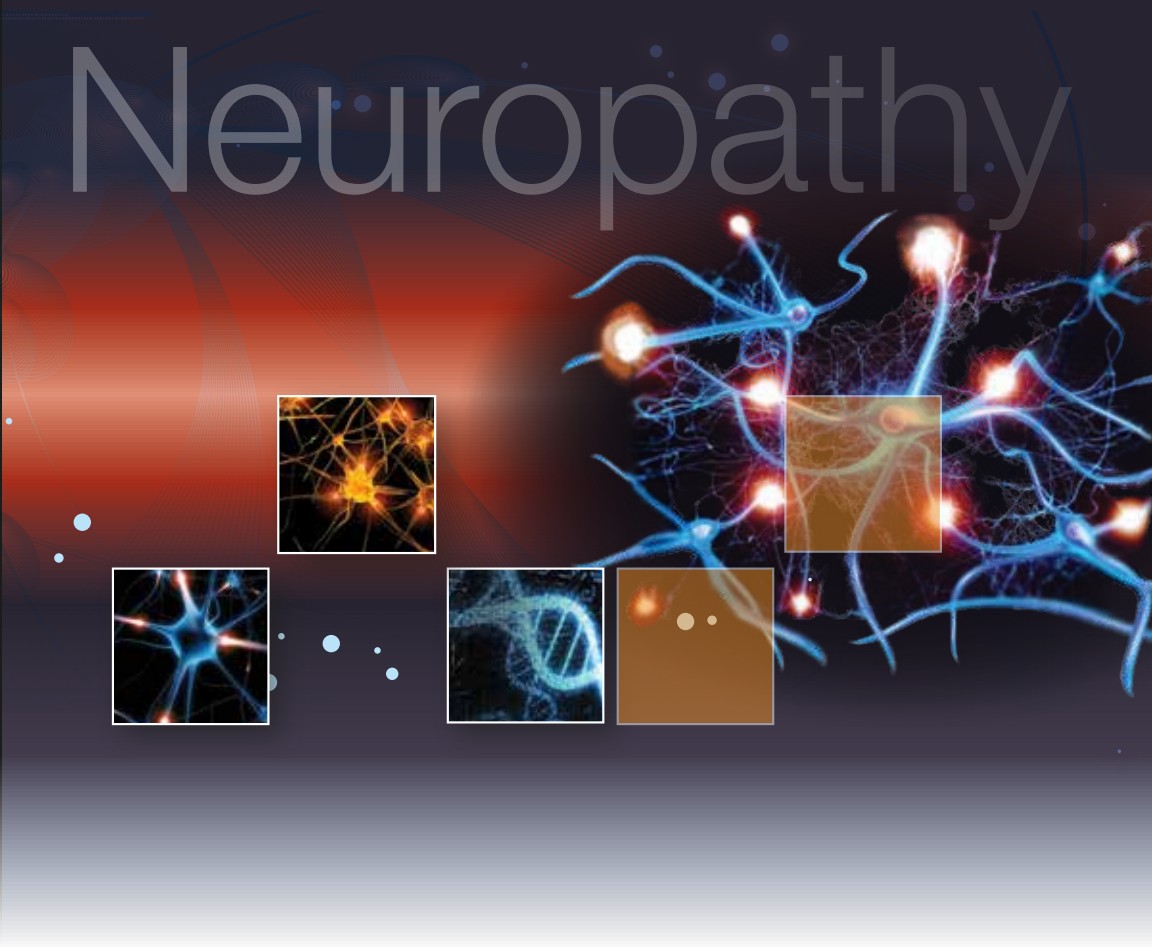


# Genetic Testing for Hereditary Neuropathy

## A Guide for Patients

GeneDx
an OPKO Health Company

KNOWING WHAT TO LOOK FOR  KNOWING WHERE TO LOOK  AND KNOWING WHAT IT MEANS

## Introduction

### What are hereditary neuropathies?

Hereditary neuropathies are a large group of inherited disorders that affect the peripheral nervous system. The peripheral nervous system is comprised of the somatic nervous system, which relays motor and sensory information to and from the central nervous system, and the autonomic nervous system, which regulates involuntary bodily functions, for example: heart rate, breathing and digestion. Symptoms of neuropathies typically include a combination of motor, sensory and/or autonomic abnormalities (as shown in Table 1). Hereditary neuropathies can be divided into three 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). CMT is the most common inherited neurological condition with a prevalence of approximately 1 in 2,500.

