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My46 Trait Profile

# WT1-related Wilms tumor

Other Names: Wilms tumor-Aniridia-Genitourinary malformation-Retardation syndrome, Denys-Drash syndrome, Frasier syndrome, Genitourinary anomalies syndrome

*Wilms tumor is the most common type of kidney cancer affecting children. There are several genetic syndromes that result in an increased risk of Wilms tumor. These genetic syndromes are caused by mutations in the WT1 gene that makes the wilms tumor protein.*

**Characteristics of WT1-related Wilms tumor**

WT1-related Wilms tumor syndromes are a group of genetic conditions in which affected individuals have an increased risk of developing a cancerous kidney tumor called Wilms tumor. Wilms tumor is most commonly found in children, but rarely can occur in adults. Four WT1-related Wilms tumor syndromes are WAGR syndrome, Denys-Drash syndrome (DDS), Frasier syndrome (FS), and Genitourinary (GU) anomalies (i.e., abnormalities of the reproductive and urinary systems) syndrome.

WAGR is an acronym that stands for the common features seen in this syndrome: Wilms tumor, Aniridia (complete or partial absence of the iris, the colored part the eye), Genitourinary abnormalities (e.g., undescended testes in boys), and Retardation (more commonly referred to as intellectual disability). Children with WAGR syndrome have about a 50% chance of developing Wilms tumor. WAGR syndrome is also associated with an increased risk for end-stage renal (kidney) disease, which may be more common and/or severe in children who have been treated for Wilms tumor. All children with WAGR syndrome have aniridia, and some children have intellectual disability and behavioral abnormalities. Most individuals with WAGR syndrome show some degree of cognitive impairment. Other medical problems that are seen in some children with WAGR syndrome include seizures, brain malformations, and muscle weakness.

DDS is a genetic condition in which children have a very high risk of developing Wilms tumor (the risk is estimated to be over 90%). Individuals with DDS may also develop kidney failure and/or kidney disease (specifically, a condition known as mesangial sclerosis). DDS can also be associated with genitourinary abnormalities, which are linked with a higher risk of developing gonadoblastoma (a tumor of the developing reproductive organs, including the ovaries and testes).

FS is a genetic condition that affects the kidneys and reproductive organs. While Wilms tumor is not usually seen in FS, several cases have been reported. Individuals with FS are at increased risk of developing kidney failure and/or kidney disease (specifically, a condition known as focal segmental glomerulosclerosis). Boys with FS may have abnormal or undermasculinized reproductive organs, while girls with FS usually have normal reproductive organs. Children with FS also have a higher risk of developing gonadoblastoma.

GU anomalies syndrome is a genetic condition in which children are at increased risk to develop Wilms tumor. GU anomalies are most common in boys, and may include undescended testicles, inguinal hernias or hypospadias (a birth defect characterized by abnormal placement of the urinary opening).

**Diagnosis/Testing**

Individuals with WT1-related Wilms tumor syndromes have a change or mutation in a gene called WT1. This gene

makes the WT1 protein which is thought to play an important role in the development of the kidneys and reproductive organs (the testes in boys and the ovaries in girls). Individuals with WAGR syndrome have a deletion (i.e., missing piece) on one of the two copies of chromosome 11. This deletion typically includes several genes, most importantly the WT1 gene and the PAX6 gene (the PAX6 gene is involved in development of the eye, and when altered or missing causes aniridia). The protein made by the WT1 gene also has a tumor suppressor function, meaning that it controls cell growth and division to prevent the formation of tumors. Mutations in the WT1 gene are thought to interfere with the normal development of the kidneys and gonads and to increase the risk for development of tumors. The most common tumors associated with mutations in the WT1 gene are Wilms tumor and gonadoblastoma.

**Management/Surveillance**

Management of WT1-related Wilms tumor syndromes generally includes surveillance for Wilms tumor. To screen for Wilms tumor, an ultrasound examination focusing on the kidneys (renal ultrasound) should be performed every three months until the affected individual is 5-7 years of age. Renal ultrasounds are safe and painless, and they do not involve the use of radiation. If a tumor is suspected, more detailed imaging is often used (e.g., CT or MRI scan) and the individual should be promptly referred to a pediatric oncologist for further management.

Some WT1-related Wilms tumor syndromes are also associated with other physical or cognitive features that require management by a multidisciplinary team of pediatric specialists. For example, some children with WT1-related tumor syndromes may have other medical problems involving the kidneys which should be managed by a pediatric nephrologist (kidney specialist). Children who have genitourinary abnormalities and/or are at increased risk to develop gonadoblastoma should be followed by a pediatric urologist. Some children may have ambiguous genitalia (i.e., a birth defect where the outer genitals do not have the usual appearance of either a boy or a girl) and should be evaluated by a pediatric endocrinologist. A neurologist and/or developmental pediatrician should be involved in the care of children who have behavioral and/or cognitive disabilities. Finally, aniridia associated with WAGR syndrome should be managed by a pediatric ophthalmologist.

**Mode of inheritance**

WT1-related Wilms tumor syndromes are inherited in an autosomal dominant pattern. This means inheriting one WT1 mutation is enough for an individual to be affected and show signs of a WT1-related Wilms tumor syndrome (e.g. WAGR syndrome, DDS, FS, GU syndrome). The mutation can be inherited from an affected parent or it can occur brand new (de novo) in an affected child.

**Risk to family members**

The risk to family members depends on whether or not the individual with a WT1-related Wilms tumor syndrome has a parent affected with the syndrome. If a parent also has a WT1-related Wilms tumor syndrome, the risk of having a child with the syndrome is 50% with each pregnancy. If a parent does not have a WT1-related Wilms tumor syndrome, the risk of other siblings being affected is very low.

**Special considerations**

In addition to the WT1-related Wilms tumor syndromes reviewed above, Wilms tumor can also occur on its own (i.e., not part of a genetic syndrome) or as part of other genetic syndromes. Other genetic syndromes that involve an increased risk for Wilms tumor include Beckwith-Wiedemann syndrome (see trait profile) and Perlman syndrome. Isolated Wilms tumor (Wilms tumor that develops in people who do not have other physical or cognitive differences) can also run in families, and is generally not caused by mutations in the WT1 gene. The genetic cause of most cases of familial isolated Wilms tumor have not yet been discovered, although research to identify these genes is ongoing.

**Resources**

International WAGR Syndrome association
http://www.wagr.org/
Genetics Home Reference: Wilms tumor, aniridia, genitourinary anomalies, and mental retardation syndrome
http://ghr.nlm.nih.gov/condition/wilms-tumor-aniridia-genitourinary-anomalies-and-mental-retardation-syndrome
Genetics Home Reference: Denys-Drash syndrome
http://ghr.nlm.nih.gov/condition/denys-drash-syndrome

Genetics Home Reference: Frasier syndrome
http://ghr.nlm.nih.gov/condition/frasier-syndrome
National Wilms Tumor Study
http://www.nwtsg.org

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