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## WAGR Syndrome: A Clinical Review of 54 Cases

Bernard V. Fischbach, MD\*; Kelly L. Trout, RN, BSN; Julia Lewis, MD\*; Catherine A. Luis; and Mohammed Sika, PhD\*

**ABSTRACT.** WAGR syndrome is a rare genetic disorder characterized by a *de novo* deletion of 11p13 and is clinically associated with Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (W-A-G-R). Although the genotypic defects in WAGR syndrome have been well established, the large variety of phenotypic manifestations of the syndrome has never been reported. We report on 54 cases of WAGR syndrome to demonstrate both the classical clinical signs and nonclassical manifestations found in a large population of individuals with this disorder. An understanding of WAGR syndrome and its clinical findings can provide important insight regarding the functions of the involved genetic region. Recommendations for diagnosis, evaluation, and surveillance of patients with WAGR syndrome are also presented. *Pediatrics* 2005;116:984-988; WAGR syndrome, Wilms' tumor, aniridia, FSGS, WT1, PAX6, genitourinary abnormalities, mental retardation, Frasier syndrome, Denys-Drash syndrome.

ABBREVIATIONS. WAGR, Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation; FSGS, focal segmental glomerulosclerosis; DDS, Denys-Drash syndrome.

The clinical association of Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) was first noted by Miller et al.<sup>1</sup> Patients invariably have a *de novo* deletion in the distal band of 11p13 as described by Riccardi et al.<sup>2</sup> and Franke et al.<sup>3</sup> WAGR syndrome is a contiguous gene deletion syndrome. The deletion of several neighboring genes, including the PAX6 ocular development gene and the Wilms' tumor gene (WT1), results in both aniridia and increased risk for Wilms' tumor (Fig 1). Abnormalities in the Wilms' tumor gene are also thought to be responsible for the genital anomalies and nephropathies often seen in this disorder. According to recent research, deficiencies in the PAX6 gene result in abnormalities not only of the eye but also possibly of the brain and pancreas.<sup>4-7</sup>

Children with WAGR syndrome generally present in the newborn period with sporadic aniridia. The combination of sporadic aniridia along with genital anomalies may alert the clinician to the possibility of

WAGR syndrome, although genitourinary anomalies are not always present, particularly in girls. For this reason, it is recommended that all infants with sporadic aniridia be evaluated carefully for WAGR syndrome. In older children, clinical diagnosis of the syndrome can be made when aniridia and 1 of the other features (genital anomalies, Wilms' tumor, or mental retardation) are present. When WAGR syndrome is suspected, a combination of lymphocyte high-resolution chromosome study and molecular cytogenetic fluorescence *in situ* hybridization is recommended to demonstrate the characteristic deletion and confirm the diagnosis.<sup>8,9</sup>

In addition to the classic features for which the syndrome is named, there are a variety of serious complications for which the disorder is less well known. The present study of 54 cases of WAGR syndrome highlights these potential complications and demonstrates the presence of clinical findings that have not been reported in conjunction with this syndrome. Diagnosis of WAGR syndrome early in life allows for prompt recognition of these complications. Timely and appropriate medical intervention can significantly improve survival and quality of life for affected individuals.

## METHODS

The Institutional Review Board approved the study protocol. The database of patients who had a diagnosis of WAGR syndrome was obtained from a nonprofit family support organization, the International WAGR Syndrome Association. With informed consent from parents or guardians, medical information was obtained from the patients' physicians, hospital records, and a survey of characteristics that was completed by parents. This data then were compiled and analyzed.

## RESULTS

A total of 54 patients, 31 male and 23 female, were included in the study. Patients ranged in age from 7 months to 42 years, with a median age of 9.2 years. Demographic data regarding race and geographic region were not available for the majority of patients. The diagnosis of WAGR syndrome was based on results of genetic testing and the classical clinical criteria of Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation. Only 5 patients did not possess at least 2 of these classic clinical findings. In 4 of the 5, aniridia in combination with the 11p13 chromosomal deletion established the diagnosis. In the other, aniridia was not present, and Wilms' tumor in combination with the deletion established the diagnosis. The 11p13 deletion was known to be present in all patients for whom genetic information was available (51 of 54). In the three patients for whom genetic testing results were not

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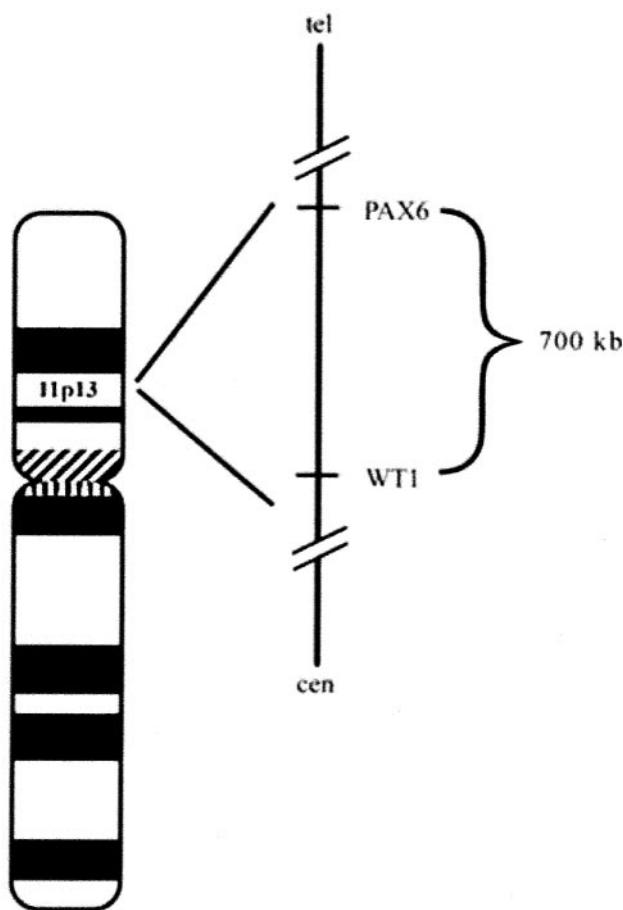


Fig 1. 11p13 genetic region.

available, at least 3 of the usual WAGR clinical criteria were present.

A total of 24 patients had all 4 classical clinical findings, 14 had 3 classical findings, and 11 had only 2 classical features of WAGR syndrome. Table 1 summarizes the classical clinical findings in our study population.

Wilms' tumor was diagnosed in a total of 31 (57%) patients. The staging of Wilms' tumor at the time of diagnosis ranged from stage I (confined to the kidney) to stage IV (metastatic disease). The treatment received by each patient varied depending on the stage of the tumor at diagnosis. Twenty-seven patients had undergone nephrectomy. Thirty-one patients had received chemotherapy, which most commonly consisted of actinomycin D and vincristine.

Aniridia was present in 53 of 54 patients. WAGR syndrome without aniridia, although rare, is not unprecedented; at least 1 other report describes a patient who had WAGR without aniridia.<sup>10</sup> Other ocular manifestations were common and included cataracts, glaucoma, and nystagmus (Table 2).

TABLE 1. Classic WAGR Clinical Findings in Study Participants

	Male	Female	Total
Wilms' tumor	19/31	12/23	31/54
Aniridia	31/31	22/23	53/54
Genitourinary anomalies	28/31	8/23	41/54
Mental retardation	24/31	15/23	39/54

The most common abnormality of the genitourinary tract was cryptorchidism, found in 60% of male patients. Internal genital anomalies, such as streak ovaries and bicornuate uterus, were found in 17% of female study participants. Ambiguous genitalia were present in 2 boys and 3 girls.

Mental retardation, defined as IQ <74, was the most common neurologic manifestation of WAGR syndrome and was found in 70% of patients. Table 2 summarizes the additional neurologic manifestations seen in patients with WAGR.

