Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

North Bristol NHS Trust

Fragile X syndrome (*FMR1*)

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Sample Required:
Adult: 5mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)

Prenatal testing MUST be arranged with the laboratory well in advance of taking sample

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, any 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

- Fragile X syndrome is the most commonly inherited cause of mental retardation, affecting approximately 1/4000 males and 1/6000 females.
- the gene involved (*FMR1*) is located on the long arm of the X-chromosome (Xq27.3) and encodes an RNA-binding protein.
- Fragile X is caused, in the vast majority of cases, by expansion of the (CGG)n repeat sequence in the 5'UTR (untranslated region) of the *FMR1* gene above 200 repeats with methylation and subsequent silencing of the gene.
- Fragile X is caused by the absence of functional *FMR1* gene product. Deletions and point mutations in the *FMR1* coding sequence have also been reported to cause the syndrome (<1% of cases).
- CGG alleles are categorized according to the CGG repeat size of the repeat region (as per ACGS Best Practice Guidelines, 2012):
  - **normal alleles** between 5 and 45 CGG repeats.
  - **intermediate alleles** (46-58 CGG repeats) are not associated with clinical features of Fragile X, but may display size instability in future generations.
  - **premutation alleles** (59-200 CGG repeats, usually unmethylated) are not associated with mental retardation, but convey an increased risk of FXTAS (Fragile X associated tremor and ataxia syndrome) and POF/POI (premature ovarian failure/insufficiency). The CGG repeat is unstable at meiosis (upon maternal transmission) therefore women who are premutation carriers are at risk of having children affected with Fragile X.
  - **full mutation alleles** (>200 CGG repeats, usually methylated) are associated with Fragile X syndrome.

Service offered

- **FRAXA PCR assay:** amplifies the CGG repeat and is used as a pre-screen for the majority of Fragile X referrals.
- **Asuragen AmplideX PCR assay:** used for males with an undetectable allele on FRAXA PCR, females with a single sized allele on the FRAXA PCR, cases with a premutation for accurate sizing, and referrals with a known confirmed family history of Fragile X. Also used for prenatal diagnosis

Referrals

- **diagnostic testing:** for (i) paediatric referrals eg developmental delay, learning/behavioural difficulties; (ii) infertility referrals: females with POF/POI; (iii) neurology referrals: patients with symptoms of tremor and ataxia (to confirm/ exclude FXTAS)
- **carrier testing:** patients with a family history of Fragile X which has been confirmed by molecular methods
- **prenatal diagnosis:** for known female carriers of a premutation or full mutation (contact the laboratory well ahead of testing to discuss sample requirements etc)

Target reporting time

- Diagnostic/carrier testing: 42 calendar days
- Prenatal diagnosis: 3 calendar days

Quality

- BGL participates in the GENQA scheme for this service

Contact the laboratory for up-to-date prices

Information document No 25 Version 8
Active date of this version: 06/07/19
DETAILS CORRECT AT DATE OF PRINTING ONLY
Approved by: Lisa Burvill-Holmes