

FEP 2.04.89 Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Effective Date: April 15, 2018

Related Policies: None

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Description

The inherited peripheral neuropathies are a heterogeneous group of diseases that may be inherited in an autosomal dominant, autosomal recessive, or X-linked dominant manner. These diseases can generally be diagnosed based on clinical presentation, nerve conduction studies, and family history. Genetic testing has been used to diagnose specific inherited peripheral neuropathies.

Hereditary Motor and Sensory Neuropathies

Most inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurologic findings to the classic picture with pes cavus and “stork legs” to a severe polyneuropathy with respiratory failure.³ CMT disease is genetically and clinically heterogeneous. Variants in more than 30 genes and more than 44 different genetic loci have been associated with the inherited neuropathies.⁴ Also, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and inheritance patterns. A 2016 cross-sectional study of 520 children and adolescents with CMT found variability in CMT-related symptoms across the 5 most commonly represented subtypes.⁵

CMT subtypes are characterized by variants in one of several myelin genes, which lead to abnormalities in myelin structure, function, or upkeep. There are 7 subtypes of CMT, with type 1 and 2 representing the most common hereditary peripheral neuropathies.

Most cases of CMT are autosomal dominant, although autosomal recessive and X-linked dominant forms exist. Most cases are CMT type 1 (approximately 40%-50% of all CMT cases, with 78%-80% of those due to *PMP22* variants).⁶ CMT type 2 is associated with 10% to 15% of CMT cases, with 20% of those due to *MFN2* variants.

A summary of the molecular genetics of CMT is outlined in Table 1.

Table 1: Molecular Genetics of CMT Variants

Locus	Gene	Protein Product	Prevalence (if known)
CMT type 1			
CMT1A	<i>PMP22</i>	Peripheral myelin protein 22	70%-80% of CMT1
CMT1B	<i>MPZ</i>	Myelin P0 protein	10%-12% of CMT1
CMT1C	<i>LITAF</i>	Lipopolysaccharide-induced tumor necrosis factor- α factor	\approx 1% of CMT1
CMT1D	<i>EGR2</i>	Early growth response protein 2	

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Locus	Gene	Protein Product	Prevalence (if known)
CMT1E	<i>PMP22</i>	Peripheral myelin protein 22 (sequence changes)	≈1% of CMT1
CMT1F/2E	<i>NEFL</i>	Neurofilament light polypeptide	
CMT type 2			
CMT2A1	<i>KIF1B</i>	Kinesin-like protein KIF1B	
CMT2A2	<i>MFN2</i>	Mitofusin-2	20% of CMT2
CMT2B	<i>RAB7A</i>	Ras-related protein Rab-7	
CMT2B1	<i>LMNA</i>	Lamin A/C	
CMT2B2	<i>MED25</i>	Mediator of RNA polymerase II transcription subunit 25	
CMT2C	<i>TRPV4</i>	Transient receptor potential cation channel subfamily V member 4	
CMT2D	<i>GARS</i>	Glycyl-tRNA synthetase	
CMT2E/1F	<i>NEFL</i>	Neurofilament light polypeptide	
CMT2F	<i>HSPB1</i>	Heat-shock protein beta-1	
CMT2G	12q12-q13	Unknown	
CMT2H/2K	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein 1	
CMT2I/2J	<i>MPZ</i>	Myelin P0 protein	
CMT2L	<i>HSPB8</i>	Heat-shock protein beta-8	
CMT2N	<i>AARS</i>	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	<i>DYNC1H1</i>	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	<i>LRSAM1</i>	E3 ubiquitin-protein ligase LRSAM1	
CMT2S	<i>IGHMBP2</i>	DNA-binding protein SMUBP-2	
CMT2T	<i>DNAJB2</i>	DnaJ homolog subfamily B member 2	
CMT2U	<i>MARS</i>	Methionine-tRNA ligase, cytoplasmic	
CMT type 4			
CMT4A	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein 1	
CMT4B1	<i>MTMR2</i>	Myotubularin-related protein 2	
CMT4B2	<i>SBF2</i>	Myotubularin-related protein 13	
CMT4C	<i>SH3TC2</i>	SH3 domain and tetratricopeptide repeats-containing protein 2	
CMT4D	<i>NDRG1</i>	Protein NDRG1	
CMT4E	<i>EGR2</i>	Early growth response protein 2	
CMT4F	<i>PRX</i>	Periaxin	
CMT4H	<i>FGD4</i>	FYVE, RhoGEF and PH domain-containing protein 4	
CMT4J	<i>FIG4</i>	Phosphatidylinositol 3, 5-bisphosphate	
X-linked CMT			
CMTX1	<i>GJB1</i>	Gap junction beta-1 protein (connexin 32)	90% of X-linked CMT
CMTX2	<i>Xp22.2</i>	Unknown	
CMTX3	<i>Xq26</i>	Unknown	
CMTX4	<i>AIFM1</i>	Apoptosis-inducing factor 1	
CMTX5	<i>PRPS1</i>	Ribose-phosphate pyrophosphokinase 1	
CMTX6	<i>PDK3</i>	Pyruvate dehydrogenase kinase isoform 3	