Renal failure has previously been reported to be common in patients with WAGR syndrome and a history of Wilms' tumor.<sup>11</sup> Nine (29%) male patients and 5 (20%) female patients had some level of renal failure, defined in this study as a reduction in glomerular filtration rate <80 mL/min. Four male patients in the study population had received renal transplantation for end-stage renal disease. The cause of these patients' renal failure included both nephrectomy (for Wilms' tumor) and glomerulonephritis, specifically focal segmental glomerulosclerosis (FSGS). Proteinuria was present in a total of 14 patients and ranged from minimal to overt nephrotic syndrome.

## DISCUSSION

Since the initial identification of the genetic mutation associated with WAGR syndrome, this region has been mapped extensively by multiple investigators and found to be vitally important in the development of multiple organ systems. The Wilms' tumor gene (WT1) is crucial in the development of the fetal kidney and is the major site of involvement in WAGR syndrome. WT1 was first identified as a tumor suppressor gene in the development of Wilms' tumor.<sup>12</sup>

Wilms' tumor is an embryonal tumor that normally affects approximately 1 in 10 000 children. In patients with WAGR syndrome, the risk has been estimated to be up to 45%.<sup>13</sup> In this study, Wilms' tumor was diagnosed in 57% (31 of 54 patients). The reason for this discrepancy is unknown. Selection bias is possible (ie, parents of children who have a diagnosis of cancer may be more likely to join a support group). Breslow et al<sup>14</sup> reported that children with aniridia or other known risk factors tended to receive a diagnosis at an earlier-than-average age (median: 17–27 months vs 38 months). This finding was mirrored in the study population, in which median age at diagnosis was 19 to 23 months. Although Wilms' tumor is considered unusual after age 5, 4 patients in the study population were older than 5 at the time of diagnosis of Wilms' tumor, and 1 of these was 25 years of age. Breslow et al<sup>15</sup> reported on 2 patients whose "reported relapses" were in fact de novo disease within the contralateral kidney. These patients developed new disease 2.4 years and 12.1 years after their initial Wilms' tumor diagnosis. These reports raise the possibility of late-appearing Wilms' tumor in some patients with WAGR syndrome and underscore the importance of screening renal ultrasounds and routine physical examinations. Renal ultrasound is recommended every 3 months from birth until age 6. After age 6, a thorough physical examination should be performed to

**TABLE 2.** Nonclassical Clinical Findings in WAGR Syndrome in Study Participants (N = 54)

Finding	n
<b>Genetic</b>	
Translocation	4
Mosaic deletion	1
<b>Ocular</b>	
Cataracts	36
Glaucoma	24
Nystagmus	22
Optic nerve hypoplasia	8
Macular/foveal hypoplasia	7
Retinal detachment	5
Strabismus	4
Ptosis	2
Corneal pannus	2
<b>Genitourinary</b>	
Cryptorchidism	19
Ambiguous genitalia	4
Hypospadias	4
Inguinal hernia	3
Streaked ovaries	2
Gonadoblastoma	2: 1 male/1 female
Bicornuate uterus	1
Hypoplastic uterus	1
Ureteral duplication	1
<b>Neurologic</b>	
Hypertonia/hypotonia	7
Epilepsy	4
Cerebral palsy	2
Enlarged ventricles	2
Agenesis of the corpus callosum	2
Central auditory processing disorder	2
Potocki Shaffer syndrome	1
Periventricular heterotopia	1
Microcephaly	1
Cerebellar hypoplasia	1
<b>Renal</b>	
Proteinuria	14
FSGS	6
Nephrogenic rests/nephroblastomatosis	2
Renal cysts	1
Unilateral renal agenesis	1
Hypoplastic kidney	1
<b>Cardiopulmonary</b>	
Asthma	8
Recurrent pneumonia	6
Patent foramen ovale	2
Pulmonary hypertension	2
Valvular hypoplasia	2
Ventricular septal defect	2
Patent ductus arteriosus	1
Tetralogy of Fallot	1
Atrial septal defect	1
<b>Head, eyes, ears, nose, and throat</b>	
Tonsillectomy/adenoidectomy	22
Tympanostomy tube placement	19
Recurrent sinusitis	15
Obstructive sleep apnea	11
Recurrent otitis media	10
Severe dental malocclusion	9
Hearing impairment	2
Micrognathia	2
Narrow palate	2
Hearing impairment	2
Cleft palate	1
<b>Behavioral</b>	
Attention-deficit/hyperactivity disorder	12
Autism, autism spectrum disorder	10
Obsessive compulsive disorder	5
Anxiety disorder	4
Depression	3
Pervasive developmental disorder, not otherwise specified	3
Attention-deficit disorder	1
Sensory integration disorder	1

