



The Fragile X Premutation: A Cause for Premature Ovarian Failure^{©2006}

There are many factors that influence or limit the number of eggs (ovarian reserve) stored in a woman's ovaries. These include genetic factors and environmental factors or a combination of both. Among women who go through menopause before the age of 40 (referred to as premature ovarian failure, or POF), 2% who do not have a family history of POF and 14% of those with familial POF carry a fragile X premutation. This is an atypical form of the *FMR1* gene, a gene located on the X-chromosome. Women with this atypical or premutation form of the *FMR1* gene have a higher chance of having POF or early menopause than women who do not have this mutation. The premutation form of the *FMR1* gene can be easily detected in blood or cheek cells via a DNA test. As you consider testing, please think about the benefits and risks to knowing this information.

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.

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 problems 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.

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

Risks:

- Women with the premutation have up to a 50% chance of having a child with the FXS mutation.
- Approximately 16% of women with the fragile X premutation will go through menopause before the age of 40, a condition known as premature ovarian failure (POF).
- There is a small risk for developing Fragile X Tremor/Ataxia Syndrome (FXTAS), a neurological disorder that causes tremors, balance problems, difficulty walking, and memory problems later in life.
- Women with the premutation will often times have other relatives who have a chance of carrying the fragile X mutation and, as a result, will also be at risk for similar health risks.

Benefits:

- If a woman is found to carry the premutation, she will have a diagnosis to explain the cause of her ovarian problems and, potentially, related symptoms of menopause present early in life.
- If a woman is considering egg donation from her relatives, this test can be used to screen for carrier status prior to their donation.
- If a woman is found to carry the premutation, she will have full information about the risk for having a child with FXS and consider prenatal diagnosis.

How will testing be done?

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

There are several research opportunities at Emory for families with FXS and POF. 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.