

## Overview

### Useful For

Establishing a molecular diagnosis for patients with distal weakness

Identifying variants within genes known to be associated with distal weakness, allowing for predictive testing of at-risk family members

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 211 genes associated with distal weakness: *AAAS, AARS1, ABCA1, ABCD1, ACTA1, AIFM1, ALDH18A1, AMACR, ANO5, AP5Z1, APOA1, APTX, ARSA, ATL1, ATL3, ATM, ATP1A1, ATP7A, B4GALNT1, BAG3, BICD2, BIN1, BSCL2, C12orf65 (MTRFR), C1orf194, CAV3, CHCHD10, CLCF1, CLTCL1, CNTNAP1, COQ4, COQ7, COX10, COX20, COX6A1, CPOX, CRLF1, CRYAB, CTDP1, CYP27A1, CYP2U1, CYP7B1, DCTN1, DDHD1, DES, DGAT2, DHH, DNAJB2, DNAJB6, DNM2, DNMT1, DST, DYNC1H1, DYSF, EGR2, ELP1, ERCC8, FA2H, FAM126A, FBLN5, FBXO38, FDX2, FGD4, FGF14, FHL1, FIG4, FLNC, FLVCR1, FMR1, FXN, GALC, GAN, GARS1, GBA2, GBE1, GBF1, GDAP1, GJB1, GLA, GM2A, GNB4, GNE, GSN, HADHA, HADHB, HARS1, HEXA, HEXB, HINT1, HK1, HMBS, HNRNPA1, HNRNPA2B1, HSPB1, HSPB8, HSPD1, IARS2, IBA57, IGHMBP2, INF2, KARS1, KIF1A, KIF5A, LAMA2, LDB3, LITAF, LMNA, LRSAM1, MARS1, MATR3, MCM3AP, MFN2, MME, MORC2, MPC1, MPV17, MPZ, MTMR2, MTPP, MYH14, MYH2, MYH7, MYOT, NAGLU, NDRG1, NEB, NEFH, NEFL, NF2, NGF, NIPA1, NTRK1, OPA1, PDK3, PDYN, PEX7, PHYH, PLA2G6, PLEKHG5, PLP1, PMP2, PMP22, PNKP, PNPLA6, POLG, PPOX, PRDM12, PRKCG, PRNP, PRPS1, PRX, PTRH2, RAB7A, REEP1, RETREG1, RNASEH1, RRM2B, RTN2, SACS, SBF1, SBF2, SCN10A, SCN11A, SCN9A, SCO2, SELENON, SETX, SH3TC2, SIGMAR1, SLC12A6, SLC25A19, SLC25A46, SLC52A2, SLC52A3, SLC5A7, SNAP29, SOD1, SORD, SOX10, SPAST, SPG11, SPG21, SPG7, SPTAN1, SPTLC1, SPTLC2, SQSTM1, SUCLA2, SURF1, TDP1, TFG, TIA1, TRIM2, TRPV4, TSFM, TTN, TTPA, TTR, TUBB3, TWNK, TYMP, UBA1, VCP, VPS13D, VRK1, VWA1, WARS1, WASHC5, WNK1, YARS1, ZFYVE26. *SMN1* exon 7 and *SMN2* exon 7 copy number are determined by droplet digital polymerase chain reaction. See [Targeted Genes and Methodology Details for Comprehensive Distal Weakness Gene Panel](#) and Method Description for additional details.*

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for distal weakness.

### Testing Algorithm

For more information see [Hereditary Peripheral Neuropathy Diagnostic Algorithm](#)

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Hereditary Peripheral Neuropathy Diagnostic Algorithm](#)
- [Molecular Genetics: Neurology Patient Information](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Targeted Genes and Methodology Details for Comprehensive Distal Weakness Gene Panel](#)

### Method Name

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Sequence Capture and Next-Generation Sequencing (NGS), Polymerase Chain Reaction (PCR), Sanger Sequencing, and Dosage Analysis by Droplet Digital Polymerase Chain Reaction (ddPCR)

**NY State Available**

Yes

**Specimen****Specimen Type**

Varies

**Ordering Guidance**

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

**Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.

**Specimen Required**

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA) or yellow top (ACD)

**Acceptable:** Any anticoagulant

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Forms**

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file.

