WFS1 gene

wolframin ER transmembrane glycoprotein

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.

Health Conditions Related to Genetic Changes

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.

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.

Other disorders

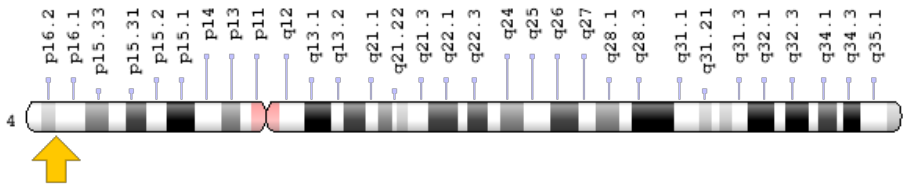
A few *WFS1* gene mutations have been found to cause a condition known as Wolfram-like syndrome that is characterized by progressive hearing loss and optic atrophy leading to vision loss, typically beginning in adolescence. Some people with this condition also develop diabetes mellitus. These features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

Chromosomal Location

Cytogenetic Location: 4p16.1, which is the short (p) arm of chromosome 4 at position 16.1

Molecular Location: base pairs 6,260,368 to 6,303,265 on chromosome 4 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- DFNA6
- DFNA14
- DFNA38
- DIDMOAD
- WFRS
- WFS
- WFS1_HUMAN
- Wolfram syndrome 1 (wolframin)

Additional Information & Resources

Educational Resources

- Florida State University: The Endoplasmic Reticulum
  http://micro.magnet.fsu.edu/cells/endoplasmicreticulum/endoplasmicreticulum.html
- The Cell, A Molecular Approach (2nd edition, 2000): The Endoplasmic Reticulum
  https://www.ncbi.nlm.nih.gov/books/NBK9889/

Clinical Information from GeneReviews

- Hereditary Hearing Loss and Deafness Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1434
- WFS1-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK4144

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28WFS1%5BTIAB%5D%29+OR+%28Wolfram+syndrome+1%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- WOLFRAM-LIKE SYNDROME, AUTOSOMAL DOMINANT
  http://omim.org/entry/614296
- WOLFRAMIN ER TRANSMEMBRANE GLYCOPROTEIN
  http://omim.org/entry/606201

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_WFS1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=WFS1%5Bgene%5D
- HGNC Gene Family: Deafness associated genes
  https://www.genenames.org/cgi-bin/genefamilies/set/1152
- HGNC Gene Symbol Report
  https://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=12762
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:7466
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/7466
- The Hereditary Hearing Loss Homepage
  https://hereditaryhearingloss.org/
- UniProt
  https://www.uniprot.org/uniprot/O76024
- WFS1 Gene Mutation and Polymorphism Database, Kresge Hearing Research Institute
  https://medicine.umich.edu/dept/khri/faculty-labs/labs/lesperance-lab/low-frequency-hearing-loss

