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. 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.

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. 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.

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.
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: