

## WAGR SYNDROME

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*The WAGR syndrome is a multiple congenital anomaly-mental retardation syndrome caused by interstitial deletion of the distal portion of chromosome 11p13. It is a contiguous gene deletion syndrome and WAGR is an acronym for the primary features: Wilms tumor, aniridia, genital anomalies, and mental retardation. Wilms tumor and male genital anomalies are caused by deletion of the *WT1* tumor-suppressor gene and aniridia is caused by deletion of *PAX6* ocular developmental gene. Mental retardation is presumed to be a consequence of the deletion of multiple as yet unidentified genes in the region. Most cases are identified by chromosome studies of children with sporadic aniridia and are caused by *de novo* deletions of 11p13, although a few familial translocations are reported. Individuals with the WAGR syndrome have a high risk for developing Wilms tumor and late-onset renal failure, and should be monitored for these complications.*

### INTRODUCTION

The observation that aniridia can be associated with Wilms tumor was made 50 years ago (Brusa and Torricelli, 1953) and confirmed 11 years later by Miller et al. (1964), who found 6 cases of aniridia among 440 individuals with Wilms tumor, noting that 3 had mental retardation. Genital anomalies were soon recognized to be a part of the association. In 1978, interstitial deletion of chromosome band 11p13 was reported in three individuals, and hence, the WAGR (Wilms tumor, aniridia, genital anomalies, and mental retardation) syndrome was proven to be a chromosomal microdeletion syndrome (Riccardi et al., 1978). It is now known that

late-onset nephropathy and end-stage renal disease are additional important features of the WAGR syndrome (Breslow et al., 2005).

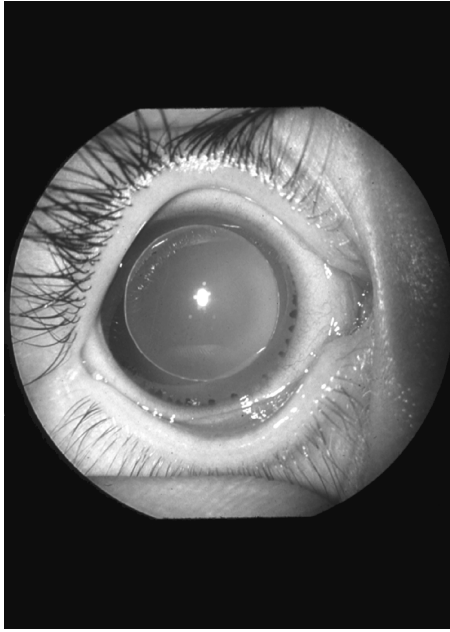
### Incidence

Although the syndrome is well-known to medical specialists and cytogeneticists, it is sufficiently rare that there are only a few hundred cases reported and incidence is not known. The most comprehensive reviews are by Turleau et al. (1984), Schinzel (2001), and Fischbach et al. (2005).

Given the high risk of malignancy and renal failure, average life span is likely reduced, but no longevity data have been published.

### Diagnostic Criteria

There are no consensus diagnostic criteria for the WAGR syndrome. As aniridia is almost constantly present and is the most distinctive feature, the clinical diagnosis of the syndrome can be made if aniridia and one of the other features are present (Fig. 59.1). External genital anomalies occur only in males (Fig. 59.2), and therefore, females with the disorder may go unrecognized when only aniridia is present at birth. Minor dysmorphism is frequently present, though there is no agreement on whether there is a recognizable facial phenotype (Fig. 59.3). Wilms tumor is reported in the literature to occur in 45–57% of individuals with WAGR syndrome (Muto et al., 2002; Fischbach et al., 2005). Data of Fischbach et al. was compiled from medical records and parent surveys of 54 individuals, who are members of the International WAGR Syndrome Association, and thus,



**FIGURE 59.1** Aniridia.

may reflect a degree of ascertainment bias. As late-onset nephropathy is now recognized as a long-term complication of the WAGR syndrome (Breslow et al., 2005), individuals with sporadic aniridia and nephropathy should be considered highly likely to have the syndrome.



**FIGURE 59.2** Genitalia of a 9-year-old boy with WAGR syndrome caused by  $del(11p13)$  showing right cryptorchidism and small phallus.

