

Galactosemia Panel

GALACTOSEMIA DNA AND GALACTOSE-1-PHOSPHATE URIDYLTRANSFERASE TO DIAGNOSE CLASSIC GALACTOSEMIA AND PREDICT CARRIER STATUS

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, and its derivatives, galactitol and galactonate.
- In classic galactosemia, the activity of *GALT* 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, 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; 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 55,000 Caucasians.
- One in 550 in Ireland's Traveller population.

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 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.

Indications for Ordering

- Follow-up of an abnormal newborn screening test for galactosemia.
- Neonatal testing of an affected individual's siblings.
- Carrier testing of parents of an affected individual.

Contraindications

- This test should not be used to monitor the dietary compliance of affected individuals.
- Rare forms of galactosemia may be caused by a deficiency of either galactokinase or galactose-4-epimerase. These enzyme deficiencies will not be detected with this test.
- If the familial mutations are not on the DNA panel, *GALT* full gene sequencing should be ordered.

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 detailing the proband's specific mutations.

Interpretation

- The diagnosis requires demonstrating galactose-1-phosphate uridylyltransferase deficiency in erythrocytes and the accumulation of metabolites (red cell galactose-1-phosphate, urine galactitol).
- Two severe *GALT* gene mutations are causative for disease. Nevertheless, not detecting two specific mutations in an affected individual does not eliminate the possibility of the disorder, as it may be caused by rare *GALT* mutations not detected by the *GALT* DNA panel.
- DNA studies are useful for the complete characterization of full/partial deficiencies and for carrier identification.
- Molecular genetic analysis of the nine common *GALT* mutations or variants has a sensitivity approaching 80 percent in Caucasians, but is reduced in other ethnicities. Other *GALT* mutations that cause classic galactosemia are individually rare and require full gene analysis for detection.

Methodology

- Measurement of uridine diphosphogalactose by calculating the oxidation of UDPG with nicotinamide dinucleotide (NAD) in the presence of UDPG-dehydrogenase to produce NADH. NADH is measured spectrophotometrically at 340 nm.
- Seven common classical *GALT* gene mutations (IVS2-2 A>G, S135L, T138M C>T, L195P T>C, K285N, Q188R, and Y209C A>G), as well as two variants (N314D and L218L) are detected by allele-specific PCR and fluorescent monitoring.

Limitations

- Other forms of galactosemia may be caused by a deficiency of either galactokinase or galactose-4-epimerase; these rare enzyme deficiencies would not be detected.
- Mutations, other than the 9 *GALT* panel mutations specified above, will not be detected.

Related Tests

- Galactosemia, *GALT* Gene Mutations (0051176)
- Galactosemia Full Gene Analysis (0051346)
- Galactose-1-Phosphate Uridyltransferase (0080125)

References

1. Elsas LJ, et al. Galactosemia: a strategy to identify new biochemical phenotypes and molecular genotypes. *Am J Hum Genet* 1995;56:630-639.
2. Scriver CR, et al. *The metabolic and molecular bases of inherited Disease*, 8th ed., volume 1. 2001. McGraw Hill. 1553-1587.
3. Pesce MA. Pitfalls in the diagnosis of transferase deficient galactosemia. *Lab Management* 1979;17:27-33.
4. Yang YP, et al. Molecular analysis in newborns from Texas affected with galactosemia. *Human Mutation* 2001;476:1-6.

Test Information

0051175 Galactosemia, Galactose-1-Phosphate Uridyltransferase & *GALT* Gene Mutations

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.