# *GALT* Gene Analysis in Galactosemia

**Clinical Features:**
Classical galactosemia is the most common disorder of galactose metabolism. Symptoms appear in the neonatal period after ingestion of galactose and include vomiting, diarrhea, failure to thrive, lethargy, hypotonia, jaundice, hepatomegaly, septicemia, cataracts, and bleeding tendencies. If a galactose-restricted diet is initiated rapidly, the neonatal symptoms resolve and the complications of liver failure, sepsis, neonatal death, and intellectual disability may be prevented. Despite adequate galactose restriction from an early age children with galactosemia are at risk for ataxia, verbal apraxia, delayed speech and developmental delay. Females with galactosemia are at risk for premature ovarian failure.

**Genetics:**
Galactosemia is caused by pathogenic variants in the *GALT* gene that encodes the galactose-1-phosphate uridyltransferase (GALT) enzyme, which is responsible for the conversion of galactose-1-phosphate and UDP-glucose into glucose-1-phosphate. GALT deficiency leads to the accumulation of galactose-1-phosphate in various organs. Patients with classic galactosemia typically have GALT enzyme activity levels that are less than 5% of control values. There are two variant forms of galactosemia. The Los Angeles (Duarte-1) variant is associated with normal or increased GALT enzyme activity and the Duarte (Duarte-2) variant is associated with approximately 50% of the normal GALT activity. The *GALT* gene is located on chromosome 9p13 and has 11 exons. The prevalence of classic galactosemia based on newborn screening programs is approximately 1 in 10,000 to 1 in 30,000.[1]

**Inheritance Pattern:**
Autosomal Recessive

**Test Methods:**
This comprehensive test includes bi-directional sequence analysis of all coding exons (1-11) and their intron-exon boundaries of the *GALT* gene. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. A variant/deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, quantitative PCR or oligo-array comparative genome hybridization (ExonArrayDx), as appropriate.

**Test Sensitivity:**
Variant analysis is expected to identify a sequence variant in greater than 95% of patients with galactosemia.[2] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

**Variant Spectrum:**

There are over 300 variants reported in *GALT* that are dispersed across the gene. Common variants exist in certain populations. Q188R is the most common variant in classic galactosemic patients of Caucasian ethnicity occurring on approximately 70% of mutant alleles and is associated with a severe clinical phenotype and undetectable GALT levels in homozygous individuals.[3,4] The S135L variant is common in African Americans with an allele frequency of approximately 60% and is associated with a milder clinical phenotype and residual GALT activity.[3,4] Both the Los Angeles and Duarte variants are associated with the N314D variant that is found in all populations with a frequency ranging from 1% to 13%.[6, 7] The Duarte variant is caused by a promoter variant, c.-116_119delGTCA, in cis with N314D, which results in an impaired regulatory domain and reduced GALT activity.[4] The Los Angeles variant is not associated with the deletion in the promoter region, but is caused when N314D is present in cis with a L218L variant.[4, 1] There is a common complex 5kb deletion which is common in the Ashkenazi Jewish population.[5] Genotype/phenotype correlations also exist for a number of other *GALT* variants.

**References:**

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