# Understanding Fragile X Syndrome

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Fragile X syndrome (FXS) is a genetic disorder that is often associated with autism spectrum disorder (ASD). Since the behavior and social deficits seen in children with FXS are the same as those found in ASD, children with Fragile X are often initially diagnosed with autism. Genetic testing is required to determine if Fragile X syndrome is the cause of the ASD. While FXS is considered the most common known genetic cause of ASD, there are hundreds of other genetic causes of ASD. That is why it is important for all children diagnosed with ASD to have genetic testing, including the Fragile X DNA test. Most studies show that about two percent of individuals diagnosed with autism have Fragile X syndrome.[1,2] In addition, 60 percent of children with Fragile X syndrome also meet the diagnostic criteria of ASD, which means these children have both FXS and ASD.[1,3]

## Genetics

Each cell in the human body contains 23 pairs of chromosomes. Individuals receive one half of each pair of chromosomes from their mother and the other half from their father. The 23rd pair of chromosomes is called the sex chromosome and it determines if a person is genetically male or female. Females have two X chromosomes (XX) and males have one X chromosome and one Y chromosome (XY). The Fragile X gene is located on the X chromosome, which is why the condition is called Fragile "X." This is important when determining the genetic history of Fragile X in your family.

Each chromosome is constructed of tightly coiled strands of DNA. DNA is made up of building blocks called nucleotides. There are four building blocks/nucleotides: Adenine (A), Cytosine (C), Guanine (G) and Thymine (T). These nucleotides are strung together, one after another, in varying sequences (i.e. GCTTACTACCG). One segment or section of DNA is called a gene and each human cell contains thousands of genes (See figure 1). Genes determine our physical characteristics and can also lead to certain illnesses and disorders. Most importantly, genes act as a set of instructions and tell the cell how to make a specific protein. Proteins are responsible for making the body function correctly. When there is a change or mutation in the DNA sequence (nucleotides) in a gene, this is called a genetic mutation.

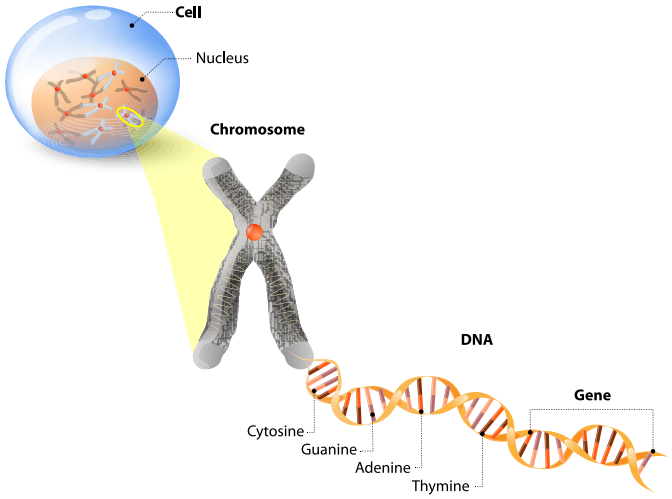
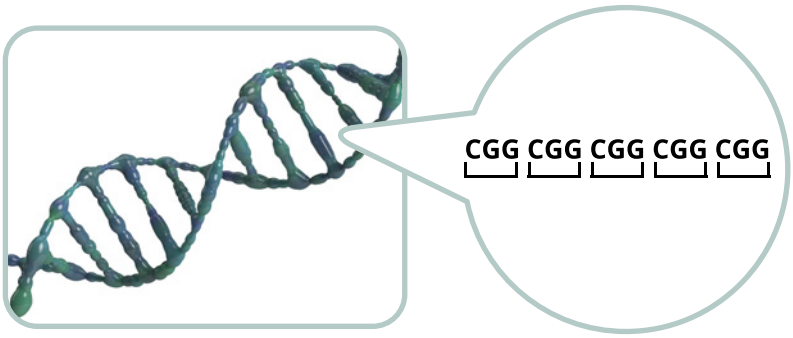



*Figure 1. The relationship between the cell, chromosome, DNA, nucleotides and the gene.*

