FRAGILE X 101

A guide for the newly-diagnosed and those already living with Fragile X.

NATIONAL **FRAGILE X** FOUNDATION

fragilex.org

Introduction

Most people first hear about Fragile X disorders when someone in their family is unexpectedly diagnosed. It is possible you have been concerned about your child's development for some time and just received a diagnosis of Fragile X syndrome. Or maybe you have been unsuccessful in getting pregnant and found out you are a Fragile X "carrier." Maybe you have an older male relative who has tremors, memory loss, or balance problems and you are starting to wonder about the cause.

Let's look at the different Fragile X disorders:

- **Fragile X syndrome (FXS)**: A genetic condition that causes intellectual disability, behavioral and learning challenges and various physical characteristics. Though FXS occurs in both genders, males are more frequently affected than females, and generally with greater severity. It is also the most common, known single gene cause of autism spectrum disorder. Individuals with FXS have a form of the Fragile X gene called a "full mutation."

- **Fragile X-associated primary ovarian insufficiency (FXPOI)**: A cause of infertility, early menopause, and other ovarian problems in women of reproductive age, FXPOI is seen in females who have a form of the Fragile X gene called a "premutation."

- **Fragile X-associated tremor/ataxia syndrome (FXTAS)**: This adult-onset (over age 50) neurological condition causes balance and memory problems, tremors, and other neurological and psychiatric symptoms in people who have Fragile X premutations. It is more common in males than females.

- **Other potential health issues for people who have Fragile X premutations:** Although people with Fragile X premutations are generally healthy, they may experience some medical issues more commonly than the general population. These problems include: high blood pressure, migraine headaches, depression, anxiety, and hypothyroidism. Researchers continue to study possible associations with these and other health issues in people with Fragile X premutations.

Genetics and Inheritance of Fragile X

Cells, Chromosomes, Genes, and DNA

The Fragile X gene can be passed on in families by and to people of either gender who have no obvious signs of Fragile X disorders. To understand how this happens, we will review basic hereditary information.

Every person's body is made up of many millions of tiny structures called cells. Within each cell is the genetic information we inherit from our parents. The genetic information is contained in "genes," and the genes are found lined up on structures called chromosomes. The genes are made from long strands of DNA. DNA is often called the "genetic code." The DNA molecules are symbolized by letters C, G, T, and A. Each gene is made from a specific sequence of DNA molecules.

Genes are often called the units of heredity because the information they contain is passed from one generation to the next. We all inherit one gene of each pair from our mother and the other gene in a pair from our father. In this way, our bodies work with a combination of instructions inherited from both our parents. Parents have no control over which genes they pass on to their children.

Thousands of genes pack together to form chromosomes. Most people have 46 chromosomes (23 pairs). There are 44 "non-sex" chromosomes, numbered in pairs from 1-22, that are the same in males and females. We call the 23rd pair the "sex" chromosomes because they determine a person's sex (male or female). Females have two "X" chromosomes. Males have one "X" and one "Y" chromosome. The Fragile X gene is on the "X" chromosome; it is on every "X" chromosome.

FMR1: The Fragile X Gene

Fragile X got its name because, under a microscope, a portion of the X chromosome from individuals with FXS appear "broken" or "fragile." As researchers studied this area of the X chromosome in individuals with FXS, they found it contained more than the normal amount of DNA. Specifically, it turned out to a higher than usual number of repetitions of the code CGG, known as a CGG repeat.

In May 1991, researchers identified the gene responsible for Fragile X. This gene, on the X chromosome, is called *FMR1*, which stands for "Fragile X Mental Retardation 1."

Note: The term "mental retardation" has since been replaced by "intellectual disability," but that is what the gene was originally named in the scientific literature.

Every person has at least one copy of the *FMR1* gene. Since women have two X chromosomes, they have two copies of the gene. Men have only one X chromosome, so they have just one copy of *FMR1*. The gene varies in length from one person to another. The variation occurs because the number of CGG repeats varies from person to person. What distinguishes people who have a Fragile X mutation from those who don't is the number of times this CGG pattern is repeated.

Most of our genes either make a protein or regulate proteins made by other genes. The *FMR1* gene is responsible for producing a protein that is important in brain development. This protein is called FMRP (Fragile X Mental Retardation Protein). In people with FXS, the extra CGG repeats cause *FMR1* to become "methylated," a chemical change that silences the gene and prevents it from making FMRP. FXS is caused by a lack of FMRP.

