FRAGILE X PREMUTATION

By Joel Snitman

About a decade ago, I learned of the existence of Fragile X. My surprising introduction to Fragile X was due to a family member found to have the premutation and one of its consequences; Fragile X Premutation, pre-ovarian insufficiency (FXPOI). The condition affects some 30% of premutation carriers and cuts off ova production at an early age. If this condition is known early enough, eggs can be harvested and frozen for later use; however, this can be done only if one is suspected of being a carrier or child of a carrier. At the time of my learning of Fragile X, no one I knew had ever heard of a Fragile X premutation. I don't think that much has changed in that regard up to today. When I sought information at the time, I found references only to Fragile X syndrome. But Fragile X syndrome only continues to affect individuals and families because Fragile X premutation continues to hide silently in the population that continues to be ignorant of its existence. If one has never heard of Fragile X premutation, one is unlikely to be genetically tested for it. Nowhere in Canada is there routine testing for Fragile X Premutation.

Fragile X Syndrome (FXS) is the most common known cause of inherited intellectual disability affecting both males and females. An article in the Journal of Assisted Reproduction and Genetics by B. Poteet and collaborators provides some statistics. These stats are confirmed by the US Centers for Disease Control on their Fragile X Syndrome Home page. In the USA, depending on whose statistics one uses, it is estimated that 1 in 1,700 males and 1 in 11,000 females. (1 to 4-5,000 male and 1 to 6-8,000 female) have a FXS diagnosis. Studies by W. Kaufmann, et al (Pediatrics 2017, 139) as well as an article from the Mind Institute, Sacramento, California (Dr. Randi Hagerman, UC Davis Health website Oct 2020) show that Fragile X syndrome (FXS) is also the most common known cause of autism or autism spectrum disorders.

As most readers will know, FXS occurs with a mutation on the FMR1 gene (recently renamed Fragile X Messenger Ribonucleoprotein 1) found on an X chromosome. The mutation is a repeating sequence of three nucleotide bases—CGG (cytosine, guanine, guanine) on a section of the DNA molecule. When the repeating sequence reaches 200 triplets the result is an individual being afflicted with a Fragile X Full Mutation known as Fragile X syndrome (FXS). But when the repeating triplet sequence falls between 55 and 199, it is known as a Premutation. At one time it was thought that the Premutation produced no effects. However, research has established that there can be significant negative impacts, known as Fragile X-related disorders. These include FXPOI, as well as Fragile X associated tremor/ataxia syndrome (FXTAS) which, in some instances, produces movement disorders and may have other serious issues as a premutation carrier ages. Recent attention has been brought to the mental health implications of the premutation. Proposed by Hagerman et al. (2018), the term Fragile X Associated Neuropsychiatric Disorders (FXAND) refers to FMR1's role in the overrepresentation of neuropsychiatric disorders, such as anxiety, depression, ADHD, autism spectrum disorders, and OCD, among premutation carriers.Having a child with FXS puts a huge emotional and financial strain on the family as well as costs to society at large. The solution is genetic testing. A rare disease is considered to be one affecting less than 1 in 2000 people; however, rare diseases are often not so rare according to Dr. Christopher McMaster from the Canadian Institutes of Health. Fragile X syndrome would fall into this category. The Premutation, however, which can lead to a full mutation in subsequent generations, is not "so rare"—running between 1 in 102 to 1 in 419 in the female population depending on ethnic groups. (Data from a table by Owens, K.M.et al FMR Premutation Frequency in a Large, Ethnically Diverse Population...American Journal Medical Genetics March 2018)

If a woman is a carrier (i.e. she has the premutation), the number of "repeats" can expand into her offspring resulting in a child with the full mutation (FXS) even though she, or her male partner, if a carrier, has no symptoms. Expansion in male carriers is not seen as much which may be part of the reason male genetic testing for Fragile X is promoted even less than that of female testing.

