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 ofgalactose-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. Current data indicates that Duarte variant galactosemia is not associated with an increased risk for complications.[8, 9] 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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the GALT gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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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 a benign amino acid substitution (N314D) 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 allele, that includes L218L and N314D, results in a higher than normal GALT enzyme activity and has not been shown to cause other clinical findings.[1, 4] 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.

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