ALBERTA PRECISION LABORATORIES
Leaders in Laboratory Medicine

Fragile X syndrome and *FMR1*-Related Disorders: Information for Health Care Providers

Fragile X syndrome is the most common inherited cause of intellectual disability in the general population

Fragile X syndrome is usually more severe in males than in females, although symptoms can be variable in both. Symptoms may include:

- ***Males*** - intellectual disability, developmental delay, behavior problems, poor eye contact, speech delay, and some subtle physical characteristics that become more obvious with age.
- ***Females*** - may have some degree of intellectual disability or learning disability, while others have no symptoms at all. It is not possible to predict which females will show symptoms or to what degree.

Genetic Cause of Fragile X Syndrome:

Fragile X syndrome is caused by an alteration in the FMR1 gene, located on the X chromosome. The gene normally contains a region of trinucleotide repeats (CGG repeats) in the range of 5 to 44 repeats. Almost all individuals with fragile X syndrome have repeat sizes over 200, also known as a full mutation. A full mutation causes inappropriate methylation resulting in inactivation of the FMR1 gene. The CGG repeat expansion is detectable by molecular genetic techniques. Rarely (<1%), fragile X syndrome is caused by a point mutation or deletion in the FMR1 gene that would not be detected by the standard testing.

Interpretation of Molecular Test Results

CGG Repeat Size	Status	Explanation
~5-44*	Normal (unaffected)	This is the normal range for repeat size. This is not consistent with a diagnosis of fragile X syndrome
~45-54*	Intermediate (large normal)	Intermediate (large normal) repeats do not cause fragile X syndrome. In rare cases, repeats of this size have demonstrated instability, but the risk of an expansion to a full mutation is low.
~54-200*	Premutation (FXTAS/POI)	This repeat size is found in carrier females and males. **See below for more information.**
Over 200	Full mutation	Repeat size consistent with a diagnosis of fragile X syndrome.

*The demarcation between the normal, large normal (intermediate) and premutation ranges is not absolute and must be interpreted in the context of the family and medical history.

What are Premutations and FMR1-related disorders?

Premutations have the potential to expand into full mutations when transmitted to the next generation. The chance of expansion is dependent on the repeat size and is more likely to occur when inherited from a female premutation carrier. Premutations are also known to be associated with other health risks:

- ***Premature ovarian insufficiency (POI)*** – defined as onset of menopause before age 40. An estimated 20% of female premutation carriers experience POI.
- ***Fragile X associated tremor/ataxia syndrome (FXTAS)*** - features of FXTAS include ataxia, tremors, other neurological finding such as: short-term memory loss, executive function deficits, dementia, parkinsonism, lower-limb proximal muscle weakness, and autonomic dysfunction. The prevalence of FXTAS is estimated at 45.5% in male premutation carriers over age 50. The risk of FXTAS is female premutation carriers over 50 is approximately 16.5%.

What are the risks to other family members?

The gene for fragile X syndrome is located on the X chromosome and transmitted in an X-linked manner. Genetic counselling is available to families for individual risk assessments.

Who should be tested for Fragile X Syndrome?

1) Individuals with unexplained intellectual disability, developmental delay or autism
2) Individuals with a documented family history of fragile X syndrome. NB: It is recommended that carrier testing for FMR-1 premutations be performed after the patient has received genetic counselling
3) Individuals with a family history of X-linked intellectual disability or possible fragile X syndrome
4) Women with unexplained premature menopause
5) Individuals with late onset progressive cerebellar ataxia and intention tremor
6) Prenatal testing for fragile X syndrome is available for known premutation carriers

Note: Carrier testing for unaffected minors is not recommended by the Canadian College of Medical Genetics, as the results do not affect medical management in childhood.

Referrals for genetic counselling can be made to:

University of Alberta Hospital
Medical Genetics Clinic
8-53 Medical Sciences Building
Edmonton, AB T6G 2H7
Fax: 780-407-6845 Tel: 780-407-7333

R.B. Lowry Genetics Clinic
Alberta Children's Hospital
28 Oki Drive NW
Calgary AB T3B 6A8
Fax: 403-955-2701 Tel: 403-955-7373

Molecular testing for Fragile X syndrome and FMR1-related disorders is available through the Calgary and Edmonton Molecular Genetic Laboratories.
Visit the Alberta Precision Laboratories Test Directory for specimen requirements and requisition forms.

Additional resources:

Fragile X Research Foundation of Canada
Phone: 905-453-9366
www.fragilexcanada.ca

National Fragile X Foundation (US)
Phone: 1-800-688-8765
www.FragileX.org

References

Hunter JE, Berry-Kravis E, Hipp H, et al. FMR1 Disorders. 1998 Jun 16 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020 [cited 2015 Nov]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1384/