Galactosemia Genetic Testing

Galactosemia type 1 is an inherited disorder of galactose metabolism resulting from galactose-1-phosphate uridyltransferase (GALT) deficiency and includes phenotypes of classic galactosemia, clinical variant galactosemia, and benign variant galactosemia. Classic galactosemia and clinical variant galactosemia may be life-threatening. Clinical findings can include diarrhea, feeding problems, failure to thrive, hepatocellular damage, bleeding, sepsis, seizures, lethargy, or neonatal death. When 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. If an infant with the disease is left untreated, liver and brain damage are irreversible. Even with adequate early treatment, individuals with classic galactosemia are at increased risk for developmental delays, speech disorders, motor function issues, cataracts and, in females, premature ovarian insufficiency. Individuals with clinical variant galactosemia who have received adequate early treatment may not be at risk for long-term complications.[1] Benign variant galactosemia, the most common form being Duarte variant galactosemia (also known as D/G galactosemia), is associated with partial deficiency in erythrocyte GALT enzyme, but is typically not associated with clinical disease; thus, dietary therapy is often not recommended.

Diagnosis of classic or clinical variant galactosemia relies on elevated erythrocyte galactose-1-phosphate concentration, reduced erythrocyte GALT enzyme activity, or detection of biallelic pathogenic *GALT* variants. Genotype/phenotype correlation helps in prognostication.[1]

Featured ARUP Testing

Galactosemia (GALT) Enzyme Activity and 9 Mutations 0051175

Method: Enzymatic Assay/Polymerase Chain Reaction (PCR)/Single Nucleotide Extensions

- Preferred initial test for the diagnosis of classic galactosemia or carrier status
- Use to assess for GALT enzyme activity and common pathogenic *GALT* variants

Galactosemia (GALT) Sequencing and Deletion/Duplication 3004716

Method: Massively Parallel Sequencing

Use to assess for additional variants when GALT enzyme activity and common *GALT* variant testing results are discordant

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Genetics

Gene

GALT (NM_000155)

Variants

Over 300 known pathogenic *GALT* variants are detectable by sequencing. Common variants detected in the U.S. are as follows:

Common *GALT* Variants in the U.S.

Variant	Frequency in U.S. Patients With Confirmed Galactosemia (%)	Additional Information
c.563A>G, p.Gln188Arg (Q188R)	49	Causal variant in 70% of individuals of northern European descent
c.404C>T, p.Ser135Leu (S135L)	7	Causal variant in 50% of individuals of African American descent African Americans with the p.Ser135/p.Ser135L genotype may have absent or barely detectable erythrocyte GALT enzyme activity Homozygosity associated with clinical variant galactosemia

n/a, not available

Variant	Frequency in U.S. Patients With Confirmed Galactosemia (%)	Additional Information
c.855G>T, p.Lys285Asn (K285N)	4	Predominant causal variant in individuals of German, Austrian, and Croatian descent
c.413C>T, p.Thr138Met (T138M)	Unknown	—
c.584T>C, p.Leu195Pro (L195P)	2	—
c.626A>G, p.Tyr209Cys (Y209C)	1	—
c.253-2A>G (IVS2-2A>G)	Unknown	Almost exclusively found in individuals of Hispanic descent
Duarte 2 (D_2) variant	n/a	Found in 5% of the general U.S. population Benign variant associated with moderate decrease in GALT activity Most common variant associated with benign variant galactosemia Duarte 2 haplotype refers to the combination of the c.-119_116delGTCA variant and four other sequence changes (c.378-27G>C, c.507+62G>A, c.508-24G>A, and c.940A>G, p.Asn314Asp) that are found together on the same chromosome
Los Angeles (LA) variant	n/a	Benign variant associated with a mild increase in GALT expression Complex allele, c.[652C>T;940A>G]; p.[Leu218=;Asn314Asp] Also known as Duarte 1 (D_1)
5 kb deletion	Unknown	Pathogenic variant common in Ashkenazi Jewish individuals

n/a, not available

Etiology

GALT is an enzyme involved in galactose utilization; other enzyme deficiencies are rare. Deficiency results in accumulation of galactose-1-phosphate, galactitol, and galactonate.