## The Genetics of Fragile X Syndrome

Fragile X syndrome is caused when there is a mutation, or change, to the gene known as the *FMR1* gene. This gene is located on the bottom end of the X chromosome. At the front end of the *FMR1* gene, there is a group of three nucleotides (CGG) that repeat over and over. Normally, the grouping of 'CGG' repeats anywhere between 5 and 45 times. The average number of CGG repetitions for the general population is about 30. If an individual has 45 to 54 CGG repetitions, they are considered to be in an intermediate or grey zone. The clinical implications of being in the grey zone are uncertain, but many individuals with autism fall into this zone. Individuals with 55 to 200 CGG repetitions, are considered to have a "premutation" of Fragile X. The premutation is not a full mutation (>200 repeats) that causes Fragile X syndrome. Individuals with a premutation usually do not have intellectual deficits but often have ADHD and anxiety in childhood. Also, about 15 percent of males with the premutation have ASD.

In adulthood many individuals with the premutation have anxiety and/or depression, but also medical difficulties such as high blood pressure, fibromyalgia, migraine headaches, early menopause or hypothyroidism. A carrier of the premutation who reaches the age of 60, is at risk of developing Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) that includes tremor in the hands and difficulties with balance. When an individual has 200 or more CGG repetitions at the beginning of the FMR1 gene, he/she is considered to have the "full mutation" or Fragile X syndrome.[1] (See figure 2)




| Number of CGG Repeats | | | |
|---|---|---|---|
| Typical | 5 | to | 45 |
| Intermediate (Grey Area) | 45 | to | 54 |
| Premutation | 55 | to | 200 |
| Full Mutation (Fragile X) | 200+ | | |

*Figure 2. CGG repeats in the FMR1 gene.*

The Fragile X gene, or *FMR1* gene, is found in every cell in the body. It is responsible for producing a major regulatory protein known as FMRP that regulates hundreds of other genes needed for normal brain development. The abundance of over 200 or more CGG repetitions causes the *FMR1* gene to shut down, or turn off, through a process known as methylation. When the gene is shut off, copies of the gene (messenger RNA or mRNA) cannot be produced, and consequently FMRP is not produced. Without the production of the FMRP protein, brain development is compromised (See figure 3). It is worth noting that individuals with the premutation make an abundance of mRNA from the FMR1 gene, which causes RNA toxicity. RNA toxicity leads to the premutation difficulties listed above, including FXTAS (See figure 4). The FMRP regulates the translation (or conversion) of mRNAs into their respective proteins for hundreds of other genes, including about 30 percent of the genes involved in ASD.[4]



With the Fragile X full mutation (more than 200 CGG repeats), the *FMR1* gene is shut off.

When the *FMR1* gene is turned off, FMRP (protein) is not produced.

