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Medical Policy Manual

Topic: Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The inherited peripheral neuropathies are the most common inherited neuromuscular disease. Genetic testing has been suggested as a way to diagnose specific inherited peripheral neuropathies.

Background

The inherited peripheral neuropathies are a clinically and genetically heterogeneous group of disorders. The estimated prevalence in aggregate is estimated at roughly 1 in 2,500 persons, making inherited peripheral neuropathies the most common inherited neuromuscular disease.[1]

Peripheral neuropathies can be subdivided into 2 major categories: primary axonopathies and primary myelinopathies, depending upon which portion of the nerve fiber is affected. Further anatomic classification includes fiber type (e.g. motor versus sensory, large versus small), and gross distribution of the nerves affected (e.g. symmetry, length-dependency).

The inherited peripheral neuropathies are divided into the hereditary motor and sensory neuropathies, hereditary neuropathy with liability to pressure palsies, and other miscellaneous, rare types (e.g. hereditary brachial plexopathy, hereditary sensory autonomic neuropathies). This policy will focus on

the hereditary motor and sensory neuropathies and hereditary neuropathy with liability to pressure palsies.

A genetic etiology of a peripheral neuropathy is generally suggested by generalized polyneuropathy, family history, lack of positive sensory symptoms, early age of onset, symmetry, associated skeletal abnormalities, and very slowly progressive clinical course.[2] A family history of at least three generations with details on health issues, cause of death, and age at death should be collected.

Hereditary Motor and Sensory Neuropathies

The majority of inherited polyneuropathies are variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurological findings to the classic picture with pes cavus and "stork legs" to a severe polyneuropathy with respiratory failure.[3] The majority of cases of CMT are autosomal dominant, although autosomal recessive and X-linked dominant forms exist. The majority of cases are CMT type 1.

Charcot-Marie-Tooth neuropathy type 1 (CMT1) is a 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 individuals usually become symptomatic between age 5 and 25 years, and lifespan is not shortened. Less than 5% of individuals 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. CMT1A accounts for 70-80% of all CMT1, and about two thirds of probands with CMT1A have inherited the disease-causing mutation and about one third have CMT1A as the result of a *de novo* mutation.

CMT1A involves duplication of the gene *PMP22*. *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.[4] Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) results in the most severe phenotype whereas 3 normal alleles (as in the heterozygous CMT1A duplication) causes a less severe phenotype.[5] CMT1B (6-10% of all CMT1) is associated with point mutations in *MPZ*, CMT1C (1-2% of all CMT1) is associated with mutations in *LITAF*, and CMT1D (<2% of all CMT1) is associated with mutations in *EGR2*. CMT1E (<5% of all CMT1) is associated with point mutations in *PMP22*. CMT2E/1F (<5% of all CMT1) is associated with mutations in *NEFL*. Molecular genetic testing is clinically available for all of these genes.[5]

Charcot-Marie-Tooth hereditary neuropathy 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.[6] Unlike CMT1, peripheral nerves are not enlarged or hypertrophic. 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 15 genes in which mutations are known to cause CMT2 subtypes are *KIF1B* (CMT2A1), *MFN2* (CMT2A2), *RAB7A* (formerly *RAB7*) (CMT2B), *LMNA* (CMT2B1), *MED25* (CMT2B2), *TRPV4* (CMTC), *GARS* (CMT2D), *NEFL* (CMT2E/1F), *HSPB1* (CMT2F), *MPZ* (CMT2I/J), *GDAP1*

(CMT2H/K), *HSPB8* (CMT2L), *AARS* (CMT2N), *DYNC1H1* (CMT2O), and *LRSAM1* (CMT2P). Molecular genetic testing is clinically available for CMT subtypes 2A1, 2A2, 2B, 2B1, 2B2, 2C, 2D, 2E, 2F, 2I, 2J, 2H/K, 2L, 2N, 2O, and 2P.[6]

Charcot-Marie-Tooth neuropathy 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.[7] 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)* detects about 90% of cases of CMTX1, which is available on a clinical basis.[7]

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)

