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WT1 Disorder

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Summary

Clinical characteristics

WT1 disorder is characterized by congenital/infantile or childhood onset of steroid-resistant nephrotic syndrome (SRNS), a progressive glomerulopathy that does not respond to standard steroid therapy. Additional common findings can include disorders of testicular development (with or without abnormalities of the external genitalia and/or müllerian structures) and Wilms tumor. Less common findings are congenital anomalies of the kidney and urinary tract (CAKUT) and gonadoblastoma. While various combinations of renal and other findings associated with a *WT1* pathogenic variant were designated as certain syndromes in the past, those designations are now recognized to be part of a phenotypic continuum and are no longer clinically helpful.

Diagnosis/testing

The diagnosis of a *WT1* disorder is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *WT1* identified by molecular genetic testing.

Management

Treatment of manifestations: SRNS: Avoid immunosuppressants; consider renin-angiotensin-aldosterone system (RAAS) inhibition. Disorder of testicular development: Management is often by a multidisciplinary team (medical geneticist, endocrinologist, urologist, and psychologist). Treat Wilms tumor with standard oncology protocols and, when applicable, nephron-sparing surgery. Treat CAKUT as per standard care. Prevent whenever possible gonadoblastoma by prophylactic gonadectomy.

Surveillance: Monitor for first appearance of the following: (1) proteinuria every six months until age ten years, yearly thereafter; (2) Wilms tumor every three months until age seven years. For ongoing issues with disorder of testicular development as per treating multidisciplinary team and for CAKUT as per treating nephrologist and/or urologist.

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Agents/circumstances to avoid: Avoid treating glomerulopathy with immunosuppressants, as they are not effective and potentially toxic.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an individual with a *WT1* disorder in order to identify as early as possible those who would benefit from prompt initiation of treatment and surveillance.

Genetic counseling

WT1 disorder is inherited in an autosomal dominant manner. Most individuals diagnosed with *WT1* disorder have the disorder as the result of an apparent *de novo WT1* pathogenic variant; in rare instances, a parent of an individual with *WT1* disorder is heterozygous for the *WT1* pathogenic variant. If a parent of the proband is affected and/or is known to have the *WT1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the *WT1* pathogenic variant is 50%. If the proband's *WT1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Once the *WT1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for *WT1* disorder have not been established.

Note: This chapter on *WT1* disorder excludes WAGR syndrome (*W*ilms tumor-*a*niridia-*g*enital anomalies-*r*etardation), caused by a contiguous gene deletion of *PAX6* and *WT1* (see *PAX6*-Related Aniridia).

Suggestive Findings

A *WT1* disorder **should be suspected** in an individual with the following clinical findings.

Clinical Findings

Steroid-resistant nephrotic syndrome. A progressive glomerulopathy that does not respond to standard steroid therapy (see Trautmann et al [2020] and Boyer et al [2021] for diagnostic clinical practice guidelines).

- Onset from infancy to the second to third decade of life
- Manifestations in the order in which they typically (but not invariably) appear:
  - **Persistent proteinuria,** defined as any one of the following lasting >3 months: 24-hour protein excretion >100 mg/m^2/day OR urine protein:creatinine ratio ≥0.2 mg/mg (0.5 if age <2 yrs) OR urine protein:creatinine ratio >20 mg/mmol (50 if age <2 yrs) [Hogg et al 2003]
  - **Steroid-resistant nephrotic syndrome (SRNS).** Nephrotic syndrome (defined as hypoalbuminemia, edema, and hyperlipidemia) that does not respond to standard steroid therapy. Note: "Congenital nephrotic syndrome" is nephrotic syndrome manifesting in the first three months of life.
  - **Chronic kidney disease (CKD),** defined as glomerular filtration rate <60 mL/min/1.73 m^2) [Hogg et al 2003]

Wilms tumor, especially in children with:

- Early-onset Wilms tumor (i.e., median age 15-19 months vs median age of 36 months in children without a *WT1* pathogenic variant) OR
- Bilateral Wilms tumors

Disorder of testicular development (See Nonsyndromic Disorders of Testicular Development.)