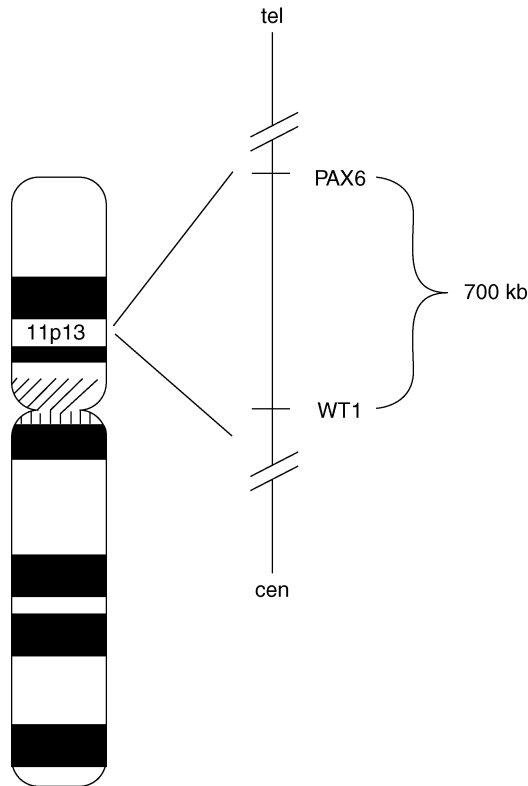


**FIGURE 59.3** A 5-year-old girl with WAGR syndrome caused by  $del(11)(p11.2p14.1)$ , showing photophobia as a result of aniridia. She was diagnosed with a Wilms tumor at age 18 months and focal segmental glomerulosclerosis at 17 years. She has multiple hereditary exostoses, type II caused by deletion of the *EXT2* gene at 11p11-12.

All newborn males with unexplained genital anomalies, including hypospadias, should have ophthalmologic evaluation for the presence of aniridia or iris hypoplasia. Most such infants will have a karyotype as part of the workup of genital abnormalities. Even if the karyotype is apparently normal, a finding of iris hypoplasia or aniridia in a male with genital anomalies establishes the diagnosis of WAGR syndrome until proven otherwise.

#### Etiology, Pathogenesis, and Genetics

The seminal discovery that WAGR syndrome is caused by deletion of band 11p13 led to the identification of the *WT1* tumor suppressor gene (Call et al., 1990; Gessler et al., 1990) and the *PAX6* ocular developmental gene (Hill et al., 1991) (Fig. 59.4). Hence, WAGR is a classical contiguous gene deletion syndrome, whereby the phenotype is caused by deletion of several neighboring genes. Approximately 90% of deletions are *de novo*, most frequently of paternal origin (Huff et al., 1990; Schinzel, 2001). A few individuals are mosaic for the deletion (Crolla and van Heynigen, 2002). The remainder are the result of familial insertional rearrangements, *de novo* unbalanced rearrangements, and one possible insertional translocation (Schinzel, 2001; Lennon et al., 2006). Of note is the observation of four published



**FIGURE 59.4** Partial map of the distal half of band 11p13, showing relative positions of *WT1* and *PAX6*.

cases (Turleau et al., 1984) and one unpublished (personal observation) case of *de novo* deletion of 11p13 associated with other apparently balanced *de novo* rearrangements. The biological basis for the frequent occurrence of *de novo* 11p13 deletion and the association with other *de novo* balanced translocations is unknown. Although the size of the deletion varies, it always includes at least the distal half of the 11p13 band.

To date, *WT1* and *PAX6* are the only genes identified in the deleted region that account for the genitourinary and ocular features. *WT1*, in addition to being a tumor suppressor gene, has a specific expression pattern in the developing genitourinary system and functions as a transcription factor essential for normal renal and gonadal development (Jadresic et al., 1990; Pelletier et al., 1991; Armstrong et al., 1993). Therefore, the genital anomalies and nephropathy as well as the risk for Wilms tumor in the WAGR syndrome are consequences of *WT1* mutations.

Although *WT1* expression is highest during urogenital embryogenesis in the condensing mesenchyme, renal vesicle, and developing podocytes, it persists in the podocytes of the adult kidney, a finding that appears to confirm the importance of *WT1* in the maintenance of glomerular function (Pritchard-Jones, 1999). Renal manifestations of haploinsufficiency of *WT1* in individuals with WAGR syndrome include not only nephropathy of adolescence/early

adulthood, but also small glomeruli and focal segmental glomerulosclerosis (Breslow et al., 2005; Fischbach et al., 2005; Dahan et al., 2007; Le Caigne et al., 2007). Focal segmental glomerulosclerosis is the renal lesion typically seen in Frasier syndrome (a genitourinary malformation syndrome caused by *WT1* mutation; see Chapter 22).

