

UPF3B–Related Disorder: A Guide for Families

Also called UPF3B–related disorder, or previously, Lujan–Fryns syndrome. Formally known as intellectual developmental disorder, X-linked syndromic 14 (MRXS14).

If your family has just received this diagnosis, start here. UPF3B-related disorder is very rare, and most doctors have never seen a case. That can feel isolating. This guide explains what the condition is, what to expect, what helps, and where to find other families. It is written for parents and caregivers, not for specialists, so we have avoided medical jargon wherever possible and explained it where we could not.

What it is	A rare genetic condition that affects brain development, causing developmental delay or intellectual disability, often alongside speech difficulties and behavioral differences.
Cause	A change (variant) in the UPF3B gene, located on the X chromosome at position Xq25.
Inheritance	X-linked recessive. It mainly affects boys. Girls are usually carriers without symptoms.
How common	Extremely rare. Roughly 43 people have been described in published medical research worldwide as of 2025. Many more are likely undiagnosed.
Is there a cure	No. There is no medicine that treats the underlying genetic cause. Therapies and support address individual symptoms and can make a meaningful difference.
Life expectancy	Not reported to be shortened. Published reports include affected adults living into middle age and beyond.

What Causes UPF3B–Related Disorder?

Every cell in the body follows instructions written in genes. Genes are copied into messages, called mRNA, which the cell reads to build proteins. Sometimes those messages contain errors. Cells have a built-in quality-control system that spots faulty messages and removes them before they can cause problems. That system is called **nonsense-mediated mRNA decay**, or NMD.

The UPF3B gene makes one of the proteins that runs this quality-control system. When UPF3B does not work properly, faulty messages are not cleared away efficiently. The brain appears to be especially sensitive to this, which is why the effects show up mainly in learning, speech, and behavior rather than in other parts of the body.

Laboratory work has shown that losing working UPF3B disrupts how young brain cells mature and how neurons grow the branching connections they use to communicate. That is the current best explanation for why a defect in a general quality-control gene produces effects specific to the brain.

How It Is Inherited

UPF3B sits on the **X chromosome**. Girls inherit two X chromosomes, one from each parent. Boys inherit one X from their mother and a Y from their father.

This is the key to understanding the pattern in families:

- **Boys have only one X chromosome.** If that single copy of UPF3B carries the variant, there is no backup, and the condition shows up.
- **Girls have two X chromosomes.** If one copy carries the variant, the second working copy usually compensates. These girls are called **carriers** and typically do not have symptoms.
- **A carrier mother** has, with each pregnancy, a 50 percent chance of passing on the changed copy. A son who inherits it will be affected. A daughter who inherits it will usually be a carrier like her mother.
- **An affected father** passes his X chromosome to all his daughters and none of his sons. So all of his daughters would be carriers, and none of his sons would be affected by his copy.

Nothing you did caused this. Genetic changes like this arise on their own during the formation of egg or sperm cells, or are passed down unknowingly through generations. Nothing a parent did or did not do before or during pregnancy caused this condition.

Carrier females are not always symptom-free. Most carriers have no symptoms, but some reports describe mild learning or behavioral differences in carrier women. This has not been studied systematically, and it is an open question in the research. If you are a carrier and have concerns about yourself, raise them with your genetics team rather than assuming they are unrelated.

Signs and Symptoms

UPF3B-related disorder looks different in different people, sometimes even between brothers or cousins carrying the exact same variant. One published family included relatives whose diagnoses ranged from a recognizable syndrome to intellectual disability with no other features at all. **No child has every sign listed below, and the presence or absence of any one feature does not confirm or rule out the diagnosis.**

Learning and development

- Developmental delay, meaning milestones such as sitting, walking, or talking come later
- Intellectual disability, most often mild to moderate, though the range is wide
- Difficulty with schoolwork, memory, or problem solving

Speech and language

- Delayed speech, sometimes significantly
- Unclear or hard-to-understand speech
- A nasal-sounding voice (sometimes described as hypernasal speech)
- In at least one reported case, speech difficulty was the main presenting problem