- 46,XY disorder of sex development (46,XY DSD)
  - External genitalia that can range over the following spectrum:
    - Ambiguous with mild-to-severe penoscrotal hypospadias with or without chordee
    - Microphallus
    - Abnormalities of scrotal formation
    - Normal-appearing female
  - Müllerian structures that on ultrasound (US) examination, MRI, and/or laparoscopy can range over the following spectrum:
    - Absent
    - Fully developed uterus and fallopian tubes
  - Gonadal findings as determined by a combination of physical examination, imaging, and hormonal testing (and on occasion histologic examination) ranging over the following spectrum:
    - Normal testis
    - Dysgenetic testis (decreased size and number of seminiferous tubules, reduced number or absence of germ cells, peritubular fibrosis, and hyperplasia of Leydig cells)
    - Streak gonad
- 46,XY complete gonadal dysgenesis (46,XY CGD)
  - External genitalia. Normal female
  - Müllerian structures. Uterus and fallopian tubes present
  - Gonadal findings. Streak gonads or dysgenetic testes

    Note: 46,XX individuals with a *WT1* disorder may have abnormalities of the müllerian structures such as bicornuate uterus and typically do not have a disorder of gonadal development.

Gonadoblastoma (germ cell tumor). Most commonly in 46,XY individuals with a disorder of testicular development

Congenital anomalies of the kidney and urinary tract (CAKUT) including:

- Duplex kidney; horseshoe kidney; kidney malrotation
- Vesico-urinary reflux; pelviureteric junction stenosis; urogenital sinus

Other. Diaphragmatic hernia

Supportive Laboratory Findings

Normal 46,XX karyotype or normal 46,XY karyotype determined by either:

- Chromosome analysis with FISH to determine the integrity of *SRY*, or
- Chromosomal microarray analysis

Establishing the Diagnosis

The diagnosis of a *WT1* disorder **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *WT1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *WT1* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *WT1* disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *WT1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Sequence analysis of the entire gene is typically performed first; however, some laboratories may choose to sequence exons 8, 9, and their intronic junctions first because more than 90% of pathogenic variants are in that region [Lipska et al 2014]. If no pathogenic variant is found, gene-targeted deletion/duplication analysis can be performed to detect intragenic deletions or duplications.

A multigene panel (for any of the following, depending on the clinical manifestations at the time of the evaluation: SRNS; hereditary [pediatric] cancers; 46,XY disorders of testicular development [see Table 2]; CAKUT) that includes *WT1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *WT1* Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
WT1	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	<10% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lipska et al [2014], Sadowski et al [2015]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Several exon and multiexon deletions have been reported (e.g., Finken et al [2015]).

Clinical Characteristics

Clinical Description

A *WT1* disorder is characterized by congenital/infantile- or childhood-onset of a progressive glomerulopathy that does not respond to standard steroid therapy. Additional common findings can include disorders of testicular development (with or without abnormalities of the external genitalia and/or müllerian structures) and Wilms tumor. Less common findings are congenital anomalies of the kidney and urinary tract (CAKUT) and gonadoblastoma (see Table 2). While various combinations of renal and other findings associated with a *WT1* pathogenic variant have in the past been designated as certain syndromes, those combinations are now recognized to be part of a phenotypic continuum and their designations are no longer clinically helpful (see Nomenclature) [Chernin et al 2010, Lipska et al 2014, Lehnhardt et al 2015, Ahn et al 2017].

Table 2. *WT1* Disorder: Select Clinical Findings

Clinical finding		Present in % of *WT1* Disorders	Comment		
Glomer-ulopathy	Persistent proteinuria	>95%	Renal hallmark of *WT1* disorder; degree may vary over time.		
	SRNS	80%	Criteria for diagnosis of SRNS [1] may not be met initially.		
	CNS	15%	Nephrotic syndrome within 1st 3 mos of life		
			External genitalia	**Müllerian structures**	**Gonadal findings**
Disorder of testicular development	46,XX DSD or CGD	See footnote 2.	Normal female	Bicornus uterus, polypose uterus	Streak gonads, hypertrophic ovaries, or normal ovaries
	46,XY DSD	63%-79% of 46,XY individuals [3]	Range: microphallus, hypospadias & cryptorchidism, ambiguous, normal-appearing female	Range: absent to normal uterus & fallopian tubes	Range: normal testis, ovotestis, dysgenetic testis, streak gonad
	46,XY CGD	18%-33% of 46,XY individuals [3]	Normal female	Uterus & fallopian tubes present	Streak gonads or dysgenetic testes

Table 2. continued from previous page.