High levels of *WT1* expression are also observed in the developing genital ridges and fetal gonads. *WT1* persists only in the Sertoli cells of the testis and in the granulosa and epithelial cells of the ovaries (Pelletier et al., 1991). The complex role of *WT1* in gonadal development is far from understood. A number of gene targets for *WT1* have been suggested, including the sex-determining gene *SRY* (Hossain and Saunders, 2001) and steroidogenic factor 1 (*Sf1*) (Wilhelm and Englert, 2002).

The high risk of Wilms tumor in individuals with WAGR syndrome is consistent with Knudson's "two hit" theory of tumorigenesis, that is, there is a constitutional deletion of one *WT1* tumor suppressor gene and all that is required for tumor development is a second spontaneous (sporadic) *WT1* mutation. Molecular genetic analysis of Wilms tumor tissue from several individuals with WAGR syndrome has revealed acquired *WT1* mutations in most tumors studied (Knudson and Strong, 1972; Baird et al., 1992; Gessler et al., 1993; Park et al., 1993). Mitotic recombination and loss of the normal chromosome followed by duplication of the deleted chromosome is one such mechanism resulting in a second hit. One study found that individuals with WAGR syndrome and a submicroscopic deletion had a twofold higher risk of developing Wilms tumor compared with those with cytogenetically visible deletions (van Heyningen et al., 2007). The authors suggested that this could be because of the greater likelihood of survival of a cell line containing two copies of a submicroscopic deletion.

The *WT1* gene has 10 exons and encodes a zinc finger protein that is thought to function as a transcription factor. In WAGR syndrome, deletion of the *WT1* gene leads to haploinsufficiency of WT1 protein and subsequent incomplete masculinization of XY individuals (usually, cryptorchidism and hypospadias), late onset renal failure (Breslow et al., 2000), and predisposition to Wilms tumor. The relatively mild genital, renal, and tumor-risk phenotype of WAGR syndrome can be contrasted to the more severe expression of this constellation of abnormalities seen in the Denys-Drash and Frasier syndromes, which are because of missense and splice-site mutations, rather than deletions or premature protein truncation mutations of the *WT1* gene (see Chapter 22). This phenotype-genotype correlation suggests a functional difference between mutant WT1 protein with a single amino acid substitution (Denys-Drash and Frasier syndromes) and haploinsufficient WT1 protein (WAGR syndrome). In other words, a *WT1* mutation produces a more severe phenotype than a *WT1* deletion. This observation supports the hypothesis that *WT1* mutations produce

a “dominant-negative effect” wherein the mutant protein actively suppresses and inactivates the influence of the wild type allele (Huff, 1996).

The *PAX6* gene, which is positioned telomeric to *WT1* in the 11p13 band, is an ocular developmental gene, which causes aniridia when mutated, deleted, or functionally different because of a position effect. The *PAX6* gene deficiency causes a panocular malformation of the eye in which the most obvious abnormality is almost complete absence of the iris (Traboulsi et al., 1998). The term “aniridia” is conventionally used to denote the entire spectrum of eye abnormalities that are caused by *PAX6* gene abnormalities. The other features include glaucoma, corneal pannus, foveal and optic nerve hypoplasia, and cataract formation. Using DNA from individuals with the WAGR syndrome, the *PAX6* gene was cloned as a candidate gene for isolated aniridia in 1991 (Hill et al., 1991). Subsequently, a large number of *PAX6* mutations have been identified in individuals with aniridia (Robinson et al., 2008). The human *PAX6* gene is a homologue of the mouse *Pax6*, mutations in which cause microphthalmia and aniridia, as well as Peters’ anomaly (a form of anterior segment dysgenesis). *Pax6* is also expressed in the mouse brain, spinal cord, and pancreas, and mice homozygous for null *Pax6* mutations die at birth, showing anophthalmia, absent noses, and severely malformed brains (Hill et al., 1991; Walther and Gruss, 1991). There is one report of an infant with a similar phenotype who was found to be a compound heterozygote for *PAX6* mutations, suggesting a critical role for this gene in human brain development (Glaser et al., 1994). Another report identified 12 individuals with typical aniridia and *PAX6* mutations who had minor anterior brain abnormalities on imaging and reduced olfaction, suggesting subtle but widespread neurodevelopmental effects of a single mutation in *PAX6* (Sisodiya et al., 2001).