In HNPP (also called tomaculous neuropathy), inadequate production of *PMP22* causes nerves to be more susceptible to trauma or minor compression/entrapment. HNPP patients rarely present symptoms before the second or third decade of life. However, some authors report presentation as early as birth or as late as the seventh decade of life.[8] The prevalence is estimated at 16 persons per 100,000 although some authors indicate a potential for underdiagnosis of the disease.[8] An estimated 50% of carriers are asymptomatic and do not display abnormal neurological findings on clinical examination.[9] HNPP is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop and episodes of numbness, muscular weakness, atrophy, and palsies due to minor compression or trauma to the peripheral nerves. The disease is benign with complete recovery occurring within a period of days to months in most cases, although an estimated 15% of patients have residual weakness following an episode.[9] Poor recovery usually involves a history of prolonged pressure on a nerve, but in these cases the remaining symptoms are typically mild.

PMP 22 is the only gene in which mutation is known to cause HNPP. A large deletion occurs in approximately 80% of patients and the remaining 20% of patients have point mutations and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. Point mutations in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome.[10] Studies have also reported that the point mutation frequency may vary considerably by ethnicity. [11] About 10-15% of mutation carriers remain clinically asymptomatic, suggesting incomplete penetrance.[12]

Treatment

Currently there is no effective therapy for the inherited peripheral neuropathies. Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain.[13] Avoidance of obesity and high-risk drugs such as vincristine is recommended in CMT patients.

Supportive treatment for HNPP can include transient bracing (e.g., a wrist splint or ankle-foot orthosis) which may become permanent in some cases of foot drop.[14] Prevention of HNPP manifestations can be accomplished by wearing protective padding (e.g., elbow or knee pads) to prevent trauma to nerves during activity. Some authors report that vincristine should also be avoided in HNPP patients.[5,14]

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

Genetic testing is considered **investigational** for all indications, including but not limited to testing to confirm a clinical diagnosis of an inherited peripheral neuropathy.

SCIENTIFIC EVIDENCE

Literature Appraisal

Validation of the clinical use of any genetic test focuses on 3 main principles:

1) Analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent

2) Clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease

3) Clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Most of the published data available for analytic and clinical validity of genetic testing for the inherited peripheral neuropathies are for duplications and deletions in the *PMP22* gene in the diagnosis of Charcot-Marie-Tooth (CMT) and hereditary neuropathy with liability to pressure palsies (HNPP), respectively.

Analytic Validity

A variety of methods, in addition to fluorescence in-situ hybridization (FISH), can be used for deletion/duplication analysis targeted specifically at *PMP22*, including quantitative polymerase chain reaction (qPCR), multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA), with high agreement between testing methods (see Table 1).

Table 1. Agreement Between CMT1A and HNPP Genetic Tests

Reference	Disorders Tested	Test Method	Confirmation Method	% agreement CMT1A; HNPP
Hung, 2007[15]	CMT1A; HNPP	CE PCR	RFLP-PCR	100%; 100%

Ravise, 2003[16]	CMT1A; HNPP	dFISH	Southern Blot	94%; 100%
Hung, 2008[17]	CMT1A; HNPP	MLPA	Competitive multiplex PCR	100%; 100%
Slater, 2004[18]	CMT1A; HNPP	MLPA	FISH	90%; 100%
Stangler, 2009[19]	CMT1A; HNPP	MLPA	FISH	100%; 100%
Hung, 2008[17]	CMT1A; HNPP	MLPA	RFLP-PCR	78%; 86%
Stangler, 2009[19]	CMT1A; HNPP	MLPA	RFLP-PCR**	88%; NA
Lin, 2006[20]	CMT1A; HNPP	DHPLC	Microsatellite analysis	100%; 100%
Aarskog, 2000[21]	CMT1A; HNPP	RT-qPCR	Clinical and EMG characteristics	89.6%; 100%
Thiel, 2003[22]	CMT1A; HNPP	RT-qPCR	Microsatellite analysis	100%; 100%
Chen, 2008[23]	CMT1A; HNPP	RT-qPCR	Microsatellite analysis	100%; 100%
Kim, 2003[24]	CMT1A; HNPP	RT-qPCR	Microsatellite analysis	100%; 100%
Choi, 2005[25]	CMT1A; HNPP	RT-qPCR	REP-PCR	100%*; 100%*

*RT-qPCR detected 4 of 13 suspected cases of HNPP and 2 of 16 suspected cases of CMT1A that were not discovered by REP-PCR
**RFLP-PCR had 1 false-negative and 3 false-positive results