Clinical finding	Present in % of *WT1* Disorders	Comment
Wilms tumor	38%-43% [3]	• Median age at diagnosis: 1.3-1.6 yrs • Significant fraction is bilateral synchronous &/or metachronous
CAKUT	~11% [3]	• Kidney: duplex, horseshoe; malrotation • Urinary tract: vesico-urinary reflux, pelviureteric junction stenosis, urinary sinus
Gonadoblastoma	5%	• To date, reported only in persons w/a disorder of testicular development • See Genotype-Phenotype Correlations for *WT1* variants assoc w/ highest risk.

46,XY CGD = 46,XY complete gonadal dysgenesis; 46,XY DSD = 46,XY disorder of sex development; CAKUT = congenital anomalies of the kidney and urinary tract; CGD = complete gonadal dysgenesis; CNS = congenital nephrotic syndrome; DSD = disorders of sex development; SRNS = steroid-resistant nephrotic syndrome

1. Nephrotic syndrome (proteinuria, hypoalbuminemia, edema, and hyperlipidemia) that does not respond to standard steroid therapy

2. Two instances of 46,XX complete gonadal dysgenesis have been reported [Ahn et al 2017, Roca et al 2019].

3. Lipska et al [2014], Lehnhardt et al [2015]

Progressive Glomerulopathy

Persistent proteinuria is the most common initial finding of the glomerulopathy. While the degree of proteinuria may fluctuate at the onset of renal involvement, it becomes progressively worse over time. The severity of the proteinuria varies among affected individuals, even within the same family. Note that individuals with end-stage renal disease (ESRD) may be anuric, and thus will not have proteinuria.

Steroid-resistant nephrotic syndrome (SRNS) – proteinuria, hypoalbuminemia, edema, and hyperlipidemia that does not respond to standard steroid therapy – is the characteristic renal finding. SRNS can precede Wilms tumor by as much as four years, present at the time of Wilms tumor diagnosis, or develop after Wilms tumor (as much as 10 years after completion of the oncology treatment) [Lipska et al 2014, Lehnhardt et al 2015].

SRNS results in irreversible and progressive decline of renal function and inevitably leads to ESRD. Congenital nephrotic syndrome (nephrotic syndrome that presents in the first 3 months of life) is more rapidly progressive, resulting in ESRD within weeks to months [Boyer et al 2021].

Typical findings of the glomerulopathy on renal biopsy are diffuse mesangial sclerosis reported primarily in children younger than age two years and focal segmental glomerulosclerosis in older individuals (usually as either isolated SRNS or SRNS in association with 46,XY complete gonadal dysgenesis). Of note, because the histologic findings do not correlate with the clinical findings and because remarkable histopathologic heterogeneity is observed even among individuals with the same *WT1* pathogenic variant [Lipska et al 2014, Lehnhardt et al 2015, Trautmann et al 2017], renal biopsy is no longer considered a first-tier diagnostic measure for patients of any age.

Wilms Tumor

Wilms tumor (nephroblastoma) is one of the most common pediatric malignant solid tumors. The estimated risk to heterozygotes who have an exonic *WT1* pathogenic variant of developing Wilms tumor is one tumor per nine years at risk. Calculation of the exact penetrance is hampered because a significant number of individuals with a *WT1* pathogenic variant undergo prophylactic nephrectomy at the time of transplantation or placement of a peritoneal dialysis catheter).

The median age at Wilms tumor diagnosis in *WT1* disorder is significantly younger (median age 1.3-1.6 years (range 0-4.5 years) compared to Wilms tumor of unknown cause.

Bilateral tumors are more frequent in individuals with a truncating *WT1* variant compared to individuals with other variants (>50% vs <15%) [Lipska et al 2014, Lehnhardt et al 2015] (see Genotype-Phenotype Correlations).

The survival rates for individuals with Wilms tumor caused by a *WT1* disorder do not differ significantly from those in individuals with Wilms tumor of unknown cause.

Genital Findings

46,XY individuals have a disorder of testicular development that is either a disorder of sex development (DSD) or complete gonadal dysgenesis (CGD) (see Table 2). 46,XY individuals with normal testes, normal male external genitalia, and normal fertility have been reported anecdotally.

46,XX individuals typically have normal ovaries, normal female external genitalia, müllerian structures that are usually normal (however, on occasion bicornuate uterus has been observed), and normal fertility (see Table 2 for details). To date, two instances of 46,XX CGD have been reported [Ahn et al 2017, Roca et al 2019].

