WT1 Gene

Subjects: Genetics & Heredity
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Wilms tumor 1: 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.

Keywords: genes

1. Normal Function

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.

2. Health Conditions Related to Genetic Changes

2.1. 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.

2.2. 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>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.

2.3. 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.

2.4. Congenital nephrotic syndrome

2.5. Cytogenetically normal acute myeloid leukemia

2.6. Prostate cancer

2.7. WAGR syndrome

The *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 *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.

2.8. Other disorders

At least two germline mutations 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 (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 *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 *WT1* gene most often cause diffuse glomerulosclerosis.

3. Other Names for This Gene

- WIT-2
- WT1_HUMAN
- WT33

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