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 pathogenic variants (Q188R, S135L, K285N, 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 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 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

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