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

CAKUT are observed in about 10% of individuals with a *WT1* disorder. The most common kidney abnormalities are duplex kidney, horseshoe kidney, kidney malrotation. The most commonly reported urinary tract anomalies are vesico-urinary reflux, ureteropelvic junction stenosis, and urogenital sinus (in a 46,XX individual in whom both the urethra and vagina open into a common channel).

Gonadoblastoma

Individuals with 46,XY disorder of testicular development (either 46,XY DSD or 46,XY CGD) are at increased risk for germ cell tumors, particularly gonadoblastoma. The observed incidence is one gonadal tumor per 30 years at risk [Lipska et al 2014].

Because of the lack of long-term follow-up data, exact penetrance and long-term outcome are unknown. The survival rates for gonadoblastoma are excellent; however, if not treated it may result in malignant transformation of germ cells. A few cases of Sertoli tumor or other malignant testicular germ cell tumors have been reported [Kitsiou-Tzeli et al 2012].

Other

Diaphragmatic defect or herniation is a rare finding in *WT1* disorder, reported in fewer than ten infants [Denamur et al 2000, Suri et al 2007, Ahn et al 2017].

Post-transplant lymphoproliferative disorder (PTLD) was reported in 7%-17% of individuals with a *WT1* disorder following kidney transplantation [Lipska et al 2014, Ahn et al 2017]. In all children undergoing kidney transplantation, the 25-year cumulative incidence of PTLD, adjusted for the competing risk of death, is 3.6% (95% CI 2.7-4.8). Because of small numbers and lack of standardized follow-up data, it is not yet possible to determine if the frequency of PTLD is higher for *WT1* disorder than for all other children undergoing renal transplantation.

Genotype-Phenotype Correlations

Recent developments have allowed delineation of genotype-phenotype correlations for the following subgroups of *WT1* variants.

Truncating pathogenic variants (all nonsense, frameshift, or splice-site variants that are not KTS intron variants; see Molecular Genetics) are associated with the following [Lipska et al 2014, Lehnhardt et al 2015]:

- Glomerulopathy. Proteinuria is typically diagnosed in the second decade of life in individuals who underwent unilateral or partial nephrectomy for Wilms tumor. The course of SRNS is slower.
- Genital anomalies secondary to a 46,XY DSD affect the vast majority of phenotypic males; 46,XY CGD is unlikely.
- The risk for bilateral Wilms tumor is the highest (odds ratio = 18.4).
- One in five individuals has congenital anomalies of the kidney and urinary tract.

Missense variants affecting nucleotides coding for amino acid residues in the DNA-binding region in exons 8 and 9 (see Molecular Genetics) are associated with the following [Lipska et al 2014]:

- The highest risk for congenital nephrotic syndrome or early-onset rapidly progressive SRNS. By age two and a half years, 50% of affected children have ESRD.
- Of 46,XY individuals, approximately 80% had 46,XY DSD and 20% 46,XY CGD [Author, personal observation].

Missense pathogenic variants in exons 8 and 9 outside the DNA-binding region are associated with an intermediate glomerulopathy phenotype that manifests before age five years and progresses to ESRD by about age ten years [Lipska et al 2014].

Certain donor splice-site pathogenic variants in intron 9 (see Molecular Genetics) are associated with the following [Chernin et al 2010, Lipska et al 2014, Lehnhardt et al 2015]:

- Later-onset and relatively slow progression of glomerulopathy that typically leads to ESRD in adolescence
- 46,XY CGD in the majority of (but not all) 46,XY individuals and 46,XY DSD in a few individuals

Penetrance

The penetrance of *WT1* disorder is high. It is age dependent, reaching about 90% by the end of puberty.

A few asymptomatic parents heterozygous for the same germline *WT1* variant in their affected offspring have been reported [Fencl et al 2012, Lipska et al 2014, Kaneko et al 2015, Boyer et al 2017]. The penetrance appears to depend on the sex of the affected parent, with higher penetrance associated with paternal origin of the *WT1* variant [Kaneko et al 2015]. However, current data on penetrance are limited because the variable expressivity of *WT1* pathogenic variants was not recognized until recently, as the asymptomatic parents of a child with a *WT1* pathogenic variant were not routinely tested.