The prevalence of classic galactosemia is 1/48,000 in the U.S.[1]

Inheritance

Autosomal recessive

Penetrance

100% for classic or clinical variant galactosemia

Test Interpretation

Methodology

Galactosemia (*GALT*) Enzyme Activity and 9 Mutations

Enzyme testing: enzymatic/liquid chromatography-tandem mass spectrometry

Genetic testing: polymerase chain reaction/single nucleotide extensions

This assay detects seven pathogenic *GALT* variants and two benign variants. The D_2 variant is predicted when c.940A>G is detected with lack of detection of c.652C>T; the LA variant is predicted when both c.940A>G and c.652C>T are identified.

- Pathogenic variants:
  - c.253-2A>G (IVS2-2A>G)
  - c.404C>T, p.Ser135Leu (S135L)
  - c.413C>T, p.Thr138Met (T138M)
  - c.563A>G, p.Gln188Arg (Q188R)
  - c.584T>C, p.Leu195Pro (L195P)
  - c.626A>G, p.Tyr209Cys (Y209C)
  - c.855G>T, p.Lys285Asn (K285N)
- Benign variants:
  - c.940A>G, p.Asn314Asp (N314D)
  - c.652C>T, p.Leu218Leu (L218L)

Galactosemia (*GALT*) Sequencing and Deletion/Duplication

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and, in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Sensitivity

Galactosemia (*GALT*) Enzyme Activity and 9 Mutations

Clinical Sensitivity

- Enzyme testing: >99% for classic galactosemia
- Genetic testing: 80% for classic galactosemic in White individuals; reduced in other ethnicities

Galactosemia (*GALT*) Sequencing and Deletion/Duplication

Clinical Sensitivity

95%

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; PPA, positive percent agreement; NPA, negative percent agreement; SNVs, single nucleotide variants

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] Deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] Duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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Results

Galactosemia (*GALT*) Enzyme Activity and 9 Mutations

Individuals affected with classic galactosemia usually have enzyme activity of ≤0.7 U/g Hb; normal enzyme activity is ≥19.4 U/g Hb. Enzyme ranges can overlap between genotypes. Possible genotype results and the expected enzyme activity levels are as follows:

Variant(s) Detected	Clinical Significance	Associated Enzyme Activity Levels
Two severely pathogenic variants (G/G)	Classic galactosemia or clinical variant galactosemia	≤0.7 U/g Hb
One pathogenic variant and one benign Duarte 2 variant (D/G)	Duarte-variant galactosemia (also known as benign variant galactosemia)	3.1-7.8 U/g Hb
One pathogenic variant (G/N)	Individual is at least a carrier of galactosemia	6.5-16.2 U/g Hb
Two Duarte 2 variants detected (D/D)	Individual is homozygous for the Duarte variant	6.4-16.5 U/g Hb
One Duarte 2 variant detected (D/N)	Individuals is at least a carrier of Duarte variant galactosemia	12.0-24.0 U/g Hb
No pathogenic variants (N/N)	Galactosemia or carrier status cannot be excluded	≥19.4 U/g Hb

Galactosemia (*GALT*) Sequencing and Deletion/Duplication

In addition to the results described in the table below, variants of unknown clinical significance may be detected.

Test Result	Interpretation
Detection of two severely pathogenic variants (G/G)	Classic galactosemia or clinical variant galactosemia
One pathogenic variant and one benign Duarte 2 variant (D/G)	Duarte variant galactosemia (also known as benign variant galactosemia)
One pathogenic variant (G/N)	Individual is at least a carrier of galactosemia In the presence of markedly reduced GALT activity, patient may have classic galactosemia or clinical variant galactosemia with a variant not detected by the panel

Test Result	Interpretation
No pathogenic variants	Galactosemia or carrier status cannot be excluded Refer to enzyme activity for follow-up testing The benign LA and D_2 variants are reported when detected

Limitations

Galactosemia (*GALT*) Enzyme Activity and 9 Mutations

- *GALT* gene variants other than the nine targeted by this assay will not be detected.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- Enzyme ranges can overlap between genotypes.

Galactosemia (*GALT*) Sequencing and Deletion/Duplication

- A negative result does not exclude a diagnosis of or carrier status for galactosemia.
- Other rare forms of galactosemia caused by deficiency of galactokinase (GALK) or galactose-4 epimerase (GALE) will not be identified.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the *GALT* gene
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes or repetitive/homologous regions
  - The 5kb deletion is detected by this assay at a reduced sensitivity; therefore, individuals of Ashkenazi Jewish ancestry may benefit from additional analysis via a different methodology for this common variant.

References

1. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last update: Mar 2021; Accessed: Dec 2021]

Related Information

Classic Galactosemia

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