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While genetic testing is performed in Canada for a range of genetic disorders/mutations, none of the testing panels include Fragile X. None of the commercial or popular genetic testing laboratories, for example, 23 and Me or Life Labs, now offer such services. The organization Genetics Education Canada-Knowledge Organization (GEC-KO) states: "General population carrier screening for FXS is not recommended." (GECKO Reproductive Genetic Carrier Screening in Canada, March 2023 via website.) If someone is particularly aware or attuned to family history and has knowledge of the existence of Fragile X, (still I suspect not widely known), that person can for specific reasons get genetic testing in Canada as well as receiving genetic counselling. If an individual or couple wishes to get tested at their own initiative and expense, there are private labs that will do this. One example is Invitae (invitae.com)

Of course, genetic testing is being done in Canada and there are panels of genetic disorders that can be run, some specific for certain ethnic groups. For those of Ashkenazi Jewish ancestry there is a panel of genetic diseases available for screening, including, for example, Tay-Sachs which is a frequently found recessive genetic disorder.

Having lunch with a couple of old friends recently, the subject came up as to what I was spending time with now that I'm retired. I mentioned that I was writing an article (this one) for the Fragile X Foundation of Canada. They responded with a "what's that?". While I was explaining what Fragile X was, the waitress came by, a woman who appeared about 25 years old. To "test my hypothesis" that most people have not heard of Fragile X, I asked her. She had never heard of it. As the discussion continued, it turns out that she is Jewish and said she had undergone the genetic testing panel for Ashkenazi Jews. As noted above she has a 1 in 102 chance of being a carrier, but a Fragile X genetic test was not included in the panel nor offered or mentioned at the time of her testing. An example of such a current panel can be seen at this Hospital for Sick Children (Toronto) website: https://www.sickkids.ca/siteassets/care--services/for-health-care-providers/lab-information-sheets/aj-screening-panel.pdf

Note that Fragile X is not included in this panel, notwithstanding that the incidence of Fragile X Premutation carriers in Ashkenazi females is more prevalent than the general population. This higher prevalence occurs also in other ethnic groups. The reasons for this omission are unclear, but rationing in the public healthcare system is a common rationale for hesitancy in the expansion of service offerings. There are, however, millions of prospects for FX testing and including this mutation in the standard genetic panel epitomizes the "ounce of prevention" advantage, if it means preventing cases of full FX Syndrome, not to mention the costs of managing FX-related disorders.

Israel is often quoted as an example of where Fragile X is accepted as an issue at the forefront. In a long discussion with Professor Lidia Gabis of Tel Aviv University and the Director of the Keshet center for Autism, I learned that in Israel any woman aged eighteen and over can be tested for Fragile X upon request, with no prescription needed and at no cost to the patient. All pregnant women are given counselling respecting Fragile X and are tested on request. The fetus can also be tested, and if prenatal testing reveals prevalence of Fragile X, the parents are given a choice to continue the pregnancy or terminate. Abortion laws in Israel, like here in Canada, consider the decision to be a private one as between the woman and her physician. I discussed the awareness of Fragile X in Israel with Dr. Gabis, who noted that OB-GYN physicians in Israel are very much aware of Fragile X and will discuss the issue with their patients, both in their family planning stages and during pregnancy. Family medicine physicians were, however, not as informed.

Where do we go from here? Over recent years, much research has gone into the mechanics of how the Fragile X mutation functions and researchers now understand a great deal about the protein involved and the mechanism at the molecular level of how the mutation reacts with this protein production or lack thereof. Perhaps therapeutic interventions are on the horizon. In the meantime, however, much more must be done in Fragile X awareness and Fragile X testing. While it is unrealistic to expect Canada's significantly stressed publicly funded health system to test every person of childbearing age for the Fragile X Premutation, it seems prudent to consider ethnic propensity when exploring preconception genetic counselling and testing. At present, people who want to be proactive and responsible about their family planning must bear the financial burden to privately test for Fragile X. However, without awareness about the existence of the disorder and its myriad implications, they cannot even be empowered to make that choice. Educating medical professionals, genetic counsellors, and the general public about the role of Fragile X will be an important step.