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GDAP1-Related Hereditary Motor and Sensory Neuropathy

Synonyms: *GDAP1*-HMSN, *GDAP1*-Related Charcot-Marie-Tooth Neuropathy

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Summary

Clinical characteristics

GDAP1-related hereditary motor and sensory neuropathy (*GDAP1*-HMSN) is a peripheral neuropathy (also known as a subtype of Charcot-Marie-Tooth disease) that typically affects the lower extremities earlier and more severely than the upper extremities. As the neuropathy progresses, the distal upper extremities also become severely affected. Proximal muscles can also become weak. Age at onset ranges from infancy to early childhood. In most cases, disease progression causes disabilities within the first or second decade of life. At the end of the second decade, most individuals are wheelchair bound. Disease progression varies considerably even within the same family. The neuropathy can be either of the demyelinating type with reduced nerve conduction velocities or the axonal type with normal nerve conduction velocities. Vocal cord paresis is common. Intelligence is normal. Life expectancy is usually normal, but on occasion may be reduced because of secondary complications.

Diagnosis/testing

Diagnosis of *GDAP1*-HMSN is based on clinical findings and confirmed by detection on molecular genetic testing of either biallelic pathogenic variants in *GDAP1* in those with autosomal recessive inheritance or a heterozygous pathogenic variant in those with autosomal dominant inheritance.

Management

Treatment of manifestations: Treatment is symptomatic and involves evaluation and management by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment may include: daily heel cord stretching exercises to prevent Achilles tendon shortening, ankle/foot orthoses, orthopedic surgery, forearm crutches or canes, wheelchairs, treatment of musculoskeletal pain with acetaminophen or nonsteroidal anti-inflammatory agents, and career and employment counseling.

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Surveillance: Regular evaluation by the multidisciplinary team to determine neurologic status and functional disability.

Agents/circumstances to avoid: Drugs and medications known to cause nerve damage; obesity.

Genetic counseling

GDAP1-HMSN is usually inherited in an autosomal recessive (AR) manner; autosomal dominant (AD) inheritance is also observed.

- *AR inheritance:* 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 relatives is possible once the pathogenic variants in an affected family member have been identified.
- *AD inheritance:* Offspring of an individual with AD *GDAP1*-HMSN have a 50% risk of inheriting the *GDAP1* pathogenic variant from their affected parent.

Prenatal testing for pregnancies at increased risk for *GDAP1*-HMSN and preimplantation genetic testing are possible for families in which the pathogenic variant(s) have been identified.

GeneReview Scope

GDAP1-Related Hereditary Motor and Sensory Neuropathy Subtype	MOI	Neuropathy Type		
		Demyelinating	Axonal	Intermediate
CMT4A	AR	X		
CMT2H	AR		X	
CMTRIA	AR			X
CMT2K	AD		X	

AD = autosomal dominant; AR = autosomal recessive; CMT = Charcot-Marie-Tooth neuropathy; CMTRIA = Charcot-Marie-Tooth Neuropathy, recessive intermediate A
MOI = mode of inheritance
Hereditary motor and sensory neuropathy is also referred to as "Charcot-Marie-Tooth neuropathy"; see Nomenclature for further discussion of term usage.

Diagnosis

Suggestive Findings

GDAP1-related hereditary motor and sensory neuropathy (*GDAP1*-HMSN) **should be suspected** in individuals with the following clinical and nerve conduction velocity findings.

Clinical findings

- Early onset of peripheral neuropathy, presenting especially with foot deformities, muscle wasting, and involvement of the sensory nerves resulting in decreased appreciation of touch, pain, and vibration. Proximal weakness usually comes later.
- Disability within the first and second decade of life consisting of foot deformity, difficulty walking and claw hand deformity.
- Vocal cord paresis manifest as a hoarse voice
- Mild-to-moderate scoliosis
- Occasional involvement of cranial nerves sometimes resulting in facial weakness.

