Women's Health and the FRAGILE X PREMUTATION

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Introduction

About 1 in 260 women are carriers of the fragile X premutation. Many people know about this genetic change because a family member may have fragile X syndrome. Much attention has been focused on fragile X syndrome. Now it's time to think about the premutation.

Women need to be aware of the health concerns related to carrying the premutation. While much is known, research in the area of premutation-related health concerns for women is changing rapidly. Staying up to date on current findings is important so you can better care for yourself and get the care you need from your healthcare providers. You may end up being your doctor's teacher!

This booklet is intended to be a women's guide to healthcare. We hope that it empowers premutation carriers of all ages by providing information and by describing research findings. This booklet is a guide for carriers, their families, and medical providers.

Fragile X is a family diagnosis. Women with the premutation deserve support for their own health.

This book is organized in a question and answer format and is divided into 5 main sections:

1. The Fragile X Premutation and its Inheritance in Families
2. Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)
3. Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) and Other Premutation Related Health Concerns
4. Family Planning
5. Health Worksheet to help you discuss the premutation with your doctor

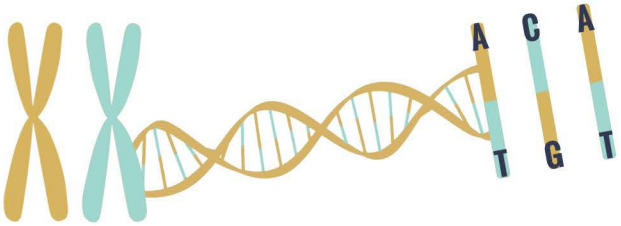
The Fragile X Premutation and its Inheritance in Families

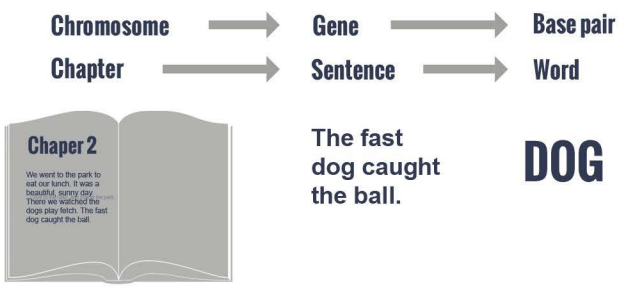
WHAT ARE GENES?

A gene is a piece of DNA that contains the information to make the molecules needed for our bodies to work properly. DNA is composed of a series of small units, or letters, labeled C, A, T, or G. Each series of letters provides the information for a specific molecule. Genes form long strands that are referred to as chromosomes.

We have 23 pairs of chromosomes in each of our cells. We received one set of 23 chromosomes from one parent, and one set from our other parent. One of these pairs is different, and is called the sex chromosomes. Females have two X chromosomes (XX) and males have one X and one Y (XY).

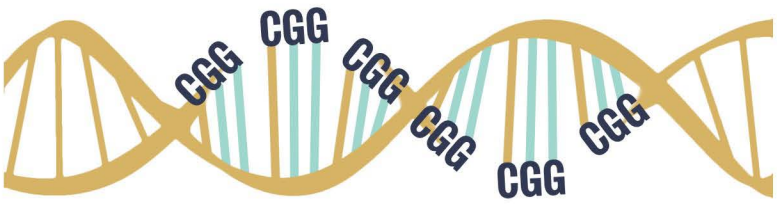
A helpful comparison is to think about our DNA as a chapter in a book. Genes are much like a sentence in a chapter. When problems occur in our genes, called mutations, they act like misspelled words or repeated words in a sentence. Sometimes they disrupt the meaning of a sentence or even a whole paragraph so it is no longer understandable. In the same way, some mutations change a gene so much that our body cannot read it anymore. These mutations may cause single health problems or may cause many body functions to be affected. The fragile X mutation is one of the changes that can affect different functions in the body. The gene that is changed by the fragile X mutation is on the X chromosome. Because of its location, the fragile X mutation leads to different health problems or different levels of disease severity in males and females.





WHAT IS THE FRAGILE X PREMUTATION?

The fragile X mutation is a type of genetic mutation called a repeat expansion. This repeat expansion occurs on the *FMR1* gene on the X chromosome. Most people have less than 55 repeated copies of three letters (CGG) within their *FMR1* gene. Fragile X premutation carriers can have between 55 and 200 copies of this CGG repeat. Individuals with the fragile X full mutation have over 200 copies of the CGG repeat and this can lead to **fragile X syndrome**.



The fast dog dog dog dog dog dog caught the ball.

About 1 in 260 women carry the fragile X premutation. People who carry the premutation have an increased chance to get specific health problems. For some associated health problems, the number of repeats a person carriers in this premutation range (55-199 repeats) will make a difference in the degree of risk. Women who are premutation carriers also have an increased risk to have a child with fragile X syndrome. Fragile X syndrome is the most common form of intellectual disability that can be passed through families.

For more information on genetics of fragile X syndrome and the premutation visit www.fragileX.org

Definition:

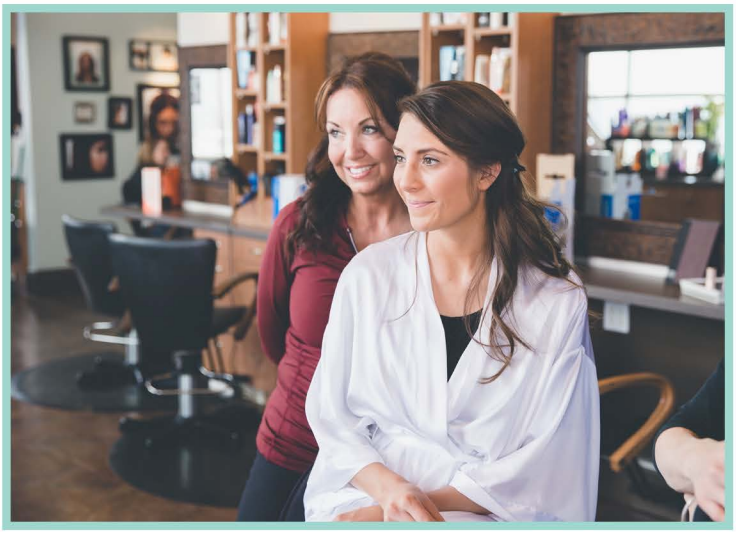
Fragile X Syndrome occurs when the repeat expansion on the *FMR1* gene is over 200 (termed the full mutation). Fragile X syndrome can cause intellectual disability, specific facial features, and behavioral challenges like autism, ADHD, and social anxiety. Fragile X syndrome can occur in both genders although males are more frequently and typically more severely affected than females.

