About Wolfram

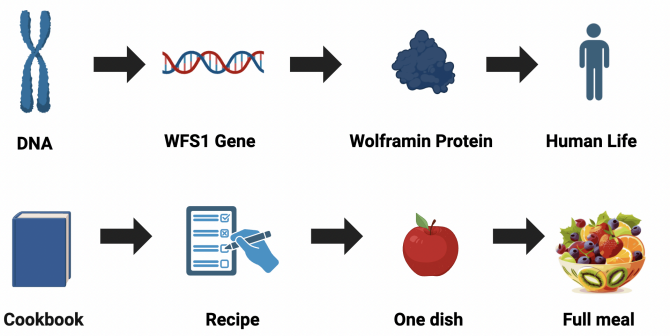
What is Wolfram Syndrome?

Wolfram syndrome (WFS) is a rare genetic disorder, affecting approximately 1 in 770,000 individuals. The primary symptoms of Wolfram Syndrome are juvenile-onset diabetes mellitus, optic nerve atrophy, deafness, diabetes insipidus and neurodegeneration. Other neurological symptoms include bladder and balance/coordination issues.

Wolfram syndrome is a spectrum disorder, meaning patients experience symptoms to varying degrees and may lack certain symptoms completely. The specific symptoms that one experiences depend on their specific mutation, among other factors, and are not always completely clear. There is no present cure for Wolfram Syndrome, and current treatment plans involve managing the unique symptoms of each patient to slow progression.

How does Wolfram Syndrome Work?

Wolfram Syndrome is an inherited genetic mutation that occurs in your DNA. You can think of your DNA like a cookbook; it contains the genetic instructions for your body's structure and function. A **gene** is like a recipe within that cookbook, containing the detailed steps required to make a specific **protein**. Just like each dish contributes to the full meal, each protein has its own unique function within your body.

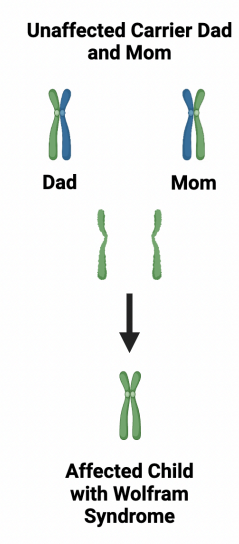


One gene that everyone has is called WFS1, and it provides the instructions to create a protein called Wolframin. Wolfram Syndrome occurs when you have a mutation in your WFS1 gene, meaning the DNA that makes up this gene is partially messed up. Since the WFS1 gene is the instruction set for the Wolframin protein, when it's messed up, the resulting protein is also messed up. This causes the cells where the Wolframin protein acts to be damaged, namely cells in your brain and pancreas. The result, over time, is the manifestation of the core symptoms of Wolfram Syndrome.

How did I get Wolfram Syndrome?

Every person receives one copy of DNA from both their mother and father. Together, these two copies make up their unique set of genetic information. This means that every person has two copies of each individual gene, including the WFS1 gene responsible for the Wolframin protein.

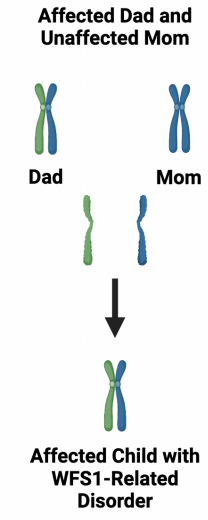
Wolfram Syndrome is called an autosomal recessive disorder, which means that it only occurs if you receive a mutated WFS1 gene from BOTH your mother and your father. If you only receive one mutated WFS1 gene and the other is normal, you are typically known as a Carrier, and do not experience any Wolfram Syndrome complications.



What is WFS1-Related Disorder?

As explained in the previous section, Wolfram Syndrome is caused when an individual receives a mutated WFS1 gene from BOTH parents. In most cases, if only a single mutated WFS1 gene is received, patients do not experience Wolfram Syndrome complications.

However, in certain cases, despite having only one mutated WFS1 gene, individuals can have what is called WFS1-Related Disorder, exhibiting “Wolfram syndrome like” symptoms. This occurs if their specific mutation happens to fall within a certain group. WFS1-Related Disorder is associated with slightly different symptoms, including early-onset hearing loss and optic atrophy, but typically no diabetes. In most cases, WFS1-Related Disorder is considered more mild than Wolfram Syndrome itself.



