Test Specific Guidelines

Charcot-Marie-Tooth Neuropathy Testing

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Introduction

Testing for Charcot-Marie-Tooth (CMT) disease is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
CMT Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
CMT Known Familial Mutation Analysis	81403
Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)	81448
PMP22 Deletion/Duplication Analysis	81324
PMP22 Known Familial Mutation Analysis	81326
PMP22 Sequencing	81325

What Is Charcot-Marie-Tooth Hereditary Neuropathy?

Definition

Charcot-Marie-Tooth Hereditary Neuropathy (CMT) is a group of inherited genetic conditions characterized by chronic motor and sensory polyneuropathy.[1]

Prevalence

CMT is the most common inherited neurological disorder. The prevalence of all CMT types is 1 in 2,500.[1,2]

Symptoms

The key finding in CMT is symmetric, slowly progressive distal motor neuropathy of the arms and legs, usually beginning in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. This is expressed as distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and pes cavus foot deformity (e.g. high arched feet).[1]

Cause

The most common cause of CMT is a large chromosome 17 duplication involving the PMP22 gene, but more than 80 different genes have been associated with CMT.[1]

As more genes causing CMT were identified and as the overlap of neuropathy phenotypes and modes of inheritance became apparent, the previous alphanumeric classification system proved unwieldy and inadequate. In 2018, Magy et al proposed a gene-based classification of inherited neuropathies, which includes a comprehensive list of CMT-associated genes and correlation with the alphanumeric classification.[3] An additional advantage of this classification system is that a patient's findings can be described in terms of mode of inheritance, neuropathy type, and gene.

Establishing a specific genetic cause of CMT hereditary neuropathy can aid in discussions of prognosis.[1]

Inheritance

CMT can be inherited in an autosomal dominant, autosomal recessive, or an X-linked manner.[1] De novo cases are reported, but the proportion ranges widely depending on the gene involved.[1]

Diagnosis

The clinical diagnosis of CMT in a symptomatic person is based on characteristic findings of peripheral neuropathy on medical history and physical examination.[1] CMT needs to be distinguished from the following entities: systemic disorders with neuropathy, other types of hereditary neuropathy, distal myopathies, hereditary sensory neuropathies (HSN), and acquired disorders.[1]

Molecular genetic testing can be used to establish a specific diagnosis, which aids in understanding the prognosis and risk assessment for family members.[1]

A 1.5Mb duplication at 17p11.2 that includes the PMP22 gene is the most common cause of CMT, accounting for up to 50% of cases.[1] Therefore, PMP22 deletion/duplication analysis is recommended as a first tier diagnostic test.[1] If negative, a multi-gene testing panel may be indicated.

Management

Management of CMT is based on the symptoms present, and is often accomplished through a multidisciplinary team.[1] Treatment addresses neurological deficits and mobility issues, often including physical and occupational therapies and orthoses to aid in walking.[1]

Survival

Life span is normal in many forms of CMT, but quality of life is often impacted by the degree of physical disability experienced.[1]

Test Information

Introduction

Testing for CMT may include known familial mutation analysis, deletion/duplication analysis, and/or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and

losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

CMT multi-gene testing panels include a wide variety of genes associated with CMT neuropathy. The following are points to consider regarding multi-gene testing panels for CMT:

- Multi-gene testing panels may include genes without clear management recommendations. A comprehensive panel with simultaneous testing of most known genes for CMT may not be cost-effective or necessary.[1,4]
- Multi-gene testing panels may vary in technical specifications (e.g. depth of coverage, large deletion/duplication analysis, etc).
- Given differences in testing methods and sensitivity, single-gene testing after a negative multi-gene testing panel may be warranted if there is a high clinical suspicion for a particular syndrome.
- The genes included on a multi-gene testing panel may vary. The medical record should document the performing laboratory and genes tested.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to CMT testing.

American Academy of Neurology

Evidence-based guidelines from the American Academy of Neurology (AAN, 2019) recommend testing for CMT, but with a tiered approach:[5]

- "Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies."
    - This is considered a level A recommendation which is defined as "established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population."

