Test Definition: PCMSP

Postmortem Inherited Congenital Myasthenia Syndrome Gene Panel, Tissue

Overview

Useful For

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

Providing a comprehensive postmortem genetic evaluation in the setting of a congenital myasthenic syndrome

Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide variants and deletions-insertions (delins) in 28 genes associated with congenital myasthenic syndromes: *AGRN, ALG14, ALG2, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, COL13A1, COLQ, DNM2, DOK7, DPAGT1, GAA, GFPT1, GMPPB, LAMB2, LRP4, MUSK, PLEC, PREPL, RAPSN, SCN4A, SLC18A3, SLC25A1, SLC5A7, SYT2, VAMP1*. See 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 congenital myasthenic syndromes.

Special Instructions

- Informed Consent for Genetic Testing
- Molecular Genetics: Neurology Patient Information
- Informed Consent for Genetic Testing for Deceased Individuals
- Informed Consent for Genetic Testing (Spanish)

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS)

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test is intended for use when whole blood is not available, and formalin-fixed, paraffin-embedded tissue is the only available specimen. If whole blood is available, consider CMSP / Inherited Congenital Myasthenic Syndrome Gene Panel,

Varies.

Specimen Required

Specimen Type: Tissue block
Collection Instructions: Submit a formalin-fixed, paraffin-embedded tissue block.
Additional Information: Testing will be attempted on blocks of any age but may be canceled if adequate DNA concentration cannot be obtained.

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)
-Informed Consent for Genetic Testing for Deceased Individuals (T782)
2. Molecular Genetics: Neurology Patient Information

Specimen Minimum Volume

See Specimen Required

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	Ambient (preferred)		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Congenital myasthenic syndromes occur as a result of compromised neuromuscular transmission. Clinical manifestations include fatigable weakness involving ocular, bulbar, and limb muscles. The severity and disease course are highly variable, but individuals usually present in infancy or early childhood. The clinical phenotype associated with a neonatal onset can include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and muscle weakness. The clinical phenotype associated with a later childhood onset can include abnormal muscle fatigue, delayed motor milestones, ptosis, and extraocular muscle weakness.

The combination of the wide variability in symptoms and age of presentation can make congenital myasthenic syndromes hard to diagnosis. Given that congenital myasthenic syndromes are a heterogeneous group of disorders, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis for individuals. Postmortem diagnosis of a hereditary form of a congenital myasthenic syndrome may assist in confirmation of the cause of death, as well as risk assessment in living family members.(1-2)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) 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 Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing (NGS) 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 but 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 as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test.

Deletions-insertions (delins) of 40 or more base pairs, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/duplication analysis is not performed due to technical limitations of the formalin-fixed paraffin-embedded specimen type.

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. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

Reclassification of Variants:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals 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.(3) 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. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Byring RF, Pihko H, Tsujino A, et al. Congenital myasthenic syndrome associated with episodic apnea and sudden infant death. Neuromuscul Disord. 2002;12(6):548-553. doi:10.1016/s0960-8966(01)00336-4
2. Imperatore V, Mencarelli MA, Fallerini C, et al. Potentially Treatable Disorder Diagnosed Post Mortem by Exome Analysis in a Boy with Respiratory Distress. Int J Mol Sci. 2016;17(3):306. Published 2016 Feb 27. doi:10.3390/ijms17030306
3. 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;17(5):405-424
4. Lyadurai SJP. Congenital myasthenic syndromes. Neurol Clin. 2020;38(3):541-552

Performance

Method Description

Next-generation sequencing (NGS) is performed to test for the presence of variants in 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 20X. Sensitivity is estimated at above 99% for single nucleotide variants and above 94% for deletions-insertions (delins) less than 40 base pairs.

There may be regions of genes that cannot be effectively evaluated by sequencing as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test.(Unpublished Mayo method)

Genes analyzed: *AGRN, ALG14, ALG2, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, COL13A1, COLQ, DNM2, DOK7, DPAGT1, GAA, GFPT1, GMPPB, LAMB2, LRP4, MUSK, PLEC, PREPL, RAPSN, SCN4A, SLC18A3, SLC25A1, SLC5A7, SYT2,* and *VAMP1*

PDF Report
No

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
FFPE tissue block: Client provided paraffin blocks (FFPE) will be returned to client after testing is complete; Extracted DNA: 3 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

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. It 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
PCMSP	Postmortem Myasthenia Panel	In Process

Result ID	Test Result Name	Result LOINC® Value

620639	Test Description	62364-5
620640	Specimen	31208-2
620641	Source	31208-2
620642	Result Summary	50397-9
620643	Result	82939-0
620644	Interpretation	69047-9
620645	Additional Results	82939-0
620646	Resources	99622-3
620647	Additional Information	48767-8
620648	Method	85069-3
620649	Genes Analyzed	82939-0
620650	Disclaimer	62364-5
620651	Released By	18771-6