

## 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

Many variants (also known as 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 variants are germline, which means they are present in cells throughout the body. The variants that cause Denys-Drash syndrome almost always occur in areas of the gene known as exon 8 and exon 9. Most of these variants result in changes in single protein building blocks (amino acids) in the WT1 protein. The most common variant 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 variants 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 variant 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

Variants 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 variants that cause Frasier syndrome are germline and almost always occur in an area of the gene known as intron 9. The most common variant 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>T. This variant and others that cause Frasier syndrome alter the way the gene's instructions are pieced together to produce the *WT1* protein.

The *WT1* gene variants 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 variant 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

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

*WT1* gene variants 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 variants 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.

### WAGR syndrome

The *WT1* gene is located in a region of chromosome 11 that is often missing (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 aniridia, genitourinary anomalies, and intellectual disability. This deletion affects one copy of the *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.

### 46,XX testicular difference of sex development

MedlinePlus Genetics provides information about 46,XX testicular difference of sex

development

### 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

### Other disorders

Germline variants in the *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 or have genitalia that appear female-typical. 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.

Variants in the *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. Variants in the *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\[geneid\]](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%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D%29>)

### Catalog of Genes and Diseases from OMIM

- WT1 TRANSCRIPTION FACTOR; WT1 (<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\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=WT1[gene]))

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## Genomic Location

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

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