Without FMRP, brain development is compromised

*Figure 3. Full mutation of the FMR1 gene causes compromised brain development.*

## *FMR1* gene - Premutation vs. Full Mutation

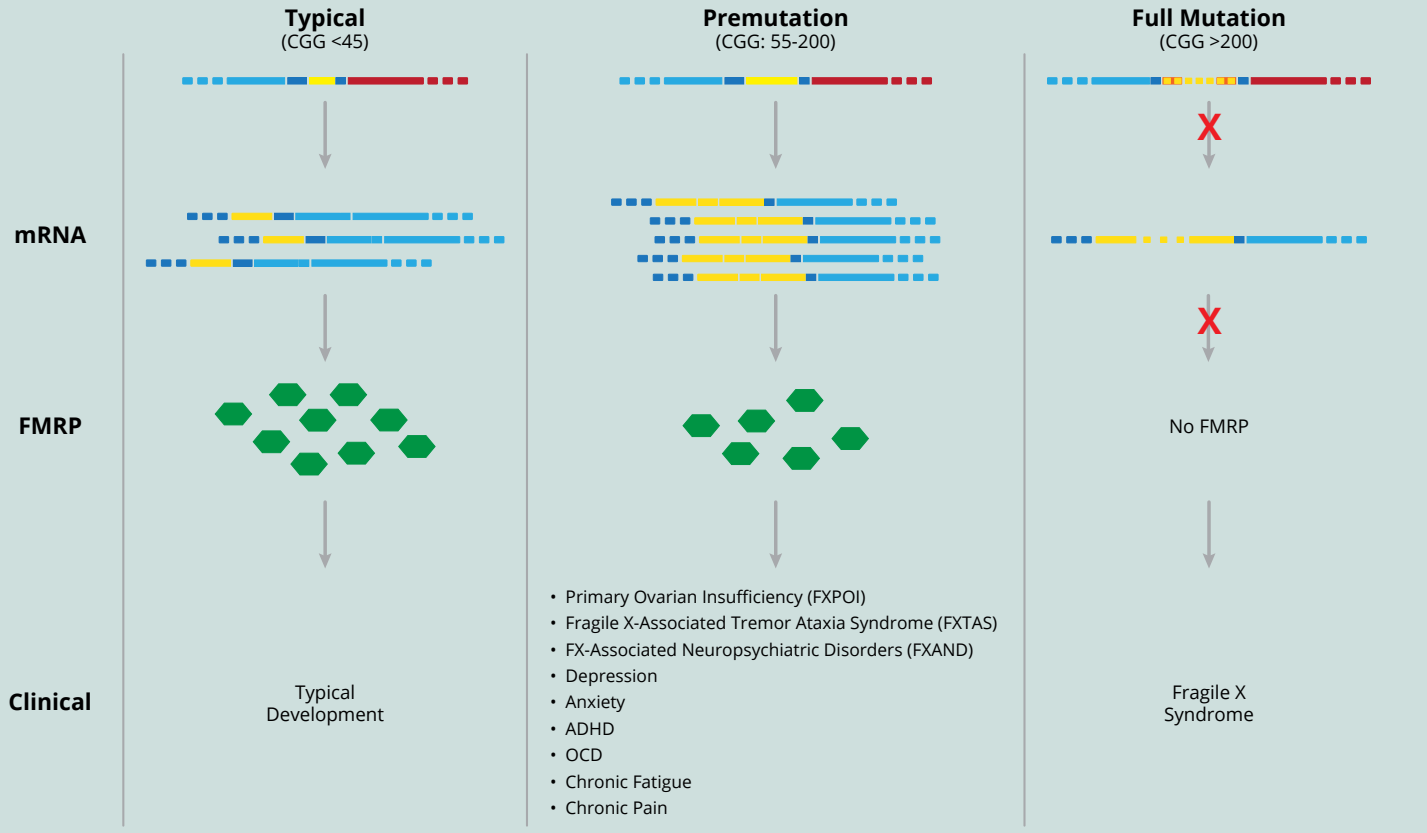



*Figure 4. A comparison between typical, premutation, and full mutation of the FMR1 gene as it relates to mRNA production, FMRP and clinical outcomes.*

As a result, when FMRP is deficient or absent, there is dysregulation of many other pathways associated with ASD. This is why there is a significant number of children with FXS that also have ASD. The association between FXS and ASD involves significant molecular overlap.[1]

## Symptoms of Fragile X Syndrome

Just as autism is diagnosed on a spectrum, the symptoms of Fragile X syndrome also vary from individual to individual. Some of the most common symptoms include the following:

- intellectual disability (IQ<70) in 85 percent of males and 30 percent of females
- anxiety (90%)
- attention deficit hyperactivity disorder (ADHD) (85% of males and 50% of females)
- poor eye contact (80 - 90 %); an individual with Fragile X finds it very uncomfortable to look other people in the eye
- hand flapping (70%)
- hand biting (50%)
- impulsive behavior (85%)
- perserveration, which means asking the same question over and over again (100% of males and 60% of females)
- prominent ears with the ears being cupped (60%)
- long face as individuals age
- high arched palate (60%)
- hyperextendable finger joints as a child (80%)
- soft and velvet-like skin with extra wrinkly skin on the palms of the hands (60%)
- enlarged testicles (2 to 3 times normal size) in males during puberty (90%)
- seizures (15 to 20%)
- autism spectrum disorder (60% in males and 20% in females)