WHAT HEALTH CONCERNS SHOULD I BE AWARE OF?

Only some women who carry the premutation experience related health problems. Your experience may differ from other carriers.

Possible conditions associated with the premutation include: 1) FXPOI- symptoms related to primary ovarian insufficiency 2) FXTAS- symptoms related to tremor/ataxia syndrome, and 3) other potential symptoms that have been reported to be more frequent among premutation carriers, like anxiety and depression. Health concerns related to the premutation are discussed in more detail in the following pages.

By knowing your fragile X status you can be better prepared to understand, recognize, and treat symptoms early.



HOW DO I KNOW IF I AM AT RISK?

A simple blood test can be ordered by your genetic counselor or physician to see if you carry the fragile X premutation. **Turn to page 29 for help with ordering the right test.**

WHY DO I NEED TO KNOW IF I AM A PREMUTATION CARRIER?

Knowing you are a carrier and knowing the size of your repeat is important. It will help you and your doctors build a health plan. It will give you information about your reproductive health and your physical health across your lifespan.

WHO SHOULD BE TESTED FOR FRAGILE X?

Many individuals may be tested by their doctor for fragile X syndrome or the premutation including:

- Individuals of either sex with intellectual or developmental delay, or autism, especially if they have any physical or behavioral characteristics of fragile X syndrome.
- Individuals with a family history of fragile X syndrome, or a male or female relative with undiagnosed intellectual disability.
- Women who are having reproductive or fertility problems associated with early ovarian insufficiency or early menopause.
- Men and women who have intention tremor or ataxia (problems with balance) starting around their 50s.
- Individuals who don't have symptoms themselves but have a significant family history of any of the above conditions

To find a genetic counselor in your area to discuss genetic testing visit www.NSGC.org.

WHY CAN SYMPTOMS DIFFER BETWEEN MEN AND WOMEN?

The fragile X mutation is on the X chromosome. Women have two X chromosomes and men have one X and one Y. Because males only have one X chromosome, if it has the premutation or full mutation, they tend to be more frequently and more severely affected. For women, the extra X chromosome (without the premutation) may offer some protection from symptoms.

WHAT DO MY TEST RESULTS MEAN?

Your test results will give you a "repeat" number. This is the number of copies of the CGG repeat you have in your *FMR1* gene. Women may have 2 numbers reported on their test results because women have two X chromosomes.

The number of repeats you carry can give you information about your chances to develop symptoms. It can also give you information about the chance of having a child with fragile X syndrome.

Match your repeat size to the chart on the following page for more personalized risk information

TABLE 1 Health Information by Premutation Length

Your repeat length	What does this mean for my health?	What does this mean for my pregnancies?
5- 44 Non carrier	Not at risk for premutation related symptoms.	Not at increased risk to have a child with fragile X syndrome.
45-54 Intermediate	Not at risk for premutation related symptoms.	Thought to have no risk to have a child with fragile X syndrome. There is a 50% chance with each pregnancy that your child will inherit your intermediate repeat. There is a chance for this repeat to expand to a premutation in your children.
55-79 **PREMUTATION**	Some chance (10%) to develop FXPOI. Up to 17% of women may develop FXTAS*.	There is a 50% chance of passing on an expanded repeat length (premutation or full mutation) in each pregnancy. The chance the premutation could expand to a full mutation ranges from 3-31%.**
80-99	Highest chance (30%) to develop FXPOI. Up to 17% of women may develop FXTAS*.	There is a 50% chance of passing on an expanded repeat length (premutation or full mutation) in each pregnancy. The chance the premutation could expand to a full mutation ranges from 60-80%.**
100-200	Moderate (20%) chance to develop FXPOI. Up to 17% of women may develop FXTAS*.	There is a 50% chance of passing on an expanded repeat length (premutation or full mutation) in each pregnancy. The chance the premutation could expand to a full mutation ranges from 95-100%.
>200 Full mutation	Not at risk for FXPOI and FXTAS. Many women will show signs of fragile X syndrome.	There is a 50% chance with each pregnancy that your child will inherit the full mutation. Males who inherit the full mutation will have fragile X syndrome. Females may or may not have symptoms of fragile X syndrome.***

*No information on risk by repeat size in women for FXTAS at this time
**Risk of expansion from premutation to full mutation also depends on AGG repeat interruptions
*** Development of fragile X syndrome in males and females also depends on methylation status and in females, X inactivation

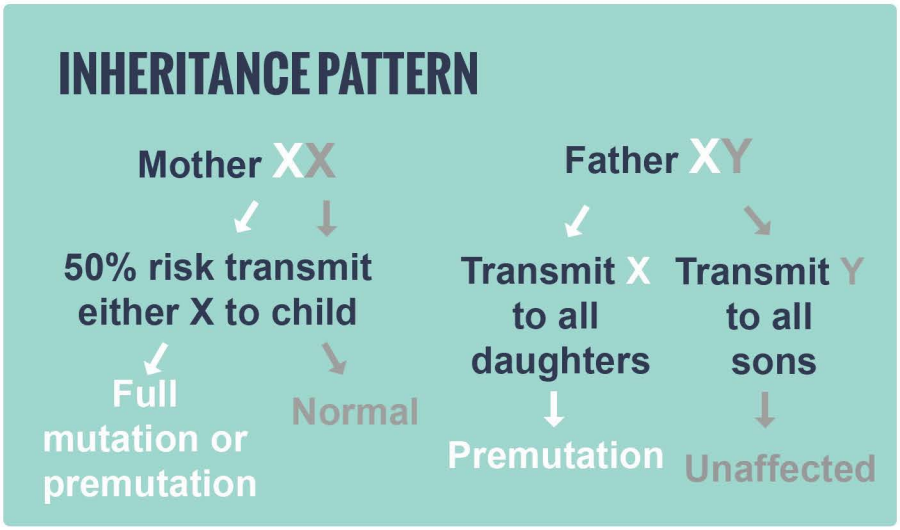
HOW DID I GET THIS GENETIC CHANGE?