Aniridia occurs in 1/50,000–1/100,000 individuals, and two-thirds of the cases occur in families with autosomal dominant aniridia caused by *PAX6* sequence alterations deletions, or position effects (Muto et al., 2002). The remaining one-third of aniridia is sporadic, some affected individuals having the WAGR syndrome and others having acquired new mutations of *PAX6*. For individuals with sporadic aniridia, who do not have visible cytogenetic 11p13 deletions, there remains a concern that there may be a cryptic deletion including not only *PAX6*, but also *WT1*, and hence, significant risk for Wilms tumor. Recently developed molecular cytogenetic methods using fluorescence *in situ* hybridization (FISH) can now be employed to identify those sporadic aniridia cases with deletion of *PAX6* who also harbor a *WT1* deletion. In view of two reports of familial WAGR syndrome, wherein the mother had only aniridia and her male offspring had aniridia and early onset Wilms tumor, it is recommended that FISH deletion testing for *PAX6* and *WT1* be offered to all individuals with aniridia, both sporadic and familial (Fantes et al., 1992; Robinson et al., 2008).

There are three characteristics of individuals with WAGR syndrome that remain unexplained, despite our current knowledge of the *WT1* and *PAX6* genes. (1) The preponderance of males with a male:female ratio of 3:2 in the review of Turleau et al. (1984) and 2.7:2 in the review of Fischbach et al. (2005). Because individuals with WAGR syndrome are ascertained primarily on the basis of aniridia, and not genital anomalies, it appears that this cannot be explained by ascertainment bias. On the other hand, it may be that males with aniridia and genital anomalies are more likely to have cytogenetic analysis specifically to evaluate for WAGR syndrome, whereas females with aniridia (without external genital anomalies) are less likely to have the same studies. (2) The occurrence of genital anomalies and tumors in females, including uterine anomalies, streak gonads, and gonadoblastomas (Andersen et al., 1978; Fischbach et al., 2005). Streak gonads and gonadoblastomas are common in XY individuals with genital ambiguity or sex-reversal as a result of *WT1* mutations, that is, individuals with Denys-Drash and Frasier syndromes, but normal female genital development is characteristic of XX females with these two conditions (see Chapter 22). Analogously, normal female genital development would also be predicted in XX females with WAGR syndrome and *WT1* deletion. (3) The development of obesity as reported in several single case reports and in 18% (10/54) of the cohort reported by Fischbach et al. (2005) is also unexplained.

Several individuals with WAGR syndrome have been reported to have hereditary multiple exostoses type II caused by deletions of 11p that include the *EXT2* gene at 11p12-p11 (Bremond-Gignat et al., 2005; McGaughan et al., 1995).

### Diagnostic Testing

Children with sporadic or familial aniridia, with or without other features of the WAGR syndrome, should have a lymphocyte high-resolution chromosome study (at least 550 bands) looking for deletion of 11p13. If the chromosomes are normal, then additional FISH studies, which can identify deletion of *PAX6* and *WT1* should be pursued. Diagnostic WAGR deletion testing using FISH is clinically available. As there are a number of reported cases with cytogenetically visible 11p13 deletions where *WT1* is not involved in the contiguous deletion, it may still be appropriate for FISH testing to be carried out to assess whether or not *WT1* is involved (see below).

As the basic question to be answered is “Does this individual have aniridia which is caused by deletion of *PAX6*, and if so, is *WT1* also deleted?,” it is important to seek expert consultation from a clinical laboratory with the capability of evaluating both genes.

If no *PAX6* deletion is found, mutation study of *PAX6*, which is clinically available, should be carried out (Robinson et al., 2008).

### Differential Diagnosis

As sporadic aniridia is the key feature that suggests the diagnosis of WAGR syndrome, the differential diagnosis primarily includes other disorders with sporadic aniridia. If standard chromosome and FISH studies are normal, the most likely diagnosis in a child with isolated sporadic aniridia is a new *PAX6* mutation, that is, new mutation for autosomal dominant aniridia. If neurological abnormalities are present and cataracts absent, one should consider Gillespie syndrome, an autosomal recessive disorder characterized by aniridia, mental retardation, and cerebellar ataxia (Gillespie, 1965). To date, no abnormalities in *PAX6* have been identified in this syndrome (Glaser et al., 1994).