The severity of anxiety in an individual with Fragile X correlates with an additional diagnosis of ASD. In general, most individuals with Fragile X are anxious. Those that are severely anxious will likely also qualify to be diagnosed with autism.[5]

## How to test for Fragile X Syndrome

Every individual who is diagnosed with autism, or who has some or all of the symptoms above, should be tested for Fragile X syndrome with a Fragile X DNA test. Autism professionals are very familiar with this test and can advise parents where the test can be conducted. This test can usually be done by a primary health care provider. After an individual is tested, the results will show how many CGG repetitions are found. This will help you determine if the child is classified as typical, intermediate, premutation, or full mutation. In addition to the Fragile X DNA test, a child with ASD should have a full genetic test, which includes a test called a "microarray." This is also called a CGH array and looks for deletions or duplications in the genome that can also lead to ASD. This is especially useful information if the Fragile X DNA test is normal. If both the Fragile X DNA test and the CGH array are normal, the geneticist will recommend either whole exome sequencing (WES) or whole genome sequencing (WGS) to identify if a point mutation — a mutation affecting only one or very few nucleotides in a gene sequence — is the cause of ASD.

## Why should I test my child for Fragile X?

**Family History** – Fragile X syndrome is a genetic mutation that is passed from a parent to a child. Assuming both parents do not have Fragile X syndrome, they might wonder how their child developed the condition. If a child is diagnosed with Fragile X syndrome (i.e., diagnosed with the full mutation) and neither parent has symptoms of Fragile X, it means that the child's mother has the premutation. Fragile X can only expand to the full mutation when it is passed from the mother. If the father has the premutation, it will only pass on to all of his daughters. The daughters are then at risk for having a child with FXS. It is also possible that the mother has the full mutation, and simply doesn't know. About 30 percent of women with the full mutation do not have an intellectual disability as the Fragile X symptoms in females are often mild and can go undetected. The Fragile X family mystery does not stop there. The mother must have received the premutation from either her mother or father. If she received it from her father, it means that all of the mother's sisters also have the premutation. If it was passed from the mother's mother, all of the mother's siblings have a 50 percent chance of inheriting the premutation or even a full mutation. These patterns link back to the fact that the Fragile X mutation is on the X chromosome. (See figure 5)