The repeat expansion is passed through families. One of your parents carried the repeat expansion and passed it to you. There is also a 50/50 chance for you to pass this repeat expansion on to your children.

When the repeat expansion is passed from parent to child, there is a chance that the number of CGG repeats will expand to a larger number. For example, if you carry 70 repeats there is a 50/50 chance that your child will get the expanded repeat as described above. This expanded repeat usually will be greater than 70 repeats and sometimes over 200. The size of the expansion most often differs for each child.

The pattern is different for men. Fathers who carry the premutation will pass it to all of their daughters and none of their sons. The premutation will almost never expand to the full mutation when passed from father to daughter.

It is important to talk about your test results with your relatives who may also be at risk. A genetic counselor can help you understand who might be at risk in your family. A genetic counselor can also help you talk with your family about this information. **Turn to page 23 for information on family planning.**



GENETICS TAKE HOME POINTS

- Fragile X-associated conditions are caused by a specific genetic mutation called a repeat expansion on the *FMR1* gene on the X chromosome.
- Women who carry the premutation are at risk for FXPOI, FXTAS, and possibly other conditions like anxiety and depression.

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

WHAT IS FXPOI?

FXPOI stands for fragile X-associated primary ovarian insufficiency. FXPOI is a group of symptoms that includes: 1) altered menstrual cycles such as irregular, skipped or stopped periods; 2) hormonal changes such as elevated **follicle stimulating hormone (FSH)** or low **anti-Müllerian hormone (AMH)**; 3) difficulty getting pregnant; and 4), symptoms of menopause such as hot flashes and vaginal dryness. On average premutation carriers go through menopause 5 years earlier (average age 46) than the general population (51 years). Sometimes, the diagnosis of "premature ovarian failure" (POF) is used, which means the stopping of periods before the age of 40.

FXPOI is a condition in which the ovaries are not functioning at full capacity. Ovaries are part of a women's reproductive system that hold all of a woman's eggs. Ovaries, together with other organs, produce hormones that are important to fertility. These hormones assist in the release of an egg each menstrual cycle.

Definition:

Follicle Stimulating Hormone (FSH) is a hormone produced by the pituitary that can be used to determine a woman's menopausal status. FSH levels vary through the menstrual cycle and play a role in fertility.

Anti-Müllerian Hormone (AMH) is a hormone produced by the early follicles in the ovary. It is a promising marker of the approximate size of the remaining egg supply.

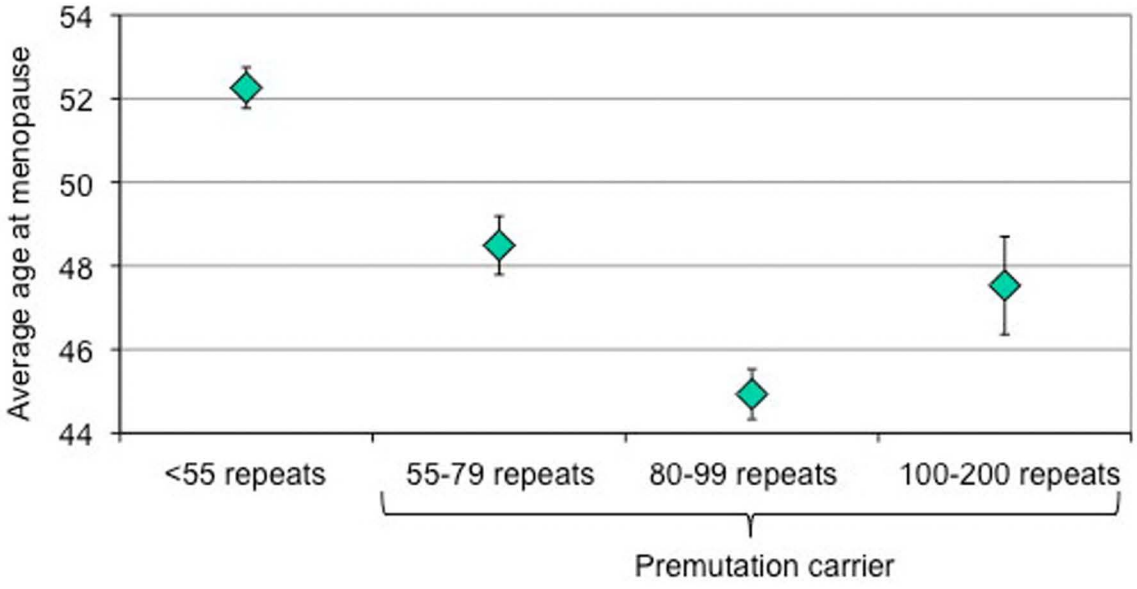
HOW IS FXPOI DIFFERENT FROM MENOPAUSE?

Menopause symptoms and FXPOI symptoms are similar. But women with FXPOI can still get pregnant. Once in a while, their ovaries may release a viable egg. In the same way, women with FXPOI can occasionally experience a return of menstrual periods. Women in menopause will not.

IS REPEAT SIZE RELATED TO FXPOI SYMPTOMS?

FXPOI affects around 1 in 5 women (20%) who carry the premutation. The chance to develop symptoms of FXPOI depends on your repeat length. The highest chance to develop these symptoms occurs in women with repeats in the mid-range, or those with 80-99 repeats. The average age of menopause by repeat length can be seen in the graph below.