Aniridia can also be seen in association with anterior segment dysgenesis, such as Peters' anomaly, with microcornea and subluxed lenses, as well as with a handful of other rare multiple malformation syndromes (Traboulsi et al., 1998).

Except for the absence of aniridia and mental retardation, there is extensive clinical overlap between Denys-Drash and Frasier syndromes (caused by mutations in *WT1*) and WAGR syndrome. All three of these syndromes share the three cardinal features of external male genital anomaly, nephropathy, and Wilms tumor, though the genitourinary features of WAGR syndrome are generally milder than in Denys-Drash syndrome and Frasier syndromes (see Chapter 22). Hence, children suspected of Denys-Drash syndrome and Frasier syndrome should have careful ophthalmological evaluation to evaluate for aniridia.

## MANIFESTATIONS AND MANAGEMENT

The most comprehensive reviews of the natural history of WAGR syndrome are by Turleau et al. (1984) based on the evaluation of 37 affected individuals and by Schinzel (2001) and Fischbach et al. (2005) based on record review and parent surveys on 54 individuals.

### Growth and Feeding

Many children with WAGR syndrome have low-normal birthweight and most have postnatal short stature and microcephaly, a growth pattern typical of children with chromosomal abnormalities (Breslow et al., 2003). Specific feeding problems have not been reported. Severe obesity in childhood has been reported (Gul et al., 2002; Fischbach et al., 2005; Lennon et al., 2006).

### Evaluation

- Children should have height and weight measured and plotted on growth charts at routine medical visits, with

the anticipation of mildly slow, but steady linear growth and the risk of obesity.

- Plateauing of growth in childhood should raise the suspicion of an underlying medical complication, such as renal insufficiency or tumor. Appropriate investigations should be initiated.
- The risk of obesity is lifelong, and adults should also be followed up regularly and weights (or BMI) compared with earlier visits.
- The common complications of obesity, such as obstructive sleep apnea and type II diabetes mellitus, should be sought in those whose weight or BMI indicate obesity.

### Treatment

- Obesity and its complications should be managed as in the general population.

### Development and Behavior

Mental retardation is almost always present in WAGR syndrome. The range of cognitive impairment is quite wide, from normal functioning in a few individuals to severe mental retardation in the majority (Schinzel, 2001). A wide range of developmental disabilities occurs, including impairments of fine and gross motor skills, language acquisition, and sensory integration (Fischbach et al., 2005).

Psychiatric and behavioral disorders are reported in most affected individuals (ages infancy–42 years). The most frequent behavioral diagnosis is attention-deficit disorder with or without hyperactivity, particularly in males. Autism, pervasive developmental disorder, anxiety, and obsessive-compulsive disorder are also described (Fischbach et al., 2005). It should be noted that these behavioral and mental health disorders are not uncommon in any population of individuals with developmental disabilities, and it is not known if the risk of these problems is higher in WAGR syndrome. There are no data as to whether there is a specific behavioral phenotype for WAGR syndrome.

### Evaluation

- Early developmental assessment should be initiated as soon as the child is medically stable. Ongoing assessments are important for educational and vocational planning.
- Most children with the WAGR syndrome have significant visual impairment as well as a developmental disorder; therefore, programs specializing in children with visual impairment should be sought.
- Providers should maintain awareness of attentional, anxiety, and autistic spectrum disorders that may develop as the child matures.

### Treatment

- Infants and children will qualify for early intervention and special education programs, including special vision services, in addition to occupational, physical, and speech therapies.
- There is no diagnosis-specific developmental intervention.
- Referral to a behavioral health professional, such as a child psychologist or psychiatrist, should be made for therapy and/or pharmacological intervention, as needed.
- Consultation with social services and support groups is usually of great value for identifying financial and program resources for the family.
- Planning for adult services, including issues of guardianship, residential options, and vocational possibilities, should occur in adolescence.