**TABLE 2.** Continued

Finding	n
<b>Musculoskeletal</b>	
Hypertense Achilles	9
Scoliosis/kyphosis	8
Metatarsal adductus	3
Hemihypertrophy	3
Talipes	2
Multiple hereditary exostoses	2
Syndactyly/clinodactyly	2
Intention tremor	1
<b>Metabolic</b>	
Obesity	10
Hyperlipidemia	3
Diabetes	2
Adrenal insufficiency	1
<b>Gastrologic</b>	
Chronic pancreatitis	3
Gastroesophageal reflux disease	1
Pyloric stenosis	1

assess for abdominal masses every 6 months until age 8 and every 6 to 12 months thereafter.<sup>16</sup> Clinicians should maintain a high index of suspicion for Wilms' tumor in patients of any age with WAGR syndrome.<sup>17</sup>

The exact mechanism by which the 11p13 deletion results in the genitourinary abnormalities seen in WAGR syndrome has not been elucidated. Disruption of WT1 in mice has been shown to arrest gonadal development. In addition, Nachtigal et al<sup>18</sup> suggested that WT1 and steroidogenic factor act together to promote expression of müllerian inhibitory substance, which functions to cause the regression of the Müllerian ducts, a key step in sex determination. In this study, 19% of male patients had abnormalities of the external genitalia, and 60% of male patients had cryptorchidism. Two female patients had external genital anomalies, and 2 female patients were found to have streaked ovaries. The 2 female patients with streaked ovaries had XX genotypes, and 1 patient developed gonadoblastoma. The variable genitourinary abnormalities in our study population demonstrate the diverse function of this genetic region as well as WT1's critical role in both gonadal and sexual differentiation.

Aniridia is a severe ocular disorder characterized by the partial or complete absence of the iris. Aniridia exists both as sporadic cases and as familial cases with an autosomal dominant mode of inheritance. Approximately one third of patients with sporadic aniridia will have WAGR syndrome.<sup>19</sup> Both forms of aniridia are caused by mutations in the PAX6 gene.

PAX6 resides on 11p13 and in addition to modifying ocular development is also involved in the development of the central nervous system.<sup>5,20</sup> A wide variety of neurologic, behavioral, and psychiatric abnormalities were present in the study population (Table 2). The PAX6 gene also plays a role in islet cell development, and mutations in this gene have been shown to lead to defects in the endocrine pancreas.<sup>6</sup> Non-insulin-dependent diabetes was present in 2 patients in the study group but in both cases was diagnosed after renal transplantation. Chronic pancreatitis occurred in 3 patients. Obesity in conjunc-

tion with WAGR syndrome has been previously noted, although not specifically described as a feature of the syndrome. In the current study, 18% (10 of 54) of patients were obese, suggesting that obesity is indeed a common feature of the disorder. The frequency and variety of ocular, neurobehavioral, and metabolic manifestations reported in the study patients demonstrate the high penetrance and variable expressivity of the PAX6 region on 11p13.<sup>20,21</sup>

A high incidence of renal failure in patients with WAGR syndrome was first noted in 2000, with a cumulative risk for renal failure at 20 years of 38.3%.<sup>11</sup> In 2003, this risk was revised upward to 53%.<sup>15</sup> In the study population, 60% of patients who were older than 12 years had evidence of renal failure. FSGS was the most common glomerular disease found, and 2 patients had renal failure with no history of Wilms' tumor. The higher incidence of glomerular disease has not previously been reported. Although the causative factor of this clinical finding has not been determined, it is likely to be multifactorial.