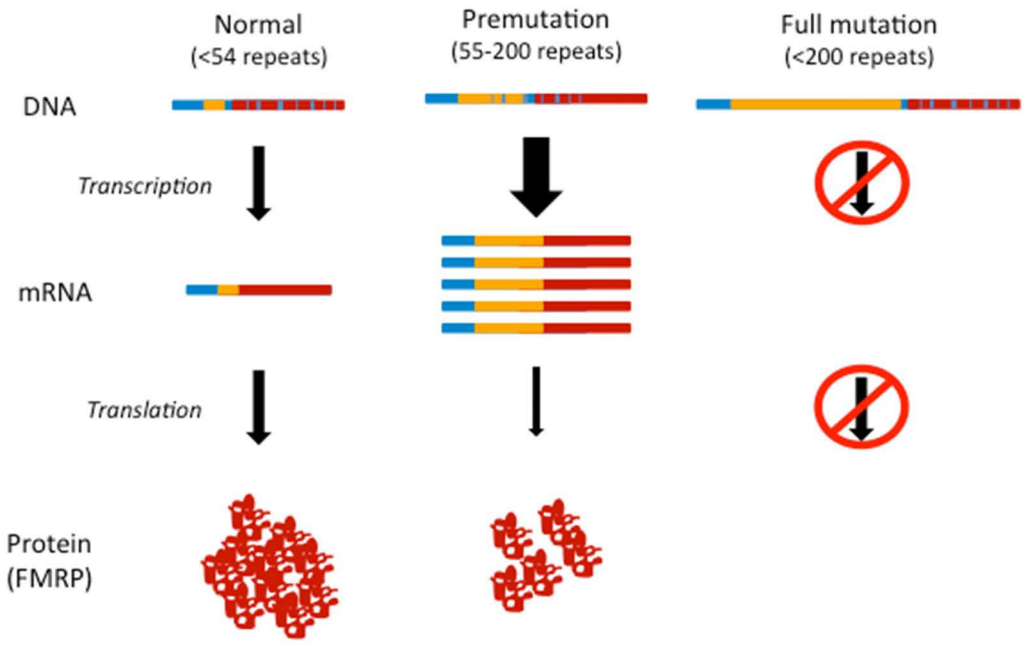
FIGURE 1 Carriers in the Middle Repeat Range have an Earlier Onset of Menopause



WHAT CAUSES FXPOI?

At this point, the cause of FXPOI is unknown. Most likely, the cause will be related to the number of CGG repeats in the **messenger RNA (mRNA)**. In addition to having an expanded number of repeats in the mRNA, premutations also produce more of the *FMR1* mRNA than those without the expansion. It is thought that both properties—too many repeats and too much *FMR1* mRNA with these expanded repeats—may cause the early loss of eggs from the ovary. This is different from fragile X syndrome, which is caused by an absence of the protein **FMRP**.

FIGURE 2 Possible Cause of Fragile X-Associated Disorders



Definition:

messenger RNA (mRNA) is a molecule that carries the information from DNA to produce proteins.

FMRP is a protein produced by the *FMR1* gene. Proteins are used by the body for structural support or to help chemical reactions take place. When proteins like FMRP are missing, the body does not perform specific tasks as well.

WHY DO I NEED TO KNOW IF I HAVE FXPOI?

FXPOI symptoms can impact many parts of your life. These include your reproductive, physical, and mental health. Recognizing the symptoms will allow you to consider treatment options. These may include hormone replacement, fertility help, or other medications as needed. Recognizing symptoms early can help you and your doctor come up with a plan to manage your needs effectively.

HOW IS FXPOI DIAGNOSED?

FXPOI is diagnosed by looking at clinical symptoms in combination with being a premutation carrier. If you are a confirmed premutation carrier, you should alert your physician to the risks and common symptoms of FXPOI. Some physicians may not be aware of this condition, so you may need to provide information to them. Hormonal tests can also be requested by your physician to help determine your current level of ovarian function. These include testing AMH and FSH levels.

Trust yourself when it comes to your health. Alert your physician to any new or unusual symptoms.

WHAT SYMPTOMS SHOULD I LOOK FOR?

Symptoms of FXPOI can mirror symptoms of menopause. Woman have a variety of experiences with FXPOI; for example, some women may have mild symptoms while other women may have more severe symptoms.

TABLE 2 Symptoms of FXPOI

Absent or irregular period 	All women should keep a log of their menstrual cycles. Note any unusual patterns or changes in flow, missed cycles, or variable cycle length from month to month (long cycles are more than 35 days and short cycles are less than 21 days).
Hot flashes 	Feeling flushed or having a sudden feeling of warmth that spreads over the upper body.
Vaginal dryness or decreased libido 	The lining of the vagina may become dry, thinner, and less flexible. Interest in sex may decrease.
Fogginess or mental haze 	Difficulty with focus or a feeling of mental cloudiness from day to day.
 **Infertility**	Difficulty getting pregnant or infertility (inability to become pregnant after 1 year of unprotected intercourse) can be common among women experiencing FXPOI. Many women need to use assistive reproductive technology such as fertility drugs or IVF.
Insomnia 	Difficulty falling asleep or staying asleep at night.
Anxiety or Depression 	Feeling depressed, irritable, anxious, or are having difficulty completing daily activities due to changes in mood. Talk with a primary care doctor or psychiatrist right away if you are having these problems.

WHAT SHOULD I DO IF I AM EXPERIENCING THESE SYMPTOMS?

If you are having any of the above symptoms, you should speak with your doctor. A primary care physician or an obstetrician / gynecologist (OB/GYN) can discuss FXPOI and the next steps with you. If you are having problems getting pregnant, you may want to discuss your options with a reproductive specialist.

Some women also find it helpful to join support groups or to talk with other women with similar experiences. Visit www.FragileX.org to find a community support group near you.

WHAT SHOULD I DO IF I AM *NOT* EXPERIENCING THESE SYMPTOMS?

Not all women have symptoms of FXPOI during their lifetime. Most will go through menopause around 50 years of age like other women. There are things you can do before you experience symptoms. Talk with your primary care doctor and your OB/GYN about the reproductive risks associated with the premutation. There are baseline hormone tests your doctor may request. They may help determine the stage of your reproductive health or whether your may have problems with fertility. You can also discuss fertility preservation with your doctor like egg or embryo freezing.

WHY IS OVARIAN INSUFFICIENCY OR EARLY MENOPAUSE A PROBLEM?

Women with FXPOI can have long-term health concerns that go beyond problems with fertility. These problems are related to having low levels of estrogen at an early age. If untreated, there is an increased risk for heart disease, early bone loss, and related problems. Also, the fluctuation of hormones that can sometimes occur in FXPOI may increase the chance for mood disorders like anxiety and depression.

Early estrogen deficiency resulting from FXPOI leads to an increased chance of low bone density, earlier onset osteoporosis, and bone fractures.

WHAT SHOULD I TELL MY DOCTOR?

You should tell your doctor that you are a fragile X premutation carrier and discuss any symptoms that may be concerning you. Bringing information about FXPOI or the fragile X premutation may help you discuss the next steps with your doctor. **See page 29 for a handout you can bring with you to your next appointment.**

Medical providers that may be able to discuss FXPOI with you: *This list does not include all possible medical providers.

