MFN2 is a key protein in mitochondrial fusion. It has been suggested that pathogenic variants in *MFN2* cause mitochondrial stress and a loss of mitochondrial fusion, resulting in axonal damage over time. Other studies have observed axonal transport deficiencies. Additionally, it has been suggested that MFN2 is important for endoplasmic reticulum / mitochondrial tethering and communication. No consistent pathogenic mechanism has yet evolved and thus no common molecular assay for pathogenicity testing exists.

Mechanism of disease causation. The mechanism of disease causation is largely unknown, and may be variant specific. Although, in general, the pathogenic variants associated with autosomal dominant inheritance appear to have a gain of function, loss of function could be the basis of loss of mitochondrial fusion, as suggested in experiments in animal and cell models.

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Chapter Notes

Revision History

- 14 May 2020 (bp) Comprehensive update posted live
- 1 August 2013 (me) Comprehensive update posted live
- 10 June 2010 (cd) Revision: edits to Agents/Circumstances to Avoid
- 12 September 2007 (me) Comprehensive update posted live
- 23 January 2006 (cd) Revision: prenatal diagnosis for *MFN2* mutations clinically available
- 18 February 2005 (me) Review posted live
- 13 September 2004 (sz) Original submission

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