WT1 gene
WT1 transcription factor

Normal Function

The WT1 gene provides instructions for making a protein that is necessary for the development of the kidneys and gonads (ovaries in females and testes in males) before birth. After birth, WT1 protein activity is limited to a structure known as the glomerulus, which filters blood through the kidneys. The WT1 protein plays a role in cell growth, the process by which cells mature to perform specific functions (differentiation), and the self-destruction of cells (apoptosis). To carry out these functions, the WT1 protein regulates the activity of other genes by attaching (binding) to specific regions of DNA. On the basis of this action, the WT1 protein is called a transcription factor.

Health Conditions Related to Genetic Changes

Denys-Drash syndrome

At least 80 mutations in the WT1 gene have been found to cause Denys-Drash syndrome, a condition that affects development of the kidneys and genitalia and most often affects males. These mutations are germline, which means they are present in cells throughout the body. The mutations that cause Denys-Drash syndrome almost always occur in areas of the gene known as exon 8 and exon 9. Most of these mutations result in changes in single protein building blocks (amino acids) in the WT1 protein. The most common mutation that causes Denys-Drash syndrome (found in about 40 percent of cases) replaces the amino acid arginine with the amino acid tryptophan at protein position 394 (written Arg394Trp or R394W).

The mutations that cause Denys-Drash syndrome lead to the production of an abnormal WT1 protein that cannot bind to DNA. As a result, the activity of certain genes is unregulated, which impairs development of the kidneys and genitalia. Abnormal development of these organs leads to the signs and symptoms of Denys-Drash syndrome.

Rarely, a mutation in exon 8 or exon 9 of the WT1 gene causes a related condition called Frasier syndrome (described below). Because these two conditions share a genetic cause and have overlapping features, some researchers have suggested that they are part of a spectrum and not two distinct conditions.
Frasier syndrome

At least seven mutations in the WT1 gene have been found to cause Frasier syndrome, a condition that affects development of the kidneys and genitalia and most often affects males. The mutations that cause Frasier syndrome are germline and almost always occur in an area of the gene known as intron 9. The most common mutation that causes Frasier syndrome (found in over half of affected individuals) changes a single DNA building block (nucleotide) in this area of the gene, written as IVS+4C\gt;T. This mutation and others that cause Frasier syndrome alter the way the gene's instructions are pieced together to produce the WT1 protein.

The WT1 gene mutations that cause Frasier syndrome lead to the production of a protein with an impaired ability to control gene activity and regulate the development of the kidneys and reproductive organs, resulting in the signs and symptoms of Frasier syndrome.

Rarely, a mutation in intron 9 of the WT1 gene causes a related condition called Denys-Drash syndrome (described above). Because these two conditions share a genetic cause and have overlapping features, some researchers have suggested that they are part of a spectrum and not two distinct conditions.

Wilms tumor

Mutations in the WT1 gene can cause Wilms tumor, a rare form of kidney cancer that occurs almost exclusively in children. Most of these mutations are somatic, which means they are acquired during a person's lifetime and present only in the tumor cells. Other WT1 gene mutations are germline.

WT1 gene mutations that cause Wilms tumor lead to a WT1 protein with a decreased ability to bind to DNA. As a result, the protein cannot regulate gene activity, leading to uncontrolled growth and division of cells in the kidney and allowing tumor development.

Many conditions caused by germline mutations in the WT1 gene, including WAGR syndrome, Denys-Drash syndrome, and Frasier syndrome (described above), are associated with an increased risk of developing Wilms tumor.

Congenital nephrotic syndrome

MedlinePlus Genetics provides information about Congenital nephrotic syndrome

Cytogenetically normal acute myeloid leukemia

MedlinePlus Genetics provides information about Cytogenetically normal acute myeloid leukemia

Prostate cancer

MedlinePlus Genetics provides information about Prostate cancer
WAGR syndrome

The \textit{WT1} gene is located in a region of chromosome 11 that is often deleted in people with WAGR syndrome, which is a disorder that affects many body systems and is named for its main features: a childhood kidney cancer known as Wilms tumor (described below), an eye problem called anirida, genitourinary anomalies, and intellectual disability. This deletion affects one copy of the \textit{WT1} gene in each cell. The loss of this gene is responsible for the genitourinary abnormalities and the increased risk of Wilms tumor in affected individuals.

