**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. The incidence of Krabbe disease within the United States and Europe is approximately one in 100,000.

**Genetics:**
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; the latter is used as an early marker to help establish the diagnosis of infantile-onset Krabbe disease. The GALC gene is located on chromosome 14q31 and has 17 exons.

**Inheritance Pattern:**
Autosomal recessive

**Test Methods:**
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the GALC 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.

**Variant Spectrum:**
Variants reported in the GALC gene include missense, nonsense, splice site, small deletions/insertions and large deletions. A 30-kb deletion, accounts for approximately 45% of pathogenic 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.\(^1\)

The R184C (c.550 C>T), D248N (c.742 G>A), and I562T (c.1685 T>C) variants have been shown to modify GALC enzyme activity, but are not sufficient to cause disease and are often observed in association with a positive newborn screen for Krabbe disease.\(^2,3,4\) The presence of one or more of these variant may further reduce enzyme function when on the same allele (in cis) with certain pathogenic variants, and these alleles have been reported in association with late-onset Krabbe disease in some individuals.\(^2,3,4\)

**References:**