

Galactosemia (*GALT*) Enzyme Activity and 9 Mutations

Indications for Ordering

- Follow-up of an abnormal newborn screening test for galactosemia
- Neonatal testing for an affected individual's sibling
- Carrier testing for parents of an affected individual
- Evaluation of a patient for galactosemia

Test Description

Galactose-1-phosphate uridylyltransferase (*GALT*) enzyme activity

- Spectrophotometric assay

GALT 9 mutations

- Polymerase chain reaction (PCR) gene amplification followed by targeted single nucleotide extension (SNE) and capillary electrophoresis to detect pathogenic variants (Q188R, S135L, K285N, T138M, L195P, Y209C, and IVS2-2 A>G) associated with classic galactosemia and two nonpathogenic variants (N314D and L218L – also known as Duarte and LA variants)

Sequencing

- Sequencing of entire *GALT* coding region, intron/exon boundaries, and partial 5'UTR

Tests to Consider

Primary test

[Galactosemia \(*GALT*\) Enzyme Activity and 9 Mutations 0051175](#)

- Preferred initial test for the diagnosis of classic galactosemia or carrier status

Related tests

[Galactose-1-Phosphate Uridylyltransferase 0080125](#)

- *GALT* enzyme
- May be used as initial screening test to diagnose individuals with classic galactosemia

[Galactosemia, \(*GALT*\) 9 Mutations 0051176](#)

- Use to clarify genotype when enzyme activity is known

[Galactosemia \(*GALT*\), Sequencing 2006697](#)

- Use when *GALT* enzyme activity is consistent with galactosemia, and the 9 pathogenic variant panel fails to identify 2 causative variants

[Galactosemia \(*GALT*\) 9 Mutations, Fetal 0051270](#)

- Useful for prenatal diagnosis of *GALT* variant only if proband has known pathogenic variant
- **Contact an ARUP genetic counselor before ordering this test for special instructions**

[Galactose-1-Phosphate in Red Blood Cells 0081296](#)

- Monitor levels, response, and compliance with dietary restriction for individuals with an established diagnosis

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a familial variant identifiable by sequencing is known

Disease Overview

Incidence

1/30,000-60,000 live births in Caucasians

- Other ethnicities vary

Age of onset

- Typically asymptomatic at birth
- Develop escalating symptoms within 3-14 days of birth following exposure to a milk-based diet

Symptoms

- Most common presenting symptoms in untreated infants
 - Hepatocellular damage
 - Food intolerance
 - Sepsis
- Other symptoms
 - Failure to thrive
 - Lethargy
 - Seizures
- If infant with disease is left untreated, liver and brain damage are irreversible
- Sequelae in treated affected individuals
 - Speech problems
 - Premature ovarian insufficiency
 - Intellectual impairment
 - Neurologic deficits
 - Cataracts

Etiology

- Galactose-1-phosphate uridylyltransferase (*GALT*) enzyme is one of the enzymes involved in galactose utilization
 - Other enzyme deficiencies are rare
- Deficiency results in accumulation of galactose-1-phosphate, galactitol, and galactonate
- Genotype/phenotype correlation helps in prognostication (GeneReviews)

Genetics

Gene – *GALT*

Inheritance – autosomal recessive

Penetrance – 100% for classic galactosemia

Structure/function

- Located on chromosome 9p13
 - 11 exons
- Encodes for *GALT* enzyme involved in galactose metabolism

Variants

- Seven pathogenic alleles (G) detected with the following frequency in individuals with classic galactosemia in the U.S. (GeneReviews)
 - Q188R – 49%
 - Causal variant in 70% of individuals of northern European descent
 - S135L – 7%
 - Causal variant in 50% of individuals of African American descent
 - K285N – 4%
 - Predominant causal variant in individuals of German, Austrian, and Croatian descent
 - T138M – unknown frequency
 - L195P – 2%
 - Y209C – 1%
 - IVS2-2 A>G – almost exclusively found in individuals of Hispanic descent
- Other frequently identified variants
 - Duarte variant (N314D) – 5% of the general U.S. population
 - Associated with moderate decrease in *GALT* activity
 - LA variant (N314D linked to L218L allele)
 - Associated with a mild increase in *GALT* expression

Test Interpretation

Galactose-1-Phosphate Uridyltransferase

Clinical sensitivity (classic galactosemia) – >99%

Results

- Individuals affected with classic galactosemia usually have <2 U/g Hb
 - Normal enzyme activity between 14.7 and 25.4 U/g Hb
- Enzyme ranges can overlap between genotypes
- Follow-up genetic testing for characterization of pathogenic variants is recommended

Galactosemia, (*GALT*) 9 Mutations

Clinical sensitivity (classic galactosemia) – 80% in Caucasians, but reduced in other ethnicities

Results

- Detection of 2 severe variants (G/G)
 - Classic galactosemia
- One pathogenic variant and one Duarte variant (D/G)
 - Duarte-variant galactosemia
- One pathogenic variant (G/N)
 - Individual is at least a carrier of classic galactosemia
 - In the presence of markedly reduced *GALT* activity, patient may have classic galactosemia with a variant not detected by the 9 variant panel
- No pathogenic variants
 - Galactosemia or carrier status cannot be excluded
 - Refer to enzyme activity for follow-up testing

Galactosemia (*GALT*), Sequencing

Sensitivity/specificity

- Clinical sensitivity (classic galactosemia) – 98%
- Analytical sensitivity and specificity – 99%

Results

- Detection of 2 severe variants (G/G)
 - Classic galactosemia
- One pathogenic variant and one Duarte variant (D/G)
 - Duarte-variant galactosemia
- One pathogenic variant (G/N)
 - Individual is at least a carrier of classic galactosemia
 - In the presence of markedly reduced *GALT* activity, patient may have classic galactosemia with a variant not detected by the 9 variant panel
- No pathogenic variants
 - Galactosemia or carrier status cannot be excluded
 - Refer to enzyme activity for follow-up testing

Limitations

- *GALT* enzyme activity ranges overlap, so molecular testing is necessary to clarify genotype
- Variants other than the 9 *GALT* panel variants specified above will not be evaluated
- Other rare forms of galactosemia caused by deficiency of galactokinase (*GALK*) or galactose-4 epimerase (*GALE*) will not be identified
- Rare diagnostic errors can occur due to primer-site variants
- Regulatory region variants, deep intronic variants, and large deletions/duplications will not be detected