Signs and Symptoms

Fragile X syndrome (FXS) is an inherited condition and one of the most common causes of inherited intellectual disability (1-2% of all ID) and autism spectrum disorders (2-3% of all ASD). Individuals with FXS commonly have:

- developmental delays, including
  - speech delays
  - cognitive/intellectual delays
  - social/behavioral problems (tantrums, ADHD/ADD, hand flapping, acting and speaking without thinking, and poor eye contact)
- autism spectrum disorder
- seizures
- flexible joints
- scoliosis
- flat feet
- macroorchidism (abnormally large testicles)
- heart issues (particularly mitral valve prolapse or aortic root dilation)
- hypotonia (decreased muscle tone)
- unique facial features, including:
  - a longer face
  - larger ears
  - a prominent forehead, and/or
  - a prominent jaw.

It is more common for males to show symptoms than females, and the symptoms in males tend to be more severe. FXS occurs in about 1 out of every 4000 males and 1 out of every 8000 females.

Genetics

FXS is caused by a repeat expansion of the *FMR1* gene, and is inherited in an X-linked pattern. The *FMR1* gene makes a protein called FMRP. One job this protein has is in the brain; it helps develop connections between nerve cells (called synapses). These connections are vital to making sure your brain can function how it's supposed to. The synapses in your brain are constantly changing in response to experiences that you have, and FMRP is thought to help regulate the evolution of these connections. This is particularly important for learning and memory.

The *FMR1* gene has a section where three letters (CGG, called a trinucleotide repeat) are repeated over and over. Everyone has these repeats in their *FMR1* gene, but how **many** repeats the gene has is important. Most people have between 5 and 40 CGG repeats in their *FMR1* gene. People who have FXS have over 200 CGG repeats (called a mutation). Having too many of these CGG repeats causes the FMRP protein that the gene makes to not work how it's supposed to. Not having enough of this working FMRP protein is what leads to the signs and symptoms of FXS.

The *FMR1* gene is located on the X chromosome. Women have two X chromosomes and males only have one (they have a Y chromosome instead of a second X chromosome), which is why it is more common to see males affected with FXS than females (females have a back-up copy of the *FMR1* gene, while males don't). Females are also usually less severely affected than males.

The number of CGG repeats that someone's *FMR1* gene has can increase (called an expansion) when it is passed down. For example, a woman could have one of her X chromosomes that has an *FMR1* gene with 80 CGG repeats, but then when she passes it down to her daughter, it expands to 120 CGG repeats. It is less common for the expansion to happen when the *FMR1* gene is passed down from someone's father. If a woman has an *FMR1* gene with over 90 CGG repeats, there is about a 94% chance that if she passes that copy of her *FMR1* gene down that it will expand to over 200 CGG repeats. This could lead to her having a son with FXS or a daughter who is a carrier for FXS (and may also have symptoms).

The AGG of it all

Some studies have shown that having what are called 'AGG interruptions' can decrease the chance that someone's *FMR1* gene will expand when it's passed down. In addition of CGG repeats, the *FMR1* gene also can contain the trinucleotide AGG within the CGG repeats (thus 'interrupting' the string of CGG repeats). Having these AGG interruptions may make the FMRP protein that the gene makes more stable and less likely to expand if it's passed down. Currently, the impact of AGG repeats on the chance for *FMR1* gene expansion are investigational and not supported by any medical guidelines, as more research is needed.

Premutation and Intermediate

The smallest number of repeats that has expanded to a mutation (200 CGG repeats) is 56. Because of this, if someone has an *FMR1* gene with between 55 and 200 CGG repeats, they are called a **premutation carrier.** *FMR1* genes that have between 45 and 55 CGG repeats

are called **intermediate**.

The *FMR1* gene in premutation carriers is still able to make FMRP protein, so they are not at risk to have FXS. However, individuals who have a premutation can be at a higher risk for Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS). Women who are premutation carriers are also at increased risk for FMR1-Related Primary Ovarian Insufficiency (FXPOI).

FXTAS is a condition characterized by tremors (trembling or shaking) and ataxia (movement, coordination, and balance difficulties). Individuals with FXTAS can also have problems with involuntary body functions (such as bladder and bowel movement control) as well as mental health issues (depression, anxiety, mood changes, etc). Average age of onset of symptoms for FXTAS is typically between 60 to 65 years of age. Males also have a higher risk for FXTAS than women (40% compared to 16-20% for women), and tend to be more severely affected.

FXPOI is characterized by a woman going through menopause (stopping of periods) before the age of 40.. Women in the general population have about a 1% risk for primary ovarian insufficiency, while women who carry a premutation have about a 20% risk. Women with FXPOI go through menopause an average of five years earlier than women without FXPOI.

Individuals who have an intermediate *FMR1* gene (45-55 CGG repeats) are not considered to be carriers, and not at risk for FXTAS or FXPOI. There have been some studies that suggest a potential increased risk for developmental or behavioral disorders, but this remains uncertain and is likely unrelated.

Diagnosis

The diagnosis of FXS is made through genetic testing that looks at the number of CGG repeats that are in the *FMR1* gene. If a male has over 200 CGG repeats in his *FMR1* gene, then he has a diagnosis of FXS. If a female has over 200 CGG repeats in one of her *FMR1* genes, then she is a carrier for FXS and may experience some symptoms. If a female has over 200 CGG repeats on BOTH of her *FMR1* genes, then she has a diagnosis of FXS. FXTAS and FXPOI are diagnosed by a combination of clinical symptoms and having between 55-200 CGG repeats in their *FMR1* gene

When to Consider Genetic Testing

Any individual who has intellectual/cognitive disability or developmental delay (where the cause is unknown) should consider testing for FXS. People with learning disabilities,

social/behavioral problems, or autism spectrum disorder should also consider seeing a medical professional to evaluate for possible FXS. Individuals with personal or family histories of FXS-related health issues (late onset tremor or ataxia of unknown cause, early menopause) may also wish to consider fragile X syndrome screening.

Treatment and/or medical management

Treatment for fragile X syndrome is primarily focused on treatment of health issues that arise, and should be tailored to each individual. Some common treatments for individuals with FXS include:

- Therapy
- Behavioral intervention
- Medications
- Speech and language therapy
- Occupational therapy
- Individualized educational support
- Early intervention

Resources

FRAXA

The National Fragile X Foundation

Fragile X Research Registry

FORWARD

References

Monaghan K, et al. ACMG Standards and Guidelines for fragile X testing: a revision to the disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics and Genomics. Genetics in Medicine. v15, n7. July 2013.

Nolin S, et al. Fragile X full mutation expansions are inhibited by one or more AGG interruptions in premutation carriers. Genetics in Medicine. V17, n5. May 2015.

Genetics Home Reference

GeneReviews