

Fabry Disease Service

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Sample Required

See **Sample requirements page** at
www.nbt.nhs.uk/genetics for full
details

Samples should be accompanied by a
FULLY completed request form
(available as download at
www.nbt.nhs.uk/genetics
or from the laboratory).

Please include details of the test
required, family history, address and
POSTCODE, NHS number, referring
clinician and centre.

Consent and Storage:

All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients
undergoing DNA testing, unless consent
for this is specifically denied.

Stored material from all referrals may be
retained for quality assurance purposes
and may be used anonymously for the
development of new tests for the
disorder in question.

Clinical Background and Genetics

- Fabry Disease (OMIM# 301500) is an X-linked lysosomal storage disease caused by deficient or absent activity of the lysosomal enzyme α -galactosidase A (α -Gal A). The α -Gal A enzyme is a lysosomal exoglycosylase.
- Hemizygous males and most heterozygous females are affected; although the onset of clinical symptoms may be later in females. Males with classical Fabry Disease have little or no residual enzyme activity, whereas females have variable levels of residual activity, which may be in the normal range. **It is recommended that females with symptoms of Fabry Disease should be referred directly for genetic analysis rather than undergoing enzyme analysis.**
- The symptoms of classical Fabry Disease, which can begin in childhood or early adolescence, include episodic painful crises (acroparaesthesia), hypohidrosis, eye changes, heat and cold intolerance, gastrointestinal symptoms and angiokeratoma. Cerebrovascular, cardiac and renal manifestations may develop later in life. Later onset atypical variants (cardiac or renal) have been described. These patients reach adulthood with no classical Fabry Disease symptoms but present with a specific phenotype later in life and have reduced, but not abolished α -Gal A levels.
- The incidence of classical Fabry Disease is reported to be 1:50,000 males (Fabry Disease is a pan-ethnic disorder), however newborn screening studies suggest that the incidence particularly for variant Fabry Disease, is much higher.
- The gene involved in Fabry Disease is *GLA*, has 7 exons and is located at X.q22.1 (OMIM#300644). The coding region spans 1.3kb and encodes a 429 amino acid protein of which the first 31 residues are a signal peptide.
- Over 600 different disease-causing *GLA* pathogenic variants have been reported, distributed throughout all exons. There are a few pathogenic variants which have been seen in multiple families e.g. c.644A>G, p.(Asn215Ser) commonly associated with the cardiac variant of Fabry Disease.

Service Offered

- Full *GLA* gene screening by direct sequence analysis (sensitivity 95%).
- Testing for familial pathogenic variants in family members as appropriate.

Referrals

-Diagnostic Testing: Clinically affected **males** should have their diagnosis confirmed by biochemical analysis prior to genetic testing. This analysis can be arranged through Vicki Warburton, Department of Biochemistry, Bristol Royal Infirmary (Tel: 0117 342 2590) or through your local Clinical Biochemistry Service (see www.metbio.net). **Females** with a suspected diagnosis of Fabry Disease can proceed directly to genetic testing, due to the unreliability of biochemical analysis. This protocol should also apply to patients with possible variant Fabry Disease.

-Carrier Testing: Once a pathogenic variant has been found in a patient, the laboratory can offer carrier testing for the mother and other at-risk relatives.

-Prenatal Testing: May be offered for heterozygous females on a case by case basis. Referrals must come through Clinical Genetics or a Metabolic Consultant.

Clinical Advice

For clinical advice contact one of the national paediatric or adult centres for inherited metabolic disease. In Bristol contact Dr Germaine Pierre, Paediatric Metabolic Consultant, Bristol Royal Hospital for Children, Bristol, BS2 8BJ (Tel: 0117 3421694)

Target reporting Times

Diagnostic screen: 42 days

Known familial variant: 42 days

Urgent: 3 days (please contact the lab prior to sending)

Please contact the laboratory for up to date prices.

Quality

BGL participates in the following external quality assurance schemes:
GenQA Fabry disease scheme, EMQN DNA Sequencing scheme and GenQA pathogenicity of sequence variants scheme.