Nerve conduction velocities (NCVs)

- **Motor NCVs**
  - Most commonly are consistent with an axonal neuropathy with normal NCVs and reduced amplitudes [Sevilla et al 2003].
  - Occasionally are consistent with either a demyelinating neuropathy with slowed NCVs (<38 m/s) [Baxter et al 2002, Nelis et al 2002, Ammar et al 2003, De Sandre-Giovannoli et al 2003] or an intermediate range (30-40 m/s) [Senderek et al 2003].
- **Sensory NCVs** are moderately reduced.

Establishing the Diagnosis

The diagnosis of HMSN **is established** in a proband with typical clinical findings; the diagnosis of *GDAP1*-HMSN is established by the detection of either biallelic *GDAP1* pathogenic variants (in those with autosomal recessive inheritance) or a heterozygous *GDAP1* pathogenic variant pathogenic variant (in those with autosomal dominant inheritance) (see Table 1) on molecular genetic testing.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or a multigene panel) and **genomic testing** (comprehensive genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *GDAP1*-HMSN is broad, individuals with the distinctive findings described in Suggestive Findings may be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other hereditary motor and sensory neuropathies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *GDAP1*-HMSN, molecular genetic testing approaches can include **single-gene testing** or use of a hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease) **multigene panel**.

- **Single-gene testing.** Sequence analysis of *GDAP1* is performed first. If only one pathogenic variant is found, gene-targeted deletion/duplication analysis can be considered; however, to date no exon or whole-gene deletions have been reported.
- **A hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease) multigene panel** that includes *GDAP1* and other genes of interest (see Charcot-Marie-Tooth Hereditary Neuropathy Overview and Differential Diagnosis) may also be considered. 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 HMSN (CMT) multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel 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. Of note, given the rarity of *GDAP1*-HMSN many panels for HMSN may not include this gene. (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 phenotype is indistinguishable from many other hereditary motor and sensory neuropathies, molecular genetic testing approaches can include **comprehensive genomic testing** (sequencing) and/or **gene-targeted testing** (multigene panel).

- **Comprehensive genomic testing** (when clinically available) includes exome sequencing and genome sequencing. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.
- **A hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease) multigene panel** may also be consdered.

Table 1. Molecular Genetic Testing Used in *GDAP1*-Related Hereditary Motor and Sensory Neuropathy

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
GDAP1	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Pathogenic variants in *GDAP1* are identified in nearly 100% of individuals with autosomal recessive CMT whose disease has been mapped to 8q13-q21.1 [Manganelli et al 2014].
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. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

GDAP1-related hereditary motor and sensory neuropathy (*GDAP1*-HMSN) can be inherited in either an autosomal recessive (AR) manner (more common) or an autosomal dominant (AD) manner. The phenotype of AR *GDAP1*-HMSN is more severe than that of AD *GDAP1*-HMSN.

Table 2. Comparison of Autosomal Recessive and Autosomal Dominant *GDAP1*-Related Hereditary Motor and Sensory Neuropathy

GDAP1-HMSN Subtype	Neuropathy Type	Clinical Severity	Age of Onset	Vocal Paresis	Disease Progression
AR *GDAP1*-HMSN (CMT4A, CMT2H, & CMTRIA)	Typically axonal; demyelinating & intermediate also observed	Aggressive	Early (onset can be infancy)	Common	Most individuals wheelchair bound by end of 2nd decade
AD *GDAP1*-HMSN (CMT2K)	Typically axonal or demyelinating; intermediate also observed	Mild relative to AR CMT	Varies from childhood to late adulthood	Rare	Slow disease progression

CMT = Charcot-Marie-Tooth neuropathy; CMTRIA = Charcot-Marie-Tooth Neuropathy, recessive intermediate A; HMSN = hereditary motor and sensory neuropathy; also referred to as "Charcot-Marie-Tooth neuropathy." See Nomenclature for further discussion of term usage.

Autosomal Recessive (AR) *GDAP1*-HMSN

AR *GDAP1*-HMSN is an aggressive severe form with early onset and unusual manifestations. The disease is confined to the peripheral nervous system. Intellect is normal.