### Ophthalmologic

Most individuals with the WAGR syndrome will have moderate to severe visual impairment as a result of the panocular effects of deletion of one copy of the *PAX6* aniridia gene. Aniridia, or iris hypoplasia, *per se* can cause photophobia. However, significant visual loss occurs because of a combination of any or all of the following: foveal hypoplasia, optic nerve hypoplasia, cataract, corneal pannus, subluxation of the lens, and secondary glaucoma (Traboulsi et al., 1998). Glaucoma develops in 50–75% and is the main cause of acquired visual loss in children with aniridia. Although glaucoma is most likely to develop in late childhood, individuals remain at risk into adulthood. Associated manifestations include pendular nystagmus, amblyopia, and strabismus. Ptosis, blepharophimosis, optic atrophy, microphthalmia, anterior segment anomalies, retinal dysplasia, and other ocular abnormalities have also been reported (Kawase et al., 2001; Schinzel, 2001). Aniridia can be missed in the newborn period, and the family may be the first to notice cataract, photophobia, unusually large pupils, or poor fixation.

### Evaluation

- Referral to an ophthalmologist experienced in the diagnosis and management of complicated aniridia should be made as soon as aniridia is diagnosed.
- Regular ophthalmological follow-up is strongly recommended for identification of evolving ophthalmic abnormalities.

### Treatment

- The management of the multiple ocular complications of aniridia, including cataract, lens subluxation, corneal

opacification, and glaucoma, requires expertise. Providers should identify local, regional, and/or national centers with the experience to provide optimal care. The International WAGR Association ([www.wagr.org](http://www.wagr.org)) is an excellent resource for this information.

- Educational programming for the visually impaired should be instituted early.
- The family should be referred to community-based services for the visually impaired.

### Oncologic

**Wilms Tumor** The high risk for Wilms tumor in children with WAGR syndrome warrants screening for this highly treatable tumor. Characteristics of 64 children with WAGR and Wilms tumor were reported as follows: median age at diagnosis 22 months (compared with 39 months in children with Wilms tumor without WAGR syndrome); 17% have bilateral disease (compared with 6% of children without WAGR syndrome). Survival at 4 years is comparable with children with Wilms tumor without WAGR syndrome. However, at 27 years survival is 46% in those with WAGR syndrome compared with 87% in those without WAGR syndrome, with later deaths resulting from end-stage renal disease (Breslow et al., 2003). Although most tumors have developed by age 6 years, the cohort of Fischbach et al. (2005) includes two individuals with late-onset Wilms tumors: one at almost 8 years and one at age 24 years, suggesting that Wilms tumor risk extends into adulthood. Of note, there appears to be two-fold elevated risk for Wilms tumor in individuals with submicroscopic *versus* cytogenetically visible 11p13 deletions (van Heyningen et al., 2007).

**Gonadoblastoma** There are several case reports of gonadoblastoma in children with WAGR syndrome, most of whom are XY individuals who likely had intra-abdominal dysgenetic gonads. However, the literature report of gonadoblastoma in an XX female with streak gonads (Andersen et al., 1978), as well as the occurrence of gonadoblastoma in one XX female in the cohort reported by Fischbach et al. (2005), suggests an increased tumor risk for all individuals with WAGR.

### Evaluation

- Based on the relatively early occurrence and estimated doubling time of Wilms tumor, a screening protocol of renal ultrasound every 3 months until age 6 years and physical examination every 6 months until age 8 years has been recommended by a committee of experts that included members of the National Wilms Tumor Study Group (Clericuzio et al., 1993). Clinicians should be aware that individuals with WAGR syndrome probably have a life-long Wilms tumor risk.

- Wilms tumor can evolve rapidly. A number of experts, including this author, are advocates of teaching parents the “daily caretaker abdominal examination” for young children with the WAGR syndrome. Most parents are eager to take an active role in their child’s care. Those that are too anxious to do the examination are fully supported in not doing so. The benefits of this practice are anecdotal: one parent of a child with WAGR syndrome found a Wilms tumor half-way through the 3-month screening interval (personal observation). As there is no evidence of an adverse effect of teaching parents the abdominal examination, it seems reasonable to offer this education as an option.
- Once a renal mass is identified, immediate referral to an oncologist should be made.
- It is considered prudent to screen females with WAGR syndrome with annual abdominal and pelvic ultrasound, beginning at the time of diagnosis.
- Gonadoblastoma in general develops in the teenage years or later, and therefore, this author recommends that screening should continue indefinitely or until gonadectomy.
- Males with normally descended testes should be examined routinely and undergo testicular biopsy if a mass or other abnormality is detected.
- Males with undescended testes should undergo testicular biopsy at the time of orchidopexy to evaluate for dysgenetic gonads. Further management is at the discretion of the pediatric urologist.