- **"Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype. 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 mutation screening."**
  - **This is considered a level C recommendation which is defined as "possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population."**
- **"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."**
  - **This is considered a level U recommendation which is defined as "data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven."**

Selected Relevant Publications

DiVincenzo et al. [2014] described their experience testing more than 17,000 patients for CMT using a commercially available comprehensive panel of 14 genes.[6] Overall, they identified a mutation in 18.5% of patients. Notably they state that "Among patients with a positive genetic finding in a CMT-related gene, 94.9% were positive in one of four genes (PMP22, GJB1, MPZ, or MFN2). The results of our study in a population in over 17,000 individuals support the initial genetic testing of four genes (PMP22, GJB1, MPZ, and MFN2) followed by an evaluation of rarer genetic causes in the diagnostic evaluation of CMT." [6]

Dohrn et al. [2017] examined over 600 patients with either a CMT phenotype, hereditary sensory neuropathy, familial amyloid neuropathy, or small fiber neuropathy using a NGS multigene panel.[2] At least one putative pathogenic mutation was identified in 121 cases (19.8%); the most frequently affected genes were PMP22, GJB1, MPZ, SH3TC2, and MFN2. Likely or known pathogenic variants in HINT1, HSPB1, NEFL, PRX, IGHMBP2, NDRG1, TTR, EGR2, FIG4, GDAP1, LMNA, LRSAM1, POLG, TRPV4, AARS, BIC2, DHTKD1, FGD4, HK1, INF2, KIF5A, PDK3, REEP1, SBF1, SBF2, SCN9A, and SPTLC2 were detected with a declining frequency. One pathogenic variant in MPZ was identified after being previously missed by Sanger sequencing. The authors conclude that panel-based NGS "is a useful, time and cost effective approach to assist clinicians in identifying the correct diagnosis and enable causative treatment considerations".[2]

Bacquet et al [2018] compared the diagnostic yield of targeted NGS with their previous step-wise Sanger sequencing strategy.[7] A cohort of 123 unrelated patients affected with diverse forms of inherited peripheral neuropathies including CMT (23% CMT1, 52% CMT2), distal hereditary motor neuropathy (9%),

hereditary sensory and autonomic neuropathy (7%), and intermediate CMT (6.5%) were evaluated using an 81-gene NGS panel. Pathogenic variants were identified in 49 of 123 patients (~40%). In this cohort, the most frequently mutated genes were: MFN2, SH3TC2, GDAP1, NEFL, GAN, KIF5A and AARS, respectively. "Panel-based NGS was more efficient in familial cases than in sporadic cases (diagnostic yield 49% vs 19%, respectively). NGS-based search for copy number variations, allowed the identification of three duplications in three patients and raised the diagnostic yield to 41%. This yield is two times higher than the one obtained previously by gene Sanger sequencing screening. The impact of panel-based NGS screening is particularly important for demyelinating CMT (CMT1) subtypes, for which the success rate reached 87% (36% only for axonal CMT2)." [7] While NGS panels were able to identify causal variants in a shorter and more cost-effective time, the authors caution that this approach, "leads to the identification of numerous variants of unknown significance, which interpretation requires interdisciplinary collaborations between molecular geneticists, clinicians and (neuro) pathologists".[7]

In a 2022 expert-authored review, the following step-wise genetic testing strategy was recommended:[1]

- Step 1: "Single-gene testing for PMP22 duplication/deletion is recommended as the first test in all probands with CMT. PMP22 duplication (a 1.5-Mb duplication at 17p11.2 that includes PMP22) accounts for as much as 50% of all CMT and, thus, PMP22 deletion/duplication analysis is recommended as the first test for all probands with CMT."
- Step 2: "A multigene panel that includes the eight most commonly involved genes (i.e.,GDAP1,GJB1,HINT1,MFN2,MPZ,PMP22, SH3CT2, and SORD) as well as some or all of the other genes listed in Table 4 is most likely to identify the genetic cause of the neuropathy while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."
- Step 3: "Comprehensive genomic testing - which does not require the clinician to determine which gene(s) are likely involved – may be considered if a genetic cause has not been identified in Step 1 and Step 2. Exome sequencing is most commonly used; genome sequencing is also possible."
- "Given the complexity of interpreting genetic test results and their implications for genetic counseling, health care providers should consider referral to a neurogenetics center or a genetic counselor specializing in neurogenetics...."
- "For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such

information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause."

Criteria

Introduction

Requests for CMT testing are reviewed using these criteria.

