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Service information: Fragile X Syndrome

Gene/Locus: *FMR1* (Xq27.3) **OMIM:** #300624 (*309550 – *FMR1* gene)

Referrals: Any relevant speciality, e.g. Paediatrics, Neurology, Gynaecology, Clinical Genetics
Testing: Diagnostic testing offered in patients suspected to have Fragile X Syndrome, also in patients with Fragile X primary ovarian insufficiency (FXPOI) or Fragile X-associated tremor/ataxia syndrome (FXTAS). Carrier testing in patients with a family history of Fragile X Syndrome.

Target Reporting Times:

• Diagnostic	28 calendar days	
• Carrier Testing	28 calendar days	
• Atypical cases		contact laboratory to discuss testing
• Urgent Testing*	3 calendar days	Prenatal diagnosis/carrier testing in pregnant women (may be longer if additional testing required)

***Please contact the laboratory for urgent testing**

Test Details:

- **PCR across the expandable *FMR1* CGG repeat region** to detect CGG repeat expansions.
- Second-stage testing involves the **Asuragen AmplideX FMR1 kit** to detect large *FMR1* gene expansions. This extra testing is required in females with two normal *FMR1* alleles of the same size and in patients with *FMR1* gene expansions. Some rare atypical cases may also need additional testing, such as Southern blotting, to determine expansion size, methylation status or the extent of any mosaicism.
- Expansion size ranges: *Normal: <46 repeats, Intermediate: 46-55 repeats- possible expansion in future generations*
  Intermediate/Premutation: 56-58, one report of a patient with 56 CGGs expanding to a full mutation in offspring
  Premutation: 59-approx. 200 repeats, high chance of expansion in offspring of females
  Full mutation: Greater than approximately 200 repeats, methylated- clinical features in males and approx. 50% of females

Service Details:

It is estimated that a full expansion mutation in exon 1 of the *FMR1* gene is responsible for over 99% of Fragile X syndrome cases. Rare cases of low level mosaicism for the expansion mutation, point mutations or deletions in the *FMR1* gene will not be detected by the above test. We estimate that the above testing procedure would fail to detect <1% of individuals with this mutation.

Sample Requirements:

- **EDTA** blood sample (1-4 ml), labelled with patient's **full name**, **date of birth** and **NHS number**, or genomic DNA (≥20 µl at ≥50 ng/µl).
- Samples should be accompanied by a **fully** completed referral card which should include the patient's full name, date of birth and NHS number.
- Please also include details of the test, relevant clinical details and full details of the referring clinician and centre
- A lithium heparin sample should also be sent to the Cytogenetics department
- Maternal samples are required in cases of prenatal diagnosis to exclude maternal cell contamination.

Consent:

Please note that in submitting a sample, it is the responsibility of the clinician to ensure that consent has been taken i) for testing, ii) for storage, and iii) for the use of this sample and the information generated to be shared with the patient's relatives and their health professionals. Following testing, a sample of the patient's DNA may also be used anonymously to validate new tests and for internal quality control purposes.

Date modified – March 2016. If printed, this document is only valid on the day of printing