Nomenclature

Frasier syndrome, **Denys-Drash syndrome**, and **Meacham syndrome** were originally described as distinct disorders on the basis of clinical findings but are now understood to represent a continuum of features caused by a *WT1* heterozygous pathogenic variant. Given the extensive clinical overlap between these clinical diagnoses and molecular characterization of their shared genetic etiology, Frasier syndrome, Denys-Drash syndrome, and Meacham syndrome are no longer useful clinical diagnoses. However, these terms may still be used in the medical literature to refer to the following general phenotypic constellations:

- **Frasier syndrome.** SRNS, 46,XY CGD, and gonadoblastoma
- **Denys-Drash syndrome.** SRNS with diffuse mesangial sclerosis on renal biopsy, Wilms tumor, and 46,XY DSD
- **Meacham syndrome.** Diaphragmatic hernia, pulmonary dysplasia, complex congenital heart defects, and genitourinary abnormalities including ambiguous genitalia and gonadal dysgenesis; in most reports, the condition was lethal early in infancy prior to development of other possible manifestations of *WT1* disorder, such as SRNS or Wilms tumor. So far, none of the reported individuals with a confirmed *WT1* pathogenic variant and a diaphragmatic defect had a complex congenital heart defect. A multigenic cause

of this syndrome, with another as-yet-unknown gene responsible for the more severe cardio-pulmonary phenotype, has been suggested [Suri et al 2007].

Male pseudohermaphroditism. The spectrum of clinical manifestations related to 46,XY disorders of testicular development with a *WT1* pathogenic variant was previously referred to using outdated terms such as "male pseudohermaphroditism."

Prevalence

The prevalence of *WT1* disorder is not known. Fewer than 500 affected individuals have been reported to date.

There are no *WT1* founder variants or biased geographic distribution in specific populations.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *WT1*.

Note: *WT1* disorder excludes WAGR syndrome (*W*ilms tumor-*a*niridia-*g*enital anomalies-*r*etardation), caused by a contiguous gene deletion of *PAX6* and *WT1* (see *PAX6*-Related Aniridia).

Differential Diagnosis

For the differential diagnosis of:

- Wilms tumor, see Wilms Tumor Predisposition;
- 46,XY disorders of testicular development, see Nonsyndromic Disorders of Testicular Development;
- Diaphragmatic hernia, see Congenital Diaphragmatic Hernia Overview.

Steroid-resistant nephrotic syndrome (SRNS) is a podocytopathy (i.e., a condition caused by dysfunction of the podocytes). To date, approximately 60 genes have been associated with hereditary podocytopathy. Up to 30% of individuals with SRNS who undergo molecular genetic testing have a heterozygous pathogenic variant or biallelic pathogenic variants in a hereditary podocytopathy gene [Trautmann et al 2018].

- The two most commonly involved genes, *NPHS1* (OMIM 256300) and *NPHS2* (OMIM 600995), encode components of the slit diaphragm and are selectively expressed in the podocyte.
- A subset of genes encode proteins that are not tissue/organ specific: these include cell signaling pathways, mitochondrial energy provision (see Primary Coenzyme Q_{10} Deficiency) and nuclear transcription factors such as *SMARCAL1* (see Schimke Immunoosseous Dysplasia), *LMX1B* (see Nail-Patella Syndrome), and *WT1*. Pathogenic variants in these genes can cause a range of phenotypes from largely kidney-limited disease to severe syndromic disorders. Note: Among individuals with isolated SRNS, *WT1* is among the top three most commonly mutated genes accounting for approximately 5% of cases [Sadowski et al 2015, Trautmann et al 2015].
- Other genes associated with hereditary podocytopathy are involved in sustaining proper functioning of the cytoskeleton and membrane protein complex linking these structures (e.g., the *COL4A3/4/5* gene family; see Alport Syndrome).

See also Genetic Steroid-Resistant Nephrotic Syndrome Overview.

