MAYO CLINIC LABORATORIES

Test Definition: GALMP

Galactosemia, GALT Gene, Variant Panel, Varies

Overview

Useful For

Second-tier test for confirming a diagnosis of galactosemia as indicated by enzymatic testing or newborn screening

Carrier testing family members of an affected individual of known genotype (has variants included in the panel)

Resolution of Duarte variant and Los Angeles (LA) variant genotypes

Genetics Test Information

This targeted genotyping panel is for 24 variants in the *GALT* gene. For details regarding the specific variants for this test, see the Targeted Variants Table in Clinical Information.

Testing Algorithm

For more information see Galactosemia Testing Algorithm

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Galactosemia Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)
- Galactosemia-Related Test List

Highlights

A targeted genotyping array is utilized to detect 24 genetic targets associated with galactosemia for the purpose of diagnostic testing or carrier screening.

Method Name

Targeted Genotyping Array

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

The recommended as a first-tier test is galactose-1-phosphate uridyltransferase enzyme analysis; order GALT /

Galactose-1-Phosphate Uridyltransferase, Blood.

This genetic variant panel is recommended for individuals with a GALT enzyme value less than 24.5 nmol/h/mg of hemoglobin.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Specimen Required

Multiple whole blood tests for galactosemia can be performed on one specimen. Prioritize order of testing when submitting specimens. See Galactosemia-Related Test List for a list of tests that can be ordered together.

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 whole blood specimen in original tube. **Do not aliquot**.

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: Biochemical Disorders Patient Information (T527)

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	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Classical galactosemia is an autosomal recessive disorder of galactose metabolism caused by genetic variants in the galactose-1-phosphate uridyltransferase (*GALT*) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, intellectual disability, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Women with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000.

Duarte variant galactosemia (compound heterozygosity for the Duarte variant, N314D and -119_-116delGTCA in cis [on the same chromosome], and a classic variant in trans [on the opposite chromosome]) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are also often treated with a low-galactose diet during infancy. The Los Angeles (LA) variant, which consists of N314D without the presence of -119_-116delGTCA, is associated with normal levels of GALT enzyme activity.

Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common *GALT* variants may be performed. If one or both disease-causing variants are not detected by targeted variant analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the *GALT* gene is available to identify private variants.

The *GALT* gene maps to 9p13. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic variant. This variant accounts for 60% to 70% of classical galactosemia alleles. The S135L variant is the most frequently observed variant in African Americans and accounts for approximately 50% of the altered alleles in this population. The K285N variant is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P variant is observed in 5% to 7% of classical galactosemia. The 5 kilobase deletion is common in individuals of Ashkenazi Jewish descent. The Duarte variant (N314D and -119_-116delGTCA) is observed in 5% of the general United States population. The rest of the variants detected by this method are all uncommon but known to be recurrent in the general population.

These variants, in addition to the LA variant, are included in this test and in GCT / Galactosemia Reflex, Blood. For more information see Galactosemia Testing Algorithm.

Table. Targeted Variants

Associated phenotype	Gene (transcript)	Variants
Galactosemia	*GALT* (NM_000155	c.-119_-116del*, c.136_140del, c.221T>C*, c.253-2A>G*, c.292G>A*, c.404C>T*, c.413C>T*, c.425T>A*, c.443G>A*,

	)	c.505C>A, c.512T>C*, c.563A>G*, c.584T>C*, c.607G>A*, c.626A>G*, c.855G>T*, c.940A>G*, c.958G>A*, c.997C>G*, c.997C>T*, c.1018G>T, c.1030C>A*, c.1138T>C* Deletion analysis of exon 1-11

*Previously detected in a known positive sample

Reference Values
An interpretive report will be provided.

Interpretation
An interpretative report will be provided.

Results should be interpreted in the context of biochemical results.

If results of the galactose-1-phosphate uridyltransferase enzyme analysis and this test are discordant, then consider GALZ / Galactosemia, *GALT* Gene, Full Gene Analysis, Varies.

Cautions
This assay will not detect all of the known disease-associated variants that cause galactosemia. Therefore, the absence of a detectable variant does not rule out the possibility that an individual is a carrier of or affected with this disease.

Many disorders may present with symptoms similar to those associated with galactosemia. Therefore, biochemical testing is recommended to establish the diagnosis of galactosemia prior to DNA analysis.

A negative result does not eliminate the risk of carrier status for any of the included conditions, due to the possibility that the patient carries a variant that is not interrogated with this assay or the rare chance of a false-negative result for a tested variant. For tested variants, the negative predictive value of this screen is greater than 98%. The patient's residual risk to be a carrier after a negative screen is dependent on ethnic background and family history.

A positive control was not available for all variants targeted on this panel. For more information regarding availability of a positive control for each variant see the Table (Targeted Variants) in Clinical Information.. The negative predictive value of these targets is unknown.

Rare variants (ie, 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.

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) This assay was designed to specifically target known pathogenic or likely pathogenic variants. In rare cases, DNA variants of undetermined significance may be identified. 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.

Multiple in-silico evaluation tools may have been used to assist in the interpretation of these results. Of note, the sensitivity and specificity of these tools for the determination of pathogenicity is currently unvalidated.

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.

Bone Marrow transplants from allogenic donors will interfere with testing. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects deidentified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

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. doi: 10.1038/gim.2015.30
2. Elsas LJ 2nd, Lai K: The molecular biology of galactosemia. Genet Med. 1998 Nov-Dec;1(1):40-48. doi: 10.1097/00125817-199811000-00009
3. Kaye CI, Committee on Genetics, Accurso F, et al: Newborn screening fact sheets. Pediatrics. 2006 Sep;118(3):e934-e963. doi: 10.1542/peds.2006-1783
4. Novelli G, Reichardt JK: Molecular basis of disorders of human galactose metabolism: past, present, and future. Mol Genet Metab. 2000 Sep-Oct;71(1-2):62-65. doi: 10.1006/mgme.2000.3073
5. Welling L, Bernstein LE, Berry GT, et al: International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017 Mar;40(2):171-176. doi: 10.1007/s10545-016-9990-5
6. Carlock G, Fischer ST, Lynch ME, et al: Developmental outcomes in Duarte galactosemia. Pediatrics. 2019 Jan;143(1):e20182516. doi: 10.1542/peds.2018-2516

Performance

Method Description

The targeted genotyping assay utilizing the ThermoFisher GeneTitan platform is used to detect 24 targets in the *GALT* gene. Confirmatory testing of homozygous results is performed as reflex tests when appropriate. For details regarding the targeted pathogenic variants identified by this test, see the Targeted Variants table in Clinical Information.

Multiplex ligation-dependent probe amplification, polymerase chain reaction (PCR), relative quantitative PCR, and Sanger sequencing are used to confirm variants detected by array when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Thursday, Sunday

Report Available

7 to 21 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

81401

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GALMP	Galactosemia Mutation Panel	42318-6

Result ID	Test Result Name	Result LOINC® Value
606344	Result Summary	50397-9
606345	Result	82939-0
606346	Interpretation	69047-9
606347	Additional Information	48767-8
606348	Method	85069-3
606349	Specimen	31208-2
606350	Source	31208-2
606351	Released By	18771-6