FMR1 Expansions

FMR1 usually has between 5 and 44 CGG repeats, with most people having 29 or 30. Three different types of *FMR1* expansions can occur: intermediate, premutation, and full mutation.

1. Intermediate or "Gray Zone"

- 45 to 54 CGG repeats. *This type of expansion is common* and found in 1 in 3 individuals in the general population.
- Intermediates are not associated with any known medical problems, and individuals with expansions in this range are not at risk to have children with Fragile X syndrome.
- In a small number of families, intermediates change slightly in the next generation and may lead to premutations in future generations.

2. Premutation

- 55 to 200 CGG repeats.
- As many as 1.5 million individuals in the U.S. are estimated to have an *FMR1* premutation.
- Premutations can be unstable and expand to full mutations when passed from a mother to her child, causing FXS.
- Females with premutations are at risk for infertility/early menopause and other ovarian disorders (FXPOI).
- Males (and to a lesser degree, females) with premutations are at risk for the adult onset neurological disorder FXTAS.

3. Full mutation

- More than 200 CGG repeats.
- An estimated 100,000 individuals in the U.S. have a full mutation
- Males with *FMR1* full mutations typically have FXS.
- About half of females with full mutations have FXS. Others may have mild learning or behavioral symptoms (e.g.: learning disabilities, anxiety, and shyness) or no obvious features of FXS.
- A full mutation causes the *FMR1* gene to "turn off" and not work properly. This occurs by a process called methylation, which is like a switch that turns off the

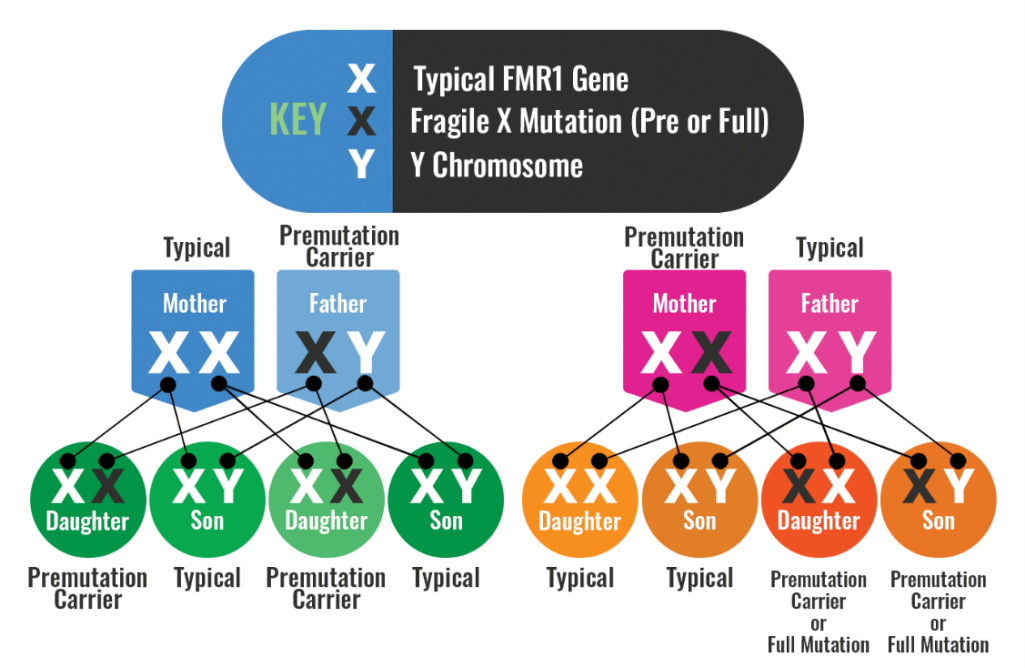
gene. (Normally the gene is “unmethylated” or switched on.) This means the gene does not produce any or enough FMRP, which is believed to be necessary for normal brain development. Current research is focusing on this protein and its function.

A small number of individuals with FXS have what is called “mosaicism.” This means they have a mixture of cells with different CGG repeat numbers and/or methylation status. For instance, a boy may have a mixture of cells, some with *FMR1* full mutations and some with premutations.