When onset of motor nerve involvement is in utero, affected newborns are hypotonic (i.e., a "floppy infant"). Onset can be in infancy, often before age two years. Affected children can show delayed achievement of motor milestones, including walking.

Initial manifestations are typically in the distal lower extremities, including the following:

- Foot deformities (high arch; hammertoe; *pes cavus* or equinovarus; severe clubfoot deformity [Bouhouche et al 2007])
- Muscle wasting
- Areflexia
- Sensory loss

Most authors describe early involvement of the upper extremities with distal muscle weakness and wasting and finger contractures (claw hands).

Sensory involvement leads to decreased appreciation in distal upper and lower limbs of touch, pain, vibration, and joint position.

In the majority of persons with AR *GDAP1*-HMSN nerve conduction velocities (NCVs) (see Suggestive Findings) are consistent with an **axonal** neuropathy. However, in a few persons NCVs are consistent with either a **demyelinating** neuropathy or an **intermediate-range** neuropathy. The clinical manifestations are not consistently distinct among these three neuropathy types.

As the neuropathy progresses the voice becomes hoarse as a result of vocal cord paresis [Sevilla et al 2003, Stojkovic et al 2004]. In some series, vocal cord paresis has been reported more often with axonal neuropathy than with demyelinating neuropathy [Cuesta et al 2002], whereas in other series the converse has been observed [Boerkoel et al 2003].

Rare manifestations of AR *GDAP1*-related neuropathy include the following:

- Spinal deformities [Birouk et al 2003, De Sandre-Giovannoli et al 2003, Sevilla et al 2003]
- Facial weakness [Boerkoel et al 2003]
- Painless lower-leg ulcers [Nelis et al 2002]

Progression of the neuropathy leads to disability of the lower and upper extremities. At the end of the second decade, most individuals are wheelchair bound. Phrenic nerve paresis has sometimes led to restrictive respiratory function [Sevilla et al 2008]. Life expectancy is usually normal, but on occasion may be reduced because of secondary complications.

Although persons with AR *GDAP1-HMSN* are usually more severely affected than those with AD inheritance, Kabzińska et al [2010] reported a founder variant in Europe (p.Leu239Phe) associated with a milder phenotype.

Intrafamilial variability in disease progression was observed in one family in which the proband was wheelchair bound by age 20 years and his sister remained ambulatory with a crutch at age 26 years [Azzedine et al 2003].

Heterozygotes in families with AR *GDAP1*-HMSN are usually unaffected; however, exceptions are two families with the p.Glu222Lys pathogenic variant in which some heterozygotes had mild manifestations [Kabzińska et al 2014].

Neuropathology. Both demyelinating and axonal peripheral nerve lesions have been observed. Prominent loss of medium-sized and large myelinated fibers has been described [Nelis et al 2002, Ammar et al 2003, Boerkoel et al 2003, Sevilla et al 2003]. Onion bulb formations as well as thinly myelinated and unmyelinated axons have been observed [Nelis et al 2002, De Sandre-Giovannoli et al 2003]. In one study, findings were interpreted as an intermediate type of neuropathy [Senderek et al 2003]. Focally folded myelin is not a feature.

Autosomal Dominant (AD) *GDAP1*-HMSN

AD *GDAP1*-HMSN – compared with AR *GDAP1*-HMSN – is typically associated with a milder phenotype that is slowly progressive.

AD *GDAP1*-HMSN has been reported in the following:

- Three Spanish families. In two families segregating the variant p.Arg120Trp and in a third family the variant p.Thr157Pro occurred *de novo* in the proband (whose paternity was confirmed) [Claramunt et al 2005].
- Eight families (in which 3 demonstrated reduced penetrance) with four different missense variants, including three families with the variant p.Arg120Trp [Zimoń et al 2011]

Onset varies from childhood to late adulthood. Difficulty with walking is the most common initial manifestation. Weakness and atrophy are usually restricted to distal muscles of the upper and lower limbs. Vocal cord paresis and thoracic scoliosis are uncommon. Disease progression is slow; affected persons generally remain ambulatory.

