

## 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: W for Wilms tumor, A for aniridia, G for genital anomalies, and R for 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 deletion of multiple as yet unidentified genes in the region. Most cases are identified by chromosome studies of children with sporadic aniridia and are due to 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

#### Incidence

The observation that aniridia is 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 part of the association as well. In 1978, interstitial deletion of chromosome band 11p13 was reported in 3 individuals, and hence the WAGR syndrome (W for Wilms tumor, A for aniridia, G for genital anomalies, and R for mental retardation) was proven to be a chromosomal microdeletion syndrome (Riccardi et al., 1978). It is now known that late-onset nephropathy is an additional important feature of the WAGR syndrome, based on data from the National Wilms' Tumor Study Group Late Effects Study (Breslow et al., 2000).

While the syndrome is well known to medical specialists and cytogeneticists, it is sufficiently rare that there are only a few hundred cases reported. The most comprehensive reviews are by Turleau et al. (1984) and Schinzel (2001).

#### Diagnostic Criteria

There are no consensus diagnostic criteria for the WAGR syndrome. There is in progress a parent survey of characteristics and medical complications in over 50 individuals with WAGR through the organization Reaching Out, The WAGR Network, and preliminary data from this survey also provide valuable information. The survey project is called MedQuest, and the data from it will be referenced here as MedQuest (2003) (personal communication from C. Luis and K. Trout, Reaching Out, The WAGR Network). Since 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 is present (Fig. 53.1). External genital anomalies occur only in males (Fig. 53.2), and therefore females with the disorder may go unrecognized if only aniridia is present at birth. Minor dysmorphology is frequently present, though there is no agreement on whether there is a recognizable facial phenotype (Fig. 53.3). Wilms tumor is reported in the literature to occur in approximately 30%; however, it has been reported in 50% of the MedQuest cohort. This estimate may well be revised in the next decade as molecular cytogenetic diagnostic tools are refined and population-based studies completed (Gronskov et al., 2001). As late-onset nephropathy is now recognized as a long-term complication of the WAGR syndrome (Breslow et al., 2000), individuals with sporadic aniridia and nephropathy should be considered highly likely to have the syndrome.

#### Etiology, Pathogenesis, and Genetics

The seminal discovery that WAGR syndrome is caused by deletion of band 11p13 led to identification of the *WT1*

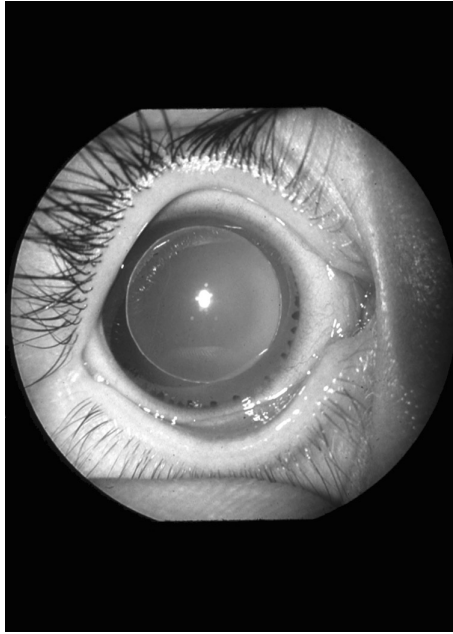


FIGURE 53.1 Aniridia.



FIGURE 53.3 A 5-year-old girl with WAGR syndrome due to del(11)(p11.2p14.1), showing photophobia due to 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 due to deletion of the *EXT2* gene at 11p11-12.



FIGURE 53.2 Genitalia of a 9-year-old boy with WAGR syndrome due to del 11p13, showing right cryptorchidism and small phallus.

tumor-suppressor gene (Call et al., 1990; Gessler et al., 1990) and the *PAX6* ocular developmental gene (Ton et al., 1991) in the region (Fig. 53.4). Hence, WAGR is a classical contiguous gene deletion syndrome, whereby the phenotype is caused by deletion of several neighboring genes in the region. Approximately 90% of deletions are *de novo*, most frequently of paternal origin (Huff et al., 1990; Schinzel, 2001). A few individuals