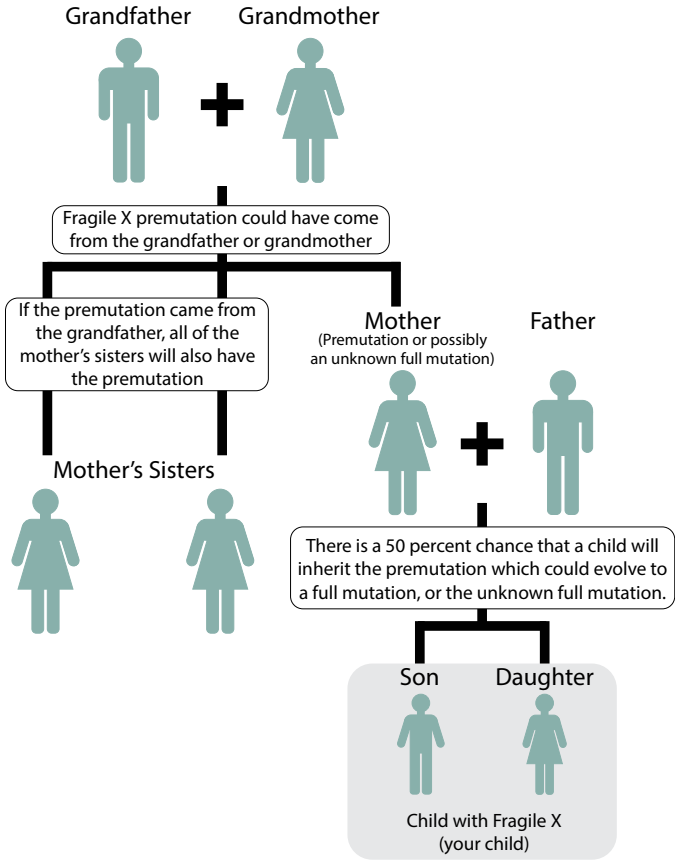



*Figure 5. The family history of Fragile X syndrome.*

Understanding the family history of Fragile X syndrome is important because it involves many family members, not just your child. You may have an uncle who was diagnosed with Parkinson's but is actually suffering from FXTAS (Fragile X-associated Tremor/Ataxia Syndrome). Perhaps you have an aunt that has migraine headaches or hypertension. You could have siblings with learning difficulties or severe anxiety. These are all Fragile X premutation symptoms. Once you have proper diagnoses, you can seek the proper treatments.

**Targeted treatments** – There are now targeted treatments that have been shown to be helpful for those with Fragile X syndrome. Metformin, a medication currently used to treat type 2 diabetes, has been shown to normalize some of the central nervous system molecular abnormalities that are associated with Fragile X syndrome.[6] CBD Oil and Gaboxodol have also been studied and show promising results.[7] Before using any medication, speak with your doctor and decide on the course of treatment that is best for your child. Targeted treatment will depend on the results seen in the Fragile X DNA test, CGH array, whole exome sequencing (WES) and whole genome sequencing (WGS) tests.

**Targeted therapy approaches** – A child with Fragile X syndrome will benefit from the therapies and interventions typical for a child with autism, such as speech therapy, occupational therapy, physical therapy and special education. These are all very important and should be investigated by parents. There are also a number of therapy approaches that are very effective for a child with Fragile X syndrome, including PROMPT therapy, Parent Implemented Language Intervention (PILI)[8] and Early Start Denver Model (ESDM).[9]

Determining if your child has Fragile X syndrome can benefit the entire family and serves as a guide for treatment. Families with a child who has Fragile X can seek genetic counselling for future pregnancies. Fragile X research is making dramatic progress in finding targeted treatments that can ameliorate or dramatically improve Fragile X syndrome. Treatments are also moving into an era of gene manipulation and genetic treatments, which can potentially reverse biological abnormalities in the future. If your child has not been tested for Fragile X, ask your doctor to do the Fragile X DNA test to find out if your child's autism symptoms could be caused by a mutation in the *FMR1* gene.

## Support for Individuals with Fragile X Syndrome

Connect with other parents whose children have Fragile X.
National Fragile X Foundation - https://info.fragilex.org/
Fraxa Research Foundation - https://www.fraxa.org/
Email Dr. Hagerman for more information rjhagerman@ucdavis.edu

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Randi J. Hagerman, M.D., is the medical director of the UC Davis MIND Institute and director of the Fragile X Research and Treatment Center. She has more than 30 years of experience in the field of neurodevelopmental disorders and is an internationally respected leader in Fragile X research. Dr. Hagerman, her husband, Dr. Paul Hagerman, and their research team are the discoverers of Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), a late-onset neurodegenerative disorder. Randi Hagerman conducts clinical research on individuals with Fragile X-associated disorders, including children and adults with Fragile X syndrome, adult males with FXTAS, and women with Fragile-X related conditions, such as Fragile X-associated primary ovarian insufficiency (FXPOI). Dr. Hagerman also conducts research that bridges the association between autism and Fragile X syndrome. Dr. Hagerman has written more than 400 peer-reviewed articles and numerous book chapters on neurodevelopmental disorders, and has written several books on Fragile X. They include *Fragile X Syndrome: Diagnosis, Treatment, and Research, 3rd edition* (2002), *Treatment of Neurodevelopmental Disorders: Targeting Neurobiological Mechanisms* (2014), *Textbook of Autism Spectrum Disorders* (in press 2020) and *Fragile X Syndrome and Premutation Disorders* (in press 2020). In 2004, The National Fragile X Foundation (NFXF) honored Randi and Paul Hagerman for their work on FXTAS, by establishing the Hagerman Award for research on FXTAS. The NFXF also honored Randi Hagerman in 2008 with a Lifetime Achievement Award.



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