April, 2022 **Fragile X Syndrome Facts**

Since many general practitioners have not encountered Fragile X syndrome we would like you to have the following information to assist you in supporting a family with Fragile X or its associated conditions.

What is Fragile X Syndrome? (The most common Cause of ID and AD.)

Fragile X syndrome results from a multiplication of part of the genetic information in the *FMR1* region of the X chromosome. Fragile X is an example of a "triplet repeat disorder". The *FMR1* gene has a region of DNA that varies in length from one person to another. It has a sequence in which the cytosine/ guanine/guanine (CGG) codons are repeated.

Worldwide studies suggest that at least **5,000** Canadians have a full mutation (>200 repeats) of Fragile X syndrome with a rate of 1:4000 for mutation male, and 1:6000 for mutation female. In addition approximately **87,000** Canadians may have the Fragile X premutation (55-200 CGG repeats) Premutation rates for female is 1:200 and male is 1:450.

- **No Fragile X:** this stretch of DNA falls within a range of length that would be considered "normal" – between 6 and 45 repeats of the CGG codon.
- **Premutation**: this stretch of DNA is somewhat longer — from 55 to 200 CGG repeats. Although a person who carries the premutation does not typically have symptoms of Fragile X syndrome, the stretch of DNA is prone to further expansion when it is passed from a woman to her children.
    - These individuals with a premutation (both male and female) are at a high risk of **Fragile X-associated Tremor Ataxia Syndrome FXTAS, Fragile X-associated primary ovarian insufficiency (FXPOI), or Fragile X-Associated Neuropsychiatric Disorders (FXAND)**. In the absence of testing in these premutation individuals their symptoms may be ignored or treated inappropriately.
    - Some of these **premutation individuals** will be hidden carriers and can pass down this genetic condition to their children who will then have the full fragile X mutation or be premutation carriers.
- **Full Mutation**: this stretch of DNA has expanded beyond a certain length (beyond 200 CGG repeats). The gene is switched off and does not produce the Fragile X messenger ribonuclear protein, FMRP. A male who inherits a full mutation exhibits Fragile X syndrome because his only X chromosome contains the full mutation in *FMR1*. A female may not be as severely affected because each cell of her body needs to use only one of its two X chromosomes and randomly inactivates the other.
    - Symptoms can include Intellectual impairment to varying degrees, delayed and abnormal speech, Attention deficit hyperactivity disorder, Anxiety and unstable moods, Autism in 50 to 60% of boys and 20-25% of girls. Long face, large ears, flat feet, hyperextensible joints, especially fingers, seizures (epilepsy) in about 15% of people.

- While there is no specific treatment for Fragile X syndrome, many of these symptoms can be treated by therapies directed at these symptoms: anxiolytics, etc.

It is important to get testing for Fragile X/CGG repeats because:

- Male babies showing developmental delays should be tested for Fragile X. This often doesn't happen until they are 3-5yo. Which results in:
    - Intervention therapies not considered at earlier age when they are seen to be more effective at an earlier age.

    - Parents often feel they are bad parents or are accused of “bad parenting”.
    - A second child might be conceived or born before their risk of carrying the Fragile X mutation has been determined.
- Getting the diagnosis may lead to feelings of guilt by parents and other family members. They need support from genetic counselors which is not often available in Canada.
- Diagnosis of premutation status in close family members should lead to earlier treatments for premutation problems and further genetic counseling to know the risks of having a child with Fragile X syndrome.
    - Helps put possible origin and causes of problems in the people with other pre-mutation consequences.
    - May prevent unnecessary, expensive, and lengthy clinical investigations of ovarian insufficiency **FXPOI**, tremor of apparently unknown origin **FXTAS** and depression and other mental illness.
- May prevent treatment that could put individuals’ health at risk e.g., **FXAND** individuals may have impaired iron metabolism and anemia. Giving these individuals an iron infusion can lead to iron deposition in the brain.
- As the child grows-up, they need a label to access treatments for specific characteristics. e.g. speech, co-ordination. This may also be required for accessing appropriate schooling. It also helps the parent to explain the characteristics of the child to teachers, educational assistants, and peers at school.
- Enables the parent to do focused research on the needs of their child. This includes reaching out to other parents and professionals. This is necessary because many pediatricians and general practitioners have no knowledge of Fragile X and genetic counselors are not widely available.
- Testing can be ordered by GP. If positive, consider referring to a genetic clinic for counselling and familial testing.
- Also consider referral to other specialists: neuro for seizure; Dev ped for behavior and learning; Cardio for cardiac malformations; ENT for ear infection.

References:

Neuropsychological changes in *FMR1* premutation carriers and onset of fragile X-associated tremor/ataxia syndrome. Jessica Famula, Emilio Ferrer, Randi J. Hagerman, Flora Tassone, Andrea Schneider, Susan M. Rivera & David Hessl Journal of Neurodevelopmental Disorders volume 14, Article number: 23 (2022)

Int J Mol Sci . 2020 Jun 20;21(12):4391Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Pathophysiology and Clinical Implications Ana Maria Cabal-Herrera , Nattaporn Tassanakijpanich , Maria Jimena Salcedo-Arellano, Randi J Hagerman

Refining the risk for fragile X–associated primary ovarian insufficiency (FXPOI) by *FMR1* CGG repeat size. Emily Graves Allen, Krista Charen, Heather S. Hipp, Lisa Shubeck, Ashima Amin, Weiya He, Sarah L. Nolin, Anne Glicksman, Nicole Tortora, Bonnie McKinnon, Katharine E. Shelly & Stephanie L. Sherman
Genetics in Medicine volume 23, pages 1648–1655 (2021)

https://fragilex.org/wp-content/uploads/Medications-Treatment-Recommendation.pdf
Medications for Individuals with Fragile X Syndrome (National Fragile-x Foundation (US).