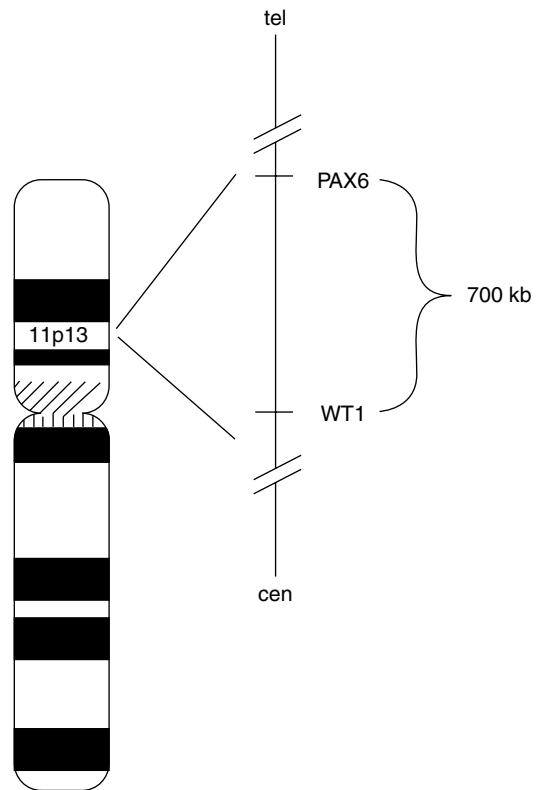


FIGURE 53.4 Partial map of the distal half of band 11p13, showing relative positions of *WT1* and *PAX6*.

are mosaic for the deletion (Crolla and van Heynigen, 2002; MedQuest, 2003). The remainder are due to familial insertional rearrangements, *de novo* unbalanced rearrangements, and one possible insertional translocation (Schinzel, 2001). Of note is the observation of four published (Turleau et al., 1984) and one unpublished (personal observation) cases 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 are unknown. While the size of the deletion varies, it always includes at least the distal half of the 11p13 band (Turleau et al., 1984).

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 (Armstrong et al., 1993; Pelletier et al., 1991; Pritchard-Jones et al., 1990). Therefore the genital anomalies and nephropathy as well as the risk for Wilms tumor seen in the WAGR syndrome are understandable consequences of *WT1* abnormalities.

While *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 maintenance of glomerular function (Pritchard-Jones, 1999). Focal glomerulosclerosis is likely the lesion that causes late-onset renal failure in WAGR syndrome as it is reported in 60% of the affected individuals over age 12 years (MedQuest, 2003), as well as in one who developed Wilms tumor (Breslow et al., 2000). Focal segmental glomerulosclerosis is the renal lesion typically seen in Frasier syndrome (a genitourinary malformation syndrome caused by *WT1* mutation; see Chapter 17) and is consistent with nephropathy expected to occur due to deletion of a *WT1* gene.

High levels of *WT1* expression are also observed in the developing genital ridges and fetal gonads. It persists only in the Sertoli cells of the testis and granulosa and epithelial cells of the ovaries (Pelletier et al., 1991). The complex role of *WT1* in gonadal development is far from being 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, i.e., there is a constitutional deletion of one *WT1* tumor-suppressor gene and all that is required for tumor development is a second spontaneous *WT1* mutation. The molecular genetic analysis of Wilms tumor tissue from several individuals with WAGR syndrome has revealed acquired *WT1* mutations in most tumors studied (Baird et al., 1992; Gessler et al., 1993; Knudson, 1972; Park et al., 1993).

The *WT1* gene has 10 exons and encodes a zinc-finger protein that is thought to function as a transcription factor. In the 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 due to missense and splice-site mutations, rather than deletions or premature protein truncation mutations, of the *WT1* gene (see Chapter 17). This phenotype-genotype correlation suggests a functional difference between mutant *WT1* protein with a single amino acid substitution (Denys-Drash and Frasier syndromes) versus 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; Little et al., 1993).