A reduction in renal mass, associated with nephrectomy for Wilms' tumor, can result in glomerular hyperfiltration. The resultant hyperfiltration is a risk factor for the development of proteinuria and secondary FSGS. In this clinical setting, the afferent arteriolar resistance decreases in the remaining nephrons and leads to an increase in single nephron glomerular filtration rate. As a result, the glomerular transcapillary pressure also increases which may be the initial insult leading to sclerosis of the remaining glomeruli.

Although this seems to be a plausible explanation for the increased prevalence of renal disease in WAGR patients, the majority of patients who have a sporadic Wilms' tumor and subsequent nephrectomy do not develop renal failure. This suggests that additional factors may contribute to the development of renal disease in patients with WAGR syndrome. In our survey, 2 patients had evidence of renal disease (FSGS) with no previous history of Wilms' tumor.

A mutation, rather than a deletion, in the WT1 gene in association with renal failure is also found in 2 additional rare genetic disorders: Denys-Drash syndrome (DDS) and Frasier syndrome.<sup>22</sup> DDS is characterized by the presence of diffuse mesangial sclerosis with renal failure at an early age, XY pseudohermaphroditism, and a high incidence of Wilms' tumor. Patients with Frasier syndrome typically have FSGS, XY pseudohermaphroditism, and a high incidence of gonadoblastoma. A plausible explanation for the increased prevalence of glomerular disease is phenotypic variation in the WT1 mutation. Within the developing kidney, WT1 is expressed in the condensed mesenchyme and glomerular epithelial cells. In the adult kidney, WT1 continues to be expressed in the podocytes of the mature glomerulus. WT1 is capable of alternative splicing which results in 4 WT1 isoforms. Two isoforms that appear to be important in the function of WT1 depend on the presence (+) or absence (-) of 3 amino acids lysine-threonine-serine (KTS), between zinc fingers 3 and 4 of the WT1 protein. -KTS protein has been shown to

**TABLE 3.** Recommendations for Health Supervision for Children With WAGR Syndrome

Evaluations/examinations: infancy to adolescence
Assess the child with sporadic aniridia for WAGR syndrome using a combination of high-resolution chromosome study and molecular cytogenetic fluorescence in situ hybridization
Assess for abdominal masses. Continue renal ultrasound for Wilms' tumor at 3-mo intervals from birth until at least age 6 and physical examination every 6 months until age 8.
Surveillance for Wilms' tumor, including abdominal palpation and assessment for hematuria and/or hypertension, should continue indefinitely.
Assess for hypotonia, hypertonia, movement disorders, and scoliosis.
Assess frequency/duration of otitis media/respiratory tract infections. Modify treatment plan as needed.
Assess for nephropathy at each office visit, beginning in early childhood. Proteinuria and/or hypertension may occur well before changes in serum creatinine and blood urea nitrogen are noted and should prompt referral to nephrology.
Assess female patients for streak ovaries with pelvic ultrasound and/or MRI.
Assess for symptoms of obstructive sleep apnea.
Assess nutritional status, with particular attention to weight management.
Begin assessment for symptoms of behavioral or psychiatric disorders by age 2.
If patient is posttreatment for Wilms' tumor, then obtain appropriate laboratory/imaging studies (Table 4)
Anticipatory guidance
Establish a medical home. Emphasize role of the family as partners in the ongoing management of medical care of the child.
Teach caregivers importance of regular ultrasound screening and how to perform abdominal palpation between office visits.
Facilitate entrance into early intervention services.
Discuss special education, and review school and classroom placement.
Review availability of local, state, and national resources for children with disabilities.
Discuss issues of transition to adulthood, including vocational training and independent living options.