Useful Definitions

Genetic mutation: a variation from the normal DNA sequence that can be inherited from a parent or occur spontaneously

Diabetes mellitus: A condition where blood sugar levels are too high, often because the body does not make enough insulin or cannot use it properly.

> **Insulin**: A hormone that helps lower blood sugar levels by helping body cells use sugar and store it for later.

Diabetes insipidus: A condition where a person passes large amounts of diluted urine, leading to constant thirst and frequent urination. This can result in dehydration and an imbalance of minerals in the body. Patients with WFS have central diabetes insipidus, which means their bodies don't make enough of a hormone called vasopressin that helps the kidneys save water.

Optic atrophy: A condition where the cells that send visual signals from the eye to the brain are dying, causing loss of color and peripheral vision. The problem is with the connection between the eye and the brain, not the eye itself.

Neurogenic bladder: A condition where the brain and nerve cells that control bladder function are disrupted, causing problems with storing or emptying urine. This can lead to symptoms such as uncontrolled urination, frequent urination, urinary retention, and increased risk of urinary tract infections.

Dominant Disorder: A disorder caused by having just one mutated gene.

Recessive Disorder: A disorder that occurs only when both copies of a gene (one from each parent) are mutated. If only one gene is mutated, the person doesn't show symptoms because the other gene works properly (they are a carrier).

Carrier: A person who has one mutated gene but does not show symptoms of the disorder. They are otherwise normal.

Frequently Asked Questions

What does a genetic mutation actually look like? Our DNA exists as a string of letters: A, T, G, and C. Every three letters represent one amino acid, which are the building blocks of proteins. Think of an amino acid as a Lego piece and the overall protein as many of these pieces put together. A fully formed protein performs specific roles in our body. If there is a genetic mutation, it means there is a mistake (a “typo”) in the letter code of our DNA. This mistake can change the amino acid building block, altering the structure of the protein. When the structure of a protein is changed, it may not function properly, leading to problems in the areas of the body where the protein normally works.

How does a mutation in the protein Wolframin impact our body, leading to clinical symptoms associated with WFS1? Wolframin is a protein located in the endoplasmic reticulum (ER) of our cells. The ER is involved in protein folding and modification, helping proteins achieve the correct shape so they can function properly. Wolframin assists with protein folding and ensures the ER is in the right conditions to function. If Wolframin is malfunctioning, the ER cannot maintain proper function, leading to a state of stress and cell death. This results in the clinical symptoms associated with Wolfram Syndrome and WFS1 Related Disorders.

How do I tell if I have WFS or WFS1-Related Disorders? The difference is based on the genetic profile. If you have two mutations in the WFS1 gene, you most likely have Wolfram Syndrome, a recessive disorder. If you have only one mutation in the WFS1 gene and still have Wolfram-like symptoms, you most likely have a WFS1-Related Disorder.

How does Wolfram Syndrome clinically manifest? Wolfram Syndrome is characterized by juvenile-onset diabetes (around age 6), optic nerve atrophy (around age 11), diabetes insipidus, hearing loss, and neurodegeneration. However, WFS is a spectrum disorder, meaning symptoms can vary widely in severity and can start at any age. Patients may experience all of the symptoms of Wolfram Syndrome or only a few. The severity of the symptoms often depends on the genetic mutations a person has.

Ashkenazi Jewish Variant: The Ashkenazi Jewish Variant is the genetic mutation c.1672C>T (p.Arg558Cys) commonly found in the Ashkenazi Jewish population. It is characterized by diabetes mellitus and optic atrophy. This variant is typically associated with a milder form of Wolfram Syndrome.

How do WFS1-Related Disorders clinically manifest? There are five types of WFS1-Related Disorders: diabetes only, hearing loss only, optic nerve atrophy & hearing loss at birth, cataracts only, and Hattersley-Urano WFS1-Related Disorder

(HU-WFS1). HU-WFS1-Related Disorder is characterized by intellectual disability, developmental delay, decreased muscle tone (hypotonia), profound hearing loss at birth, congenital cataracts, and neonatal diabetes.