Test Definition: GRHPZ

GRHPR Gene, Full Gene Analysis

Overview

Useful For

Confirming a diagnosis of primary hyperoxaluria type 2 (PH2)

Carrier testing for individuals with a family history of PH2 in the absence of known mutations in the family

Testing Algorithm

See Hyperoxaluria Diagnostic Algorithm in Special Instructions.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Hyperoxaluria Diagnostic Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequence Analysis and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

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.

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 in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521) in Special Instructions

3. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

-Inborn Errors of Metabolism Test Request (T798)

-Renal Diagnostics Test Request (T830)

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Primary hyperoxaluria type 2 (PH2) is a hereditary disorder of glyoxylate metabolism caused by deficiency of the hepatic enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR). Absence of GRHPR activity results in excess oxalate and usually L-glycerate excreted in the urine leading to nephrolithiasis (kidney stones) and sometimes renal failure.

Onset of PH2 is typically in childhood or adolescence with symptoms related to kidney stones. In some cases, kidney failure may be the initial presenting feature. Nephrocalcinosis, as seen by renal ultrasound, is observed less frequently in individuals with PH2 than primary hyperoxaluria type 1 (PH1). End-stage renal disease (ESRD) is also less common and of later onset than PH1; however, once ESRD develops, oxalate deposition in other organs such as bone, retina, and myocardium can occur.

While the exact prevalence and incidence of PH2 are not known, it is thought that PH2 is less common than PH1, which has an estimated prevalence rate of 1 to 3 per million population and an incidence of 0.1 per million/year.

Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate in a timed, 24-hour urine collection is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, Urine). In very young children (incapable of performing a timed collection), random urine oxalate to creatinine ratios may be used for determination of oxalate excretion. In patients with reduced kidney function, POXA / Oxalate, Plasma is also recommended. Urinary excretion of oxalate of >1.0 mmol/1.73 m(2)/24 hours is strongly suggestive of, but not diagnostic, for primary hyperoxaluria as there are other forms of inherited hyperoxaluria (PH1 and non-PH1/PH2) and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glycerate in the presence of hyperoxaluria is suggestive of PH2. Caution is warranted in interpretation of urine oxalate excretion in patients with reduced kidney function as urine oxalate concentrations may be lower due to reduced glomerular filtration rate. Historically, the diagnosis of PH2 was confirmed by GRHPR enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases.

PH2 is inherited as an autosomal recessive disorder caused by mutations in the *GRHPR* gene, which encodes the enzyme GRHPR. Two common *GRHPR* mutations have been identified: c.103delG and c.403_404+2delAAGT. These mutations account for about one-third of the mutant alleles described in the Northern European Caucasian population and about 15% in the Asian population. Direct sequencing of the *GRHPR* gene will identify these 2 mutations as well as other less common or novel mutations associated with PH2.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of primary hyperoxaluria type 2 (PH2) may have a mutation that is not identified by this method (eg, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of PH2. For carrier testing, it is important to first document the presence of a *PH2* gene mutation in an affected family member.

In addition to disease-related probes, this test utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

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

Technical Limitations:

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

Due to the limitations of Next Generation Sequencing, small deletions and insertions may not be detected by this test. If a diagnosis of one of the syndromes on this panel is still suspected, contact a molecular genetic counselor in the Genomics Laboratory at 800-533-1710 for more information regarding follow-up testing options.

Rare polymorphisms 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.

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.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently unvalidated.

Unless reported or predicted to cause disease, alterations in protein coding genes that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review likely pathogenic alterations or variants of uncertain significance that have been previously detected and reported. 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.

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. Primary Hyperoxaluria Type 2-GeneReviews-NCBI Bookshelf. Available from URL: http://www.ncbi.nlm.nih.gov/books/NBK2692/, accessed 8-7-2012

3. Rumsby G, Williams E, Coulter-Mackie M: Evaluation of mutation screening as a first line test for the diagnosis of the primary hyperoxalurias. Kidney Int 2004;66(3):959-963

4. Cregeen DP, Williams EL, Hulton S, Rumsby G: Molecular analysis of the glyoxylate reductase (*GRHPR*) gene and description of mutations underlying primary hyperoxaluria type 2. Hum Mutat 2003;22(6):497

5. Laboratory and molecular diagnosis of primary hyperoxaluria and oxalosis. Mayo Medical Laboratories' Communique, April 2007

Performance

Method Description

Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *GRHPR* gene. Additionally, gene dosage analysis (multiplex ligation-dependent probe amplification) is used to test for the presence of large deletions and duplications in this gene.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly; Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

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 U.S. Food and Drug Administration.

CPT Code Information

81479-Unlisted molecular pathology procedure

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
GRHPZ	GRHPR Gene, Full Gene Analysis	94202-9

Result ID	Test Result Name	Result LOINC Value
53491	Result Summary	50397-9
53492	Result	82939-0
53493	Interpretation	69047-9
53494	Additional Information	48767-8
53495	Specimen	31208-2
53496	Source	31208-2
53497	Released By	18771-6