Test Definition: RABMP

Inherited Rhabdomyolysis and Metabolic Myopathy Panel, Varies

Overview

Useful For

Establishing a molecular diagnosis for patients with rhabdomyolysis and metabolic myopathy

Identifying variants within genes known to be associated with rhabdomyolysis and metabolic myopathy, 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 83 genes associated with rhabdomyolysis and metabolic myopathy: *ABHD5, ACAD9, ACADM, ACADS, ACADVL, AGK, AGL, ALDOA, ANO5, ATP2A1, CASQ1, CAVIN1, CHCHD10, COQ2, COQ4, COQ6, COQ8A, COQ9, CPT2, CTDP1, DGUOK, DMD, DNA2, DYSF, ENO3, ETFA, ETFB, ETFDH, FBXL4, FDX2, FKRP, FKTN, FLAD1, GAA, GBE1, GFER, GYG1, GYS1, HADHA, HADHB, ISCU, LAMP2, LDHA, LPIN1, MGME1, MRPS25, MSTO1, OPA1, PDSS1, PDSS2, PFKM, PGAM2, PGK1, PGM1, PHKA1, PNPLA2, PNPLA8, POLG, POLG2, PRKAG2, PUS1, PYGM, RBCK1, RNASEH1, RRM2B, RYR1, SCN4A, SDHA, SLC22A5, SLC25A20, SLC25A4, SLC25A42, SUCLA2, SUCLG1, TANGO2, TK2, TMEM65, TRIM32, TSFM, TTC19, TWNK, VMA21,* and *YARS2*. For more information see Method Description and Targeted Genes and Methodology Details for Inherited Rhabdomyolysis and Metabolic Myopathy Gene Panel.

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

Testing Algorithm

For information see Neuromuscular Myopathy Testing Algorithm.

Special Instructions

- Informed Consent for Genetic Testing
- Molecular Genetics: Neurology Patient Information
- Neuromuscular Myopathy Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Inherited Rhabdomyolysis and Metabolic Myopathy 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.

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.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: None
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. 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.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA

yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2 mL with skirted conical base
Acceptable: Matrix tube, 1 mL
Collection Instructions:
1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

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

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	Varies		

Clinical & Interpretive

Clinical Information

Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers, which leads to leakage of potentially toxic cellular contents into the blood stream. The clinical severity can range from asymptomatic creatine kinase elevation to a

life-threatening disease. The clinical features include acute-onset myalgia, transient muscle weakness, and pigmenturia. Genetic causes of rhabdomyolysis include metabolic myopathy, mitochondrial disorders, disorders of intramuscular calcium release, and muscular dystrophies.

Metabolic myopathies are a diverse group of inherited biochemical diseases involving limitation of the use of fuels by skeletal muscle to generate energy. Metabolic myopathies include disorders of fatty acid oxidation, disorders of glycogen and glucase metabolism, and mitochondrial respiratory chain disease. Biochemical testing in multiple tissue types, including blood, urine, and muscle, can help to determine which category of muscle disease is most likely.

Disorders of fatty acid oxidation are one category of metabolic myopathies characterized by hypoketotic hypoglycemia, hepatic dysfunction, skeletal myopathy, dilated and hypertrophic cardiomyopathy, and sudden or unexpected death. Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation during periods of fasting. Biochemical testing such as urine organic acids, plasma acylcarnitines, and fatty acids can aid in diagnosis. These test results are influenced by dietary factors and the clinical status of the patient, which often leads to incomplete diagnostic information or even false-negative results.

Disorders of glycogen and glucose metabolism are another category of metabolic myopathies primarily affecting muscle and resulting in exercise intolerance, recurrent rhabdomyolysis, and myoglobinuria. Creatine kinase level is typically elevated during a major event. Muscle biopsy is often performed to verify absence of enzyme activity for the specific type of glycogenosis disease.

Polyglucosan body disease involves progressive neurogenic bladder, spasticity and weakness causing gait difficulties from either primary muscle or nerve involvements, sensory loss mainly in the distal lower extremities, and mild cognitive difficulties such as executive dysfunction. Mitochondrial myopathies due to coenzyme Q10 deficiency are a group of heterogenous diseases. These mitochondrial diseases are characterized by muscle weakness, exercise intolerance, elevated creatine kinase, and abnormal muscle biopsy findings.

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.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

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 health care prefessional 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. Scalco RS, Gardiner AR, Pitceathly RD, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015 2;10:51

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 deletions-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 Inherited Rhabdomyolysis and Metabolic Myopathy 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:
ABHD5, ACAD9, ACADM, ACADS, ACADVL, AGK, AGL, ALDOA, ANO5, ATP2A1, CASQ1, CAVIN1, CHCHD10, COQ2, COQ4, COQ6, COQ8A, COQ9, CPT2, CTDP1, DGUOK, DMD, DNA2, DYSF, ENO3, ETFA, ETFB, ETFDH, FBXL4, FDX2, FKRP, FKTN, FLAD1, GAA, GBE1, GFER, GYG1, GYS1, HADHA, HADHB, ISCU, LAMP2, LDHA, LPIN1, MGME1, MRPS25, MSTO1, OPA1, PDSS1, PDSS2, PFKM, PGAM2, PGK1, PGM1, PHKA1, PNPLA2, PNPLA8, POLG, POLG2, PRKAG2, PUS1, PYGM, RBCK1, RNASEH1, RRM2B, RYR1, SCN4A, SDHA, SLC22A5, SLC25A20, SLC25A4, SLC25A42, SUCLA2, SUCLG1, TANGO2, TK2, TMEM65, TRIM32, TSFM, TTC19, TWNK, VMA21, YARS2

PDF Report
No

Day(s) Performed
Varies

Report Available
14 to 21 days

Specimen Retention Time
Whole Blood: 30 days (if available); 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

RABMP	Rhabdo/Metabolic Myopathy Panel	102118-7

Result ID	Test Result Name	Result LOINC® Value
617702	Test Description	62364-5
617703	Specimen	31208-2
617704	Source	31208-2
617705	Result Summary	50397-9
617706	Result	82939-0
617707	Interpretation	69047-9
618190	Additional Results	82939-0
617708	Resources	99622-3
617709	Additional Information	48767-8
617710	Method	85069-3
617711	Genes Analyzed	48018-6
617712	Disclaimer	62364-5
617713	Released By	18771-6