Genotype-Phenotype Correlations

Possible genotype-phenotype correlations have been reported but are not common enough to be confirmed. An exception is the founder variant in eastern Europe, p.Leu239Phe, which appears to be associated with a comparably milder phenotype [Kabzińska et al 2010].

The *GDAP1* pathogenic variant, p.Glu222Lys, may be uniquely associated with both AR *GDAP1*-HMSN and (in rare cases) AD *GDAP1*-HMSN [Kabzińska et al 2014].

Co-occurrence of pathogenic variants in genes causing two different types of HMSN. The co-occurrence of two HMSN-related pathogenic variants presumably resulted in an additive effect and suggests consideration of simultaneous variants in two HMSN-related genes as an explanation in unusual or severe cases:

- ***GDAP1* and *MFN2*.** Kostera-Pruszczyk et al [2014] reported a child with severe HMSN who was found to be heterozygous for the *GDAP1* pathogenic variant, p.His123Arg, and the *MFN2* pathogenic variant, p.Thr236Met. The co-occurrence of pathogenic variants in these two genes was also reported by Cassereau et al [2011] and Vital et al [2012].
- ***GDAP1* and *PRX*.** Auer-Grumbach et al [2008] reported two novel *GDAP1* and *PRX* variants associated with early-onset HMSN.

Penetrance

Reduced penetrance has been reported in AD *GDAP1*-HMSN. Several heterozygotes have been reported to be mildly affected or asymptomatic at an advanced age [Zimoń et al 2011].

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, *GDAP1*-related hereditary motor and sensory neuropathy has been referred to in the past as:

- CMT4A, autosomal recessive, demyelinating HMSN
- CMT2H, autosomal recessive, axonal HMSN
- CMTRIA, autosomal recessive, intermediate HMSN
- CMT2K, autosomal dominant, axonal HMSN

However, classification using these clinically defined parameters becomes difficult when pathogenic variants in a single gene (e.g., *GDAP1*) are associated with more than one mode of inheritance (e.g., both autosomal dominant and autosomal recessive inheritance), and/or more than one neuropathy type (axonal, demyelinating, and/or intermediate). To disambiguate, the general term *GDAP1*-related hereditary motor and sensory neuropathy (*GDAP1*-HMSN) is used in this *GeneReview*. For further review of nomenclature, see the Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Prevalence

Currently, autosomal recessive *GDAP1*-HMSN is considered one of the most common autosomal recessive hereditary neuropathies.

Molecular genetic testing has shown the following proportion of individuals with HMSN (also known as CMT) with *GDAP1* pathogenic variants:

- Three of 69 (4.3%) unrelated Czech individuals with autosomal recessive CMT [Baránková et al 2007]
- Eight of 197 (5.4%) individuals in an Italian population with CMT [Manganelli et al 2014]
- Five of 174 (2.8%) families from Europe with autosomal recessive CMT screened for thirteen genes known to be associated with AR-HMSN [Zimoń et al 2015]
- 1% of 1000 individuals with an inherited peripheral neuropathy in Japan [Yoshimura et al 2017]

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* have been associated with pathogenic variants in *GDAP1*.

Differential Diagnosis

See Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Vocal cord paresis, which is often seen in autosomal recessive *GDAP1*-related HMSN, also occurs in other types of CMT, such as *TRPV4*-related hereditary neuropathy.

