



## Service Description for Fragile X Syndrome

### 1 Background

**Fragile X Syndrome (FRAX)** is an X-linked syndrome of mild to severe mental Retardation [OMIM #300624]. Clinical features include macroorchidism in post-pubertal males, long face, coarse features, large everted ears, behavioural disturbances. Clinical presentation is very variable and can be subtle in younger prepubescent children, making diagnosis difficult.

The Fragile X Mental Retardation (FMR1) gene, is located on the X chromosome at Xq27.3. Approximately 99% of Fragile X cases are caused by an increase in the number of CGG triplet repeats near exon 1 of the gene.

The number of CGG repeats are classified as shown in the table below.

Number of CGG repeats: [www.emqn.org/emqn/BestPractice.html](http://www.emqn.org/emqn/BestPractice.html)

Status	Number of CGG repeats
Normal/Unaffected	<50 approx.
Intermediate	50 - 58 approx.
Premutation	58 - 200 approx.
Affected/Full mutation	More than 200 (and methylated)

The genetic test detects increases in the number of CGG triplet repeats above the normal range.

The prevalence of a Fragile X full mutation is 1 in 4000 - 9000 [males] and 7000 - 15000 [females]. The prevalence of a Fragile X premutation is 1 in 810 - 1100 [males] and 1 in 246 - 468 [females].

### Two distinct adult onset disorders are described for certain individuals with a Fragile X premutation:

**Fragile X-associated tremor/ataxia syndrome (FXTAS)** is progressive neurodegenerative disorder characterized by late-onset progressive cerebellar ataxia and intention tremor in both middle aged & elderly males and females. Other neurologic findings include short-term memory loss, executive function deficits, cognitive decline, dementia, parkinsonism, peripheral neuropathy, lower-limb proximal muscle weakness, and autonomic dysfunction. The prevalence of FXTAS is estimated at 40% overall for males (> 50 yrs) with premutations and the penetrance is aged related. The prevalence of FXTAS in females is less than that for males.

**Premature ovarian failure (POF)** or **primary ovarian insufficiency (POI)** is defined as cessation of menses before the age of 40 in a woman with an FMR1 premutation. POF/ POI occurs with a penetrance of approximately 20% in female with a FMR1 premutation.

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Dublin, Ireland  
**Division of Molecular Genetics**

## 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:

1. Patient's symptoms
2. Any family history, including names, dates of birth, relationship, and genetic test results if available.

**Note:** 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.

**It is recommended that a sample (Lithium Heparin tube) is also submitted to the Cytogenetics Laboratory for routine karyotyping.**

### **C Restrictions on testing**

Testing would not usually be considered for asymptomatic children under 16 years of age.

As from July 2008 due to current staffing restrictions Fragile X testing is currently only available for confirmed Fragile X families, for all individuals with query FXTAS and query POF/ POI & all query affected children under 12 months\* (with or without a family history of Fragile X).

\*Children under 4 to 6 months are not routinely tested for Fragile X; please contact the NCMG for further information.

### **D Tests offered**

Prenatal testing must be arranged in advance with the laboratory, through a Clinical Genetics department if possible.

#### **Diagnostic test:**

To determine whether a patient is affected with:

Fragile X Syndrome- full mutation)

Fragile X-associated tremor/ataxia syndrome (FXTAS) – premutation

Premature ovarian failure (POF) or primary ovarian insufficiency (POI) - premutation

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**Carrier test:**

To determine whether a person without symptoms in a known Fragile X syndrome family carries a premutation (i.e. approx 58-200 CGG repeats). Such tests are only performed in conjunction with a counselling programme run by the National Centre for Medical Genetics. Patients should be referred to the Director, Prof. A. Green.

In a female carrying a premutation the number of CGG repeats can increase to a full mutation when passed on to offspring.

In a male carrying a premutation the number of CGG repeats does not increase significantly upon transmission, so a premutation is passed on to offspring.

**Prenatal diagnosis:**

To determine whether a foetus has inherited the full mutation; once a premutation or full mutation has been identified in the mother. Prenatal diagnosis can only be performed in conjunction with a counselling programme run by the National Centre for Medical Genetics. Patients should be referred to the Director, Prof. A. Green.

***E Diagnostic Sensitivity of tests***

The sensitivity of the diagnostic test is approximately 99%.

In very rare cases, Fragile X Syndrome may result from:  
Point mutations or deletions in the FMR1 (FRAXA) gene.  
Mosaicism (the presence of both normal and expanded alleles).  
These rare events cannot be excluded by the test.

Rare families have been described in which CGG expansions in the nearby FMR2 (FRAXE) locus appear to be responsible for developmental delay/mental retardation (OMIM #309548). Expansions at the FMR2 locus are not detected by the test.

***F Interpretation:***

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

The results of the genetic test indicate whether a person has the normal number of CGG repeats, is carrying a premutation, or has a full mutation.

A diagnostic test for a male showing a full mutation confirms a diagnosis of Fragile X. Approximately 30-50% of females with a full mutation on one of their X chromosomes will suffer from mental retardation (less severe than seen in affected males).

***G Target reporting times:***

As reporting times are constantly evolving, please refer to [www.genetics.ie/molecular](http://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 13/01/2010):

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Query affected males: 2-4 months  
Query affected females: 4-6 months  
Prenatal diagnosis (CVS): 4 weeks  
Prenatal diagnosis (Amniocentesis): 6 weeks  
Query carrier status females & males (confirmed familial mutation): 4-6 months  
FXTAS & POF/ POI: 2-4 months

- 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***

Not applicable.

#### ***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/2006_NCMG_Referral_Form.pdf)  
<http://www.genetics.ie/pir/SampleIdentificationPolicyWeb.pdf>  
[http://www.genetics.ie/pir/sending\\_samples.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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