- Genetic Counselor
- Medical Geneticist
- OB/GYN
- Reproductive or Fertility Specialist

WHAT TESTS SHOULD MY DOCTORS ORDER TO DETERMINE IF I AM EXPERIENCING FXPOI?

Your doctor may perform a physical exam and/or order blood tests to rule out other conditions, such as pregnancy or thyroid disease. Sometimes hormonal tests are available to determine if you are experiencing FXPOI.

- Your doctor may order a blood test that measures FSH. FSH causes your ovaries to produce estrogen. When your ovaries slow down their production of estrogen, your levels of FSH increase. High FSH levels indicate that you are approaching menopause or ovarian insufficiency.

- Testing AMH is another way to determine the response of the ovaries to hormones. AMH can help give you information about fertility. When AMH levels are low or cannot be detected, it may indicate that you could have trouble getting pregnant.

IS THERE A TREATMENT FOR FXPOI?

There is no treatment available specific to FXPOI. Your doctor may manage your symptoms with methods similar to those used for menopause. Women with FXPOI should talk to their doctors about hormone replacement therapy to help replace the estrogen their body is no longer making.

WHAT CAN I DO NOW TO PREVENT SYMPTOMS?

Lifestyle choices can greatly influence your health risks. Stay healthy by reducing stress, eating well, and not smoking.

FXPOI TAKE HOME POINTS

- FXPOI is a condition where the ovaries are not functioning at full capacity
- Symptoms may include irregular periods, reduced fertility, symptoms of menopause like hot flashes, or stopping of periods before age 40
- Recognizing symptoms early can help you and your doctor come up with a plan to effectively manage your concerns

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) and Other Premutation Related Health Concerns

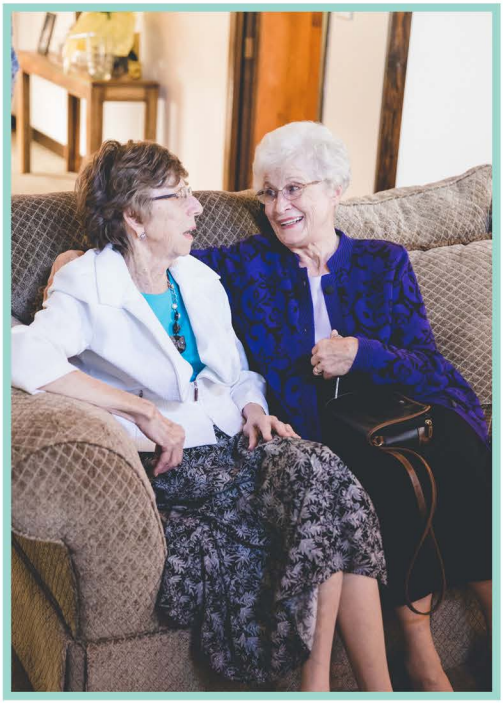
WHAT IS FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)?

FXTAS is a brain and movement disorder that typically starts later in life (50 years or older). The symptoms usually worsen over time and can be a combination of changes in movement and thinking. Many individuals with FXTAS are mistakenly diagnosed with Parkinson's disease or Alzheimer's disease when symptoms start. **See Table 3 for a list and description of symptoms.**

Medical Providers that may be able to discuss FXTAS with you:

*This list does not include all possible medical providers.

- Genetic Counselor
- Medical Geneticist
- Neurologist



CAN WOMEN GET FXTAS?

Women and men who carry the premutation are at risk for FXTAS later in life. Men with the premutation are more often affected than women. There is a lifetime risk of about 30-40% for men who carry the premutation and 8%-17% in women. Research suggests that FXTAS symptoms may look different in women compared with men. Specific presentation of FXTAS in women is still being researched. In general, symptoms in women with the premutation may be less severe and may occur at a later age than men.

TABLE 3 Symptoms of FXTAS

Tremor	Shaking or trembling of limbs when performing voluntary movements such as reaching for objects, writing, or pouring.
Ataxia	Problems with balance and coordination.
Parkinsonism	Movements commonly seen in Parkinson's disease. These include slow movements (bradykinesia), tremor when resting, impaired speech, or muscle stiffness.
Dementia and/or cognitive decline	Decline in mental ability that can be severe enough to affect daily life. Can include loss of memory (especially short term), difficulty with language, loss of focus, or difficulty with visual perception.
Mood changes	Instability in mood, irritability, personality changes, anger, or psychiatric symptoms like depression or anxiety.
Loss of executive functioning	Difficulty controlling behavior, for example, trouble planning and performing actions. Difficulty developing problem solving strategies. Loss of impulse control, trouble with focus, and lack of flexibility with change.

IS REPEAT SIZE RELATED TO FXTAS SYMPTOMS?

Individuals with longer premutation repeat lengths seem to have a greater chance of developing FXTAS, but most studies have only looked at males with FXTAS.

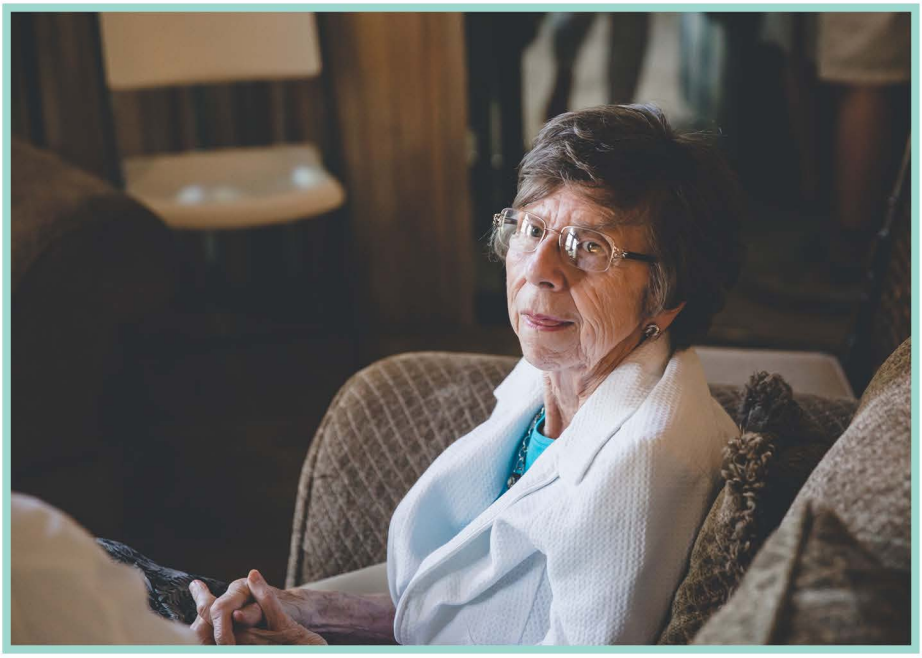
WHAT CAUSES FXTAS?