### Treatment

- Treatment for Wilms tumor usually follows national protocols, and will be managed by the oncologist, usually a pediatric oncologist. Prognosis for Wilms tumor is excellent, and over 85% of all affected individuals are cured following treatment with a combination of surgery and chemotherapy, with additional radiation therapy for advanced disease (Dome and Coppes, 2002).
- Prompt removal of intra-abdominal streak gonads is indicated if a diagnosis of XY sex reversal is made in a phenotypic female with WAGR syndrome.
- The removal of histologically dysgenetic gonads in males with ambiguous genitalia should be strongly considered, at the discretion of the managing pediatric urologist.
- Males with WAGR syndrome and intra-abdominal gonads who have normal testicular biopsy can be managed by bringing the testes into the scrotum (orchidopexy) and examining them routinely.
- Gonadectomy is recommended if streak gonads are identified in XX females.

### Genitourinary

**Genital Anomalies** Genital anomalies are usually present in males, presenting typically as cryptorchidism, hypospadias, small penis, and/or hypoplastic scrotum. Occasionally, males have more severe genital ambiguity, including involvement of internal genitalia, and may be given a female gender assignment. Complete sex reversal has been reported in an XY individual with otherwise normal female internal and external genitalia, but absent ovaries (Le Caigne et al., 2007).

Although there are no reports of female external genital anomalies, a variety of internal genital anomalies, including streak gonads, uterine malformation (hypoplastic *vs* unicornuate), and absent uterus and ovaries have been observed in females (Andersen et al., 1978; Nicholson et al., 1996; Schinzel, 2001; Fischbach et al., 2005). Hence, in contrast to Denys-Drash and Frasier syndromes (disorders that are also caused by abnormalities in the *WT1* gene), females with the WAGR syndrome may have developmental genital anomalies (see Chapter 22). Several females have had normal menstruation.

**Nephropathy** A 20-year follow-up of individuals with Wilms tumor and WAGR syndrome demonstrated that 36% of 37 individuals with WAGR and unilateral Wilms tumor had end-stage renal disease. Of the 10 individuals with WAGR and bilateral Wilms tumors, 90% had end-stage renal disease. Most instances of renal failure were relatively late, occurring during or after adolescence (Breslow et al., 2005). Hence, individuals with the WAGR syndrome should be monitored for signs of nephropathy throughout the lifespan.

In the Fischbach et al. (2005) cohort of 54 individuals with WAGR, about 25% had some degree of renal insufficiency, and four had undergone renal transplantation for end-stage renal disease. An additional six individuals were found to have focal segmental glomerulosclerosis.

### Evaluation

- A heightened index of suspicion for internal genital tract anomalies in XX females with WAGR syndrome should prompt ultrasound investigation of genitourinary symptoms such as dysuria, urinary tract infections, abdominal/pelvic pain, or mass. More detailed imaging with CT or MRI may be necessary, depending on the physical and ultrasound findings.
- Other than the testicular evaluation outlined above, there is no information on evaluations of internal genital anomalies in males with WAGR.
- Periodic screening for nephropathy, looking for proteinuria and hypertension, should be carried out every 6 months throughout life.

- Once nephropathy is diagnosed, the individual should be referred to an experienced nephrologist for management through to end-stage renal disease.

### Treatment

- For those males with significant genital ambiguity, the issue of gender assignment may affect the parents primarily, as mentally retarded children with XY who are raised as females may not comprehend the social implications of being genetically “male.” It is recommended that providers refer to the “Consensus Statement on Management of Intersex Disorders,” which covers investigation and management of disorders of sex development (Houk et al., 2006).
- XY individuals with WAGR syndrome who need surgical correction of genital anomalies are usually referred to pediatric urology or surgery.
- Intra-abdominal dysgenetic gonads should be prophylactically removed to prevent gonadoblastoma.
- Although there are no published data on pubertal development in individuals with WAGR syndrome, this author recommends that adolescents and adults be referred to pediatric/adult endocrinology if puberty is delayed or incomplete.
- Nephropathy is treated as in the general population.
- The majority of individuals with WAGR and end-stage renal disease have had renal transplantation. This is a complex decision and some families will decide against transplantation.

