FMR1-related syndrome
This guide is not meant to take the place of medical advice.

Please consult with your doctor about your genetic results and health care choices. The information in this guide was up to date at the time it was written in 2020. But new information may come to light with new research. You may find it helpful to share this guide with friends and family members or doctors and teachers of the person who has FMR1-related syndrome.
What is FMR1-related syndrome?

FMR1-related syndrome happens when there are changes to the FMR1 gene. These changes can keep the gene from working as it should.

There are two types of changes to the FMR1 gene — those that happen inside the gene itself, which are very rare, and those that happen near the gene, which are more common.

Changes near the gene lead to a condition called fragile X syndrome.

In some cases, changes within the FMR1 gene also lead to fragile X syndrome. In other cases, people who have changes within the FMR1 gene may have some symptoms of fragile X syndrome, but not all. This is referred to as FMR1-related syndrome. Males who have changes that affect FMR1 usually have more severe symptoms than females.

SPARK detects changes that happen within the FMR1 gene. SPARK does not detect changes that happen outside of the FMR1 gene that typically cause fragile X syndrome.

This guide provides information on genetic changes that happen within the FMR1 gene.

More information on fragile X syndrome can be found at the following links:

- **GeneReviews**
  www.ncbi.nlm.nih.gov/books/NBK1384

- **National Organization for Rare Disorders**
  www.rarediseases.org/rare-diseases/fragile-x-syndrome

- **National Fragile X Foundation**
  www.fragilex.org/understanding-fragile-x/fragile-x-syndrome

**Key role**
The FMR1 gene plays a key role in the communication between brain cells.

**Symptoms**
Because the FMR1 gene is important in the development and function of brain cells, many people who have FMR1-related syndrome have:

- Intellectual disability
- Developmental delay
- Autism
What causes FMR1-related syndrome?

Our genes contain the instructions, or code, that tell our cells how to grow, develop, and work. Genes are arranged in structures in our cells called chromosomes. Chromosomes and genes usually come in pairs, with one copy from the mother, from the egg, and one copy from the father, from the sperm.

We each have 23 pairs of chromosomes. One pair, called the X and Y chromosomes, differs between biological males and biological females. Biological females have two copies of the X chromosome and all its genes, one from their mother and one from their father. Biological males have one copy of the X chromosome and all its genes, from their mother, and one copy of the Y chromosome and its genes, from their father.

In most cases, parents pass on exact copies of the gene to their child. But the process of copying genes is not perfect. A change in the genetic code can lead to physical issues, developmental issues, or both.

The FMR1 gene is located on the X chromosome, so changes in this gene can affect biological males and biological females in different ways. Biological males have only one copy of the gene, so they tend to have more severe symptoms than females.

In some cases, FMR1-related syndrome is inherited. In other cases, it results from a random change in the FMR1 gene in the sperm or egg during development. This change to the genetic code is called a ‘de novo’, or new, change. The child can be the first in the family to have the gene change. SPARK detects only de novo changes in the FMR1 gene.
De novo changes can take place in any gene. We all have some de novo changes, most of which don’t affect our health. But because FMR1 plays a key role in development, de novo changes in this gene can have a meaningful effect.

Research shows that FMR1-related syndrome is often the result of a de novo change in FMR1. Many parents who have had their genes tested do not have the FMR1 gene change found in their child who has the syndrome. In some cases, FMR1-related syndrome happens because the gene change was passed down from a parent. More information on the inheritance of FMR1 changes can be found at the following links:

- **GeneReview**
  www.ncbi.nlm.nih.gov/books/NBK1384
- **National Organization for Rare Disorders**
  www.rarediseases.org/rare-diseases/fragile-x-syndrome
Why does my child or I have a change in the FMR1 gene?

No parent causes their child's FMR1-related syndrome. We know this because no parent has any control over the gene changes that they do or do not pass on to their children. Please keep in mind that nothing a parent does before or during the pregnancy causes this to happen. The gene change takes place on its own and cannot be predicted or stopped.
What are the chances that other family members or future children will have FMR1-related syndrome?

