

## An Overview:

Understanding  
Fragile X

## ■ What Is Fragile X?

Fragile X (FX) is a group of genetic conditions that can impact families in many ways. It includes fragile X syndrome (FXS), the most common cause of inherited mental impairment, ranging from learning disabilities to severe cognitive or intellectual challenges (often still referred to as mental retardation) including autism or "autistic-like" behavior. Symptoms can include physical characteristics, behavioral deficits, and delays in motor and speech/language development.

FX also includes fragile X-associated tremor ataxia syndrome (FXTAS), a condition affecting balance, tremor, and memory in carriers older than 50 years; FXTAS primarily affects male carriers but, rarely, female carriers are affected. In female carriers, FX can also cause infertility due to a condition that is sometimes called "early menopause" and is medically referred to as premature ovarian failure or primary ovarian insufficiency.

FX can be passed on in a family by carriers with no apparent sign of the condition. In some families it has affected numerous family members through the generations, while in others, it initially seems to have caused problems in only one person.

## ■ What Causes Fragile X?

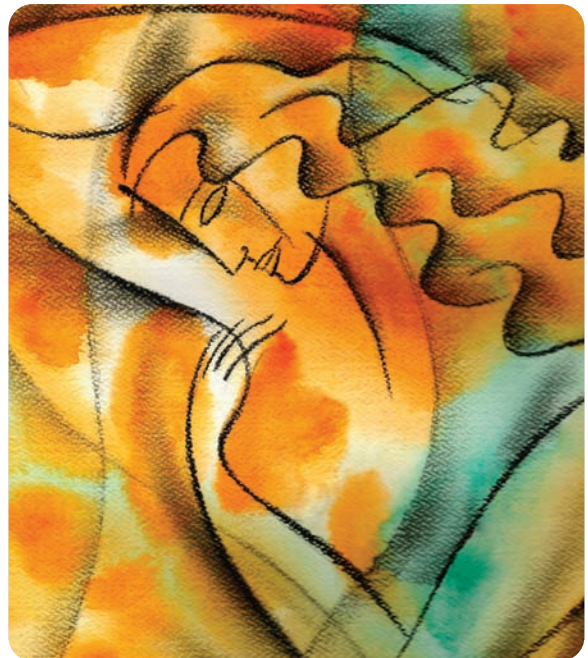
FX occurs when a gene (*FMR1*) becomes altered, or mutated. The mutation in the *FMR1* gene is an expansion of the specific chemical components of DNA (CGG). Although everyone has an *FMR1* gene with approximately 5 to 40 CGG repeats, people who are carriers of FX have between 55 and 200 repeats: this is called a "premutation." Most carriers are unaffected intellectually because they have normal levels of the *FMR1* protein.

In individuals with FXS, the number of CGG repeats is over 200. This expanded number of repeats is called a "full mutation" and it causes the *FMR1* gene to "turn off" or not work properly. An *FMR1* gene that is turned off doesn't produce enough, or any, of the protein that it is designed to produce. This protein is known to be critical to intellectual development and functioning.

Females can inherit the FX gene from their mother or their father. Males can only inherit FXS from their mother.

## ■ What Is Fragile X Syndrome?

FXS is the most common known cause of inherited mental impairment. People with FXS share a range of intellectual,



behavioral, and physical features. Both males and females can be affected. Approximately 1 in 250 females and 1 in 800 males carry the gene mutation that causes FXS. Many are unaware that they are carriers. FXS affects people of all ethnic groups worldwide.

Females with a full mutation usually have milder symptoms than males with a full mutation. Since females have two X chromosomes, the unaffected X chromosome can sometimes compensate for the one with the FX mutation, causing milder symptoms.

## ■ What Is Fragile X-Associated Tremor/Ataxia Syndrome?

Carriers of the FX gene premutation are generally thought to be spared the problems associated with the full mutation. However, a neurological disorder called FXTAS was identified in 2002, which involves progressively severe tremors and difficulty with walking and balance, and affects some older premutation carriers; more men than

women are affected. Although this neurological disorder occurs by a different mechanism than FXS and affects different individuals, it is caused by the same gene. At this time there is no cure for FXTAS; however, having the proper diagnosis can help medical professionals provide medication and therapeutic interventions.

### ■ Characteristics of Fragile X Syndrome

The clinical characteristics of FXS can be divided into three major areas: cognitive, physical, and behavioral. Males are usually more severely affected than females. Approximately 1 in 3,600 males and 1 in 4,000 to 6,000 females have mental impairment due to FXS.

**Cognitive:** The spectrum of intellectual involvement ranges from learning difficulties to severe cognitive disabilities and autism. Common problems include delayed milestones (walking, talking, toileting), attention deficits, and hyperactivity.

**Physical:** Adult males often have a long face, large and/or prominent ears, and enlarged testicles (macroorchidism). Problems with loose connective tissue (ie, ligaments) are frequent, including double-jointed fingers, flat feet, and a heart murmur (mitral valve prolapse). Females and younger children may also have some of these features, or they may look no different from the general population.

**Behavioral:** Behavior ranges from socially engaging and friendly to autistic-like and occasionally aggressive. People with FXS can become easily overwhelmed by sensory stimuli such as crowds, noises, or light touch.

### ■ Diagnosis

It is believed that many affected children and adults are undiagnosed. The following individuals should be considered for *FMR1* testing to rule out FXS or FXTAS:

- Individuals with mental impairment or autism of unknown cause
- Individuals with significant hyperactivity, learning disabilities, and/or mild cognitive deficits
- Individuals with any of the physical or behavioral features of FXS or FXTAS, regardless of gender or family history
- Any person who has a family member with a diagnosis of FXS or FXTAS, or a family history of mental impairment
- Women with unexplained infertility or primary ovarian insufficiency (also called premature menopause or premature ovarian failure)

The testing for FXS and FXTAS involves taking a blood test. It is very important to request the *FMR1* gene test, which is a direct DNA test for FX, and to ask that both PCR (polymerase chain reaction) and Southern Blot testing be

performed. When these tests are performed together, the diagnosis can be more than 99% accurate.

When specifically requested, the DNA test also can detect mutations in the *FMR1* gene in a developing fetus. Prenatal diagnosis for FXS can be performed from 10 to 20 weeks' gestation. All couples with a family history of FX or unexplained mental impairment on either side of their family may want to seek genetic counseling prior to becoming pregnant or early in a pregnancy in order to discuss their prenatal diagnostic options.

### ■ Genetic Counseling

Individuals diagnosed with FXS or FXTAS, individuals who learn someone in their family has either condition, and individuals with unexplained mental impairment within their family should receive genetic counseling. A genetic counselor familiar with FX can offer extensive information and support regarding testing, inheritance patterns, and available family planning options. Genetic counselors can also help families cope with a positive diagnosis.

### ■ Treatment for Fragile X Syndrome

At this time there is no cure for FXS; however, many treatments are available. Treatment is primarily provided through various forms of therapy including special education, speech and language therapy, occupational therapy, and physical therapy.

Medication is often helpful in managing hyperactivity and short attention spans. Other medications can be helpful for aggression, anxiety, and depression. In order to create and provide an optimal educational, therapeutic, or vocational program, it is important to assess both an individual's overall development and the best informational resources available. For help accessing these resources, please contact the National Fragile X Foundation (see below).

#### THE NATIONAL FRAGILE X FOUNDATION

The National Fragile X Foundation unites the Fragile X community to:

- Enrich lives through education and emotional support
- Promote public and professional awareness
- Advance research toward improved treatments and a cure for Fragile X

*This handout was created by*

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