FRAGILE X SYNDROME - OMIM 300624
Related disorders: Fragile X- Associated Tremor/Ataxia Syndrome (FXTAS) – OMIM 300623 and FMR1- Associated Primary Ovarian Insufficiency (FXPOI) – OMIM 311360

INTRODUCTION
Fragile X syndrome is probably the most common single gene cause of learning disability in humans, with an estimated prevalence in males of between 1 in 4000 to 1 in 6000. It is an X-linked disorder caused by loss of function mutations in the FMR1 gene which is localised to Xq27.3 and encodes the RNA-binding protein FMRP. The most common mutation (>99% of cases) is a large expansion of an unstable CGG repeat tract in the first untranslated exon of FMR1, although other rare mutations including deletions and point mutations within FMR1 have also been reported.

Full mutations (>200 CGG repeats) result in hypermethylation of the DNA in and around the CGG tract, suppressed gene transcription and no FMRP production. In males, this causes moderate to severe intellectual and social impairment together with syndromic features, including large ears and head, long face and macro-orchidism. A full mutation in females leads to a variable phenotype, ranging from apparently intellectually normal (~50% of cases) to moderate mental and social impairment in the remainder, probably due to differences in the proportions of active and inactive normal and mutant X chromosomes present in different tissues.

Premutations (59-200 CGG repeats – and unmethylated) do not cause Fragile X syndrome but cause different disease phenotypes at lower penetrance: POI in females (~20% of carriers) and FXTAS predominantly in males. However, premutations are likely to be unstable and may expand to a full mutation in one generation.

TESTING
- Diagnostic: Clinically affected patients
- Carrier: Relatives of clinically affected patients in whom a FMR1 CGG expansion has been identified
- Prenatal: At risk of having an affected child (known female carrier of a FMR1 CGG expansion)

REFERRALS
- From Clinical Genetics, Paediatrics and Psychiatry/Psychology for Fragile X; Clinical Genetics and Obstetrics for POI; Clinical Genetics and Neurology for FXTAS; Clinical Genetics for carrier tests.
- Prenatal referrals must be discussed with the laboratory and, where possible, arranged in advance.

STRATEGY AND TECHNICAL INFORMATION
- Fluorescent PCR across the FMR1 (CGG)n repeat for CGG repeat size determination
  - Detects expansions up to ~120 repeats in length
- Asuragen PCR
  - Detects normal, premutation and full mutations alleles. Does not interrogate methylation status.
- Southern blot analysis of the FMR1 (CGG)n repeat using Eco Rl/Eagl restriction enzymes and probe StB12.3
  - Confirms the presence of (CGG)n expansions and enables size estimation of large expansions >200 repeats
  - Allows determination of methylation status
  - Will not resolve small expansions <60 (CGG)n repeats in size
- Linked marker analysis
  - Provides a second independent test for prenatal diagnosis, also enables exclusion of maternal contamination
- If Karyotype analysis is also required then a separate blood sample, in lithium heparin, must be sent to the Cytogenetics Laboratory at the address below.

TARGET REPORTING TIMES
Diagnostic test: 10 days (PCR)
Carrier test: 40 days (PCR, Asuragen and Southern blot)
Prenatal: 40 days (PCR, Asuragen and Southern blot)

N.B Details are correct for the date of printing only – last updated 22/04/2015