Management

See Trautmann et al [2020] and Boyer et al [2021] for clinical practice recommendations for the management of children with steroid-resistant nephrotic syndrome.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *WT1* disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in an Individual with a *WT1* Disorder

System/Concern		Evaluation	Comment
Glomer-ulopathy	Persistent proteinuria	Urine protein:creatinine ratio	For evidence of proteinuria
	SRNS CKD CNS	• 24-hr urine protein test • Serum protein, albumin, creatinine, cholesterol, IgG, C3 • Blood pressure measurements	For evidence of proteinuria, hypertension, & CKD [1]
Disorder of testicular development		Karyotype w/FISH for *SRY* or CMA (to determine chromosomal sex)	To be performed in all persons w/ambiguous genitalia & all prepubertal phenotypic females
		Pelvic US	Eval of gonadal localization & character
		Hormonal studies	For children who have not undergone gonadectomy: hormonal studies as directed by a pediatric endocrinologist
Wilms tumor		Abdominal US	Metachronous & synchronous tumors may be unilateral or bilateral.
CAKUT		Abdominal US	To identify duplex kidney, horseshoe kidney, kidney malrotation, &/or signs of obstructive nephropathy due to vesicoureteral reflux & ureteropelvic junction stenosis
Diaphragmatic hernia		AP & lateral chest x-ray to detect a small diaphragmatic hernia. Larger ones would probably be clinically apparent due to respiratory distress.	Eval for diaphragmatic defect especially prior to start of peritoneal dialysis
Genetic counseling		By genetics professionals [2]	To inform patients & families re nature, MOI, & implications of *WT1* disorder in order to facilitate medical & personal decision making
Family support/ Resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

CAKUT = congenital anomalies of the kidney and urinary tract; CKD = chronic kidney disease; CMA = chromosomal microarray analysis; CNS = congenital nephrotic syndrome; MOI = mode of inheritance; SRNS = steroid-resistant nephrotic syndrome; US = ultrasound

1. Trautmann et al [2020] (SRNS); Boyer et al [2021] (CNS)

2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with a *WT1* Disorder

Manifestation/Concern		Treatment	Considerations/Other
Glomer-ulopathy	Persistent proteinuria	Consider renin-angiotensin-aldosterone system (RAAS) inhibition: ACE inhibitor, AT1 receptor blocker. [1]	• Avoid immunosuppressants, which are ineffective & potentially toxic. [1] • Nephropathy does not recur post renal transplantation. [2]
	SRNS CKD CNS		
Disorder of testicular development		See Nonsyndromic Disorders of Testicular Development.	Management is often by a multidisciplinary team incl medical geneticist, endocrinologist, urologist, & psychologist.
Wilms tumor		Standard oncology protocols; surgery w/ nephron-sparing approach whenever applicable	Bilateral prophylactic nephrectomy after reaching ESRD (i.e., at time of kidney transplantation or placement of a peritoneal dialysis catheter) [3]
CAKUT		Urologic intervention may be applicable.	Per treating nephrologist &/or urologist
Gonadoblastoma		Gonadectomy per DSD team	No consensus re timing of surgery
Diaphragmatic hernia		As per treating surgeon	Repair to be performed prior to start of peritoneal dialysis

CAKUT = congenital anomalies of the kidney and urinary tract; CKD = chronic kidney disease; CNS = congenital nephrotic syndrome; DSD = disorders of sex development; ESRD = end-stage renal disease; SRNS = steroid-resistant nephrotic syndrome
1. Trautmann et al [2020] (SRNS); Boyer et al [2021] (CNS)
2. For a child to be eligible for kidney transplantation, most centers require that children weigh 10 kg and/or be at least one year post-completion of treatment for Wilms tumor.
3. Gariépy-Assal et al [2018]

Surveillance

Table 5. Recommended Surveillance for Individuals with a *WT1* Disorder

System/Concern		Evaluation	Frequency
Glomer-ulopathy	Persistent proteinuria / SRNS	Monitor for 1st appearance of proteinuria.	Every 6 mos until age 10 yrs; annually after age 10 yrs [1]
	CNS	Monitor for 1st appearance of proteinuria.	During first 3 mos of life [2]
	CKD	Monitor progression of known CKD.	Every 2 yrs
Disorder of testicular development		Monitor timing & progression of puberty.	Per treating multidisciplinary team (medical geneticist, endocrinologist, urologist, psychologist)
Wilms tumor		Monitor for 1st appearance of Wilms tumor.	Abdominal US every 3 mos until age 7 yrs [3]
CAKUT		Follow up of known kidney &/or urinary tract anomalies	Per treating nephrologist &/or urologist