Adapted from Bird (2016).⁶

CMT: Charcot-Marie-Tooth.

The clinical features of CMT are briefly summarized.

CMT Type 1

CMT type 1 (CMT1) is an autosomal dominant, demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity. It is usually slowly progressive and often associated with pes cavus foot deformity, bilateral foot drop, and palpably enlarged nerves, especially the ulnar nerve at the olecranon groove and the greater auricular nerve. Affected people usually become symptomatic between ages 5 and 25 years, and lifespan is not shortened. Less than 5% of people become wheelchair-dependent. CMT1 is inherited in an autosomal dominant manner. The CMT1 subtypes (CMT 1A-E) are separated by molecular findings and are often clinically indistinguishable.

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CMT1A accounts for 70% to 80% of all CMT1, and about two-thirds of probands with CMT1A have inherited the disease-causing variant, and about one-third have CMT1A as the result of a de novo variant.

CMT1A involves duplication of the *PMP22* gene. *PMP22* encodes an integral membrane protein, peripheral membrane protein 22, which is a major component of myelin in the peripheral nervous system. The phenotypes associated with this disease arise because of abnormal *PMP22* gene dosage effects.⁷ Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) result in the most severe phenotype, whereas 3 normal alleles (as in the heterozygous CMT1A duplication) cause a less severe phenotype.⁸

CMT Type 2

CMT type 2 (CMT2) is a non-demyelinating (axonal) peripheral neuropathy characterized by distal muscle weakness and atrophy, mild sensory loss, and normal or near-normal nerve conduction velocities. Clinically, CMT2 is similar to CMT1, although typically less severe.⁹ The subtypes of CMT2 are similar clinically and distinguished only by molecular genetic findings. CMT2B1, CMT2B2, and CMT2H/K are inherited in an autosomal recessive manner; all other subtypes of CMT2 are inherited in an autosomal dominant manner. The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with variants in the *MFN2* gene.

X-Linked CMT

CMT X type 1 (CMTX1) is characterized by a moderate-to-severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females.¹⁰ Sensorineural deafness and central nervous system symptoms also occur in some families. CMTX1 is inherited in an X-linked dominant manner. Molecular genetic testing of *GJB1* (Cx32), which is available on a clinical basis, detects about 90% of cases of CMTX1.¹⁰

CMT Type 4

CMT type 4 is a form of hereditary motor and sensory neuropathy that is inherited in an autosomal recessive fashion and occurs secondary to myelinopathy or axonopathy. It occurs more rarely than the other forms of CMT neuropathy, but some forms may be rapidly progressive and/or associated with severe weakness.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for the diagnosis of inherited peripheral neuropathies is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Multiple laboratories offer individual variant testing for genes involved in hereditary sensory and motor neuropathies, which would typically involve sequencing analysis via Sanger sequencing or next-generation sequencing followed by deletion/duplication analysis (ie, with array comparative genomic hybridization) to detect large deletions or duplications. For the detection of variants in *MFN2*, whole gene or select exome sequence analysis is typically used to identify SNVs, in addition to or followed by deletion or duplication analysis for the detection of large deletions or duplications.