Each family is different. A geneticist or genetic counselor can give you advice on the chance that this will happen again in your family. The risks shown below are for new or de novo changes in the FMR1 gene. For more information on the risks associated with inheriting changes in the FMR1 gene, please consult with your doctor or genetic counselor.

The risk of having another child who has FMR1-related syndrome depends on the genes of both birth parents.

- Biological females who have changes in the FMR1 gene and are pregnant with a daughter have a 50 percent chance of passing on the gene change and a 50 percent chance of passing on the working copy of the gene. If they are pregnant with a son, the child has a 50 percent chance of inheriting the gene change and the syndrome.

For a symptom-free sibling, a brother or sister, of someone who has FMR1-related syndrome, the risk of having a child who has the syndrome depends on the symptom-free sibling’s genes and their parents’ genes.

- If neither parent has the same gene change found in their child who has the syndrome, the symptom-free sibling has a nearly 0 percent chance of having a child who has FMR1-related syndrome.
- If the mother has the same gene change found in her child who has the syndrome, the symptom-free sibling has a small chance of also having the same gene change. If the symptom-free sibling has the same gene change as their sibling who has the syndrome, the symptom-free sibling’s chance of having a son who has FMR1-related syndrome is 50 percent.

For a person who has FMR1-related syndrome, the risk of having a child who has the syndrome is about 50 percent.
How many people have FMR1-related syndrome?

People who have changes that are specifically within the FMR1 gene are quite rare. Just 20 people had been described in the medical literature as of 2020. These people may or may not have all of the symptoms of fragile X syndrome. About 1 in 4,000 males have fragile X syndrome. About 1 in 6,000 to 1 in 8,000 females have fragile X syndrome.

Do people who have FMR1-related syndrome look different?

Males who have FMR1-related syndrome may look different. Appearance can vary and features may become more noticeable over time. Features can include:

- Long face
- High, wide forehead
- Ears that stick out
- Loose joints
- Large testes
How is FMR1-related syndrome treated?

Scientists and doctors have only just begun to study FMR1-related syndrome. At this point, there are no medicines designed to treat the syndrome. A genetic diagnosis can help people decide on the best way to track the condition and manage therapies. Doctors can refer people to specialists for:

- Physical exams and brain studies.
- Genetics consults.
- Development and behavior studies.
- Other issues, as needed.

A developmental pediatrician, neurologist, or psychologist can follow progress over time and can help:

- Suggest the right therapies. This can include physical, occupational, speech, or behavioral therapy.
- Guide individualized education plans (IEPs).

Specialists advise that therapies for FMR1-related syndrome should begin as early as possible, ideally before a child begins school.

If seizures happen, consult a neurologist. There are many types of seizures, and not all types are easy to spot. To learn more, you can refer to resources such as the Epilepsy Foundation’s website: epilepsy.com/learn/types-seizures.
This section includes a summary of information from major published articles describing 21 males who have FMR1-related syndrome. It highlights how many males have different symptoms. To learn more about the article, see the Sources and references section of this guide.

Behavior and development concerns linked to FMR1-related syndrome

Learning
Everyone who has been studied to date that has FMR1-related syndrome has intellectual disability and developmental delay.

Speech
Language issues are common.

Behavior
Many people have autism or attention deficit hyperactivity disorder, also called ADHD.
Medical and physical concerns linked to FMR1-related syndrome

Joints and spine
People who have FMR1-related syndrome often have loose joints.

Brain
Some people have seizures.

Other
Some males have large testicles.
Where can I find support and resources?

FMR1-related syndrome involves the FMR1 gene, which is also involved in fragile X syndrome.

FRAXA Research Foundation
www.fraxa.org

National Fragile X Foundation
www.fragilex.org

National Fragile X Foundation Facebook page
www.facebook.com/natlfragilex
Sources and References

The content in this guide comes from published reviews about FMR1-related syndrome. Below you can find details about each review, as well as links to summaries or, in some cases, the full article.