CAKUT = congenital anomalies of the kidney and urinary tract; CKD = chronic kidney disease; CNS = congenital nephrotic syndrome; SRNS = steroid-resistant nephrotic syndrome; US = ultrasound
1. Trautmann et al [2020]
2. Boyer et al [2021]
3. Mussa et al [2019]

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual with a *WT1* disorder in order to identify as early as possible those who would benefit from prompt initiation of treatment and surveillance.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Because renal disease may progress during pregnancy, a pregnant woman with a *WT1* disorder should be referred promptly to a perinatal center experienced in the care of pregnant women with chronic kidney disease.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

WT1 disorder is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with a *WT1* disorder have the disorder as the result of an apparent *de novo WT1* pathogenic variant.
- In rare cases, a parent of an individual with *WT1* disorder is heterozygous for the pathogenic variant identified in the proband. Intrafamilial clinical variability is observed in *WT1* disorder and a heterozygous parent may be asymptomatic or have clinical manifestations of the disorder.
  - Fencl et al [2012] describe monozygotic twins presenting with congenital nephrotic syndrome born to an asymptomatic father age 41 years with the same *WT1* pathogenic variant.
  - Guaragna et al [2013] describe two families with vertical transmission of isolated *WT1*-related steroid-resistant nephrotic syndrome from an affected parent to an affected child.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo WT1* pathogenic variant.
- If the *WT1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Parental mosaicism has been reported [Beltcheva et al 2016].

- The family history of some individuals diagnosed with a *WT1* disorder may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

  Note: If the parent is the individual in whom the *WT1* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected or asymptomatic [Beltcheva et al 2016].

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *WT1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the *WT1* pathogenic variant is 50%. Although a sib who inherits a pathogenic variant is likely to have clinical manifestations of *WT1* disorder, the phenotype in a heterozygous sib cannot be reliably predicted because both intrafamilial clinical variability and reduced penetrance are observed in *WT1* disorder (see Penetrance) [Fencl et al 2012, Kaneko et al 2015, Boyer et al 2017].
- If the proband has a known *WT1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Beltcheva et al 2016].
- If the parents have not been tested for the *WT1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for a *WT1* disorder because of the possibility of reduced penetrance in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a *WT1* disorder has a 50% chance of inheriting the *WT1* pathogenic variant. It should be noted however, that most individuals with a disorder of testicular development are infertile.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *WT1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternative paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption may also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *WT1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Rare Renal: Information on Rare Kidney Diseases**
  Steroid Resistant Nephrotic Syndrome – Patient Information
- **European Rare Kidney Disease Reference Network (ERKNet)**
  Phone: 49 0 6221 56-34191
  Email: contact@erknet.org
  www.erknet.org
- **NephCure Kidney International**
  Phone: 866-NephCure; 866-637-4287
  Email: info@nephcure.org
  nephcure.org
- **National Registry of Rare Kidney Diseases (RaDaR)**
  RaDaR

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. WT1 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
WT1	11p13	Wilms tumor protein	WT1 database	WT1	WT1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for WT1 Disorder (View All in OMIM)

136680	FRASIER SYNDROME
194070	WILMS TUMOR 1; WT1
194080	DENYS-DRASH SYNDROME; DDS
256370	NEPHROTIC SYNDROME, TYPE 4; NPHS4
607102	WT1 TRANSCRIPTION FACTOR; WT1
608978	MEACHAM SYNDROME

Molecular Pathogenesis

WT1 encodes a regulatory protein comprising a proline- and glutamine-rich interaction domain and four zinc fingers (exons 7-9) which determine the sequence specificity of this critical transcription factor [Wang et al 2018]. Expression of *WT1* occurs for the most part in kidney progenitors and podocytes; in the urogenital ridge and gonadal progenitors [Wilm & Muñoz-Chapuli 2016]. More than 30 WT1 isoforms are derived from alternative splicing as well as alternative translation start sites and RNA editing; their relative ratios regulate particular processes of urogenital differentiation.

WT1 is a major transcription factor involved in cell differentiation and survival in the developing kidney, urinary tract, and gonads. WT1 regulates the expression of numerous target genes, including many genes encoding proteins that localize to the slit diaphragm of the glomeruli such as nephrin and podocin. WT1 controls the polarity of podocytes, cytoskeleton arrangement, and cell-matrix adhesion of the podocytes. It has a tumor-suppressor as well as an oncogenic role in tumor formation [Dong et al 2015].

