GALC Gene Analysis in Krabbe Disease

Clinical Features:
Krabbe disease is a neurodegenerative lysosomal storage disorder with a classical infantile-onset and a late-onset form. About 85-90% of individuals with Krabbe disease have the infantile-onset form, and 10-15% have the late-onset form.[1] Individuals with the infantile-onset form present with spasticity, hypertonia, developmental delay, and extreme irritability before the age of six months with a rapid progression and severe mental and motor regression. Eventually they progress into a decerebrate state with no voluntary movement and death, usually by 2 years of age. Late-onset patients can be asymptomatic until onset at 1 year to the fifth decade. Early signs may include vision loss, a decline in intellect, and loss of manual dexterity and weakness. The onset and course of the disease is variable, even between members of the same family.[1]

Krabbe disease is caused by pathogenic variants in the GALC gene that encodes galactocerebrosidase (GALC); a lysosomal enzyme responsible for the breakdown of certain galactolipids including β-galactosylcerebroside and psychosine. GALC deficiency causes a toxic accumulation of psychosine, which causes death of myelin-forming cells causing demyelination in both the central and peripheral nervous systems.[2] The GALC gene is located on chromosome 14q31 and has 17 exons. The incidence of Krabbe disease within the United States and Europe is approximately one in 100,000.[1]

Inheritance Pattern/Genetics:
Autosomal recessive

Test Methods:
Variant analysis of the *GALC* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons (1-17) and corresponding intron/exon boundaries. 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:
In four studies of 45 patients with Krabbe disease from diverse ethnic backgrounds, variants were identified on over 90% (83/90) of alleles.[3, 4, 5, 6]

Over 70 sequence changes, including polymorphisms, have been identified in the GALC gene including missense, nonsense, splice site and small deletions/insertions.[1] A 30-kb deletion, accounts for approximately 45% of mutant alleles in patients with the infantile form of Krabbe disease of European ancestry and 35% of alleles in individuals of Mexican ancestry.[1]

This 30-kb deletion results in the infantile form of disease when homozygous or heterozygous with another severe GALC variant.[1] A c.857 G>A variant is often found in patients with late-onset Krabbe disease and one copy of this variant, even when present with the 30-kb deletion on the second allele results in late-onset disease.[1]

References:

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