play a role in the regulation of transcription, and +KTS proteins are involved in RNA splicing. In Frasier syndrome, which is classically associated with FSGS, the ratio of +KTS/-KTS is lower than normal due to diminished +KTS. The decreased +KTS/-KTS ratio has not been demonstrated in patients with WAGR syndrome, but if present may also explain the higher incidence of FSGS and renal disease in the WAGR population.<sup>16,24</sup> Other researchers have hypothesized a genotype-phenotype correlation of these 3 syndromes, with the point mutations of WT1 in DDS and Frasier syndrome resulting in a more severe phenotype than the WT1 deletion of WAGR syndrome.<sup>11,23</sup> This study group demonstrates that the characteristic phenotype for WAGR syndrome includes genitourinary abnormalities in both male and female individuals, as well as a high risk for late-onset renal failure as a result of FSGS. The clinical findings of this study support the hypothesis that these syndromes represent a gradation of phenotype associated with WT1 mutations.

#### Changes in Clinical Evaluation and Follow-up

Children who present with sporadic aniridia are typically screened for WAGR syndrome, with genetic testing consisting of lymphocyte high-resolu-

**TABLE 4.** Recommended Annual Follow-up for Wilms' Tumor Survivors: the National Wilms Tumor Study Group

Laboratory tests: CBC, WBC/differential, liver function tests (AST, ALT, AlkPhos, bilirubin) renal function tests (BUN, plasma creatinine, GFR), urinalysis, 24-h urine collection
Blood pressure
If child received Ifosfamide (Cisplatin): blood and urine pH, electrolyte plasma and urine levels (K, P, bicarbonate and uric acid)
If child received Adriamycin (doxorubicin): echocardiogram and MUGA scan. Refer to cardiology as needed.

CBC indicates complete blood count; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; GFR, glomerular filtration rate.

Warwick A, Grigoriev Y. Recommended annual followup for Wilms tumor survivors. The National Wilms Tumor Study Group, 2003.

tion chromosome study. However, very small deletions that may not be detected even with high-resolution techniques can occur. The addition of fluorescence in situ hybridization increases the likelihood of detecting very small deletions and should be included in the evaluation of the child with sporadic aniridia.

Once the diagnosis of WAGR syndrome is confirmed, ultrasound screening for Wilms' tumor is usually initiated and continued until age 6. Because this study and others have demonstrated rare Wilms' tumor recurrences years after original diagnosis, a reasonable case could be made for lifelong Wilms' tumor surveillance. No official guidelines exist, but frequent abdominal palpation in children and periodic ultrasound evaluation in all patients may be appropriate, along with prompt evaluation of symptoms such as hypertension and hematuria.

Although the renal failure now associated with WAGR syndrome has occurred primarily in adolescents and young adults, it is possible that early indications of renal insufficiency, such as proteinuria or mild hypertension, may be present in children with the disorder. Treatment with angiotensin-converting enzyme inhibitors early in the disease process has been shown to delay the progression of FSGS in many patients.<sup>25</sup> Additional study is needed to determine whether a similar benefit may be achieved in children with WAGR syndrome and pre-end-stage renal disease. Measurement of blood pressure and dipstick urine screening for proteinuria can be accomplished at routine office visits beginning in early childhood. Periodic laboratory evaluation of serum creatinine and blood urea nitrogen should also be considered.

Finally, patients should be evaluated for other manifestations of WAGR syndrome (Table 2). Tables 3 and 4 provide guidelines for health supervision of children with WAGR syndrome, along with suggestions for facilitating medical care, education, and integration into the family and community.

### CONCLUSION

Although WAGR syndrome is a rare disorder, knowledge of its classical presentation and nonclassical manifestations is helpful for both the medical specialist and the primary care provider. The present study broadens the nonclassical phenotype of individuals with WAGR syndrome and highlights the importance of early diagnosis of both the syndrome

and its potential complications. The malformations and functional anomalies found in this study also correlate well with reports from other researchers on the phenotypic expression of abnormalities in the WT1 and PAX6 genes and demonstrate the potential for additional research into this genetic region.

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