While AR *GDAP1*-HMSN is considered one of the most common causes of autosomal recessive CMT, *SH3TC2*-HMSN is equally common in some studies [Rudnik-Schöneborn et al 2016].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *GDAP1*-related hereditary motor and sensory neuropathy (*GDAP1*-HMSN), the following evaluations are recommended:

- Neurologic examination to determine extent of weakness and atrophy, *pes cavus*, gait stability, and sensory loss
- Physical therapy and occupational therapy assessments regarding muscle weakness and gait and need for ankle foot orthoses, walking aids, and/or a wheelchair [Kennedy et al 2016]
- Speech therapy assessment if hoarseness is present or vocal cord paresis is suspected
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Individuals with *GDAP1*-HMSN are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists [Corrado et al 2016, McCorquodale et al 2016]. Treatment is symptomatic and may include the following [Mathis et al [2015]:

- Daily heel cord stretching exercises to prevent Achilles tendon shortening.
- Exercise within the affected individual's capability

  Note: (1) Fatigue may improve with exercise; (2) unconfirmed anecdotal observations suggest benefit from the stimulant modafinil [Carter et al 2006, Ramdharry et al 2012].
- Ankle/foot orthoses (AFOs) to correct foot drop and aid walking [Guillebastre et al 2011, Phillips et al 2012]
- Orthopedic surgery to correct severe *pes cavus* deformity [Boffeli & Tabatt 2015, Faldini et al 2015, Ferraro et al 2017]
- Forearm crutches or canes for gait stability
- Wheelchair for mobility because of gait instability
- Treatment of musculoskeletal pain with acetaminophen or nonsteroidal anti-inflammatory drugs [Kroenke et al 2009]
- Treatment of neuropathic pain with tricyclic antidepressants or drugs such as carbamazepine or gabapentin [Shy 2006, Bril et al 2011, Ribiere et al 2012, Jeong et al 2013]
- Weight control to avoid obesity, which has a negative effect on gait and balance
- Career and employment counseling because of persistent weakness of hands and/or feet
- Individual psychotherapy, group therapy, and/or antidepressant medication for depression [Cordeiro et al 2014]

Treatment may require involvement of specialists to evaluate and manage potential complications, including the following:

- Lower urinary tract involvement [Krhut et al 2014]
- Obstructive sleep apnea and restless legs [Boentert et al 2014]
- Pulmonary compromise and/or phrenic nerve involvement [Aboussouan et al 2007]
- Vocal cord paresis
- Hip dysplasia [Bamford et al 2009, Novais et al 2014]

Note: No special diet (including supplements with essential fatty acids, vitamin E, or creatine) has been shown to be beneficial [Mathis et al 2015].

Surveillance

Regular evaluations to determine:

- Neurologic status and need for treatment (or change in treatment) for musculoskeletal and/or neuropathic pain;
- Functional disability and need for change in physical therapy regime and/or augmentative devices for activities of daily living and mobility;
- Need for change in diet to control weight;
- Need to involve specialists to evaluate and treat potential complications.

Agents/Circumstances to Avoid

The following should be avoided:

- Obesity because of its negative effect on gait and balance
- Medications that are toxic or potentially toxic to persons with HMSN (CMT) 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

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives in order to identify as early as possible those who would benefit from prompt initiation of treatment and knowledge about agents/circumstances to avoid.

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

Therapies Under Investigation

Mathis et al [2015] discuss more speculative possible future therapies for HMSN including neurotrophic factors, targeting transport defects, enhancement of autophagy-lysosomal pathways, and neuroregeneration.

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

GDAP1-related hereditary motor and sensory neuropathy (*GDAP1*-HMSN) is inherited in an autosomal recessive manner (AR *GDAP1*-HMSN) or, less frequently, autosomal dominant manner (AD *GDAP1*-HMSN).

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with AR *GDAP1*-HMSN are obligate heterozygotes for a *GDAP1* pathogenic variant.
- Heterozygotes are typically asymptomatic (see Clinical Description).

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not heterozygous.
- The phenotype is generally consistent among family members with the same genotype; however, intrafamilial variability has been observed in one family with AR *GDAP1*-HMSN [Azzedine et al 2003].
- Heterozygotes are typically asymptomatic (see Clinical Description).

Offspring of a proband. The offspring of an individual with AR *GDAP1*-HMSN are obligate heterozygotes for a *GDAP1* pathogenic variant and are typically asymptomatic (see Clinical Description).