The *PAX6* gene, which is positioned telomeric to *WT1* in the 11p13 band, is an ocular developmental gene that, when mutated, deleted, or functionally different due to a position effect, causes aniridia. 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 of aniridia include glaucoma, corneal pannus, foveal and optic nerve hypoplasia, and cataract formation. Using deoxyribonucleic acid (DNA) from individuals with the WAGR syndrome, the *PAX6* gene was cloned as a candidate gene for isolated aniridia in 1991 (Ton et al., 1991). Subsequently, a large number of *PAX6* mutations have been identified in individuals with aniridia (van Heynigen and Williamson, 2002). The human *PAX6* gene is a homolog of the mouse *Pax6*, mutations that cause microphthalmia and aniridia, as well as Peters' anomaly (a form of anterior segment dysgenesis) in the mouse. *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., 1994a). Twelve individuals with typical aniridia and *PAX6* mutations were reported to have 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 to 1/100,000 individuals, and two-thirds of cases occur in families with autosomal dominant aniridia due to *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 can now be employed to identify those sporadic aniridia cases with deletion of *PAX6* who also harbor a *WT1*

deletion (Crolla and van Heynigen, 2002; Fantès et al., 1992; Muto et al., 2002).

There are two 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 Turleau's review and 2.5:2 in the MedQuest data (MedQuest, 2003; Turleau et al., 1984). Since 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; MedQuest, 2003). Streak gonads and gonadoblastomas are common in XY individuals with genital ambiguity or sex reversal due to *WT1* mutations, i.e., Denys-Drash and Frasier syndromes, but normal female genital development is characteristic of these XX females (see Chapter 17). Analogously, normal female genital development would also be predicted in XX females with WAGR syndrome and *WT1* deletion.

Two children with WAGR syndrome (one from MedQuest and one published) have been reported with hereditary multiple exostoses, type II, due to deletions of 11p that include the *EXT2* gene at 11p11-12 (McGaughan et al., 1995).

### Diagnostic Testing

Children with sporadic 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 fluorescent *in situ* hybridization studies that can identify deletion of *PAX6* and *WT1* should be pursued. Diagnostic WAGR deletion testing is commercially 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 fluorescent *in situ* hybridization to be carried out to assess whether or not *WT1* is involved (see below).

The basic question to be answered is: Does this individual have aniridia that is caused by deletion of *PAX6*, and if so, is *WT1* also deleted? It is important to seek expert consultation from a clinical or research geneticist and a laboratory with the capability of evaluating both genes. Published researchers in this specialized area can be approached regarding testing.

If no *PAX6* deletion is found, mutation studies should be carried out. A high proportion of the known *PAX6* intragenic mutations are recorded in a mutation database (<http://pax6.hgu.mrc.ac.uk/>). Of the 228 mutations in that database, 69 are *de novo* in the affected child.

### Differential Diagnosis

Since 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 fluorescent *in situ* hybridization studies are normal, the most likely diagnosis in a child with isolated sporadic aniridia is a new *PAX6* mutation, i.e., new mutation for autosomal dominant aniridia (personal observation). If neurologic abnormalities are present and cataracts absent, one should consider the 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., 1994b).

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 syndrome (see Chapter 17). Hence children suspected of Denys-Drash syndrome and Frasier syndrome should have careful ophthalmologic 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 evaluation of 37 affected individuals, and Schinzel (2001). As noted above in the introduction, unpublished data from over 50 children with WAGR syndrome will be cited as MedQuest (2003).

### Growth and Feeding

Many children with WAGR syndrome have low-normal birth weight and most have postnatal short stature and microcephaly, which is a growth pattern typical of children with chromosomal abnormalities (Schinzel, 2001). Specific feeding problems have not been reported. Severe obesity in childhood has been reported several times (Gul et al., 2002) and is also noted in 10 of 54 children with WAGR syndrome in MedQuest, suggesting that obesity is a clinical feature of the syndrome.

### Evaluation

- Children should be followed on standard growth curves, with the anticipation of mildly slow but steady linear growth and the risk of obesity.
- Plateauing of growth should raise the suspicion of an underlying medical complication, such as renal insufficiency or tumor. Appropriate investigations should be initiated.