A number of genetic panel tests for the assessment of peripheral neuropathies are commercially available. For example, GeneDx (Gaithersburg, MD) offers an Axonal CMT panel, which uses next-generation sequencing and exon array comparative genomic hybridization. The genes tested include:

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*AARS, BSCL2, DNM2, DYNC1H1, GARS, GDAP1, GJB1, HSPB1, HSPB8, LMNA, LRSAM1, MED25, MFN2, MPZ, NEFL, PRPS1, RAB7A, and TRPV4.*²² InterGenetics (Athens, Greece) offers a next-generation sequencing panel for neuropathy that includes 42 genes involved in CMT, along with other hereditary neuropathies. Fulgent Clinical Diagnostics Lab offers a broader NGS panel for CMT that includes 48 genes associated with CMT and other neuropathies and myopathies.

POLICY STATEMENT

Genetic testing is considered **medically necessary** when the diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to signs and/or symptoms, but a definitive diagnosis cannot be made without genetic testing.

Genetic testing for an inherited peripheral neuropathy is considered **investigational** for all other indications.

POLICY GUIDELINES

This policy addresses the hereditary motor and sensory peripheral neuropathies, of which peripheral neuropathy is the primary clinical manifestation. A number of other hereditary disorders may have neuropathy as an associated finding but typically have other central nervous system and occasional other systemic findings. Examples include Refsum disease, various lysosomal storage diseases, and mitochondrial disorders.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

For individuals with suspected inherited motor and sensory peripheral neuropathy who receive testing for genes associated with inherited peripheral neuropathies, the evidence includes case-control and genome-wide association studies. Relevant outcomes are test accuracy and validity, symptoms, and change in disease status. For the evaluation of hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies, the diagnostic testing yield is likely to be high, particularly when sequential testing is used based on patient phenotype. However, the clinical utility of

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genetic testing to confirm a diagnosis in a patient with a clinical diagnosis of an inherited peripheral neuropathy is unknown. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies was identified. However, a chain of evidence supports the use of genetic testing to establish a diagnosis in cases of suspected inherited motor or sensory neuropathy, when a diagnosis cannot be made by other methods, to initiate supportive therapies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Academy of Neurology et al

In 2009, the American Academy of Neurology and 2 other specialty societies published an evidence-based, tiered approach for the evaluation of distal symmetric polyneuropathy and suspected hereditary neuropathies, which concluded the following (see Table 2).³

Table 2: Recommendations on Distal Symmetric Polyneuropathy and Suspected Hereditary Neuropathies

Recommendation	LOE ^a
"Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies"	A
"Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype"	C
"Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 screening"	
"There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype"	U

LOE: level of evidence.

^a Grade A: established as effective, ineffective, or harmful for the given condition in the specified population; grade C: possibly effective, ineffective, or harmful for the given condition in the specified population; grade U: data inadequate or conflicting; given current knowledge.

The American Academy of Neurology website indicates the recommendations were reaffirmed in 2013 and in November 2017 indicated an update is in progress.

American Academy of Family Physicians

In 2010, the American Academy of Family Physicians recommended genetic testing for a patient with suspected peripheral neuropathy, if basic blood tests are negative, electrodiagnostic studies suggest an axonal etiology, and diseases such as diabetes, toxic medications, thyroid disease, and vasculitides can be ruled out.³²

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
March 2018	New Policy	Genetic testing for inherited motor and sensory neuropathies may be considered medically necessary when the disease is suspected. Genetic testing for an inherited peripheral neuropathy is considered investigational for all other indications.

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