



Service Description for Friedreich Ataxia (FRDA)

1 Background

Friedreich Ataxia (FRDA, OMIM 229300) is the one of the most common hereditary ataxias with an estimated prevalence of 1 in 50,000 in Caucasian populations. The carrier frequency for FRDA in the European population is estimated to be 1 in 90.

FRDA is characterised by progressive ataxia, areflexia of the legs, pyramidal weakness and impaired sense of vibration. Cardiomyopathy and diabetes are also seen with variable penetrance. FRDA is an autosomal recessive disorder and the majority of patients (98%) have a homozygous expansion mutation of a (GAA)_n repeat within intron 1 of the Frataxin gene, FXN). The normal range is 9-33 repeats and the size range associated with disease is 66 to 1,700 repeats, but the majority of pathogenic alleles contain 600 to 1,200 repeats. A number of point mutations have been reported in patients who are heterozygous for the expansion. To date, no FRDA patients without at least one expansion have been reported.

2 Standard service

A Essential referral information:

In addition to supplying standard patient identification and referral information (see Section I below), the following should be clearly indicated:

- Patient's symptoms, if any, so that we can determine if a diagnostic or carrier test is required
- Any family history, including names, dates of birth and genetics test results if available.

It is the responsibility of the referring clinician to ensure consent has been obtained for testing and storage

B Samples required:

Generally 5-10ml of EDTA blood (FBC bottle) is required. Sample identification policy is detailed at (see Section I below).

Blood specimens must be appropriately packaged (see Section I), and preferably sent by courier to arrive as soon as possible. Do not freeze prior or during postage.

Please note that extracted DNA is stored from patient's samples at the National Centre for Medical Genetics, and kept indefinitely unless a written request for its disposal is received from the patient or their parent/guardian.

C Restrictions on testing

Carrier or presymptomatic testing is not offered for minors (children under the age of 16) except in cases of early onset FRDA, but only where an index case has previously been identified. A referral to Clinical Genetics is recommended prior to presymptomatic testing. This policy is consistent with international guidelines for genetic testing of children.

Important note: The complete history of this document including its owner, author and revision date can be found on Q-Pulse

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National Centre for Medical Genetics
Dublin, Ireland
Division of Molecular Genetics

D Tests offered:

Standard analysis is to test for GAA expansion mutations in the FXN gene. Three types of test may be performed:

- Diagnostic tests for patients with clinical symptoms suggestive of FRDA
- Carrier tests for asymptomatic individuals who have a family history of FRDA or whose partner may be a carrier
- Predictive tests / presymptomatic diagnosis may be possible in families, especially in cases of early onset FRDA, but only where an index case has previously been identified. A referral to Clinical Genetics is recommended prior to presymptomatic testing

Analysis methodology uses Long PCR based on Filla *et al.* (1996) *Am. J. Hum. Genet.* **59(3)**: 554-560 and Triplet Primed PCR based on Warner *et al.* (1996) *J. Med. Genet.* **33**: 1022-1026

E Diagnostic Sensitivity of tests:

The PCR-based tests used allow for the detection and relative sizing of the GAA repeat in both the normal and pathogenic size ranges. Approximately 98% of patients with Friedreich Ataxia have no normal sized alleles and have 2 alleles with a GAA expansion in the pathogenic size range (66 – 1,700 repeats). Approximately 2% of individuals with FRDA have an expanded GAA repeat mutation in one allele and an intragenic inactivating *FXN* mutation (e.g., point mutation or deletion outside of the GAA repeat region) in the other allele.

F Interpretation:

Results are given in the form of a written interpretative report to the referring clinician.

G Target reporting times:

As reporting times are constantly evolving, please refer to www.genetics.ie/molecular, or contact the molecular genetics laboratory, to receive up-to-date information on anticipated reporting times for your referral.

The following are current target reporting times for each category of test offered (information correct as of 11/12/2009): Routine = 3 months, Urgent = 1 month.

- Please contact the laboratory if you have not received a report within a week of your patient being due back in clinic.
- Please note it is our policy not to issue verbal results.
- Request for copies of reports on the day that your patient is in clinic cannot normally be accommodated. We usually require 24 hours notice in which to fax a copy of a report.

H Further tests

Where appropriate, point mutation analysis (sequencing) may be performed in patients who have clinical symptoms but who only have one GAA expansion mutation. This further screening must be specifically requested by the clinician following receipt of the initial report on the GAA expansion analysis.

Please contact the laboratory if it is appropriate to perform other tests, for example into spinocerebellar ataxia (SCA) genes or mitochondrial disorders.

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I Web Links to Related Documents

Standard referral information/NCMG request form
Sample/Patient identification policy
Packaging of specimens for transport

http://www.genetics.ie/pir/2006_NCMG_Referral_Form.pdf
<http://www.genetics.ie/pir/SampleIdentificationPolicyWeb.pdf>
http://www.genetics.ie/pir/sending_samples.pdf

Please note that hard copies of the above documents may be requested from:

Division of Molecular Genetics, National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin 12. Tel: 01 4096733; Fax: 01 4096971

The NCMG Molecular Genetics laboratory participates in external QA schemes run by the UK NEQAS for Molecular Genetics, the European Molecular Genetics Quality Network (EMQN), and the Cystic Fibrosis European Network. Results of assessments are available for inspection upon request.

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