The cause of FXTAS is still unknown, but is probably similar to FXPOI. It is clear that high levels of *FMR1* mRNA with the long premutation repeats lead to brain loss, but why this happens is still unknown.

HOW IS FXTAS DIAGNOSED?

The diagnosis of FXTAS is based on symptoms as well as findings from a brain scan (MRI) in premutation carriers. FXTAS may be more difficult to diagnose in women because of a milder clinical presentation. If you are a premutation carrier, you should alert your physician to the risks and common symptoms of FXTAS. Some doctors may not be aware of this condition, so you may need to provide information to them. Specific criteria that may help diagnose FXTAS are listed below and can be discussed with a neurologist.

	Brain Findings (MRI)	Clinical Findings
Major	• MRI white matter lesions in the middle cerebellar peduncles • MRI white matter lesions in the splenium of the corpus callosum	• Intention tremor • Gait ataxia
Minor	• MRI lesions involving cerebral white matter • Moderate to severe generalized brain atrophy (loss of cells in the brain)	• Parkinsonism • Moderate to severe short-term memory deficit • Executive function deficit • Neuropathy



IS THERE TREATMENT FOR FXTAS?

There is no treatment specific to FXTAS. However, you can speak with a neurologist about options to lessen the burden of symptoms. Some neurologists may recommend things such as medication, physical therapy, exercise, or meditation.

WHAT CAN I EXPECT IN THE EARLY STAGES OF FXTAS?

Typically intention tremors or difficulty with balance and coordination are among the first symptoms to develop. However, there is no one way people experience FXTAS. Most information we have about the course (natural history) of FXTAS has been studied in men. Women may experience a different course of the disease.

There is no one way people experience FXTAS. More research is needed to know how FXTAS presents in women.

WHAT CAN I EXPECT IN THE LATER STAGES OF FXTAS?

Symptoms in the later stages of FXTAS can be difficult to hear if you or a family member are experiencing early signs or symptoms. No one can effectively predict how severely someone may be affected or how long someone might live after symptoms start.

For some, symptoms progress slowly and may take 10-20 years to become disabling. For others, symptoms may progress more rapidly with a decline in abilities in just a few years.

Right now most of our information on what to expect in the later stages comes from studying men with FXTAS. For male premutation carriers, onset of tremor and ataxia is around 60 years of age. Motor symptoms may interfer with routine activities after an average of 15 years. This may present as more frequent falls or dependency on walking aids.

Those with FXTAS also experience cognitive decline. This may initially be loss of memory or inability to focus. It may progress to frustration or anger, personality changes, difficulty with language, or loss of daily living skills that were once easily performed. Average life expectancy following symptoms was 21 years in a study of males with FXTAS.

OTHER HEALTH CONCERNS

Other health concerns have been reported in connection with the fragile X premutation. However, more research is needed to determine which symptoms are associated with the premutation and which are not.

Individuals with the premutation may be more likely to develop depression or anxiety. If you or a family member are experiencing prolonged feeling of sadness, frustration, or difficulty controlling stress or anxiety, seek help from a psychiatrist or primary care physician.

For women, some health conditions possibly related to the premutation include thyroid disease, neuropathy (numbness), fibromyalgia (chronic pain and tiredness), and migraines. More information is needed before we will know the exact connection between these conditions and the premutation.

FXTAS TAKE HOME POINTS

- FXTAS is a disorder affecting adult premutation carriers. It causes a decline in movement and thinking.
- It is important to pay attention to your mental health. Premutation carriers may be at risk for depression and anxiety.

Family Planning

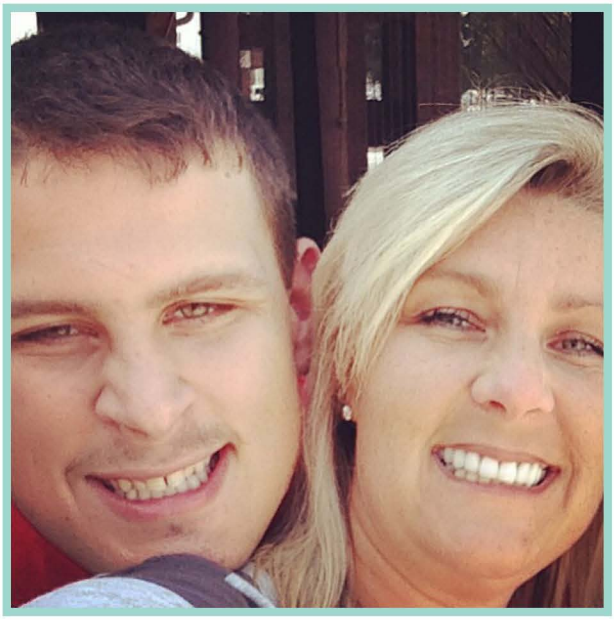
The fragile X premutation can have implications for your pregnancies, children, and other relatives. **See the chart on page 8 for more specific information based on your premutation repeat size.** With each pregnancy, premutation carriers have a 50% chance to pass on the fragile X mutation, either as a premutation or a full mutation. If a child inherits the full mutation, they have a high chance of being affected with fragile X syndrome. Expansion of the premutation to the full mutation occurs when it is passed from mother to child. Expansion of the premutation to the full mutation has not been seen when passed from father to daugher in any families studied to date.

WHAT IS FRAGILE X SYNDROME?

Fragile X syndrome occurs when the repeat expansion on the *FMR1* gene is more than 200 (termed the full mutation). Fragile X syndrome can cause intellectual disability, specific facial features, and behavioral challenges like autism, ADHD, and social anxiety. Fragile X syndrome can occur in both genders, although males are more frequently and severely affected than females.