Other family members. Each sib of the proband's parents are at a 50% risk of being heterozygous for a *GDAP1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GDAP1* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with AD *GDAP1*-HMSN have an affected parent.
- The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Molecular genetic testing of the parents for the *GDAP1* pathogenic variant identified in the proband is recommended.
- If the *GDAP1* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (though theoretically possible, no instances of germline mosaicism have been reported).

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 has the *GDAP1* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Intrafamilial clinical variability and reduced penetrance have been observed [Zimoń et al 2011].
- If the *GDAP1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with AD *GDAP1*-HMSN has a 50% chance of inheriting the 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 *GDAP1* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GDAP1* 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
- **TREAT-NMD**
  Institute of Translational and Clinical Research
  University of Newcastle upon Tyne
  International Centre for Life
  Newcastle upon Tyne NE1 3BZ
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  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

- **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. GDAP1-Related Hereditary Motor and Sensory Neuropathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GDAP1	8q21.11	Ganglioside-induced differentiation-associated protein 1	GDAP1 homepage - Leiden Muscular Dystrophy pages	GDAP1	GDAP1

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 GDAP1-Related Hereditary Motor and Sensory Neuropathy (View All in OMIM)

606598	GANGLIOSIDE-INDUCED DIFFERENTIATION-ASSOCIATED PROTEIN 1; GDAP1
608340	CHARCOT-MARIE-TOOTH DISEASE, RECESSIVE INTERMEDIATE A; CMTRIA

Gene structure. *GDAP1* comprises six exons spanning about 14 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date, more than 80 pathogenic variants have been identified. Known pathogenic variants include deletions, insertions, and nonsense, missense, and splice site variants throughout the gene (see Table A).

The following variants have been detected in specific populations:

- p.Gln163Ter in a Hispanic population [Boerkoel et al 2003]
- p.Leu239Phe in central and eastern European populations [Kabzińska et al 2010]

Note: A number of *GDAP1* pathogenic variants associated with AD *GDAP1*-HMSN (formerly known as CMT2K) have been described. See CMT Overview [Claramunt et al 2005, Chung et al 2008, Sahin-Calapoglu et al 2009].

The *GDAP1* pathogenic variant, p.Glu222Lys, may be uniquely associated with both AR *GDAP1*-HMSN and (in rare cases) AD *GDAP1*-HMSN [Kabzińska et al 2014].

Table 3. Selected *GDAP1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.347T>G	p.Met116Arg	NM_018972.2 NP_061845.2
c.358C>T	p.Arg120Trp	
c.368A>G	p.His123Arg	
c.469A>C	p.Thr157Pro	
c.487C>T	p.Gln163Ter	
c.715C>T	p.Leu239Phe	

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. The protein ganglioside-induced differentiation-associated protein-1 comprises 358 amino acids. It contains a glutathione-S-transferase (GST) domain and belongs to a new class of GST-like proteins, which have a transmembrane domain in the C-terminal extension [Marco et al 2004]. Pedrola et al [2005] investigated a human neuroblastoma cell line that transiently over-expressed GDAP1 and found co-localization with mitochondrial marker proteins. Western blots of subcellular fractions confirmed this finding. They also showed that C-terminal transmembrane domains are necessary for the correct localization in mitochondria; however, missense variants did not change the mitochondrial pattern of the wild-type protein [Pedrola et al 2005].

Niemann et al [2005] showed that GDAP1 is located in the mitochondrial outer membrane and regulates the mitochondrial network. GDAP1 induces fragmentation (fission) of mitochondria, the opposite function of mitofusin-2, encoded by *MFN2*, pathogenic variants in which cause CMT2A.

Abnormal gene product. Loss of ganglioside-induced differentiation-associated protein-1 results in loss of mitochondrial fragmentation activity. Disease-associated missense variants also result in reduced activity [Niemann et al 2005, Pareyson et al 2015]. Pathogenic variants have been reported in all regions of the protein. Variants associated with AR and AD disease include both loss-of-function and missense variants

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