NHS North Bristol NHS Trust

Fragile X syndrome (*FMR1*)

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

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

See sample requirements page at: https://www.nbt.nhs.uk/severn-pathology/pathology-services/bristol-genetics-laboratory-bgl/bgl-sample-requirements for full details. Samples should be accompanied by a **FULLY** completed request form, available to download at: https://www.nbt.nhs.uk/sites/default/files/BGL%20request%20form.pdf or by request from the laboratory. Please include details of the test required, any family history, address (including postcode), NHS number and name of referring clinician and referral 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 (OMIM 300624) 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 (at Xq27.3) and encodes an RNA-binding protein. Fragile X syndrome 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 to more than 200 repeats with methylation, and subsequent silencing, of the gene. Clinical features of Fragile X syndrome are caused by the absence of any functional *FMR1* gene product. Deletions and point mutations in the *FMR1* coding sequence can also 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 contain between 5 and 45 CGG repeats

Intermediate alleles contain 46 to 58 CGG repeats; these are not associated with any of the clinical features of Fragile X syndrome but may display size instability in future generations

Premutation alleles contain 59 to 200 CGG repeats and are usually unmethylated. These are not associated with mental retardation but convey an increased risk of Fragile X associated tremor and ataxia syndrome (FXTAS; OMIM 300623) and premature ovarian failure/insufficiency (POF/POI; OMIM 311360) in female carriers. The CGG repeat is unstable at meiosis (upon maternal transmission) and women who are premutation carriers are at risk of having children affected with Fragile X syndrome.

Full mutation alleles contain >200 CGG repeats and are usually methylated. Full mutation alleles are associated with Fragile X syndrome.

Service offered
The **FRAXA PCR assay** amplifies the CGG repeat and is used as a pre-screen for the majority of Fragile X referrals. Normal male results and two allele female results are reported.

The **Asuragen AmplideX PCR assay** is used for any sample that doesn't give a normal result on the FRAXA PCR assay and can include: males with an undetectable allele, females with a single allele, referrals with a confirmed family history of Fragile X detectable by molecular methods, possible mosaic results and prenatal samples.

Referrals
Diagnostic testing
- paediatric referrals e.g. developmental delay as a second line test after microarray CGH
- infertility referrals: females with POF/POI
- neurology referrals: patients with symptoms of tremor and ataxia (to confirm/ exclude FXTAS; OMIM 300623)

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: nbn-tr.geneticsenquiries@nhs.net