### Neurologic

Given the widespread expression of the *PAX6* gene in the central nervous system, there is a surprising paucity of neurological abnormalities, other than mental retardation, reported in individuals with WAGR syndrome. In the Fischbach cohort of 54 individuals (Fischbach et al., 2005), a variety of motor impairments (e.g., infantile hypotonia, hypertonia, and/or incoordination) were reported. Epilepsy and absent corpus callosum have also been reported. Interestingly, anosmia has been identified in individuals with autosomal dominant aniridia (caused by mutation in the *PAX6* gene) and is associated with absence or hypoplasia of the anterior commissure on magnetic resonance imaging (Sisodiya et al., 2001). Similarly, one would predict reduced olfaction in individuals with WAGR syndrome, and this history should be sought by providers.

### Evaluation

- Children and adults should have routine examinations for neurological status that are standard of care for

any individual with significant developmental disabilities.

- Sense of smell should be evaluated although there are no published data on the frequency of reduced olfaction.

### Treatment

- Standard treatment of seizures should be provided.

### Musculoskeletal

Congenital clubfoot deformity and duplication of halluces have been reported infrequently (Bremond-Gigna et al., 2005; Fischbach et al., 2005; Manoukian et al., 2005). Several individuals have developed neuromuscular kyphosis/scoliosis and Achilles tendon shortening.

### Evaluation

- Newborn examination will identify congenital limb abnormalities, such as duplicated halluces.
- Children should be monitored periodically for progressive spinal abnormalities and heel cord tightness.

### Treatment

- Standard pediatric orthopedic care should be sought for identified abnormalities.

### Ears and Hearing

Frequent and chronic middle ear and sinus infections occur with very high frequency and these should be anticipated in individuals with WAGR syndrome. Despite the high frequency of ear infections, only a few affected individuals are reported to have hearing loss.

### Evaluation

- Prompt evaluation of suspected ear and sinus infections, as well as ongoing monitoring for middle ear effusion, is warranted.
- Hearing should be tested by an audiologist in those with recurrent ear infections, as in the general population.

### Treatment

- Referral to an experienced pediatric otolaryngologist may be necessary.
- Standard treatment of ear and sinus infections is recommended.

## Respiratory

Reactive airway disease is reported in 15% of individuals (Fischbach et al., 2005).

### Evaluation

- Reactive airway disease should be evaluated as in the general population.

### Treatment

- Standard steroid and bronchodilator therapy should be employed.

## Cardiovascular

A variety of congenital heart defects have been reported. In a series of 54 individuals with WAGR syndrome, 11 cardiovascular abnormalities, ranging from patent foramen ovale to tetralogy of Fallot were reported (Fischbach et al., 2005).

### Evaluation

- Pediatric cardiology evaluation is recommended at the time of diagnosis of WAGR syndrome.

### Treatment

- Standard treatment for congenital heart disease should be offered.

## Miscellaneous

A variety of congenital anomalies have been reported infrequently, including renal cysts and horseshoe kidney. Cleft palate and tracheomalacia have been seen. Diaphragmatic hernia has been reported several times, and because *WT1* is expressed in the pleural and abdominal mesothelium, the association of WAGR with diaphragmatic hernia is not unexpected (Schinzel, 2001; Scott et al., 2005). Fischbach et al. (2005) noted dental abnormalities, including severe malocclusion, delayed loss of primary teeth, and micrognathia. Sleep apnea requiring treatment with continuous positive airway pressure, hyperlipidemia, and pancreatitis have also been reported with low frequency (Fischbach et al., 2005).

Children with deletions encompassing the *EXT2* gene at 11p11-12 should be monitored for complications of hereditary multiple exostoses. In addition to the complications caused by the exostoses *per se* (including long bone deformities and impingement on joints, nerves, and blood vessels), there is a 0.5–2% risk of malignant transformation of a hereditary exostosis into a chondrosarcoma.

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## RESOURCES

### Support Groups

#### The International WAGR Syndrome Association

Information and Support for Families and Professionals  
P.O. Box 392

Allen Park, Michigan 48101

USA

Web site: [www.wagr.org](http://www.wagr.org)

#### The Aniridia Network International

International Internet-based support group for people with aniridia and their families.

Web site: [www.aniridia.org](http://www.aniridia.org)

#### Asociacion Espanola de Aniridia

Web site: [www.aniridia.com](http://www.aniridia.com)

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