Table 1: Symptoms of Hereditary Neuropathies

| Phenotype | Description |
|---|---|
| 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<br>• Paresthesia and/or loss of sensation<br>• Foot drop<br>• Depressed deep tendon reflexes<br>• Hammer toes<br>• Pes cavus (high arches) |
| Hereditary Motor Neuropathy | • Primary motor symptoms and a lack of sensory and autonomic symptoms<br>• Progressive weakness and atrophy of the distal muscles<br>• Decreased or absent reflexes<br>• Abnormal nerve conduction studies<br>• Foot deformities<br>• Less common features include: vocal cord and diaphragm paralysis |
| Hereditary Sensory and Autonomic Neuropathy | • Progressive loss of sensation<br>• Altered perception of pain, temperature, and touch<br>• Distal muscle weakness<br>• Depressed reflexes<br>• Excessive sweating<br>• Gastroesophageal reflux<br>• Postural hypotension<br>• Apnea<br>• Incontinence<br>• Self-mutilation<br>• Deafness |

### What causes hereditary neuropathies?

Genetic causes of neuropathy must be distinguished from 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.

Genetic forms of neuropathy can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. Sometimes there are multiple affected relatives in a family, and other times there is a single affected family member who is the first case in the family.

### How are hereditary neuropathies diagnosed?

The diagnosis of a hereditary neuropathy is based on a combination of personal health history, family health history, complete neurological exam and neurological and genetic 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 1)
- Neurological testing can include:
  - Nerve conduction velocity (NCV)
  - Electromyography (EMG)
  - Nerve biopsy
- Genetic testing:
  - If the medical and family history, physical exam or clinical evaluations suggest a genetic cause, then genetic testing should be offered.

## Genetic Testing for Hereditary Neuropathies

### How is genetic testing for hereditary neuropathies performed?

The Hereditary Neuropathy gene panel is a test ordered by your physician. GeneDx will extract DNA from the blood sample and analyze it by searching for variants in a number of genes associated with Charcot-Marie-Tooth, distal hereditary motor neuropathy, and hereditary sensory and autonomic neuropathy. The GeneDx panel includes sequencing and deletion/duplication testing for all genes on the panel. After the test is finished, your physician will receive the results and discuss them with you.

### How is genetic testing for hereditary neuropathies helpful?

Identifying the genetic cause of your neuropathy is important for several reasons, such as helping with treatment decisions and providing information to family members about their chance to develop neuropathy. Here is a list of ways that genetic testing for neuropathy may benefit you and your family:

- Can establish the genetic cause of neuropathy
- Provides information about prognosis
- May prevent the need for other costly and/or painful testing
- Confirms the inheritance pattern and allows for more accurate risk assessment of family members
- Permits predictive testing for asymptomatic family members when there is a known disease-causing variant associated with a genetic form of neuropathy
- Enables clinical monitoring, follow-up, and optimal treatment when symptoms develop in an individual with a positive genetic result
- Allows accurate genetic counseling, recurrence risk determination, and family planning

### Who should have genetic testing for hereditary neuropathies?

Genetic testing is appropriate for anyone with a suspected genetic cause of their neuropathy. The chance of having a hereditary neuropathy is higher if you have other family members who have similar symptoms. If there are affected and unaffected individuals in a family, it is best to do genetic testing on an affected family member first. If the testing identifies a disease-causing variant in a person with neuropathy, then other at-risk family members can be tested.

### What makes the GeneDx test different from others?

GeneDx leads the community in genetic testing with over 14 years of experience, competitive turnaround times, patient friendly billing policy and thoroughly researched and thoughtfully written reports.

### How long does it take to complete the test?

It takes approximately 8 weeks to complete the test. This is from the time the lab receives the blood sample to the time your physician receives the results.

### What type of test results can I expect?

Three types of results are possible:

- A positive result indicates that the genetic test revealed a pathogenic variant in a gene associated with a hereditary neuropathy. This finding confirms the cause of your neuropathy and provides valuable information to your physician and family members. Knowledge of your specific genetic variant can help your physician clarify the prognosis and assist in treatment and management of your hereditary neuropathy. At-risk relatives (children, siblings and parents) may then be offered genetic testing to clarify their risk for hereditary neuropathy. If a family member is found to be positive for the familial variant, this individual may be at risk for hereditary neuropathy and should be referred for a neurological evaluation. It is important to note that there may be variability in symptoms, age of onset, severity, and response to therapy, even within families.

- A negative result indicates that the genetic test did not identify a pathogenic variant in any of the genes tested. However, this does not mean that the patient does not have hereditary neuropathy, and management should be based on clinical symptoms. Reasons for a negative result could be: (1) there may be a pathogenic variant in a gene not included in the panel, (2) there may be a pathogenic variant in a region of a gene that was not included in the test, or (3) there may be a non-genetic cause of the neuropathy.

  If an asymptomatic individual is negative for a pathogenic variant identified in a family member with neuropathy, the result is considered a "true negative." This indicates that the individual is not at increased genetic risk for the familial neuropathy syndrome and instead has the same risk to develop neuropathy as a person in the general population. Specific clinical monitoring for the development of neuropathy is not necessary in individuals with a "true negative" result.