Medical providers that may be able to discuss family planning with you: *This list does not include all possible medical providers

- Genetic Counselor
- Medical Geneticist
- OB/GYN
- Reproductive Specialist



WHAT TESTING OPTIONS ARE AVAILABLE BEFORE PREGNANCY?

If your premutation size has fewer than 90 repeats, you can ask for a test that checks how often the CGG repeats are interrupted by a different repeat, an AGG. This information can tell you more accurately about the chances of passing on the full mutation to your children.

Research has found that having an AGG between the CGG repeats in the premutation makes it more stable, or in other words, less likely to expand to the full mutation when passed to a child. This test is usually only done for premutation carriers with fewer than 90 repeats because this is when the AGG interruptions have the largest effect on stability.

There are also options available before pregnancy to reduce the chances of having a child with fragile X syndrome including **IVF/PGD**, egg donation, or adoption. These options can be discussed in more detail with a genetic counselor, OB/GYN, or reproductive specialist.

Definition:

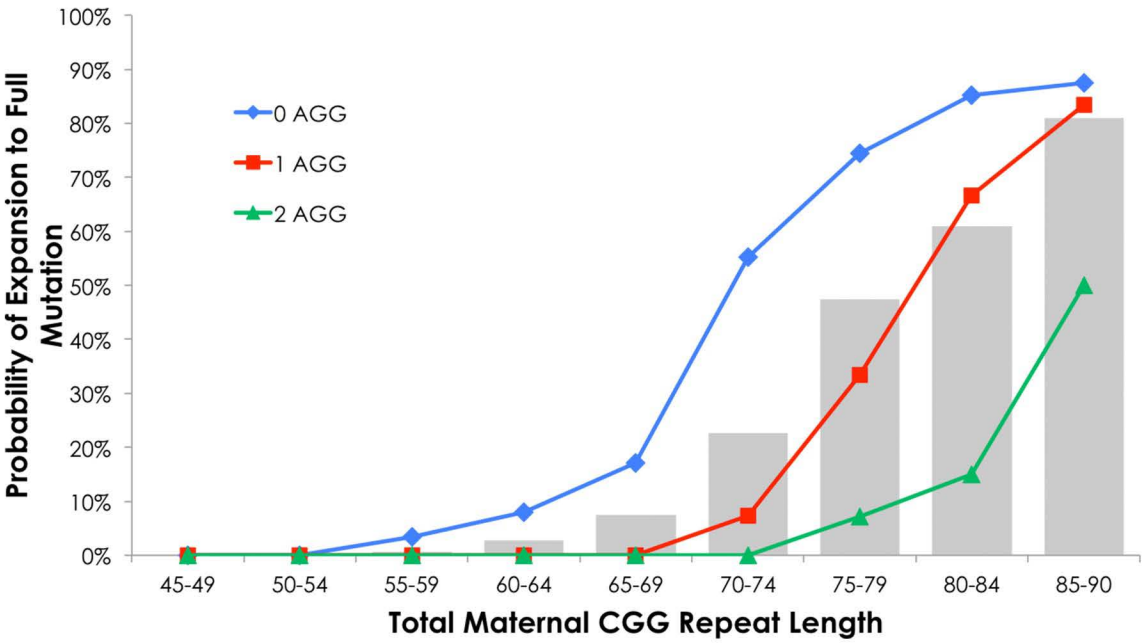
IVF stands for in vitro fertilization. This is a process where the egg and sperm are mixed in a laboratory dish for fertilization. Following this process the embryo is transferred to the uterus.

PGD stands for preimplantation genetic diagnosis. This is the process of removing a cell from an IVF embryo and testing it for genetic changes. Generally an embryo without the genetic mutation is then transferred to the uterus.

FIGURE 3 Chance for Expansion to Full Mutation using AGG Interruptions

AGG repeat interruptions can give you more information about the chance for the premutation to expand to the full mutation with each pregnancy. This graph compares the chance to expand using only premutation length versus using premutation length with AGG number.

For example, if you carry between 75-79 repeats the chance for the premutation to expand to the full mutation based on your repeat length is about 50% (grey bar). For this same premutation length the chance to expand with 2 AGGs is less than 10% (green line), with 1 AGG is approximately 30% (red line), and with 0 AGGs is approximately 75% (blue line).



Nolin et al, Genetics in Medicine, 2014

WHAT TESTING OPTIONS ARE AVAILABLE DURING PREGNANCY?

Diagnostic testing can be done during pregnancy to determine if your child carries the full mutation. There are two different procedures to obtain a sample from the placenta or baby. Chorionic villus sampling (CVS) is performed between 11-13 weeks. Amniocentesis is performed at 15 weeks and later.

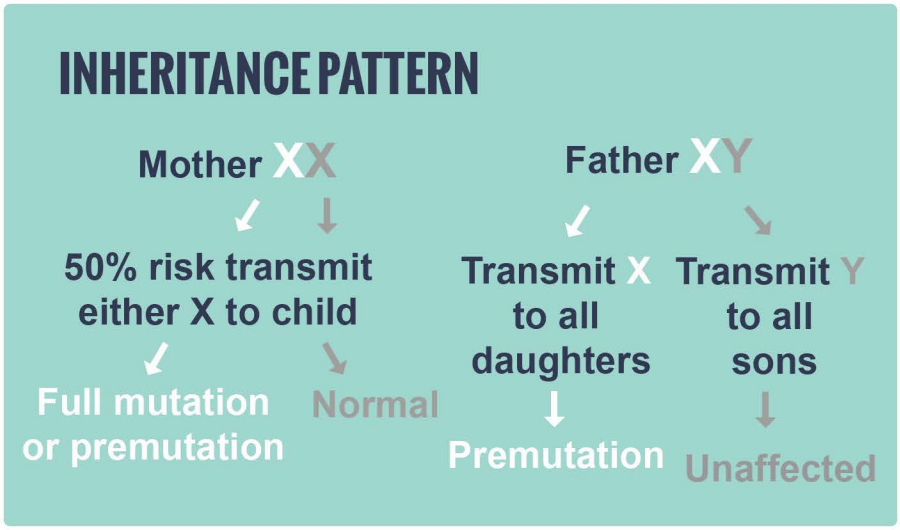
Both of these options are invasive procedures that collect some of the cells from the baby or placenta and pose a small risk to the pregnancy. If you have an amniocentesis or CVS ask your doctor to test for the fragile X repeat expansion. Results can help you prepare for or make decisions about the pregnancy.