The following documents are available:

- [Informed Consent for Genetic Testing](#) (T576)
- [Informed Consent for Genetic Testing \(Spanish\)](#) (T826)
- 2. [Molecular Genetics: Neurology Patient Information](#)

**Specimen Minimum Volume**

1 mL

**Reject Due To**

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

**Clinical & Interpretive****Clinical Information**

Peripheral neuropathy and distal myopathy are well-established inherited neuromuscular disorders characterized by progressive weakness and atrophy of the distal limb muscles.

Inherited peripheral neuropathies are common neurologic disorders that represent a spectrum of diseases with different etiologies. Based on the pattern of inheritance and nerve conduction studies, there are 3 major categories of inherited peripheral neuropathies with isolated nerve involvement. The first group is hereditary motor and sensory neuropathy, also referred to as Charcot Marie Tooth (CMT). Individuals with CMT typically present with slowly progressive muscle weakness and atrophy primarily affecting the distal extremities. The second group is hereditary sensory and autonomic neuropathy (HSAN) or hereditary sensory neuropathy if autonomic dysfunction is absent. They predominantly feature slowly progressive loss of multimodal sensation and autonomic dysfunction, with the most common features of HSANs being the loss of sensation of pain and temperature. The third group is distal hereditary motor neuropathy, which is characterized by length-dependent lower motor neuron dysfunction. The clinical phenotype is variable but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. Inherited peripheral neuropathies may also show involvement of the central nervous system (brain or spinal cord), as in hereditary spastic paraplegia with neuropathy or be part of a systemic syndromic or metabolic disorder. It is important to note that this assay includes testing for *TTR*-associated with familial amyloidosis.

Distal myopathies are characterized by distal weakness and atrophy that starts in the muscles of the hands or feet and lack of cranial involvement or sensory loss. Distal myopathies are classified based on clinical features, inheritance pattern, and histopathological findings, such as the presence of rimmed vacuoles. Categories of distal myopathies include late adult-onset autosomal dominant forms, adult-onset autosomal dominant forms, early-onset autosomal dominant forms, early-onset autosomal recessive forms, and early adult-onset autosomal recessive forms. Additionally, inclusion body myositis presents with distal muscle weakness and may be in the differential with the distal myopathies.

Given the considerable overlap in clinical phenotype of various disorders with distal weakness, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis.

**Reference Values**

An interpretive report will be provided.

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**Interpretation**

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.<sup>(1)</sup> Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Cautions**

Clinical Correlations:

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:

Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:

This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the [Targeted Genes and Methodology Details for Comprehensive Distal Weakness Gene Panel](#) for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a

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laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

**Reclassification of Variants:**

At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

**Variant Evaluation:**

Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.<sup>(1)</sup> Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

**Clinical Reference**

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015 May;17(5):405-424
2. Klein CJ, Duan X, Shy ME: Inherited neuropathies: Clinical overview and update. *Muscle Nerve*. 2013 Oct;48(4):604-622
3. Udd B: Distal myopathies. *Curr Neurol Neurosci Rep*. 2014 Mar;14(3):434. doi: 10.1007/s11910-013-0434-4
4. Savarese M, Sarparanta J, Vihola A, et al: Panorama of the distal myopathies. *Acta Myol*. 2020 Dec 1;39(4):245-265. doi: 10.36185/2532-1900-028

**Performance****Method Description**

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in

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coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletion/insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See [Targeted Genes and Methodology Details for Comprehensive Distal Weakness Gene Panel](#) for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered. (Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Droplet digital PCR is performed for detection and quantification of *SMN1* exon 7 and *SMN2* exon 7 associated with spinal muscular atrophy.

