

Galactosemia Sequencing

TO DETECT RARE GALACTOSE-1-PHOSPHATE URIDYLTRANSFERASE (GALT) GENE MUTATIONS NOT DETECTABLE ON A STANDARD PANEL

Disease Overview

- Galactosemia is a disorder of carbohydrate metabolism caused by a deficiency of enzymes involved in galactose utilization.
- The most common cause of galactosemia is a deficiency of the galactose-1-phosphate uridylyltransferase (GALT) enzyme resulting in accumulation of galactose-1-phosphate, galactose, galactitol, and galactonate.
- In classic galactosemia, GALT activity is nearly absent.
- Affected infants present at 3–14 days old with poor feeding, vomiting, diarrhea, jaundice, lethargy progressing to coma, and abdominal distension with hepatomegaly usually followed by progressive liver failure. Risk is also increased for *Escherichia coli* or other gram-negative neonatal sepsis.
- Elimination of galactose from the diet reverses growth failure, renal and hepatic dysfunction, and cataracts. However, patients can still have ovarian failure (primary or secondary amenorrhea), mental retardation, speech dyspraxia, ataxia, and learning disabilities. Diet must be continued for life.
- Patients are periodically monitored by measuring levels of galactose-1-phosphate in red blood cells; intrinsic production may cause abnormally high values even with dietary galactose restriction.
- When the diagnosis is not made at birth, liver disease and brain damage may become irreversible.

Epidemiology

- One in 30,000–60,000 for classic galactosemia in Caucasians; varies in other populations.

Genetics

- Autosomal recessive.
- GALT is located on chromosome 9p13, has 11 exons, and codes a 379 amino acid protein.
- More than 190 GALT mutations have been reported.
- Q188R and S135L are the most common mutations in individuals of European and African descent, respectively.
- The N314D (Duarte, D) variant is present in 5 percent of North Americans and reduces enzymatic activity by 50 percent; therefore, it is not considered a classic galactosemia allele (G).
- Compound DG heterozygotes (one N314D Duarte allele and one classic galactosemia allele) have about 25 percent of normal GALT activity, yet are often treated with galactose restriction in the first year of life. These patients usually have no sequelae due to the variant form of galactosemia.

- DD patients with 50 percent of normal GALT activity are not treated and have no symptoms of galactosemia.

Indication for Ordering

Affected individuals with only one or no GALT gene mutations identified on a DNA panel.

Contraindications

- This test should only be performed after an individual's GALT enzyme level is found to be consistent with galactosemia disease and the GALT DNA panel has failed to find two common causative mutations.
- If a full sibling to the proband has gene mutations other than those on the GALT panel, targeted sequencing for the specific GALT mutations would be more cost-effective than full-gene sequencing.

Additional Ordering Notes

If there is a positive family history of classic galactosemia, please provide information on the relationship of the proband to the individual being tested, as well as details regarding the proband's specific mutations.

Interpretation

Two severe GALT gene mutations are causative for disease. Gene sequencing occasionally reveals a mutation with little or no previously reported information. In these cases, interpretive information may be based on the patient's GALT enzyme activity, the specific amino acid change, and conservation among species.

Methodology

- PCR followed by bidirectional sequencing of the entire coding region, intron/exon boundaries, and the 5'-UTR of the GALT gene.
- Analytic sensitivity and specificity are greater than 99 percent.

Limitations

- Other forms of galactosemia may be caused by a deficiency of either galactokinase or galactose-4-epimerase; these rare enzyme deficiencies will not be detected by this test.
- Large GALT gene deletions or deep intronic mutations are not detected by this assay.

Related Tests

- Galactosemia, (*GALT*) Enzyme Activity & 9 Mutations ([0051175](#))
- Galactose-1-Phosphate Uridyltransferase ([0080125](#))
- Galactosemia, (*GALT*) 9 Mutations ([0051176](#))
- Galactose-1-Phosphate in Red Blood Cells ([0081296](#))

References

1. Elsas LJ, et al. Galactosemia: a strategy to identify new biochemical phenotypes and molecular genotypes. *Am J Hum Genet* 1995;56:630–9.
2. Scriver CR, et al. 2001. *The metabolic and molecular bases of inherited disease, 8th ed.*, volume 1. New York: McGraw Hill. 1553–87.
3. Tyfield L, et al. Classical galactosemia and mutations at the galactose-1-phosphate uridyl transferase (*GALT*) gene. *Human Mutation* 1999;13:417–30.
4. Yang YP, et al. Molecular analysis in newborns from Texas affected with galactosemia. *Human Mutation* 2002;19:82–3.
5. Galactosemia mutation database. http://www.arup.utah.edu/database/galactosemia/GALT_welcome.php (accessed on June 12, 2009).

Test Information

0051346

Galactosemia (*GALT*) Sequencing

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.