CE=capillary electrophoresis, RFLP=restriction fragment length polymorphism, d=direct, MLPA= multiplex ligation-dependent probe amplification, DHPLC= denaturing high-performance liquid chromatography, REP=repeat

Analytic performance of several molecular analytic methods was presented in a review by Aretz et al.[26] The reported analytic sensitivity and specificity were given as almost 100% (tests considered included MLPA, qPCR, FISH, and direct sequencing). Further evidence is provided by another review where segregation studies followed by several prospective cohort studies have also documented that currently available genetic testing results for CMT are unequivocal for diagnosis of established pathogenic mutations, providing a specificity of 100% (i.e., no false positives) and high sensitivity.[3]

Clinical Validity

The clinical sensitivity of the diagnostic test for CMT and HNPP can be dependent on variable factors such as the age or family history of the patient. A general estimation of the clinical sensitivity was presented in a report by Aretz et al. on hereditary motor and sensory neuropathy and HNPP with a variety of analytic methods (MLPA, multiplex amplicon quantification [MAQ], qPCR, Southern blot, FISH, PFGE, dHPLC, high-resolution melting, restriction analysis and direct sequencing).[26] The clinical sensitivity (i.e., proportion of positive tests if the disease is present) for the detection of deletions/duplications to *PMP22* was reported to be about 50% and 1% for point mutations. The clinical specificity (i.e., proportion of negative tests if the disease is not present) was reported to be nearly 100%.

An evidence-based review by England and colleagues on the role of laboratory and genetic tests in the evaluation of distal symmetric polyneuropathies concluded that genetic testing was established as useful for the accurate diagnosis and classification of hereditary polyneuropathies in patients with a cryptogenic polyneuropathy who exhibit a classical hereditary neuropathy phenotype.[3] Six studies

included in the review showed that when the test for CMT1A duplication was restricted to patients with clinically probable CMT1 (i.e., autosomal dominant, primary demyelinating polyneuropathy), the yield is 54-80% as compared to testing a cohort of patients suspected of having any variety of hereditary peripheral neuropathy where the yield was only 25-59% (average of 43%).

Few genotype-phenotype correlations for CMT type 2 are known. Considerable variability of phenotype has been observed within families with CMT2A, therefore the clinical validity of testing is unknown.[6]

Clinical Utility

The clinical utility of genetic testing for the hereditary peripheral neuropathies depends on how the results can be used to improve patient management. Published data for the clinical utility of genetic testing for the inherited peripheral neuropathies is lacking.

In a discussion of the clinical utility of the molecular diagnostic methods for these neuropathies, Aretz et al. suggested that the avoidance of any unnecessary therapy due to an undefined diagnosis, sparing other family members from testing, and avoidance of certain risk factors (e.g., obesity or certain occupations and activities) are potential benefits.[26]

The likelihood that genetic testing for this condition will alter patient management is low. Because the diagnosis of an inherited peripheral neuropathy can generally be made clinically and the inherited peripheral neuropathies have no specific therapy, the incremental benefit of a genetic confirmation of these disorders is not known.

Clinical Practice Guidelines

American Academy of Neurology (AAN)

The AAN published an evidence-based, tiered approach[3] for the evaluation of distal symmetric polyneuropathy, and for suspected hereditary neuropathies, which concluded that:

- genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies (level A classification of recommendations- established as effective, ineffective, or harmful for the given condition in the specified population)
- genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (level C- possibly effective, ineffective, or harmful for the given condition in the specified population)
- 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 (level U-data inadequate or conflicting; given current knowledge)

American Academy of Family Physicians (AAFP)

The AAFP recommends genetic testing in 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.[27]

Summary

The inherited peripheral neuropathies are a heterogeneous group of diseases which can generally be diagnosed based on clinical presentation, nerve conduction studies, and family history. The analytic validity of mutation testing for these diseases is high. The specificity has also been reported to be high, with variable sensitivity.

However, the clinical utility of genetic testing to confirm an inherited peripheral neuropathy has not been established; it is unknown how genotyping results impact patient management, treatment plans, or health outcomes. Therefore, genetic testing for inherited peripheral neuropathies are considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
	81325	;full gene sequencing
	81326	;family variant
HCPCS	None	