

Krabbe Disease Testing via *GALC* Exons 11-17 (502T/Del) Deletion (Test #632)

Brief Description of Clinical Features: Krabbe disease or Globoid Cell Leukodystrophy (OMIM 245200) results from deficiency of Galactocerebrosidase, a lysosomal enzyme involved in the metabolism of galactosylceramide. Galactosylceramide is a component of the myelin sheath and, with deficient Galactocerebrosidase activity, this complex lipid is known to accumulate in globoid cells. Accompanying the appearance of globoid cells is loss of myelin and associated progressive neurological deterioration leading to death (Wenger et al. *in Scriver et al. Metabolic and Molecular Basis of Human Disease*. 3669-3694, 2001). Most cases present in early infancy with non specific signs such as irritability and delays in reaching developmental milestones. The clinical course is rapid, spanning 1 to 3 years, and includes hypersensitivity to external stimuli, hypertonicity, motor and mental deterioration, blindness and deafness. Less commonly the disease presents later in life with neurological signs including weakness, vision loss and mental changes (Sato et al. *Neurol* 49:1392-1399, 1997; Kolodny et al. *Dev Neurosci* 13:232-239, 1991). Disease progression in later onset cases is typically protracted although an initial rapid deterioration is common (Loonen et al. *Neuropediatrics* 16:137-142, 1985).

Genetics: Krabbe disease is inherited in an autosomal recessive manner with intrafamilial variability of the clinical symptoms. Over 50 *GALC* mutations, mostly missense, have been reported. The most common mutation in patients of European decent, however, is a large deletion encompassing exons 11 through 17 of *GALC* (Luzi et al. *Hum Mol Genet* 4:2335-2338, 1995; Rafi et al. *Hum Mol Genet* 4:1285-1289, 1995). This deletion (referred to as 502T/del) accounts for approximately 50% of all disease alleles in northern European patients (Kleijer et al. *J Inherit Metab Dis* 20:587-594, 1997), and is similarly common in patients from the USA including those with Mexican ancestry (Wenger, Krabbe Disease, *GeneReviews*, 2007). Late onset cases frequently have at least one copy of a c.809G>A (p.Gly270Asp) mutation (Kolodny et al. *Am J Hum Genet* 57:A217, 1995).

Description of This Particular Test: Galactocerebrosidase is coded by exons 1-17 of the *GALC* gene on chromosome 14q31. Testing involves determination of the 502T/del status as described by Luzi et al. (1995). A separate test is available to evaluate the entire *GALC* coding region by direct sequence analysis (see Test #631).

Indication for Testing: *In vitro* Galactocerebrosidase enzyme activity in patient leukocytes that is <5% of normal values; infantile onset progressive neurological deterioration; cerebral atrophy. Note that enzyme measurement is not suitable to determine carrier status.

Sensitivity of test: Diminished Galactocerebrosidase activity due to *GALC* mutations is the only cause of Krabbe disease and late onset Globoid Cell Leukodystrophy. Analytical sensitivity for deletion testing and sequence analysis should be high in cases with demonstrated enzyme deficiency. The exon 11-17 deletion accounts for approximately half of all disease alleles.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: *GALC* Exons 11-17 Deletion Testing \$190

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x1	83898	\$ 30	Separation x1	83894	\$ 30
Interpretation/Report	83912	\$ 60			

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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