Fragile X syndrome (FXS) is an inherited genetic condition characterized by intellectual disability, developmental delays, and distinctive facial features. Cognitive symptoms include developmental delay, intellectual delay (ranging from mild to severe), and learning delays. Individuals with FXS also have a higher chance for behavioral differences, such as attention deficit hyperactivity disorder (ADHD), anxiety, hand biting, hand flapping, poor eye contact, and autism spectrum disorders. Physically, many (but not all) people with FXS have distinctive facial features (protruding ears, long face, prominent forehead and chin, large head), hyperflexible joints, soft skin, and a heart condition called mitral valve prolapse.

Causes

FXS is caused by a harmful change (called a pathogenic variant) in the *FMR1* gene. The *FMR1* gene is responsible for making 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 is made up of three letters that repeat themselves over and over (called a trinucleotide). It is normal to have these three letters (CGG) repeated in the *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. Having too many of these CGG repeats cause 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.

Premutation Carriers

Individuals with number of repeats in the 55 to 200 range are considered to be *premutation carriers*. While most premutation carriers have no signs or symptoms of FXS, they are at risk for fragile X tremor ataxia syndrome (FXTAS), which causes ataxia, or loss of control of body movements. FXTAS typically occurs in men who are premutation carriers, and can progressively get worse over time.

Women who are premutation carriers are also at an increased risk for fragile X associated primary ovarian insufficiency (FXPOI), which is menopause prior to 40 years of age. FXPOI occurs in about 20% of women who are premutation carriers.

If someone is a premutation carrier, it is possible for the number of CGG repeats to increase when they pass that gene down to any children they have. For example, Sarah is a FXS premutation carrier that has 150 CGG repeats on one of her X chromosomes. She has a son who inherited that X chromosome from her, but when she passed it down to him the number of CGG repeats had increased to 210. This means that he would have FXS. It is difficult to predict how the number of CGG repeats can expand in future generations, but talking with a genetics professional, such as a genetic counselor, can be helpful to gather more detailed information about this.

Inheritance

FXS is inherited in an X-linked dominant pattern because the *FMR1* gene is located on the X chromosome. X-linked dominant means that one non-working copy of a gene on the X chromosome is enough to cause FXS. Men only have one copy of their X chromosome, and therefore only one copy of all the genes that are on the X chromosome. If they inherit an X-linked dominant condition, they will be affected. Because women have two X chromosomes, they have one non-working copy of the gene and one working copy of the gene. However, since having only one broken copy of the gene causes X-linked dominant conditions, women who inherit a non-working gene for X-linked dominant conditions often also show symptoms. It is common for men with FXS to be more severely affected than women.

It is estimated that 1 in 4000 males and 1 in 8000 females has FXS.

Medical Management for FXS

Currently, there is no cure for FXS. However, life expectancy is not expected to be affected as the health concerns associated with FXS are not usually life-threatening or life-limiting. Management of FXS often focuses on early developmental intervention including specialized education with individualized attention as well as early behavioral and other supportive therapies. There are also specialized FXS clinics in many parts of the country that help guide medication options that may more specifically address the health concerns that are more common in people with FXS.

For individuals with FXTAS, management can include medications, supportive care for gait disturbance, counseling, and rehabilitation treatments. For individuals with FXPOI, endocrine evaluations are recommended along with genetic counseling to discuss reproductive options.

Click here to learn more about scheduling a genetic counseling appointment for pregnancy-related questions.

Click here to learn more about scheduling a genetic counseling appointment for infertility or preconception questions.

Click here to learn more about scheduling a genetic counseling appointment for questions about pediatric or adult genetic conditions.

Additional Resources

National Fragile X Foundation

GeneReviews

Genetics Home Reference