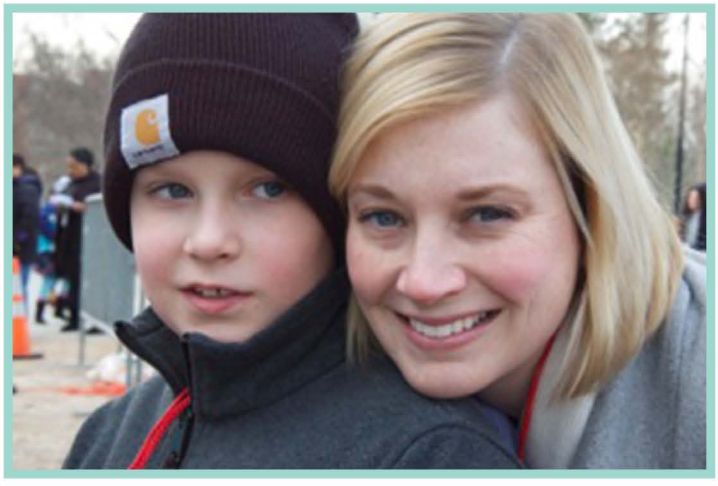
WHAT OTHER FAMILY MEMBERS ARE AT RISK?

If you are a premutation carrier, your family members may also be carriers of the fragile X premutation or full mutation.

The fragile X mutation is passed through families. Since the mutation is located on the X chromosome, it has a unique pattern of inheritance. One of your parents will carry the mutation and your brothers or sisters may also carry the mutation. This is also true for more extended family members, like grandparents, aunts/uncles and cousins. Those who have inherited the premutation will be at risk for FXPOI, FXTAS, and other health conditions related to the fragile X premutation. Some may have inherited the full mutation and they will be at risk for fragile X syndrome.

Inheritance of the fragile X repeat expansion is complex. Speak with a genetic counselor to get more information about your family. They can also help you talk with your family members and to help them learn more about the fragile X mutation and how it may affect their health.





HOW CAN I CONNECT WITH OTHER WOMEN WHO CARRY THE PREMUTATION?

Being diagnosed as a premutation carrier can be confusing and overwhelming. Many woman are interested in connecting with other premutation carriers for support or information.This can be done through your local Fragile X Community Support Network. Visit the National Fragile X Foundation website for more information. If opportunities are not yet available in your location, consider starting a group or connection that meets your needs.

Fragile X is a family diagnosis!

FAMILY PLANNING TAKE HOME POINTS

- The fragile X premutation can have implications for your pregnancies, children, and other relatives.
- Testing is available before and during pregnancy to determine the chance to pass on the full mutation.

Resources

www.FragileX.org- The National Fragile X Foundation is an organization created to support families with fragile X-associated disorders. From this website you can find a family organization or connect with other premutation carriers.

www.FRAXA.org- FRAXA research foundation is a resource for families to receive educational materials, guidance, and other fragile X associated resources. FRAXA provides a lot of support for research through funding, meetings, and conferences.

www.NSGC.org- The National Society of Genetic Counselors website is a great resource to find a genetic counselor in your area.

Build Your Plan for Better Health

Trust yourself! When it comes to your health, you are the best judge. Talk with your doctor if you are experiencing any new or concerning symptoms.

GENETICS

Genetic testing for the fragile X premutation should be considered in an individual with a personal or family history of fragile X syndrome, intellectual delay or autism, symptoms of primary ovarian insufficiency or fertility problems, or late onset tremor or ataxia.

What's your repeat size?

Who can order this testing? Almost any healthcare provider including genetic counselors, primary care physicians, or OB/GYN's can order fragile X carrier testing. Talk with your doctor about whether or not your insurance will cover this test. For information to bring to your physician about fragile X testing see: *http://www.fragilex.org/fragile-x-associated-disorders/testing/*

Have your doctor order the following test from a certified genetics laboratory:
Fragile X: CGG repeat analysis.
Once you have your repeat size you can compare your results to the table on page 8 for health information or speak with a genetic counselor for more information (Locate a counselor in your area at www.NSGC.org)

INFORMATION FOR PREMUTATION CARRIERS

FXPOI

Whether or not you are currently experiencing symptoms, consider discussing the following with your primary care physician or OB/GYN

	FSH	AMH
Baseline		
Follow up		

Before symptoms:

1. Create a menstrual diary to track your cycle length. Example: Jan-28 days
2. Check baseline hormone levels: FSH AMH

After symptoms:
Circle the symptoms you are experiencing on the list to the side.
Bring this list to your doctor. Depending on the symptoms you are experiencing your doctor may want to check or consider the following:

1. Bone density
2. Hormone replacement therapy
3. Calcium supplements

Circle any symptoms you are experiencing:

FXPOI

- Hot Flashes
- Infertility
- Mental Fogginess
- Absent or irregular periods
- Other
- Vaginal Dryness

FXTAS

Circle the symptoms you are experiencing on the list to the side.
Bring this list to a neurologist to discuss next steps

FXTAS

- Intention tremor
- Memory Loss
- Trouble performing daily activities
- Ataxia
- Other
- Parkinsonisn

FAMILY PLANNING

There are many options available to assist with family planning. You can discuss these with your OB/GYN or genetic counselor.

Before pregnancy

1. Check your repeat length and possibly your AGG interruptions (follow up with a genetic counselor for more information).
2. There are options available before pregnancy to reduce the chance of passing on the full mutation including IVF/PGD, egg donation, or adoption

During Pregnancy

1. Diagnostic testing can be performed to learn if your child carries the full mutation: CVS (10-13 weeks) or amniocentesis (after 15 weeks).

OTHER THINGS TO CONSIDER

1. Lifestyle choices can greatly influence the health risks from the premutation. Stay healthy by reducing stress, eating well, and not smoking.
2. Don't ignore symptoms of depression and anxiety. See a primary care physician or psychiatrist right away.
3. Support groups can be a helpful way to connect with other women who carry the premutation.
4. Check out your local groups on www.fragileX.org or consider starting one in your area.