### Treatment

- Obesity and its complications (e.g., obstructive sleep apnea) should be watched for and 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 more severe mental retardation in the majority (Schinzel, 2001). The MedQuest survey found not only mental retardation in the vast majority of individuals, but also psychiatric and behavioral disorders in most children (ages 3–19 years). The most frequently reported diagnosis is attention deficit disorder with or without hyperactivity, particularly in males. Autism, pervasive developmental disorder, anxiety, and obsessive-compulsive disorder are also reported. 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 as yet unknown if the risk of these problems is higher in WAGR syndrome. There are no data on whether there is a specific behavioral phenotype for WAGR syndrome.

### Evaluation

- In view of the high likelihood of significant developmental disorder in a child with WAGR syndrome, early developmental assessment and intervention should be initiated as soon as the child is medically stable.
- 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

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

## Ophthalmologic

Most individuals with the WAGR syndrome will have moderate to severe visual impairment, due to the panocular effects of deletion of one copy of the *PAX6* aniridia gene. The aniridia, or iris hypoplasia, per se can cause photophobia. However, significant visual loss occurs due to 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% of cases and is the main cause of acquired visual loss in children with aniridia. While glaucoma is most likely to develop in late childhood, individuals remain at risk into adulthood (Traboulsi

et al., 1998). 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). It is not infrequent that aniridia is 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. In the MedQuest study, 14 of 54 children were not diagnosed until over a month of age.

### 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 WAGR Network ([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 precise risk for Wilms tumor in children with WAGR syndrome is not known, but Turleau's original estimate of about 30% is still cited in the literature (Pritchard-Jones, 2002; Turleau et al., 1984). In the MedQuest survey of 54 individuals, the risk for Wilms tumor was 50%, with more males than females developing Wilms tumor (62% of males, 40% of females). The MedQuest survey includes 2 individuals with late-onset Wilms tumors: one at age 24 years and one at almost 8 years, suggesting that Wilms tumor risk extends into adulthood (MedQuest, 2003).

### 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 has been recommended by a committee of experts that included members from the National Wilms' Tumor Study Group (Clericuzio et al., 1993).
- Wilms tumor can evolve rapidly, and it is recommended that caretakers be shown how to perform daily abdominal palpation in addition to ultrasound screening (personal observation).
- Once a renal mass is identified, referral to an oncologist should be made.

### 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).

**Gonadoblastoma** There are several case reports of gonadoblastoma in children with WAGR syndrome, most of whom are XY individuals who likely had dysgenetic gonads (Schinzel, 2001; Turleau et al., 1984). However, the literature report of gonadoblastoma in an XX female with streak gonads (Andersen et al., 1978) suggests an increased tumor risk for all individuals with WAGR.

### Evaluation

- Based on the occurrence of streak gonads and gonadoblastoma in several XX females, it would be prudent to screen females with WAGR syndrome with annual abdominal and pelvic ultrasound.
- Gonadoblastoma in general develops in the teenage years or later, and therefore screening should continue indefinitely or until gonadectomy.

### Treatment

- Removal of intra-abdominal streak gonads is indicated as soon as the diagnosis of XY sex reversal in phenotypic females with WAGR syndrome is made.
- The removal of histologically dysgenetic gonads in males with ambiguous genitalia is also recommended.
- Males with WAGR syndrome and intra-abdominal gonads who have normal testicular biopsy can be managed by bringing the testes into the scrotum and examining them routinely (American Academy of Pediatrics, 2000). Males with normally descended testes should be examined routinely and undergo testicular biopsy if a mass or other abnormality is detected.
- Gonadectomy is recommended if streak gonads are identified in XX females.

### Genitourinary

Long-term follow-up of children with Wilms tumor who had sporadic aniridia (presumed WAGR syndrome) reveals that 38% (10 of 46) developed renal failure about 20 years after Wilms tumor diagnosis. The estimated cumulative risk for renal failure was over 60% after 25 years, and hence individuals with the WAGR syndrome should be monitored for signs of nephropathy throughout the life span (Breslow et al., 2000). In the MedQuest survey, 60% of children over age 12 years had developed renal failure (MedQuest, 2003).

Genital anomalies are usually present in males, presenting typically as cryptorchidism, hypospadias, small penis, and/or hypoplastic scrotum (Schinzel, 2001; Turleau et al., 1984).