Sources for This Summary

- Aloi C, Salina A, Pasquali L, Lugani F, Perri K, Russo C, Tallone R, Ghiggeri GM, Lorini R, d'Annunzio G. Wolfram syndrome: new mutations, different phenotype. PLoS One. 2012;7(1): e29150. doi: 10.1371/journal.pone.0029150. Epub 2012 Jan 4.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22238590
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3251553/
- Bespalova IN, Van Camp G, Bom SJ, Brown DJ, Cryns K, DeWan AT, Erson AE, Flothmann K, Kunst HP, Kurnool P, Sivakumaran TA, Cremers CW, Leal SM, Burmeister M, Lesperance MM. Mutations in the Wolfram syndrome 1 gene (WFS1) are a common cause of low frequency sensorineural hearing loss. Hum Mol Genet. 2001 Oct 15;10(22):2501-8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11709537
- Cryns K, Pfister M, Pennings RJ, Bom SJ, Flothmann K, Caethoven G, Kremer H, Schatteman I, Köln KA, Tóth T, Kupka S, Blin N, Nürnberg P, Thiele H, van de Heyning PH, Reardon W, Stephens D, Cremers CW, Smith RJ, Van Camp G. Mutations in the WFS1 gene that cause low-frequency sensorineural hearing loss are small non-inactivating mutations. Hum Genet. 2002 May;110(5): 389-94. Epub 2002 Apr 9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12073007
- Cryns K, Sivakumaran TA, Van den Ouweland JM, Pennings RJ, Cremers CW, Flothmann K, Young TL, Smith RJ, Lesperance MM, Van Camp G. Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. Hum Mutat. 2003 Oct;22(4):275-87. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12955714
- Cryns K, Thys S, Van Laer L, Oka Y, Pfister M, Van Nassauw L, Smith RJ, Timmermans JP, Van Camp G. The WFS1 gene, responsible for low frequency sensorineural hearing loss and Wolfram syndrome, is expressed in a variety of inner ear cells. Histochem Cell Biol. 2003 Mar;119(3):247-56. Epub 2003 Feb 19.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12649740
- Eiberg H, Hansen L, Kjer B, Hansen T, Pedersen O, Bille M, Rosenberg T, Tranebjaerg L. Autosomal dominant optic atrophy associated with hearing impairment and impaired glucose regulation caused by a missense mutation in the WFS1 gene. J Med Genet. 2006 May;43(5): 435-40.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16648378
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2649014/
- Finsterer J, Fellinger J. Nuclear and mitochondrial genes mutated in nonsyndromic impaired hearing. Int J Pediatr Otorhinolaryngol. 2005 May;69(5):621-47. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15850684
- Gürtler N, Kim Y, Mhatre A, Schlegel C, Mathis A, Daniels R, Shelton C, Lalwani AK. Two families with nonsyndromic low-frequency hearing loss harbor novel mutations in Wolfram syndrome gene 1. J Mol Med (Berl). 2005 Jul;83(7):553-60. Epub 2005 May 24.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15912360
- Hofmann S, Bauer MF. Wolfram syndrome-associated mutations lead to instability and proteasomal degradation of wolframin. FEBS Lett. 2006 Jul 10;580(16):4000-4. Epub 2006 Jun 22.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16806192
- Hofmann S, Philbrook C, Gerbitz KD, Bauer MF. Wolfram syndrome: structural and functional analyses of mutant and wild-type wolframin, the WFS1 gene product. Hum Mol Genet. 2003 Aug 15;12(16):2003-12.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12913071

- Hogewind BF, Pennings RJ, Hol FA, Kunst HP, Hoefsloot EH, Cruysberg JR, Cremers CW. Autosomal dominant optic neuropathy and sensorineual hearing loss associated with a novel mutation of WFS1. Mol Vis. 2010 Jan 12;16:26-35.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20069065
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2805421/
- Rendtorff ND, Lodahl M, Boulahbel H, Johansen IR, Pandya A, Welch KO, Norris VW, Arnos KS, Bitner-Glindzicz M, Emery SB, Mets MB, Fagerheim T, Eriksson K, Hansen L, Bruhn H, Möller C, Lindholm S, Ensgaard S, Lesperance MM, Tranebjaerg L. Identification of p.A684V missense mutation in the WFS1 gene as a frequent cause of autosomal dominant optic atrophy and hearing impairment. Am J Med Genet A. 2011 Jun;155A(6):1298-313. doi: 10.1002/ajmg.a.33970. Epub 2011 Apr 28.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21538838
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100366/
- Rigoli L, Lombardo F, Di Bella C. Wolfram syndrome and WFS1 gene. Clin Genet. 2011 Feb;79(2): 103-17. doi: 10.1111/j.1399-0004.2010.01522.x. Epub 2010 Aug 26. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20738327
- Valéro R, Bannwarth S, Roman S, Paquis-Flucklinger V, Vialettes B. Autosomal dominant transmission of diabetes and congenital hearing impairment secondary to a missense mutation in the WFS1 gene. Diabet Med. 2008 Jun;25(6):657-61. doi: 10.1111/j.1464-5491.2008.02448.x.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18544103

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/WFS1

Reviewed: April 2012
Published: October 16, 2018

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services