How Fragile X is Inherited

Fragile X is called an X-linked disorder because the *FMR1* gene is located on the X chromosome. X-linked conditions are inherited in a special way. A woman who carries the gene that causes an X-linked condition has a 50-50 chance of passing it to a child, whether it is a son or daughter. This is because she has two X chromosomes, and she passes one or the other on in each pregnancy. However, a man with the same X-linked gene passes it to all of his daughters and to none of his sons. This is because he passes his only X chromosome to all his daughters and his Y chromosome to all his sons.

When a father passes his premutation to his daughters, the CGG count usually stays in the premutation range. If a mother passes her X with the premutation to her children, the CGG repeat number can stay in the same range or can increase into the full mutation range. The higher the mother’s CGG repeat number, the greater the chance for it to expand to a full mutation in the next generation. Females with an *FMR1* premutation can inherit it from either parent, whereas males can inherit it only from their mothers.



Characteristics - Fragile X Syndrome

Certain physical and behavioral characteristics are associated with FXS in both males and females. Facial features of FXS tend to be more noticeable as children get older. The following physical, learning, and behavioral characteristics of FXS are usually more evident in males, but females can also demonstrate a range of features.

Common Features of Fragile X Syndrome

Physical Features

- Large ears
- Low muscle tone
- High palate (roof of mouth)
- Flat feet
- Seizures
- Crossed/lazy eyes
- Tendency for ear infections
- Flexible joints, particularly of the hands and wrists
- Long face
- Large testicles (in males at puberty)

Cognitive/Behavioral Features

- Learning and intellectual disabilities
- Attention deficits and hyperactivity (ADHD)
- Hand flapping and/or biting
- Poor eye contact
- Shyness, anxiety
- Behavior issues
- Speech and language delays
- Motor delay (late crawling, walking, toileting)
- Difficulty with transitions
- Increased sensitivity to sounds, touch, crowds, certain foods, and textures
- Autism spectrum disorder (ASD)

It is important to remember that every individual with FXS is unique. Therefore, people with FXS may exhibit very few to many of the features described.

Females with a Full Mutation

The effects of a full mutation in females can range from quite minimal to significant learning and intellectual disabilities, though these disabilities do not occur with the same frequency as in males. This is because females with a full mutation have a normal functioning *FMR1* gene on their other X chromosome, which means they usually produce some FMRP.

Their normal Fragile X gene may thus compensate for or "cover up" some effects of the full mutation. In addition to the learning and developmental issues listed above, some of the symptoms reported in females with full mutations include difficulty with math, reading maps and graphs, picking up "social cues," social anxiety, depression, and other mental health issues. Females with full mutations are not at risk for FXPOI or at higher risk for infertility than the general population.

Treatments for FXS

Research and clinical experience have shown that children with FXS may benefit from the following treatments and interventions:

- Early intervention programs
- Speech and occupational therapies
- Behavioral therapies
- Special education
- Medications for symptom-specific issues such as anxiety, ADHD, seizures, etc.

Adolescents and adults with FXS also benefit from educational opportunities that help them acquire appropriate life skills. These programs can begin in high school and extend into adulthood and should include education and guidance in matters of employment, social activity, recreation, and sexuality.

The NFXF Consensus Documents can help you and your doctors/clinicians determine the best treatment options. They are available at fragilex.org/consensus.

Fragile X-associated Primary Ovarian Insufficiency (FXPOI)

FXPOI occurs in about a quarter of females with Fragile X premutations. It can cause irregular or absent menstrual periods, reduced fertility, infertility, and premature or early menopause—these are all effects of abnormal ovarian functioning.

It is important for women or teens with a premutation to keep track of their menstrual cycles and to discuss the potential for FXPOI with their health care providers. Because of the decrease in estrogen production (which is common in those with any type of ovarian insufficiency), blood hormone levels may be helpful in assessing those at risk for FXPOI. Women with FXPOI should be followed by an OB/GYN or reproductive endocrinologist familiar with ovarian insufficiency.

When women discover they are infertile, they can experience a profound grief reaction. Often, their long-held dreams of becoming pregnant and having biological children are now lost. In addition, the fact that if a pregnancy were to be conceived, there would be a risk for FXS can complicate the options and the decisions faced by a carrier and her partner.

Treatments

Women with FXPOI should discuss medical interventions with their doctor. They may need to consider treatment such as hormone therapies if they are experiencing discomfort from the symptoms of ovarian insufficiency (hot flashes, etc.). Couples who wish to pursue infertility treatments or learn about their reproductive options should meet with a reproductive endocrinologist and genetic counselor familiar with FXD to discuss these issues. Support groups such as IPOFA (ipofa.org) or RESOLVE (resolve.org) can also be of help to infertile couples.

Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)

FXTAS is an adult-onset neurological condition that occurs in some people who have *FMR1* premutations. Though it occurs more commonly in male carriers, some females also develop features of FXTAS.

FXTAS is sometimes misdiagnosed as Parkinson's Disease, Alzheimer's Disease, or a stroke.

The features of FXTAS include balance problems (ataxia), shaky hands (tremors), memory loss, mood instability or irritability, numbness of the extremities (neuropathy),

lack of normal inhibitions, and cognitive decline. Some, but not all people with FXTAS, also show specific findings on magnetic resonance imaging (MRI).

Some of the psychological, cognitive, or neurological features of FXTAS are often attributed to the aging process and not initially recognized as symptoms of the condition. This is especially true for symptoms such as impulsivity, short-term memory loss, depression, mood instability, or irritability. It is important to pay attention to any unexplained personality or neurological changes in older adults at risk for FXTAS.

The symptoms of FXTAS tend to progress over time. Some individuals remain stable over many years with only minimal symptoms, while others can decline steadily and/or rapidly.

The diagnosis of FXTAS can be confusing and frightening. Neurologists are still in the early stages of understanding its impacts and range of treatments with Fragile X disorders can affect multiple people in different generations, and this can cause stress and tension in families. Sometimes the routine of caring for a child with FXS is complicated by the emergence of additional demands to take care of the newly diagnosed adult with FXTAS.

Treatments

Current treatments for FXTAS include physical and occupational therapy and various medications to control tremors, ataxia, depression, and dementia. As with the other Fragile X conditions, ongoing consultations with a knowledgeable physician are invaluable in helping to manage FXTAS symptoms to the person's greatest possible benefit.

Fragile X Clinics

All the clinics in the Fragile X Clinical and Research Consortium (FXCRC) provide medical services – including medication evaluation and consultation – supervised by a medical doctor. Multidisciplinary services and/or referrals, such as occupational therapy, speech and language therapy, behavioral therapy, and genetic counseling are available within the institutions or through referral.

Many of the clinics also participate in collaborative research efforts with other Fragile X clinics and professionals.

The FXCRC was created in 2006 by the NFXF in response to the growing needs of families whose members have Fragile X.

Find a clinic near you at fragilex.org/clinics.

Research

The NFXF keeps the public well-informed about the latest research and clinical trials and created and manages the NFXF Biobank[tm] and the Collaborative Biomarker Project, which is helping provide vital data for Fragile X researchers around the world.

The NFXF periodically assists with research recruitment through a variety of means including emails and social media postings. If you are interested in participating in research and/or clinical trials, you can visit fragilex.org/research-recruitment.

Support from the NFXF

Receiving a diagnosis of a Fragile X disorder presents a distinct challenge for individuals and their families. The challenge relates to both known and unknown effects of the specific conditions. Having a child or other family member with a Fragile X disorder or any disability means extra work—sometimes a lot of it. Anyone diagnosed with a Fragile X condition will find his or her (and entire family's) life changed.

However, as countless families who have lived with Fragile X disorders can readily attest, a changed life does not mean it will be a bad life—just a different life.

Fragile X disorders affect people all over the world, which has given rise to support groups on every continent.

Researchers around the world are studying and seeking ways to reduce the impact of Fragile X disorders. They make substantial and inspiring progress every year.

The National Fragile X Foundation (NFXF) is here to help you by providing the latest information and guidance. All questions are welcome. Rest assured that your question is not too simple or trivial. We are here to help you wherever you are in your journey and the NFXF has more resources than ever to assist you in obtaining an answer.

Our website, fragilex.org, has the largest and most trustworthy collection of news and information about Fragile X. To receive regular updates, follow us on social media on Facebook and subscribe to our email newsletter. You can also call or email for individual responses to any of your questions or concerns.

Perhaps the most important point to remember is this: *You're not alone.*

- ✓ Community Support Network: fragilex.org/community
- ✓ Phone: 1-800-688-8765
- ✓ Email:treatment@fragilex.org
- ✓ Website: fragilex.org
- ✓ Facebook: facebook.com/natlfragilex
- ✓ Twitter: @NFXFoundation
- ✓ Instagram: instagram.com/nfxfoundation