Genetic Testing for Hereditary Neuropathy

A Guide for Clinicians
Introduction

The inherited neuropathies are a large group of genetically and phenotypically heterogeneous disorders affecting the peripheral nervous system.

Hereditary neuropathies are categorized by involvement of motor, sensory and/or autonomic nerve fibers (Dyck et al., 2005). They can be divided into 3 main categories: hereditary motor and sensory neuropathies (HMSN), also known as Charcot-Marie-Tooth (CMT) disease, hereditary motor neuropathy, and hereditary sensory and autonomic neuropathy (HSAN) (see Table 1). The peripheral neuropathies have overlapping symptoms including muscle weakness, foot deformities, depressed or absent reflexes and loss of sensation. In addition to genetic causes, there are many non-genetic, or acquired, causes of neuropathy, including: diabetes mellitus, trauma, alcohol, vitamin B12 deficiency, thyroid disease, vasculitis, HIV infection, leprosy, neurosyphilis, amyloid neuropathies and other inflammatory and immune related neuropathies. The diagnostic process aims to determine if an individual’s symptoms are due to an acquired or genetic form of neuropathy. The elucidation of a specific diagnosis and etiology is mainly based on age of onset, family history, neurologic studies; such as nerve conduction studies, blood tests, and genetic testing.

Hereditary Neuropathy Panel at GeneDx

<table>
<thead>
<tr>
<th>Charcot-Marie-Tooth Disease</th>
<th>Hereditary Sensory Neuropathies</th>
<th>Other Hereditary Neuropathies</th>
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</thead>
<tbody>
<tr>
<td>AARS, DNMT1, DYNC1H1, EGR2, FGD4, FIG4, GARS, GDAP1, GJB1, HSPB1, HSPB8, LITAF, LMNA, LRSAM1, MED25, MFN2, MPZ, MTMR2, NDRG1, NEFL, PDK3, PMP22, PRPS1, PRX, RAB7A, SBF2, SH3TC2, TRPV4</td>
<td>ATL1, DNMT1, FAM134B, IKBKAP, KIF1A, NGF, NTRK1, SCN9A, SPTLC1, SPTLC2, WNK1</td>
<td>ATP7A, BSCL2, DNAJB2, GAN, GLA, IGHMBP2, PLEKHG5, REEP1, SLC12A6, TFG, TTR</td>
</tr>
</tbody>
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Large PMP22 deletions are responsible for approximately 80% of cases of hereditary neuropathy with liability to pressure palsy (HNPP), and duplications of the PMP22 gene are responsible for approximately 70% of Charcot-Marie-Tooth Type 1 (CMT1) cases. PMP22 deletion/duplication testing is available as part of the panel and as a separate test.
Genetics of Hereditary Neuropathies

Currently, over seventy genes have been described in the literature to cause inherited neuropathies (Rossor et al., 2013). Genetic forms of neuropathy can be inherited in autosomal dominant, autosomal recessive or X-linked inheritance patterns. They can also be sporadic without a family history of neuropathy and may be the result of a new (de novo) mutation in a patient. A genetic diagnosis is identified in approximately 50-70% of individuals with Charcot-Marie-Tooth disease (Vallat et al., 2013), 30% of individuals with hereditary sensory and autonomic neuropathy (HSAN) (Rotthier et al., 2012), and 20% of individuals with distal motor neuropathy (Rossor et al, 2012). Pathogenic mutations in some genes have been associated with multiple phenotypes or clinical patterns. For example, mutations in the GARS gene can be associated with Charcot-Marie-Tooth type 2D or with distal spinal muscular atrophy type V, and mutations in the GDAP1 gene can be inherited in an autosomal dominant or autosomal recessive manner and have been associated with axonal, demyelinating or intermediate nerve conduction velocity tests (Barhoumi et al., 2001; Cuesta et al., 2002).

Diagnosis of Hereditary Neuropathies

The diagnosis of a genetic neuropathy is based on a combination of personal health history, family health history, complete neurological exam and neurological tests.

- Clinical and Family History:
  - The medical and family history may indicate whether the neuropathy is likely due to an acquired or genetic cause
  - The mode of inheritance can be helpful in differentiating possible diagnoses
  - Physical examination may reveal symptoms of sensory, autonomic or motor neuropathy (see Table 2)

- Neurological testing can include:
  - Nerve conduction velocity (NCV)
  - Electromyography (EMG)
  - Nerve biopsy

- Genetic testing:
  - If the medical and family history, physical exam, or clinical evaluation suggest a genetic cause, then genetic testing should be offered.
### Table 2: Inherited Neuropathy Phenotypes

<table>
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<th>Phenotype</th>
<th>Description</th>
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| Hereditary Motor and Sensory Neuropathy (HMSN) more commonly known as Charcot Marie Tooth (CMT) | • Progressive distal muscle weakness with feet and legs most severely affected  
• Paresthesia and/or loss of sensation  
• Foot drop  
• Depressed deep tendon reflexes  
• Hammer toes  
• Pes cavus (high arches)                                                                                       |
| Hereditary Motor Neuropathy                         | • Primary motor symptoms and a lack of sensory and autonomic symptoms  
• Progressive weakness and atrophy of the distal muscles  
• Decreased or absent reflexes  
• Reduced motor amplitude potentials on NCV  
• Foot deformities  
• Less common features include: vocal cord and diaphragm paralysis, pyramidal tract signs                                |
| Hereditary Sensory and Autonomic Neuropathy         | • Progressive loss of sensation  
• Altered perception of pain, temperature, and touch which can lead to hyperkeratosis, chronic ulcers, dystrophic nails, osteomyelitis  
• Distal muscle weakness  
• Depressed reflexes  
• Excessive sweating  
• Gastroesophageal reflux  
• Postural hypotension  
• Apnea  
• Incontinence  
• Self-mutilation  
• Deafness                                                                                                       |
Algorithm for Peripheral Neuropathy Testing

