Test Definition: KETGP

Ketone Disorders Gene Panel

Overview

Useful For

Follow up for abnormal biochemical results suggestive of a ketone disorder

Establishing a molecular diagnosis for patients with ketone disorders

Identifying variants within genes known to be associated with ketone disorders, 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 9 genes associated with ketone disorders: *ACAA2*, *ACAT1*, *ACAT2*, *AKT2*, *BDH1*, *HMGCL*, *HMGCS2*, *OXCT1*, *SLC16A1*. See Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for ketone disorders.

Additional first tier testing may be considered/recommended.Â For more information see Advisory Information.

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name

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

NY State Available

No

Specimen

Specimen Type

Varies

Ordering Guidance

The recommended first-tier biochemical testing for ketone disorders includes urine organic acids and plasma acylcarnitine profile. OrderÂ OAU / Organic Acids Screen, Urine and ACRN / Acylcarnitines, Quantitative, Plasma.

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:

Preferred: 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 specimen in original tube.

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 in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)

2. Molecular Genetics: Biochemical Disorders Patient Information(T527) in Special Instructions

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 and Interpretive

Clinical Information

Ketones are a chemical energy source used by tissues when glucose is low. Disorders of impaired ketone body metabolism include beta-ketothiolase (BKT) deficiency and succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency. Disorders of ketogenesis are mitochondrial 3-hydroxy-3-methyglutaric acid CoA (HMG-CoA) synthase (mHS) and HMG-CoA lyase (HL) deficiencies.

BKT deficiency is caused by impaired activity of the enzyme acetoacetyl-CoA thiolase. Individuals with BKT deficiency are typically asymptomatic at birth, and symptoms are likely to develop from 6 to 18 months of age with illness or fasting, which appear as episodes of decompensation and severe ketoacidosis, vomiting, dehydration, and lethargy. Children are usually asymptomatic between episodes.

SCOT deficiency is a more severe ketone utilization disorder, as all experience recurrent ketoacidotic episodes, and most individuals have chronic ketosis. About 50% of infants with SCOT deficiency present in the first week of life, and the remaining 50% present between 6 to 24 months of age.

mHS deficiency is due to reduced activity of a mitochondrial enzyme mHS. Infants with mHS deficiency have episodes of hypoketotic hypoglycemia, which can progress to coma. In mHS deficiency, there is no diagnostic pattern of organic acids in urine. The only biochemical diagnostic test is enzyme assay of mHS in liver.

HL deficiency is due to reduced activity of mitochondrial and peroxisomal enzyme HL. Infants and children with HL deficiency also experience hypoketotic hypoglycemic episodes, and long-term impacts of these episodes can include epilepsy, intellectual disability, and white matter changes in the brain, usually due to hypoglycemia. Urine organic acids of individuals with HL are characteristic and demonstrate high levels of HMG and leucine metabolites.

All 4 of these ketone disorders are inherited in an autosomal recessive manner. BKT deficiency is caused by variants in *ACAT1*, and SCOT deficiency is caused by variants in the *OCT1*. HMG-CoA synthase deficiency is due to variants in *HMGCS2*, and HMG-CoA lyase deficiency is due to variants in *HMGCL*.

An additional disorder that impacts ketone metabolism and is included in this panel is monocarboxylate transporter 1 deficiency, due to 2 variants in *SLC16A1* and resulting in severe episodes of ketoacidosis with illness or fasting.

Treatment for these ketone disorders involves avoidance of fasting and provision of oral or intravenous carbohydrate to correct hypoglycemia and ketoacidosis. Long term neurologic sequelae occur in some individuals and are a consequence of hypoglycemia during ketoacidotic episodes.

Urine organic acids (OAU / Organic Acids Screen, Random, Urine) and plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma) are the recommended first-tier tests for assessment of ketone disorders. However, as these may be normal in all but severe BKT deficiency, molecular genetic testing is a rapid and effective tool to diagnose individuals with ketone disorder.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) 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 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 further testing options, for assistance in general test selection, or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted 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, 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 specific clinical disorders are suspected, evaluation by alternative methods can be considered.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, these 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.

There may be regions of genes that cannot be effectively amplified for 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 assay will not reliably detect insertions/deletions (indels) of 40 or more base pairs (bp), including Alu insertions, long interspersed nuclear elements (LINES), and short interspersed nuclear elements (SINES). The bioinformatics software pipeline is verified to detect 95% of deletions up to 75 bp and insertions up to 47 bp.

Additionally, low level mosaic variants may not be detected.

This test is not designed 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.

Reclassification of Variants-Policy:

At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Variant Evaluation:

Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) 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. Intronic and synonymous sequence variants not predicted to impact splicing or otherwise contribute to disease are not 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. Mitchell GA, Fukao T: Inborn errors of ketone body metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease McGraw-Hill Education; 2019. Accessed January 07,2020. Available at

http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087757

3. Hori T, Yamaguchi S, Shinkaku H, et al: Inborn errors of ketone body utilization. Pediatr Int. 2015;57(1):41-48

4. Fukao T, Mitchell G, Sass JO, Hori T, Orii K, Aoyama Y: Ketone body metabolism and its defects. J Inherit Metab Dis. 2014;37(4):541-551

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed. 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 amplified for 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 may be performed by alternate methodologies based on internal laboratory criteria..

PCR-based methods and/or Sanger sequencing is used to confirm variants detected by NGS when appropriate.(Unpublished Mayo method)

Genes analyzed: *ACAA2*, *ACAT1*, *ACAT2*, *AKT2*, *BDH1*, *HMGCL*, *HMGCS2*, *OXCT1*, *SLC16A1.*

PDF Report

No

Day(s) Performed

Varies

Report Available

3 to 4 weeks

Specimen Retention Time

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

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
KETGP	Ketone Disorders Gene Panel	In Process

Result ID	Test Result Name	Result LOINC Value
608692	Test Description	62364-5
608693	Specimen	31208-2
608694	Source	31208-2
608695	Result Summary	50397-9
608696	Result	82939-0
608697	Interpretation	69047-9
608698	Resources	In Process
608699	Additional Information	48767-8
608700	Method	85069-3
608701	Genes Analyzed	48018-6
608702	Disclaimer	62364-5
608703	Released By	18771-6