Occasionally males have more severe genital ambiguity, including involvement of internal genitalia, and may be given a female gender assignment. All newborn males with unexplained genital anomalies should have ophthalmologic evaluation for the presence of aniridia or iris hypoplasia. Most will have a karyotype as part of the workup of genital abnormalities, and, 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.

While 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; MedQuest, 2003; Nicholson et al., 1996; Schinzel, 2001). 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. Menstruation has occurred normally in several females (MedQuest, 2003).

### Evaluation

- Pediatric and adult providers should periodically screen all individuals with WAGR for nephropathy. As proteinuria is usually the first sign, urinalysis every 6 months is recommended.
- Once nephropathy is diagnosed, the child should be put under the care of an experienced nephrologist for management through to end-stage renal failure.
- The evaluation of newborns with genital anomalies is well established and should include a search for internal genital anomalies. The reader is referred to excellent reviews by the American Academy of Pediatrics Committee on Genetics and others (American Academy of Pediatrics, 2000; Aaronson, 2002).
- Providers should be aware of the possibility of internal genital tract anomalies in XX females and investigate genitourinary symptoms such as dysuria, urinary tract infections, abdominal/pelvic pain, or mass promptly by ultrasonography. More detailed imaging with computed tomography (CT) or magnetic resonance imaging (MRI) may be necessary, depending on the physical and ultrasound findings.

### Treatment

- Management of nephropathy does not differ from that in the general population.
- The majority of individuals with WAGR and end-stage renal disease have had renal transplantation (Breslow et al., 2000; MedQuest, 2003)
- 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.
- For those males with significant genital ambiguity, the issue of gender assignment will affect the parents primarily, as most XY children raised as females will not

comprehend the social implications of being genetically “male.”

### Neurological

Given the widespread expression of the *PAX6* gene in the central nervous system, there is a surprising paucity of neurological abnormalities reported in individuals with WAGR syndrome, other than mental retardation. In the MedQuest survey, 60% of children had motor impairments (e.g., infantile hypotonia, hypertonia, and/or incoordination), several developed neuromuscular kyphosis/scoliosis, 10% were reported to have absence seizures, and one child had partial agenesis of the corpus callosum. 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). One would predict similarly 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.

#### Treatment

- Standard treatment of kyphosis, scoliosis, and seizures are used.

### Ears and Hearing

Frequent and chronic middle ear and sinus infections occur with very high frequency in the MedQuest survey population, suggesting that these should be anticipated in individuals with WAGR syndrome. Despite the high frequency of ear infections, only 10% of 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 in those with recurrent ear infections, as in the general population.

#### Treatment

- In addition to antibiotic therapy and ear ventilation tubes, nearly 40% of children reported in MedQuest have required adenotonsillectomy and/or sinus surgery.

### Respiratory

Reactive airway disease is reported in 15% of individuals (MedQuest, 2003).

#### Evaluation

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

#### Treatment

- Standard steroid and bronchodilator therapy should be employed.

#### Miscellaneous

A variety of congenital anomalies have been reported infrequently, including congenital heart defects, renal cysts and anomalies, diaphragmatic hernia, cleft palate, and tracheomalacia (Schinzel, 2001). The MedQuest survey also 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 were each found in about 5% of the MedQuest cohort.

Children with deletions encompassing the *EXT2* gene at 11p11-12 should be monitored for complications of hereditary multiple exostoses. In addition to the complications due to 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.

### RESOURCES

#### Support Groups

##### Reaching Out, the WAGR Network

Information and support for families and professionals

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

##### The USA Aniridia Network

Jill Nerby

1138 N. Germantown Parkway

Suite 101 PMB 109

Cordova, TN 38106

Email: [USAniridiaNET@aol.com](mailto:USAniridiaNET@aol.com)

Web site: [www.home.attbi.colm/~usann/](http://www.home.attbi.colm/~usann/)

##### The Aniridia Network

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Colchester CO4 3XU UK

Email: [hannah@aniridia-network.net](mailto:hannah@aniridia-network.net)

Web site: [www.aniridia-network.net/](http://www.aniridia-network.net/)

##### Asociacion Espanola de Aniridia

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28003 Madrid (Spain)

Web site: <http://www.aniridia.com>

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