Peripheral Neuropathy
- Acquired
  - Diabetes mellitus
  - Autoimmune disorder
  - Nutritional diseases
  - Alcoholism
  - Toxin exposure
  - Appropriate laboratory testing
- Inherited
  - PMP22 del/dup testing
  - Hereditary neuropathy panel
  - Mitochondrial disorder?
- CNS + peripheral features
  - Comprehensive mitochondrial disorder panel
  - Consider whole exome sequencing
Possible Genetic Test Results and What They Mean

There are three possible outcomes of genetic testing: a positive result, a negative result, or an inconclusive result.

Positive

A positive result indicates that a disease-causing mutation was identified in the individual who was tested. This finding confirms the diagnosis as well as identifying the genetic cause. A genetic diagnosis provides valuable information to the physician and family members about treatment, prognosis, and recurrence risk. First-degree relatives (e.g., children, siblings, and parents) of a patient with a positive genetic test result can then be offered predictive genetic testing. If a family member is found to be positive for the familial mutation(s), depending on the mode of inheritance, this individual may also be at risk for neuropathy and should be referred for further evaluation. It is important to note that there can be variability in symptoms, age of onset, and disease severity even among members of the same family who have the same genetic mutation.
Negative

A negative genetic test result in an individual with neuropathy does not rule out a genetic cause. Possible reasons for a negative result could be (1) the patient has a mutation in a gene not included in the testing panel, (2) the patient may have a mutation in a part of a neuropathy gene that was not covered by the test, or (3) the patient does not have a heritable form of neuropathy. A negative genetic test result in an individual with neuropathy indicates that predictive testing of asymptomatic family members with the same test will not be informative. However, family members of a clinically affected individual with negative test results may still be at risk neuropathy based on the family history.

If an asymptomatic individual tests negative for a disease-causing mutation identified in a family member with neuropathy, the individual is expected to have the same risk to develop neuropathy as a person in the general population. Specific clinical monitoring for the development of neuropathy may be reduced or eliminated in these individuals.

Variant of Unknown Significance (VUS)

One of the most difficult results to interpret is the finding of a variant of unknown clinical significance (VUS). This result indicates that the role of the genetic change in causing neuropathies has not clearly been established. In some cases, testing of other family members may help clarify the clinical significance of a VUS. If other relatives with neuropathy are found to have the same variant, it is more likely that the variant is disease-causing. The greater the number of affected family members who carry the VUS, the greater the likelihood that the identified variant is pathogenic. If, on the other hand, an individual is the only affected family member, the finding that the VUS identified at GeneDx is de novo (was not inherited from a parent) supports the interpretation that the variant is likely disease-causing.

In some cases, an individual may be found to have a single mutation in a gene associated with an autosomal recessive disorder. In this case, the results are inconclusive as the individual may be a heterozygous carrier of a single mutation, or they may have a second mutation in that gene which was not detected by the test. For individuals who have a single mutation identified in an autosomal recessive disorder, clinical correlation is required and additional testing may be necessary.
Interpretation of Variants of Unknown Significance

At GeneDx we have a multi-step process of evaluating variants that includes:

- Review of published literature
- Review of publicly available and internal mutation databases
- The frequency of the variant in the population
- Evolutionary conservation
- In silico prediction models
- Consideration of the reported mutation spectrum for the gene
- Segregation of the variant with the disease in the family

Resources for Patients

You can find more information at the following websites:

- Genereviews: www.ncbi.nlm.nih.gov/books/NBK1116/
- OMIM: http://www.omim.org/

Search for Research Studies for Neuropathy

- Clinical trials: http://clinicaltrials.gov/
- Inherited Neuropathies Consortium: http://rarediseasesnetwork.epi.usf.edu/INC/about/mission.htm

Patient Support Organization

- Charcot-Marie-Tooth Association: http://cmtausa.org/
- Hereditary Neuropathy Foundation: www.hnf-cure.org
- Muscular Dystrophy Association: http://mda.org/
- The Neuropathy Association: http://www.neuropathy.org

Genetic Counseling

- National Society of Genetic Counselors: www.nsgc.org


About GeneDx

GeneDx is a highly respected genetic testing company founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients and clinicians concerned with rare inherited disorders. GeneDx offers sequencing and deletion/duplication testing for inherited cardiac disorders, mitochondrial disorders, neurological disorders, inherited cancer disorders, prenatal disorders and other rare genetic disorders. GeneDx also offers whole exome sequencing, next-generation and microarray-based testing. At GeneDx, our technical services are matched by our scientific expertise and customer support. Our growing staff includes more than 70 geneticists and genetic counselors specialized in clinical genetics, molecular genetics, metabolic genetics and cytogenetics who are just a phone call or email away. We invite you to visit our website www.genedx.com to learn more about us and the services we offer.