

NE THAMES REGIONAL MOLECULAR GENETICS SERVICE

Krabbe disease (Globoid Cell Leukodystrophy)

Contact details

Molecular Genetics
GOSH NHS Trust
Level 6
York House
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+44 (0) 20 7762 6888
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+44 (0) 20 7813 8196

Samples required

5ml venous blood in plastic EDTA bottles (>1ml from neonates)

Prenatals must be arranged in advance, through a Clinical Genetics department if possible. Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis

A completed DNA request card should accompany all samples.

Introduction

Krabbe disease (MIM #245200) is an autosomal recessive inborn error of metabolism caused by deficiency of the enzyme galactosylceramidase (galactocerebrosidase). Galactosylceramidase (EC 3.2.1.46) is a lysosomal enzyme involved in the catabolism of galactosylceramide, a major lipid in myelin, kidney, and epithelial cells of the small intestine and colon. Enzyme deficiency results in the build-up of undigested fats affecting growth of the nerve's protective myelin sheath and causes severe degeneration of mental and motor skills. The disease may be diagnosed by its characteristic grouping of certain cells (multinucleated globoid cells), nerve demyelination and degeneration, and destruction of brain cells. Special stains for myelin (e.g; luxol fast blue) may be used to aid diagnosis. Definitive testing is by direct enzyme analysis.

Infants with Krabbe disease are normal at birth. Symptoms begin between the ages of 3 and 6 months with irritability, inexplicable crying, fevers, limb stiffness, seizures, feeding difficulties, vomiting, and slowing of mental and motor development. In infants, the disease is generally fatal before age 2. There are also juvenile- and adult-onset cases of Krabbe disease, which have similar symptoms but slower progression and significantly longer lifespan. Although there is no cure for Krabbe disease, bone marrow transplantation has been shown to benefit mild cases early in the course of the disease. The incidence of Krabbe disease is around 1 in 100,000–200,000 births.

The *GALC* gene is situated at 14q31 and consists of 17 exons. A recurrent 30kb deletion has been described which extends from intron 10 to intron 17 of the *GALC* gene and in the homozygous state is associated with infantile onset disease. The allele frequency of this deletion in Krabbe patients is reported to be approximately 50% in Dutch patients and 35% in non-Dutch European patients (Kleijer, WJ *et al.* (1997) *J Inher Metab Dis* 20:587-594).

Referrals

- Clinically affected patients should have their diagnosis confirmed by enzyme analysis; such patients may then be referred for mutation analysis. If the necessary patient samples are unavailable genetic testing can be undertaken in the parents of the affected child. Information regarding ethnic origin is useful.
- Carrier testing can be offered to adult relatives of affected patients once a disease causing mutation has been identified.

Prenatal testing

Prenatal testing is available for families in whom the 30kb deletion has been identified or in whom appropriate family studies have been undertaken - please contact the laboratory to discuss.

Service offered

Testing for the common 30kb deletion by three-primer PCR analysis. Other disease causing mutations are heterogeneous and testing is not currently offered as part of this diagnostic service.

Target reporting time

2 weeks for routine deletion mutation test in the index case and family member carrier testing. For urgent samples please contact the laboratory.

Contact details for Biochemistry/ Enzyme Unit:

Enzyme Unit, Chemical Pathology, Great Ormond Street Hospital, London, WC1N 3JH
Tel: +44 (0) 20 7405 9200 (x2509)

Patient details

To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, address and ethnic origin), details of any relevant family history and full contact details for the referring clinician