

# WFS1 Gene

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Contributor: Hongliu Chen

Wolframin ER transmembrane glycoprotein.

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## 1. Normal Function

The *WFS1* gene provides instructions for producing a protein called wolframin that is thought to regulate the amount of calcium in cells. A proper calcium balance is important for many different cellular functions, including cell-to-cell communication, the tensing (contraction) of muscles, and protein processing. The wolframin protein is found in many different tissues, such as the pancreas, brain, heart, bones, muscles, lungs, liver, and kidneys.

Within cells, wolframin is located in the membrane of a structure called the endoplasmic reticulum. Among its many activities, the endoplasmic reticulum folds and modifies newly formed proteins so they have the correct 3-dimensional shape to function properly. The endoplasmic reticulum also helps transport proteins and other molecules to specific sites within the cell or to the cell surface. Wolframin is thought to play a role in protein folding and aid in the maintenance of endoplasmic reticulum function by regulating calcium levels. In the pancreas, wolframin may help fold a protein precursor of insulin (called proinsulin) into the mature hormone that controls blood glucose levels. In the inner ear, wolframin may help maintain the proper levels of calcium ions or other charged particles that are essential for hearing.

## 2. Health Conditions Related to Genetic Changes

### 2.1. Nonsyndromic Hearing Loss

More than 30 *WFS1* gene mutations have been identified in individuals with a form of nonsyndromic hearing loss called DFNA6. People with this condition have hearing loss without related signs and symptoms affecting other parts of the body. Individuals with DFNA6 nonsyndromic deafness cannot hear low tones (low-frequency sounds), such as sounds from a tuba or the "m" in moon. Most *WFS1* gene mutations change single protein building blocks (amino acids) used to make wolframin. *WFS1* gene mutations probably result in a wolframin protein with an altered 3-dimensional shape, which could affect its function. It is thought that the loss of cells in the inner ear, along with the disruption of the normal function of cells in the part of the brain responsible for hearing, lead to hearing loss in affected individuals. Researchers also suggest that altered wolframin disturbs the balance of calcium in the inner ear, which interferes with the hearing process.

### 2.2. Wolfram Syndrome

At least 200 mutations in the *WFS1* gene have been found to cause Wolfram syndrome. This condition is characterized by a lack of insulin leading to increased blood sugar (diabetes mellitus), a degeneration of nerves that carry information from the eyes to the brain (optic atrophy), and a number of other features involving the urinary tract, the brain, and hearing. Mutations in both copies of the *WFS1* gene in each cell are necessary to cause Wolfram syndrome. Some mutations delete or insert pieces of DNA in the *WFS1* gene, causing no functional wolframin to be made. Other mutations change single protein building blocks (amino acids) in the wolframin protein, reducing the protein's function. As a result, calcium levels within cells are not regulated and the endoplasmic reticulum does not function correctly.

When the endoplasmic reticulum cannot function, the cell triggers its own cell death (apoptosis). The death of cells in the pancreas, specifically cells that make insulin (beta cells), causes diabetes mellitus in people with Wolfram syndrome. The gradual loss of cells along the optic nerve eventually leads to blindness in affected individuals. The death of cells in other body systems likely causes the various signs and symptoms of Wolfram syndrome.

## 2.3. Other Disorders

A few *WFS1* gene mutations have been found to cause a condition known as Wolfram-like syndrome that is characterized by progressive hearing loss and optic atrophy leading to vision loss, typically beginning in adolescence. Some people with this condition also develop diabetes mellitus. These features are common in Wolfram syndrome, and Wolfram-like syndrome is considered a mild version of that condition.

Wolfram-like syndrome is caused by one *WFS1* gene mutation in each cell. These mutations replace single amino acids in the wolframin protein, leading to a decrease in protein function. A reduction in functional wolframin protein leads to cell death, specifically affecting cells along the optic nerve, cells within the inner ear, and beta cells in the pancreas. A loss of these cells contributes to the features of Wolfram-like syndrome. The second copy of the *WFS1* gene that does not have a mutation produces normal wolframin. The presence of some normal wolframin in each cell likely explains why Wolfram-like syndrome is less severe than Wolfram syndrome.

## 3. Other Names for This Gene

- DFNA14
- DFNA38
- DFNA6
- DIDMOAD
- WFRS
- WFS
- WFS1\_HUMAN
- Wolfram syndrome 1 (wolframin)

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