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
- Sequelaes 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
  o 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)
  o Q188R – 49%
    ▪ Causal mutation in 70% of individuals of northern European descent
  o S135L – 7%
    ▪ Causal mutation in 50% of individuals of African American descent
  o K285N – 4%
    ▪ Predominant causal mutation in individuals of German, Austrian, and Croatian descent
  o T138M – unknown frequency
  o L195P – 2%
  o Y209C – 1%
  o IVS2-2 A>G – almost exclusively found in individuals of Hispanic descent
• Other frequently identified variants
  o Duarte variant (N314D) – 5% of the general U.S. population
    ▪ Associated with moderate decrease in GALT activity
  o 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
  o 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)
  o Classic galactosemia
• One mutation and one Duarte variant (D/G)
  o Duarte-variant galactosemia
• One mutation (G/N)
  o 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
  o 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)
  o Classic galactosemia
• One mutation and one Duarte variant (D/G)
  o Duarte-variant galactosemia
• One mutation (G/N)
  o 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
  o 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