Test Definition: LGCMP

Inherited Limb-Girdle Muscular Dystrophy and Congenital Myasthenic Syndrome Gene Panel, Varies

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Overview

Useful For

Establishing a molecular diagnosis for patients with limb-girdle muscular dystrophy or congenital myasthenic syndrome

Identifying variants within genes known to be associated with limb-girdle muscular dystrophy or congenital myasthenic syndrome, 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 65 genes associated with limb-girdle muscular dystrophy and congenital myasthenic syndrome: *AGRN, ALG14, ALG2, ANO5, BIN1, BVES, CAPN3, CAV3, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, COL13A1, COL6A1, COL6A2, COL6A3, COLQ, CRPPA, DAG1, DES, DNAJB6, DNM2, DOK7, DPAGT1, DPM3, DYSF, FKRP, FKTN, GAA, GFPT1, GMPPB, HNRNPDL, LAMA2, LAMB2, LMNA, LRP4, MUSK, MYOT, PLEC, POGLUT1, POMGNT1, POMGNT2, POMK, POMT1, POMT2, PREPL, RAPSN, SCN4A, SGCA, SGCB, SGCD, SGCG, SLC18A3, SLC25A1, SLC5A7, SYT2, TCAP, TNPO3, TOR1AIP1, TRAPPC11, TRIM32, TTN, VAMP1, VCP*. For more information see Method Description and Targeted Genes and Methodology Details for Inherited Limb-Girdle Muscular Dystrophy and Congenital Myasthenic Syndrome Gene Panel.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for limb-girdle muscular dystrophy and congenital myasthenic syndrome.

Testing Algorithm

For more information see Neuromuscular Myopathy Testing Algorithm

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Neuromuscular Myopathy Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Inherited Limb-Girdle Muscular Dystrophy and Congenital Myasthenic Syndrome Gene Panel

Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

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 Variant, 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. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.
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
Additional Information: To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

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
3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

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

The limb-girdle muscular dystrophies (LGMD) are a heterogeneous group of muscular dystrophies that show progressive weakness and muscle atrophy, predominantly affecting the hips, shoulders, and proximal extremity muscles. There is wide variability in age of onset, severity, and clinical presentation within the LGMD spectrum.

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 clinical overlap of limb-girdle muscular dystrophy and limb-girdle congenital myasthenic syndromes can make these conditions difficult to distinguish clinically. Misdiagnoses can lead to diagnostic delays of several decades, impacting prognostic predictions and appropriate management. This multigene panel can be an efficient and cost-effective way to establish a molecular diagnosis.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) 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. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a 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:
Currently, 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.(1) 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;17(5):405-424
2. Nicolau S, Milone M, Liewluck T. Guidelines for genetic testing of muscle and neuromuscular junction disorders. Muscle Nerve. 2021;64(3):255-269
3. Mitsuhashi S, Kang PB. Update on the genetics of limb girdle muscular dystrophy. Semin Pediatr Neurol. 2012;19(4):211-218.
4. Iyadurai SJP. Congenital myasthenic syndromes. Neurol Clin. 2020;38(3):541-552

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are 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 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-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 the Inherited Limb-Girdle Muscular Dystrophy and Congenital Myasthenic Syndrome 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.

Genes analyzed: *AGRN, ALG14, ALG2, ANO5, BIN1, BVES, CAPN3, CAV3, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, COL13A1, COL6A1, COL6A2, COL6A3, COLQ, CRPPA, DAG1, DES, DNAJB6, DNM2, DOK7, DPAGT1, DPM3, DYSF, FKRP, FKTN, GAA, GFPT1, GMPPB, HNRNPDL, LAMA2, LAMB2, LMNA, LRP4, MUSK, MYOT, PLEC, POGLUT1, POMGNT1, POMGNT2, POMK, POMT1, POMT2, PREPL, RAPSN, SCN4A, SGCA, SGCB, SGCD, SGCG, SLC18A3, SLC25A1, SLC5A7, SYT2, TCAP, TNPO3, TOR1AIP1, TRAPPC11, TRIM32, TTN, VAMP1,* and *VCP*

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

21 to 28 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. 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

LGCMP	LGMD and CMS Gene Panel	In Process

Result ID	**Test Result Name**	**Result LOINC® Value**
617624	Test Description	62364-5
617625	Specimen	31208-2
617626	Source	31208-2
617627	Result Summary	50397-9
617628	Result	82939-0
617629	Interpretation	69047-9
618184	Additional Results	82939-0
617630	Resources	99622-3
617631	Additional Information	48767-8
617632	Method	85069-3
617633	Genes Analyzed	48018-6
617634	Disclaimer	62364-5
617635	Released By	18771-6