Mechanism of disease causation

- **Dominant-negative mechanism.** *WT1* disorder is caused by a dominant-negative mechanism. For example, missense, nonsense, and frameshift variants that affect the zinc finger region may result in the loss, reduction, or altered specificity of WT1 isoforms to bind target DNAs. The numerous WT1 isoforms, derived from alternative splicing, alternative translation start sites, and RNA editing likely have varying effects in different tissues during development. For example, two common pathogenic variants with intron splice-site nucleotide changes (see Table 6) alter the ratio of alternative transcripts. Physiologically, an alternative donor splice site in intron 9 of *WT1* results in addition of three amino acid residues – lysine (K), threonine (T) and serine(S), referred to as the KTS splice variant – between the third and fourth zinc finger domains. Disruption of this splice site due to single-nucleotide variants at positions +4 or +5 of intron 9 alters the ratio of the WT1 isoforms with and without the KTS insert (+KTS/-KTS, respectively). Affected individuals have significantly fewer +KTS splice variants, resulting in a decreased ratio of +KTS/-KTS isoforms, a regulatory factor involved in proper testicular development in 46,XY individuals.
- **Tumor suppressor mechanism.** Consistent with the Knudson two-hit model of tumorigenesis and previous observations, children with a germline loss-of-function *WT1* variant are at very high risk for Wilms tumor (see Wilms Tumor Predisposition). See also Cancer and Benign Tumors.

***WT1*-specific laboratory technical considerations.** Because of high GC content, the sequencing of exon 1 of *WT1* is problematic. The numerous transcripts and their isoforms resulting from alternative splicing and translation start sites result in a single variant having many HGVS-approved names depending on the reference sequence. As there is no consensus in the literature or databases as to the "canonic" protein sequence, care must be taken when interpreting numbers of residues. In this chapter, amino acid positions are given according to NP_077742.3 (see Table 6).

Notable *WT1* variants. Variants discussed in the Genotype-Phenotype Correlations section include the following:

- Missense variants affecting nucleotides coding for DNA-binding helices of Zinc fingers 2 and 3 (residues: 439-454[RSDQLKRHQRRHTGVK]) from exon 8 and 467-474(RSDHLKTH) from exon 9 (reference sequence NP_077742.3)
- Certain splice site pathogenic single-nucleotide variants in the splice donor site of intron 9 change the ratio of +KTS/-KTS isoforms (See Table 6.)

Note: Originally, *WT1* pathogenic variants were subclassified as exon variants (presumably Denys-Drash syndrome-type) and KTS intron variants (presumably Frasier syndrome-type) (see Nomenclature).

A few recurrent pathogenic variants, both exon and intron, have been identified (see Table 6).

Table 6. Notable *WT1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_024426.6 NP_077742.3	c.1399C>T [1]	p.Arg467Trp [1]	The most common pathogenic variant
	c.1447+4C>T [2]	NA	Common pathogenic variant; typical for 46,XY CGD [Barbaux et al 1997]
	c.1447+5G>A [3]	NA	Common pathogenic variant; typical for 46,XY CGD [Barbaux et al 1997]

46,XY CGD = 46,XY complete gonadal dysgenesis
Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Alternate variant designations (e.g., c.1384C>T, 1180C>T, p. Arg462Trp, Arg394Trp). Originally reported as p.Arg394Trp [Pelletier et al 1991]. See ClinVar and Ensembl sites for rs121907900.
2. Alternate variant designations (e.g., 1432+4C>T, IVS9+4C>T). See ClinVar and Ensembl for rs587776577.
3. Alternate variant designations using other reference sequences (e.g., 1432+5G>A; IVS9+5G>A). See ClinVar and Ensembl for rs587776576.

Cancer and Benign Tumors

Somatic *WT1* variants have been described in sporadic Wilms tumors as well as in a significant proportion of other cancers, in particular desmoplastic small round cell tumor of childhood and leukemia.

Loss-of-function *WT1* variants are reported in about 15% of sporadic Wilms tumors.

In hematologic malignancies, somatic *WT1* variants are noted in about 6% to 15% of *de novo* acute myeloid leukemia (AML) and are associated with poor prognosis.

The *EWS-WT1* gene fusion is pathognomonic for desmoplastic small round cell tumor, an extremely rare aggressive soft tissue malignancy [Charlton & Pritchard-Jones 2016].

Chapter Notes

Author Notes

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