SickKids® | Genome Diagnostics

# FRAXE MOLECULAR ANALYSIS

FRAXE is a form of non-syndromic X-linked intellectual disability. The FRAXE phenotype is quite variable, and tends to include slow learning (mild intellectual disability), hyperactivity, attention problems and language delay. The gene associated with FRAXE is called *FMR2.* The normal gene contains a three base pair sequence, which is repeated on each X chromosome (called a CCG repeat). The principal mutation causing FRAXE is an expansion of the CCG repeat sequence within the *FMR-2* gene.

## GENETICS

FRAXE results from the expansion of CCG repeats leading to abnormal methylation and interfering with *FMR2* expression. In typical individuals the number of CCG repeats within the *FMR2* gene ranges in size from 6-30 repeats, whereas patients affected with FRAXE show expansion ranges of 200 repeats or greater (full mutation). Individuals with a premutation (~61-199 repeats) usually do not show symptoms but the premutation may expand to a full mutation in later generations.

## WHO SHOULD BE TESTED?

- Individuals of either sex with a family history of FRAXE (pedigree required).
- Individuals of either sex with intellectual disability, developmental delay, and/or learning or social difficulties, especially if they have any behavioural characteristics of FRAXE, PLUS a family history suggestive of X-linked intellectual disability (pedigree required).

## TEST METHODS

- PCR amplification to detect alleles in the normal, intermediate, and premutation range.
- Southern blot analysis with methylation sensitive enzymes to detect expanded alleles and methylation status of the *FMR2* gene.

## TEST SENSITIVITY

Expansion of the *FMR2* repeat occurs in over 99% of individuals affected with FRAXE. These cases will be detected by current testing procedures in place in the Genome Diagnostics Laboratory.

## POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

| Repeat size | # of CCG repeats | Clinical Phenotype | Transmission |
|---|---|---|---|
| Normal | ~6 to 30 | Normal | Stably transmitted |
| Intermediate | ~31 to 60 | Normal | May increase in size in subsequent generations |
| Premutation | ~ 61 to 199 | Possibly Symptomatic | Risk of expansion to full mutation |
| Full mutation | 200 and over | Symptoms of FRAXE | |

*For More Information*

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/ Item # 300806

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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*1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of FRAXE.*

*2. FMR2 repeat sizes in the inconclusive expansion range may be found in normal individuals, but indicate a premutation in others. Analysis of multiple family members may be necessary in order to distinguish between these two possibilities.*

*3. The clinical course or severity of symptoms cannot be predicted by molecular analysis.*

*4. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.*

*5. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration.. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.*