Genes analyzed: *AAAS, AARS1, ABCA1, ABCD1, ACTA1, AIFM1, ALDH18A1, AMACR, ANO5, AP5Z1, APOA1, APTX, ARSA, ATL1, ATL3, ATM, ATP1A1, ATP7A, B4GALNT1, BAG3, BICD2, BIN1, BSCL2, C12orf65 (MTRFR), C1orf194, CAV3, CHCHD10, CLCF1, CLTCL1, CNTNAP1, COQ4, COQ7, COX10, COX20, COX6A1, CPOX, CRLF1, CRYAB, CTDP1, CYP27A1, CYP2U1, CYP7B1, DCTN1, DDHD1, DES, DGAT2, DHH, DNAJB2, DNAJB6, DNM2, DNMT1, DST, DYNC1H1, DYSF, EGR2, ELP1, ERCC8, FA2H, FAM126A, FBLN5, FBXO38, FDX2, FGD4, FGF14, FHL1, FIG4, FLNC, FLVCR1, FMR1, FXN, GALC, GAN, GARS1, GBA2, GBE1, GBF1, GDAP1, GJB1, GLA, GM2A, GNB4, GNE, GSN, HADHA, HADHB, HARS1, HEXA, HEXB, HINT1, HK1, HMBS, HNRNPA1, HNRNPA2B1, HSPB1, HSPB8, HSPD1, IARS2, IBA57, IGHMBP2, INF2, KARS1, KIF1A, KIF5A, LAMA2, LDB3, LITAF, LMNA, LRSAM1, MARS1, MATR3, MCM3AP, MFN2, MME, MORC2, MPC1, MPV17, MPZ, MTMR2, MTPP, MYH14, MYH2, MYH7, MYOT, NAGLU, NDRG1, NEB, NEFH, NEFL, NF2, NGF, NIPA1, NTRK1, OPA1, PDK3, PDYN, PEX7, PHYH, PLA2G6, PLEKHG5, PLP1, PMP2, PMP22, PNKP, PNPLA6, POLG, PPOX, PRDM12, PRKCG, PRNP, PRPS1, PRX, PTRH2, RAB7A, REEP1, RETREG1, RNASEH1, RRM2B, RTN2, SACS, SBF1, SBF2, SCN10A, SCN11A, SCN9A, SCO2, SELENON, SETX, SH3TC2, SIGMAR1, SLC12A6, SLC25A19, SLC25A46, SLC52A2, SLC52A3, SLC5A7, SNAP29, SOD1, SORD, SOX10, SPAST, SPG11, SPG21, SPG7, SPTAN1, SPTLC1, SPTLC2, SQSTM1, SUCLA2, SURF1, TDP1, TFG, TIA1, TRIM2, TRPV4, TSFM, TTN, TTPA, TTR, TUBB3, TWNK, TYMP, UBA1, VCP, VPS13D, VRK1, VWA1, WARS1, WASHC5, WNK1, YARS1, and ZFYVE26*

**PDF Report**

Supplemental

**Day(s) Performed**

Varies

**Report Available**

28 to 42 days

**Specimen Retention Time**

Whole blood: 2 weeks (if available); Extracted DNA: 3 months

## Performing Laboratory Location

Rochester

## Fees & Codes

### Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

### Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

### CPT Code Information

81443

### LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
DWPAN	Distal Weakness Gene Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
617546	Test Description	62364-5
617547	Specimen	31208-2
617548	Source	31208-2
617549	Result Summary	50397-9
617550	Result	82939-0
617551	Interpretation	69047-9
618178	Additional Results	In Process
617552	Resources	99622-3
617553	Additional Information	48767-8
617554	Method	85069-3
617555	Genes Analyzed	48018-6
617556	Disclaimer	62364-5
617557	Released By	18771-6