GALK1 Gene Analysis in Galactokinase Deficiency

Clinical Features:
Galactokinase deficiency is an inborn error of galactose metabolism. Untreated patients develop early onset, bilateral cataracts, which at this time appears to be the only consistent abnormality in galactokinase deficiency. Rarely, additional clinical symptoms have been reported including asymptomatic hypoglycemia, mental retardation, failure to thrive, seizures, deafness, hepatomegaly, and hypercholesterolemia; however, it is unclear whether these additional abnormalities are a result of galactokinase enzyme deficiency.[1,2] In one report of 18 affected patients, the authors report that additional symptoms seemed to be more prevalent in patients who were non-compliant with treatment.[1] Treatment of patients with a lactose-free, reduced-galactose diet results in prevention or, in some cases, regression of cataracts.[1] Estimates of the frequency of galactokinase deficiency range from 1 in 2,200,00 to 1 in 40,000.[1] The highest incidence has been found in the Romani population where the carrier frequency is estimated to be 1 in 47.[3]

Genetics:
Galactokinase deficiency is caused by pathogenic variants in the *GALK1* gene encoding the galactokinase enzyme that converts α-D-galactose to galactose-1-phosphate in the galactose metabolic pathway. In galactokinase deficient neonates who are milk fed, galactose levels in the body are highly elevated, and alternate pathways of galactose metabolism are activated leading to accumulation of galactitol. Cataracts develop as a result of the accumulation of galactitol in the lens of the eye and subsequent osmotic disruption of the lens fibers.[4] The *GALK1* gene is located on chromosome 17q24 and has 8 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *GALK1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *GALK1* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:

In four separate studies each including between 4 and 14 patients with galactokinase deficiency based on deficient galactokinase enzyme activity, variants were identified on 72 of 76 *GALK1* alleles (95%).[1, 5, 6, 7] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

The majority of *GALK1* variants are missense variants with small deletions/insertions also reported. A nucleotide substitution in the regulatory region, c.-22 T>C, has been found in Korean individuals with elevated galactokinase enzyme activity who were identified due to a positive newborn screen for galactosemia.[8] The majority of variants are private; however, the p.P28T variant has been identified as a founder mutation in the Romani population, the p.Q382X variant occurs frequently in the Costa Rican population, and the p.A198V variant occurs in Japanese and Korean populations.[1]

References:

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