EMORY UNIVERSITY SCHOOL OF MEDICINE
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Fragile X Syndrome

What is Fragile X Syndrome?

Fragile X syndrome (FXS) is the most common *inherited* form of mental retardation, affecting approximately 1 in 4000 males and 1 in 8000 females. Males typically present with developmental and language delays, behavioral and emotional problems, hyperactivity, autistic-like behavior and moderate to severe mental retardation (IQ of 30-50). Physical characteristics include a long face, large ears, a prominent jaw, and enlarged testicles. Often these physical features become more apparent during puberty. Females typically present with a milder presentation because of the X-linked nature of the mutation. Males have one X chromosome and one Y chromosome, whereas females have two X chromosomes. Features in females include learning disabilities typically involving math, attention difficulties, emotional problems (anxiety, depression, &/or shyness), and poor social skills. Individuals with fragile X syndrome typically have minimal serious medical issues and generally live a normal lifespan. There is currently no cure or specific treatment available for FXS; however, therapy is available to help maximize an individual's potential. In addition, ongoing research at Emory University is focused on understanding the mutation to help develop possible treatment approaches.

Genetics of the fragile X mutation

Fragile X is caused by an abnormality (mutation) in a single gene, the *FMR1* gene, located on the X chromosome. Each individual has 23 pairs of chromosomes, or 46 individual chromosomes. One pair, called sex chromosomes, determines if a person will be a male or a female. Females have two X chromosomes, whereas males have one X chromosome and one Y chromosome.

The *FMR1* gene exists in three different forms: normal, premutation and full mutation. The three forms differ based on the length of a DNA sequence that is repeated (CGG repeat), similar to a genetic "stutter," in which a small section of the genetic material within the gene is repeated too many times. The *FMR1* gene is responsible for making the FMR protein, which functions in communication between nerve cells in the brain.

Individuals in the normal range have 6-50 copies of the CGG repeat, with the average being around 30. The number of CGG repeats varies from individual to individual. When in the repeat of 6-50 range, the repeat number is usually passed from parent to child in a stable manner. For example, if a father has 30 copies of the CGG repeat, then his daughter will also have 30 CGG repeats.

Individuals who have between 55 and 200 repeats do not express fragile X-associated symptoms and are referred to as **premutation carriers**; however, premutation carriers are at increased risk for other disorders, such as premature ovarian failure and fragile X associated tremor ataxia syndrome (see below for additional information). Approximately 1 in 250 women and 1 in 800 men are carriers of the premutation form of the gene. The fragile X mutation is inherited in an X-linked pattern, although it is more complicated because of the unstable repeat sequence. The premutation is not transmitted in a stable manner from parent to child and the number of repeats could expand or increase in each generation. For men who carry the premutation, ALL of his daughters will be fragile X mutation carriers. Almost always, the daughters will carry the premutation form of the gene. These daughters will have up to a 50% chance of having a child with FXS. Sons of men with the premutation will NOT inherit the mutation and will NOT be carriers. For women who carry the premutation, their sons and daughters have up to a 50% chance of carrying the fragile X mutation. The chance that the premutation expands to the full mutation and leads to FXS depends on the repeat size carried by the mother.

Finally, when the number of CGG repeats exceeds 200, a chemical change occurs in the cells (methylation), which turns off the *FMR1* gene. If the gene is turned off, the protein cannot be made.

This form of the gene is called the **full mutation** because it causes the symptoms of fragile X syndrome (FXS). Approximately 1/3-1/2 of females with the full mutation shows clinical symptoms of fragile X syndrome.

As a man, what does it mean to my health if I am a premutation carrier?

- ALL daughters of men with the premutation will be carriers. These women will have up to a 50% chance of having a child who carries the fragile X mutation, either as a premutation or a full mutation. All sons of men with the premutation will NOT have FXS and will NOT be carriers.
- Men with the premutation are at increased risk for developing Fragile X Tremor/Ataxia Syndrome (FXTAS).

Fragile X Tremor/Ataxia Syndrome (FXTAS)

FXTAS is a neurological disorder that causes tremors, balance problems, difficulty walking, and dementia after age 50. This neurological disorder occurs by a completely separate mechanism to FXS.

As a woman, what does it mean to my health if I am a premutation carrier?

- Women with the premutation have up to a 50% chance of having a premutation carrier or an affected child with each pregnancy, depending upon the size of the woman's premutation.
- Women are at increased risk for early menopause (occurring between the ages of 40 and 45).
- Approximately 21% of premutation women experience premature ovarian failure (POF). This is a 21-fold increase above the general population risk of 1%. Among general population women who have POF, 2% with sporadic POF and 14% with familial POF carry the premutation.
- Women with the premutation are at increased risk for developing FXTAS, although it is typically a milder presentation than in male premutation carriers.
- You may have relatives who are also carriers who have similar health risks.

Premature Ovarian Failure (POF)

POF is a condition in which the ovaries stop functioning normally in a woman younger than age 40. Symptoms of POF include absent or irregular periods, hot flashes, night sweats, and occasionally infertility. POF is NOT menopause in that women with POF can STILL get pregnant in approximately 5-10% of cases without treatment.

How can I get tested?

The *FMR1* DNA test is a blood test that can determine if you are at risk for FXS, POF, or FXTAS. To make sure this is the right test for you or your family member, please discuss your concerns with your health care provider or a genetics specialist. In addition, you can discuss your concerns and/or schedule an appointment in the **Emory Fragile X Center** by calling Shelley Dills at **(404) 778-8524**.

There is fragile X syndrome in my (friend's) family, how can I help?

There are several research opportunities at Emory for families with fragile X syndrome. Please contact our research coordinator at **404-778-8479** or visit our website at www.genetics.emory.edu for more information.

Resources

- The National Fragile X Foundation: The NFXF provides patient friendly information on their website at www.fragilex.org or by calling (800) 688-8765.

- The Fragile X Association of Georgia: This parent led association can provide information, support, and guidance for newly diagnosed families in Georgia. For more information e-mail parent sources at frax@bellsouth.net

- FRAXA – The Fragile X Research Foundation: Their mission is to find effective treatments and a cure for all children and adults with Fragile X. To obtain additional information, visit their website at www.fraxa.org.