# 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 uridyltransferase (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 mutations (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 Uridyltransferase 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 mutation panel fails to identify 2 causative mutations

Galactosemia (*GALT*) 9 Mutations, Fetal 0051270

- Useful for prenatal diagnosis of *GALT* mutation only if proband has known mutation
- **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 mutation 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 uridyltransferase (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

**Mutations**

- Seven pathogenic alleles (G) detected with the following frequency in individuals with classic galactosemia in the U.S. (GeneReviews)
  - Q188R – 49%
    - Causal mutation in 70% of individuals of northern European descent
  - S135L – 7%
    - Causal mutation in 50% of individuals of African American descent
  - K285N – 4%
    - Predominant causal mutation 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 mutations is recommended

**Galactosemia, (*GALT)* 9 Mutations**

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

**Results**

- Detection of 2 severe mutations (G/G)
  - Classic galactosemia
- One mutation and one Duarte variant (D/G)
  - Duarte-variant galactosemia
- One mutation (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 mutation not detected by the 9 mutation panel
- No mutations
  - 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 mutations (G/G)
  - Classic galactosemia
- One mutation and one Duarte variant (D/G)
  - Duarte-variant galactosemia
- One mutation (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 mutation not detected by the 9 mutation panel
- No mutations
  - Galactosemia or carrier status cannot be excluded
    - Refer to enzyme activity for follow-up testing

**Limitations**

- GALT enzyme activity ranges overlap, so mutation testing is necessary to clarify genotype
- Mutations other than the 9 *GALT* panel mutations 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 mutations
- Regulatory region mutations, deep intronic mutations, and large deletions/duplications will not be detected