Behavior and mental health

- Autism or autism-like behaviors, including social and sensory differences
- ADHD, meaning difficulty with attention, impulsivity, or hyperactivity
- Anxiety or difficulty with change and transitions
- In some individuals, usually in adolescence or adulthood, a serious mental health condition called schizophrenia has been reported

Movement and physical features

- Low muscle tone (hypotonia), often noticed as a "floppy" baby
- A tall, slender build with long limbs and fingers, sometimes called a marfanoid appearance
- A longer, narrower face
- Curvature of the spine (scoliosis)
- Seizures in some individuals

Brain imaging

- Some individuals have differences visible on an MRI scan, most often involving the corpus callosum, the band of fibers connecting the two halves of the brain
- Other reported findings include changes in the anterior commissure, olfactory bulbs, and hippocampus, and in one individual, mild cerebellar atrophy
- Many affected individuals have normal brain imaging. An MRI is not required to make the diagnosis, and a normal scan does not rule it out

How often do these features occur?

Feature	Reported in roughly
Developmental delay or intellectual disability	95%
Autism or autism-spectrum features	24%
Seizures, or low muscle tone	22%
Scoliosis or related spine curvature	21%

These percentages come from published case series summarized in the Simons Searchlight UPF3B gene guide. They are based on a small number of described individuals, so they should be read as a rough guide rather than a prediction for any one person. As more people are diagnosed, these numbers are likely to change.

How It Is Diagnosed

UPF3B-related disorder cannot be diagnosed by appearance or symptoms alone. It requires genetic testing. The usual path looks like this:

- **Chromosomal microarray.** Often the first genetic test ordered. It looks for missing or extra pieces of chromosomes. Think of it as scanning a book for missing or duplicated chapters. This test will not usually find a UPF3B variant, but it rules out other common causes.
- **Exome or genome sequencing.** This reads the individual letters of the genetic code, more like proofreading every sentence to find one misspelled word. **This is the test that identifies UPF3B variants.**
- **Testing other family members.** Once a variant is found, the mother is usually offered carrier testing, and other relatives may be tested as well. This can explain difficulties in relatives that were never understood.

About the cost of testing. In the United States, Texas Medicaid and most private insurance plans cover comprehensive genetic testing, including exome sequencing, for children with unexplained developmental delay or intellectual disability. If cost has been presented as a barrier, ask your doctor's office or genetics clinic to check your specific coverage before ruling testing out.

What Helps: Care, Therapy, and Support

There is no medicine that corrects the underlying genetic change. However, a diagnosis opens the door to targeted support, and many of the difficulties associated with this condition respond well to therapy, especially when started early.

Specialists to consider

- **Developmental pediatrician**, to coordinate overall care and monitor progress
- **Genetic counselor**, to explain results and discuss implications for relatives
- **Neurologist**, particularly if there are seizures
- **Speech–language pathologist**, for speech clarity, language, and communication
- **Occupational therapist**, for daily living skills and sensory needs
- **Physical therapist**, especially with low muscle tone
- **Psychologist or behavioral therapist**, for autism features, ADHD, and anxiety
- **Orthopedist**, if scoliosis is present or develops

Therapies that commonly help

- **Early intervention**. In the United States, children under 3 may qualify for free early intervention services regardless of income. Ask your pediatrician how to request an evaluation.
- **Speech therapy**. Often the highest-value therapy for this condition given how frequently speech is affected. Some children benefit from communication devices or sign supports alongside spoken language.
- **Occupational and physical therapy**. For coordination, muscle tone, handwriting, and everyday independence.
- **Behavioral support**. For attention, anxiety, transitions, and sensory needs.

School and education

- In the United States, a child with a diagnosed condition affecting learning is usually eligible for an **Individualized Education Program (IEP)** or a **504 plan**. These are legal documents that require the school to provide specific supports.
- Bring the genetic diagnosis letter to the school meeting. A named genetic condition often makes it easier to establish eligibility than a general description of delays.
- Useful accommodations often include extended time, speech therapy in school, small-group instruction, and a communication plan between home and teachers.

Monitoring over time

- **Spine**. Ask for periodic checks for scoliosis, particularly through growth spurts in adolescence.
- **Seizures**. Report any staring spells, unusual movements, or unexplained lapses to your doctor. Not all seizures look dramatic.
- **Mental health in adolescence and adulthood**. Because psychiatric symptoms have been reported in some individuals, changes in mood, thinking, or behavior during the teenage years or later deserve prompt attention rather than being dismissed as part of the condition.