- A variant of unknown significance (VUS) result indicates an inconclusive finding. This means that there is not enough evidence at this time to conclude whether or not the DNA change that was identified causes disease. To further clarify the clinical significance of the variant, it may be helpful to test other family members, such as other affected relatives or the patient's parents.

### How will I learn my test results?

GeneDx will provide the results to the physician who ordered the test. Your physician will share the results with you and discuss them in the context of your health care.

### Will my insurance cover this test?

GeneDx accepts all commercial insurance. GeneDx will bill your insurance company and appeal for payment. GeneDx is a Medicare provider and therefore is able to accept Medicare patient samples. A completed Advance Beneficiary Notice (ABN) is required for Medicare patients. In most cases, Medicaid will not cover genetic testing for these conditions, as Medicaid coverage varies by state. For more information, please visit our website at www.genedx.com/neurology or call us at 301-519-2100.

### What if I do not have insurance?

If you do not have health insurance or cannot afford to pay the full cost of testing, GeneDx provides a generous financial assistance program, including a significantly discounted price. For more information, call us at 301-519-2100.

### Do my family members need to be tested?

A physician or genetic counselor will help determine if testing other relatives is appropriate. If a pathogenic variant is identified in one of the genes on the Hereditary Neuropathy Panel, then other members of your family may also be at risk to have this variant. In most cases, your family members can be tested for the specific familial variant and do not need the full Hereditary Neuropathy Panel. The cost and turnaround time are significantly reduced when family members get tested for a specific variant, instead of the full gene panel.

If a pathogenic variant in is not identified, genetic counseling is available for other family members to evaluate their risk of an inherited neuropathy. If a genetic test result is negative for an affected individual, predictive genetic testing of family members is not indicated.

### Does GeneDx test family members?

Yes, GeneDx offers variant-specific testing for known familial variant(s). If a family member has been tested at another lab, in most cases GeneDx can still test for the known familial variant; however, a blood specimen from the affected relative may be required as a positive control. For more information, please call one of our genetic counselors at 301-519-2100.

### Does GeneDx perform prenatal testing?

Yes, GeneDx can provide prenatal testing for a known familial variant in most genes for families who have had previous genetic testing performed in a CLIA laboratory. For more information, please call one of our genetic counselors at 301-519-2100.

### Can my health insurer or employer discriminate against me based on my test results?

The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, is a federal law that protects Americans from discrimination by health insurance companies and employers based on their genetic information. The President signed the act into federal law on May 21, 2008. The parts of the law relating to health insurers took effect on May 2009, and those relating to employers took effect on November 2009.

However, this law does not cover life insurance, disability insurance, or long-term care insurance. GINA also does not apply to members of the United States military, to veterans obtaining healthcare through the Department of Veterans Affairs (VA), or to the Indian Health Service. For more information, please visit www.genome.gov/10002328.

### How can this testing be ordered by my physician?

Your physician can order this test by taking the following steps:

- Download neurology requisition forms from the GeneDx website: **www.genedx.com/neurology**
- Complete all the forms with the required information
- Ship completed forms along with 2mL–7mL whole blood in EDTA purple/lavender top tube to the following address:

  GeneDx
  207 Perry Parkway
  Gaithersburg, MD 20877

We also provide shipping kits to physicians when requested. To order a neurology shipping kit, please visit our website at **www.genedx.com/supplies**, call us at 301-519-2100, or email us at **zebras@genedx.com**.

## Where can I find more information?

You can find more information at the following websites:

- GeneReviews: www.ncbi.nlm.nih.gov/books/NBK1116
- National Institutes of Health Genetics Home Reference(NIH/GHR): http://ghr.nlm.nih.gov
- National Institute of Neurological Disorders and Stroke: www.ninds.nih.gov/disorders/neuropathy_hereditary/neuropathy_ hereditary.htm
- 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 Organizations

- 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 was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients diagnosed with rare disorders and the clinicians treating these conditions. Today, GeneDx has grown into a global industry leader in genomics, having provided testing to patients and their families in over 55 countries. Led by its world-renowned whole exome sequencing program, and an unparalleled comprehensive genetic testing menu, GeneDx has a continued expertise in rare and ultra-rare disorders. Additionally, GeneDx also offers a number of other genetic testing services, including: diagnostic testing for hereditary cancers, cardiac, mitochondrial, and neurological disorders, prenatal diagnostics, and targeted variant testing. At GeneDx, our technical services are backed by our unmatched scientific expertise and our superior customer support. Our growing staff includes more than 30 geneticists and 100 genetic counselors specializing in clinical genetics, molecular genetics, metabolic genetics, and cytogenetics who are just a phone call or email away to assist you with your questions and testing needs. We invite you to visit our website: www.genedx.com to learn more about us.

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