MAYO CLINIC LABORATORIES

Test Definition: KRABZ

Krabbe Disease, Full Gene Analysis and Large (30 kb) Deletion, Varies

Overview

Useful For

Second-tier test for confirming a diagnosis of Krabbe disease

Carrier testing for individuals with a family history of Krabbe disease in the absence of known sequence variants in the family

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

Testing includes full gene sequencing of the *GALC* gene.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

The following are available:
-Newborn Screen Follow-up for Krabbe Disease: Galactocerebrosidase
-Newborn Screen Follow-up for Krabbe Disease: Galactocerebrosidase and Psychosine
-Newborn Screening Act Sheet Krabbe Disease: Decreased Galactocerebrosidase

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Blood Spot Collection Card-Spanish Instructions
- Newborn Screening Act Sheet Krabbe Disease: Decreased Galactocerebrosidase
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Newborn Screen Follow-up for Krabbe Disease: Galactocerebrosidase
- Newborn Screen Follow-up for Krabbe Disease: Galactocerebrosidase and Psychosine
- Blood Spot Collection Instructions

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type
Varies

Ordering Guidance
The recommended first-tier test for Krabbe disease is GALCW / Galactocerebrosidase, Leukocytes, however this test is not reliable for detection of carriers.

For ongoing therapeutic monitoring for patients with Krabbe disease or for second tier newborn screening, order PSY / Psychosine, Blood Spot.

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.

Submit only 1 of the following specimens:

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

Specimen Type: Cultured fibroblasts
Container/Tube: T-75 or T-25 flask
Specimen Volume: 1 Full T-75 or 2 full T-25 flasks
Specimen Stability Information: Ambient (preferred)/Refrigerated <24 hours
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Skin biopsy
Supplies: Fibroblast Biopsy Transport Media (T115)
Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

Specimen Volume: 4-mm punch
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Acceptable:
Specimen Type: Blood spot
Supplies: Card - Blood Spot Collection (Filter Paper) (T493)
Container/Tube:
Preferred: Collection card (Whatman Protein Saver 903 Paper)
Acceptable: PerkinElmer 226 (formerly Ahlstrom 226) filter paper or blood spot collection card

Specimen Volume: 2 to 5 Blood spots
Collection Instructions:
1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see How to Collect Dried Blood Spot Samples.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.
Specimen Stability Information: Ambient (preferred)/Refrigerated
Additional Information:
1. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.
2. For collection instructions, see Blood Spot Collection Instructions
3. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)
4. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)

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

Blood: 1 mL
Blood Spots: 3

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

Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). GALC is encoded by the *GALC* gene located on 14q31. Krabbe disease occurs in approximately 1 in 100,000 live births with a carrier frequency of about 1 in 150 in the general population. Deficiency of GALC activity leads to an accumulation of galactosylceramide in globoid cells (multinucleated macrophages) causing severe demyelination throughout the brain. The toxic metabolite galactosylsphingosine (psychosine), an apoptotic compound, accumulates in oligodendrocytes and Schwann cells and contributes to disease pathogenicity.

Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration follows, with death usually occurring by age 13 months. There are later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression. The clinical course of Krabbe disease can be variable even within the same family. Treatment is mostly supportive, although hematopoietic stem cell transplantation has shown some success if treatment begins before neurologic damage has occurred.

The recommended first-tier test for Krabbe disease is GALCW / Galactocerebrosidase, Leukocytes.
Individuals with GALC activity below the reference range for these assays are more likely to have variants in the *GALC* gene that are identifiable by molecular genetic testing. The above test is not reliable for detection of carriers of Krabbe disease. Additionally, measurement of the psychosine biomarker can aid in diagnosis and ongoing therapeutic monitoring (PSY / Psychosine, Blood Spot).

This assay includes DNA sequencing of all 17 exons within the *GALC* gene as well as evaluation for the common 30-kb deletion spanning intron 10 through the end of the gene. This deletion accounts for a significant proportion of disease alleles that contribute to infantile Krabbe disease. While enzyme activity is not predictive of age of onset, there are known genotype-phenotype correlations. Individuals who are homozygous for the deletion or compound heterozygous for the deletion and a second *GALC* alteration (with the exception of late-onset variants) are predicted to have infantile Krabbe disease. The c.857G->A (p.Gly286Asp) alteration, on the other hand, is only associated with a late-onset phenotype.

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

This analysis does not exclude a diagnosis of atypical Krabbe disease due to saposin A deficiency.

A small percentage of individuals who are carriers or have a diagnosis of Krabbe disease may have a variant that is not identifiable by this method (eg, large genomic deletions, promoter alterations). The absence of a variant, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of Krabbe disease.

In some cases, DNA alterations of undetermined significance may be identified.

Rare alterations exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

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

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. Orsini JJ, Escolar ML, Wasserstein MP, Caggana M: Krabbe disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated October 11, 2018. Accessed June 30, 2020. Available at ncbi.nlm.nih.gov/books/NBK1238/
3. Luzi P, Rafi MA, Wenger DA: Structure and organization of the human galactocerebrosidase (*GALC*) gene. Genomics. 1995;26:407-409
4. Luzi P, Rafi MA, Wenger DA: Characterization of the large deletion in the *GALC* gene found in patients with Krabbe disease. Hum Mol Genet. 1995;4(12):2335-2338
5. Spiegel R, Bach G, Sury V, et al: A mutation in the saposin A coding region of the prosaposin gene in an infant presenting as Krabbe disease: report of saposin A deficiency in humans. Molec Genet Metab. 2005,84:160-166

Performance

Method Description

Bidirectional sequence analysis is performed to test for the presence of a sequence variant in all coding regions and intron/exon boundaries of the *GALC* gene. Additionally, a PCR-based assay is used to examine DNA for the presence of a 30-kb deletion encompassing exon 11 through the end of the *GALC* gene.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Varies

Report Available

14 to 20 days

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

81406 GALC (galactosylceramidase) (eg, Krabbe disease), full gene sequence
88233-Tissue culture, skin or solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
KRABZ	Krabbe Disease, Full Gene Analysis	87738-1

Result ID	Test Result Name	Result LOINC® Value
53505	Result Summary	50397-9
53506	Result	82939-0
53507	Interpretation	69047-9
53508	Additional Information	48767-8
53509	Specimen	31208-2
53510	Source	31208-2
53511	Released By	18771-6