Known Familial Mutation Analysis

- **Previous Genetic Testing:**
  - **No previous genetic testing that would detect the familial mutation, and**
  - **Pathogenic CMT-related mutation in a 1st or 2nd degree biologic relative, AND**
- **Diagnostic Testing for Symptomatic Individuals:**
  - **Distal muscle weakness and atrophy, or**
  - **Weak ankle dorsiflexion (e.g. foot drop), or**
  - **Distal sensory loss, or**
  - **Depressed or absent tendon reflexes, or**
  - **Foot deformity (e.g. high arches, hammer toes, pes cavus), or**
  - **Electrodiagnostic studies consistent with a peripheral neuropathy, OR**
- **Predisposition Testing for Presymptomatic/Asymptomatic Individuals:**
  - **Age 18 years or older**

PMP22 Deletion/Duplication Analysis

- **Previous Genetic Testing:**
  - **No previous PMP22 deletion/duplication analysis, and**
  - **No known CMT-related mutation in the member's family, AND**
- **Diagnostic Testing for Symptomatic Individuals:**
  - **Distal muscle weakness and atrophy, or**
  - **Weak ankle dorsiflexion (e.g. foot drop), or**
  - **Distal sensory loss, or**
  - **Depressed or absent tendon reflexes, or**
  - **Foot deformity (e.g. high arches, hammer toes, pes cavus), AND**

- **The member does not have a known underlying cause for their neuropathy (e.g. diabetic neuropathy, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy, known mutation), AND**
- **Member's electrodiagnostic studies are consistent with a primary demyelinating neuropathy**

CMT Neuropathy Multigene Panel

When a multi-gene panel is being requested and will be billed with the appropriate CPT panel code, 81448, the panel will be considered medically necessary when the following criteria are met:

- **Previous Genetic Testing:**
  - **No previous CMT neuropathy multi-gene panel testing, and**
  - **No known CMT-related mutation in the member's family, AND**
- **Diagnostic Testing for Symptomatic Individuals:**
  - **Distal muscle weakness and atrophy, or**
  - **Weak ankle dorsiflexion (e.g. foot drop), or**
  - **Distal sensory loss, or**
  - **Depressed or absent tendon reflexes, or**
  - **Foot deformity (e.g. high arches, hammer toes, pes cavus), AND**
- **The member does not have a known underlying cause for their neuropathy (e.g. diabetic neuropathy, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy, known mutation), AND**
- **The panel includes the genes with the highest diagnostic yield for the member's suspected CMT neuropathy subtype, AND**
- **Member's electrodiagnostic studies are consistent with an axonal neuropathy or combined axonal and demyelinating neuropathy (e.g., CMT1 is NOT the most likely diagnosis), OR**
- **Member's electrodiagnostic studies are consistent with a primary demyelinating neuropathy (e.g., CMT1 is the most likely diagnosis) and PMP22 deletion/duplication analysis was previously performed and was negative**

Billing and Reimbursement Considerations

- **When separate procedure codes will be billed for individual CMT-related genes (e.g., Tier 1 MoPath codes 81200-81355 or Tier 2 MoPath codes 81400-81408), the entire panel will be approved if the above criteria are met. However, the laboratory will be redirected to the use of an appropriate panel CPT code, 81448, for billing purposes.**

- The billed amount should not exceed the list price of the test.
- Broad CMT neuropathy panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.
- Genetic testing is only necessary once per lifetime. Therefore, a single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- If the laboratory will not accept redirection to 81448 due to their panel not sequencing at least 5 genes, the medical necessity of each billed component procedure will be assessed independently.
    - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining individual components will not be reimbursable.
    - When the test is billed with multiple stacked codes, only sequencing of the following genes may be considered for reimbursement, based on electrodiagnostic findings and the family history:
        - Primary demyelinating neuropathy with negative PMP22 deletion/duplication analysis (CMT1 suspected): MPZ, PMP22, LITAF (SIMPLE) and EGR2.
        - Primary axonal neuropathy (CMT2 suspected): MFN2, MPZ and HSPB1 (HSP27). If there is no evidence of male-to-male transmission in the family, GJB1 (for CMTX) is also reimbursable.
        - Combined axonal and demyelinating neuropathy (intermediate CMT suspected): DNM2, YARS, MPZ, and GNB4.

References

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