Galactosemia (GALT) Enzyme Activity and 9 Mutations

Galactosemia can result in life-threatening complications including feeding problems, failure to thrive, hepatocellular damage, bleeding, and *E. coli* sepsis in untreated infants. If a lactose-restricted diet is provided during the first 10 days of life, the neonatal signs usually quickly resolve and the complications of liver failure, sepsis, and neonatal death are prevented; however, despite adequate treatment from an early age, children with classic galactosemia remain at increased risk for developmental delays, speech problems (termed childhood apraxia of speech and dysarthria), and abnormalities of motor function.[1]

Disease Overview

Incidence

1/30,000-60,000 live births in White individuals

- 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
  - Death
- 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) is an enzyme involved in galactose utilization

Tests to Consider

Galactosemia (GALT) Enzyme Activity and 9 Mutations (Extended TAT as of 11/20/20-no referral available) 0051175

Method: Enzymatic/Polymerase Chain Reaction/Single Nucleotide Extensions

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

Related Tests

Galactose-1-Phosphate Uridyltransferase (GALT Enzyme), RBC 3001790

Method: Enzymatic/Liquid Chromatography-Tandem Mass Spectrometry

May be used as initial screening test to diagnose individuals with classic galactosemia

Galactosemia, (GALT) 9 Mutations 0051176

Method: Polymerase Chain Reaction/Single Nucleotide Extensions

Use to clarify genotype when enzyme activity is known

Galactosemia (GALT), Sequencing 2006697

Method: Sequencing

Use when GALT enzyme activity is consistent with galactosemia, and the nine pathogenic variant panel fails to identify two causative variants

Galactosemia (GALT) 9 Mutations, Fetal 0051270

Method: Polymerase Chain Reaction/Single Nucleotide Extensions

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

Method: Gas Chromatography-Mass Spectrometry (GC-MS)

- Other enzyme deficiencies are rare
- Deficiency results in accumulation of galactose-1-phosphate, galactitol, and galactonate
- Genotype/phenotype correlation helps in prognostication[1]

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

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a familial variant identifiable by sequencing is known

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

- Over 300 known pathogenic variants detectable by full gene sequencing
- Seven pathogenic alleles (G) detected with the following frequency in individuals with classic galactosemia in the U.S.[1]
  - 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 ≤0.7 U/g Hb
  - Normal enzyme activity is ≥19.4 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 White individuals, and reduced in other ethnicities

Results

- Detection of two 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 nine 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 two 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 nine 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 nine *GALT* panel variants specified above will not be evaluated on the Galactosemia (*GALT*) 9 Mutations panel
- 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

References

1. Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Mar 2017; Accessed: Feb 2020]

Related Information

Classic Galactosemia

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