Family Planning

Many families want to understand what a diagnosis means for future pregnancies and for other relatives. This is a conversation to have with a **genetic counselor**, who can look at your specific family and your specific variant and give you accurate numbers.

A genetic counselor can discuss:

- Carrier testing for the mother, sisters, aunts, and adult daughters
- What the chances are for future pregnancies in your particular family
- The range of options available before or during a pregnancy
- How to talk with relatives about testing, which can be an emotionally complicated conversation

These are personal decisions that depend on your family's values and circumstances. A genetic counselor's role is to give you accurate information and support your choices, not to direct them.

Questions to Ask Your Care Team

- What exactly is my child's variant, and is it considered definitely disease-causing?
- Was this variant inherited, or did it arise new in my child?
- Should other family members be tested? Who, and how do we arrange it?
- Which therapies should we start now, and how do we get referrals?
- Does my child need an MRI, an EEG, or a spine check? How often?
- What should I report to you between visits?
- Can you write a letter supporting our school accommodation request?
- Are there research studies or registries we could join?

Connecting With Other Families

Because this condition is so rare, most families have never met another family affected by it. Two things are worth doing.

- **Join the Simons Searchlight registry.** Simons Searchlight is a free international research registry for UPF3B and more than 180 other rare neurodevelopmental conditions. Joining is optional and confidential. It connects your family to researchers studying this condition and helps build the natural history data that future families will depend on.
Visit simonssearchlight.org/gene-guide/upf3b
- **Reach out to us.** The UPF3B Project was founded by a family affected by this condition. We personally respond to every message from a newly diagnosed family.
Visit upf3b.org or email hello@upf3b.org

Words You May Hear

Variant

A change in the spelling of a gene. Some cause no problems, some, like this one, cause a condition.

Pathogenic

A variant known to cause disease, as opposed to a harmless difference.

Carrier

Someone with a changed gene copy who does not show symptoms, usually because a second working copy compensates.

Proband

The first person in a family to be diagnosed. Testing of relatives starts from this person.

De novo

A variant that appeared new in a child rather than being inherited from either parent.

X-linked recessive

The gene is on the X chromosome, and one working copy is enough to prevent symptoms. This is why boys are affected more often.

Chromosomal microarray

A test looking for missing or extra chunks of chromosomes. Often the first genetic test ordered.

Exome sequencing

A test that reads the protein-coding letters of your genes. This is the test that finds UPF3B variants.

Hypotonia

Low muscle tone. Often described as a baby feeling "floppy."

Marfanoid habitus

A tall, slender body type with long limbs and fingers. A description of build, not a separate diagnosis.

Nonsense-mediated mRNA decay

The cell's quality-control system for clearing out faulty genetic messages. UPF3B is part of it.

Corpus callosum

The band of nerve fibers connecting the left and right halves of the brain. Sometimes formed differently in this condition.

Where This Information Comes From

This guide summarizes information from the Simons Searchlight UPF3B Gene Guide (updated 2025) and from published medical research, including: Tarpey et al., 2007, Nature Genetics (the original description of UPF3B variants); Laumonnier et al., 2010, Molecular Psychiatry; Lynch et al., 2012, European Journal of Medical Genetics; Szyska et al., 2012, Psychiatric Genetics; Xu et al., 2013, Clinical Genetics; Jolly et al., 2013, Human Molecular Genetics; Tejada et al., 2019, Frontiers in Genetics; and Romano et al., 2024, American Journal of Medical Genetics Part A, which provides the most current review of reported features. Full citations and links are available at upf3b.org/research.

This guide is not medical advice. It is general information about a rare condition and cannot account for your child's individual situation. Please discuss your child's genetic results, symptoms, and care decisions with your own doctor and genetics team. Research on UPF3B is still early and this information will change as more is learned.

Review and version. Medical content reviewed by Shayanne Martin, MPH, UT Health San Antonio. Version 1, October 2026. We plan to publish Spanish and Hindi translations of this guide. If you spot an error or something that is unclear, please tell us at hello@upf3b.org so we can correct it.