Other disorders

At least two germline mutations in the \textit{WT1} gene have been found to cause Meacham syndrome. This condition is characterized by abnormalities in the development of the male genitalia, heart, and diaphragm. Individuals with this condition have a typical male chromosome pattern (46,XY) but have external genitalia that do not look clearly male or clearly female (ambiguous genitalia) or have genitalia that appear completely female. Additionally, the internal reproductive organs are female, but they do not develop normally. Individuals with Meacham syndrome typically have heart defects of varying severity that are present from birth. They also have a hole in the muscle that separates the abdomen from the chest cavity (the diaphragm), which is called a congenital diaphragmatic hernia. Meacham syndrome is typically fatal in infancy. Approximately a dozen individuals have been diagnosed with Meacham syndrome.

Mutations in the \textit{WT1} gene can also cause a condition called isolated nephrotic syndrome. This condition is characterized by an inability of the kidneys to filter waste products from the blood, which leads to protein in the urine, swelling (edema) of the abdomen, and ultimately, kidney failure. Isolated nephrotic syndrome includes diffuse glomerulosclerosis, in which scar tissue forms throughout the clusters of tiny blood vessels (glomeruli) in the kidneys, and focal segmental glomerulosclerosis, in which glomeruli in only certain areas of the kidneys experience scarring. Mutations in the \textit{WT1} gene most often cause diffuse glomerulosclerosis.

Other Names for This Gene

- WIT-2
- WT1\_HUMAN
- WT33

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of WT1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=7490[geneid])

Scientific Articles on PubMed
PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28WT1%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29 %29+AND+english%5Blam%5D+AND+human%5Bmh%5D+AND+%22last+720+days %22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- WT1 TRANSCRIPTION FACTOR (https://omim.org/entry/607102)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/7490)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=WT1[gene])

References

- Al-Hussain T, Ali A, Akhtar M. Wilms tumor: an update. Adv Anat Pathol. 2014 May; 21(3):166-73. doi: 10.1097/PAP.0000000000000017. Review. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/24713986)
- Andrade JG, Guaragna MS, Soardi FC, Guerra-Júnior G, Mello MP, Maciel-Guerra AT. Clinical and genetic findings of five patients with WT1-related disorders. Arq Bras Endocrinol Metabol. 2008 Nov;52(8):1236-43. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19169475)
- Ariyaratana S, Loeb DM. The role of the Wilms tumour gene (WT1) in normal and malignant haematopoiesis. Expert Rev Mol Med. 2007 May 24;9(14):1-17. Review. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17524167)
- Deng C, Dai R, Li X, Liu F. Genetic variation frequencies in Wilms' tumor: A meta-analysis and systematic review. Cancer Sci. 2016 May;107(5):690-9. doi:10. 1111/cas.12910. Epub 2016 Mar 18. Review. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/26892980) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4970837/)
- Heathcott RW, Morison IM, Gubler MC, Corbett R, Reeve AE. A review of the phenotypic variation due to the Denys-Drash syndrome-associated germline WT1 mutation R362X. Hum Mutat. 2002 Apr;19(4):462. Review. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11933209)
- Miller-Hodges E, Hohenstein P. WT1 in disease: shifting the epithelial-mesenchymal balance. J Pathol. 2012 Jan;226(2):229-40. doi:10.1002/path.2977. Epub 2011 Sep 29. Review. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21959952)
- Salvatorelli L, Parenti R, Leone G, Musumeci G, Vasquez E, Magro G. Wilmstumor 1 (WT1) protein: Diagnostic utility in pediatric tumors. Acta Histochem.2015 May-Jun; 117(4-5):367-78. doi: 10.1016/j.acthis.2015.03.010. Epub 2015 Apr14. Review. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25881478)
• Suri M, Kelehan P, O'Neill D, Vadeyar S, Grant J, Ahmed SF, Tolmie J, McCann E, Lam W, Smith S, Fitzpatrick D, Hastie ND, Reardon W. WT1 mutations in Meacham syndrome suggest a coelomic mesothelial origin of the cardiac and diaphragmatic malformations. Am J Med Genet A. 2007 Oct 1;143A(19):2312-20. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17853480)

• Yang L, Han Y, Suarez Saiz F, Minden MD. A tumor suppressor and oncogene: the WT1 story. Leukemia. 2007 May;21(5):868-76. Epub 2007 Mar 15. Review. Erratum in: Leukemia. 2007 Jul;21(7):1603. Suarez Saiz, F [corrected to Suarez Saiz, F]. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17361230)

Genomic Location

The WT1 gene is found on chromosome 11 (https://medlineplus.gov/genetics/chromosome/11/).

Last updated September 1, 2018