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Aniridia**

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Kelly Trout, BSN, RN

**Health Consultant
International WAGR Syndrome Association**

**Program Manager, IWSA Patient Registry
Coordination of Rare Diseases at Sanford**

Let's say you have a new patient: a 3-month old infant who's just been diagnosed with WAGR syndrome. You – and her parents – were hoping it was “just” sporadic aniridia. That's more than complicated enough. But genetic testing has revealed WAGR syndrome, and WAGR involves not only many serious systemic conditions but often involves significant intellectual disability as well. So now you're wondering: what kind of future does this child have?

So I want to show you some things you may not have seen before. Not just new information, I want to give you a **view** of the future for these patients that is, surprisingly, full of hope.



As ophthalmologists, you are the first line of defense for these patients. You are typically the first referral made by the primary care manager, and you may be the **ONLY** one to recognize the possibility of WAGR syndrome, and refer for genetic testing. By doing so, you may literally save their life.

You also see these patients throughout their lifespan. So all their lives, you have the opportunity to play a role in recognizing the conditions associated with this disorder.



Evidence

Expert opinion

Case reports

Cohort studies

Natural history studies

Peer-reviewed articles

RCTs

Systematic reviews

Let's start with the evidence basis for the information I'm going to share with you. Of course there's a hierarchy for the quality of evidence for clinical recommendations. In the case of very rare disorders like WAGR, Randomized Controlled Trials and Systematic Reviews simply don't exist – so other levels of evidence have to suffice.

The best pieces of evidence we have at this point come from:

WAGR Syndrome: A Clinical Review of 54 Cases






Bernard V. Fischbach, Kelly L. Trout, Julia Lewis, Catherine A. Luis, Mohammed Sika

Article Figures & Data Info & Metrics Comments

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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.

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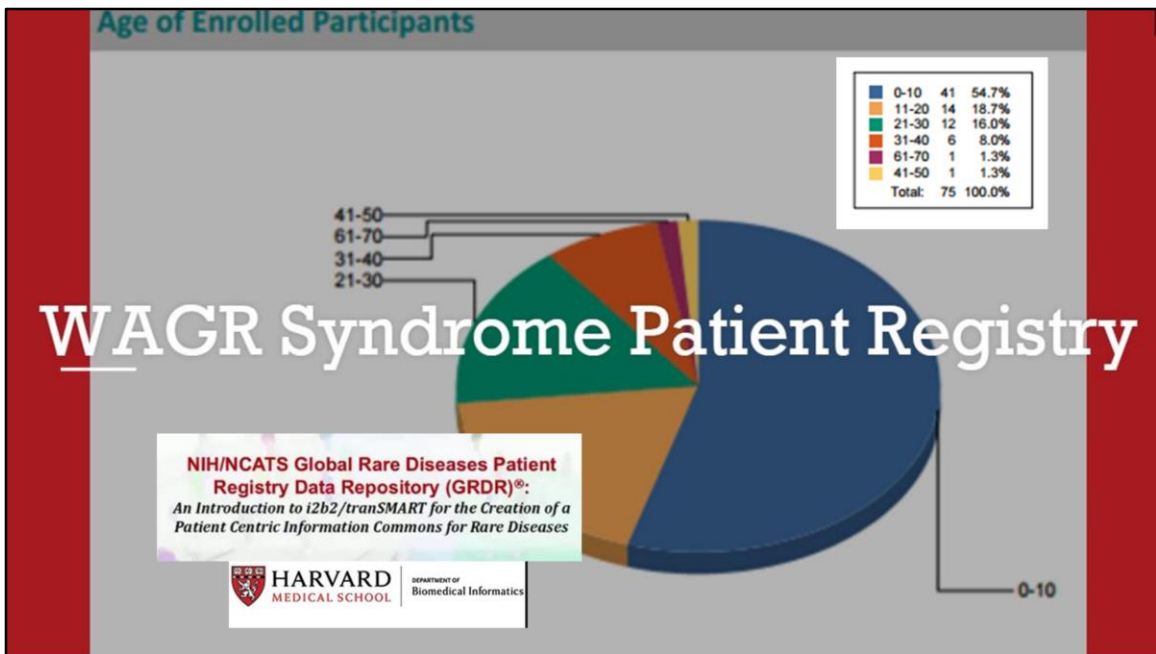
A clinical review of 54 cases of the disorder, published in the journal *Pediatrics* in 2005. Before this review, most of the available data on WAGR syndrome came from case reports. This article confirmed much of that data, but expanded the conditions associated with it beyond just the W, the A, the G, and the R.

National Institutes of Health
**Study of WAGR syndrome, 11p Deletions, and
Aniridia**
2006 – 2014



More progress in our understanding of the disorder has come from the US National Institutes of Health. Beginning in 2006, Joan Han (whom you'll hear from this morning) began a genotype/phenotype correlation study of WAGR syndrome, 11p deletions and aniridia.

This study involved extensive clinical testing, and identified a wide variety of new information.



Finally, a natural history study was launched in January, 2015. This Registry was developed as part of the NIH Global Rare Disease Registry and Data Repository project (GRDR), and is collecting comprehensive phenotypic data on patients with WAGR syndrome from around the world.

The Registry is housed in an online, secure platform and uses Common Data Elements and standardized data collection developed by the NIH.

Our hope is that this registry will provide not only additional data, but will also allow for prospective study – on Wilms tumor, for example, or aniridia. In fact, de-identified data from the Registry is currently available to any researcher, through a remarkable and very dynamic portal created for the GRDR by the Department of Biomedical Informatics at Harvard. Identified data can be obtained with IRB approval.

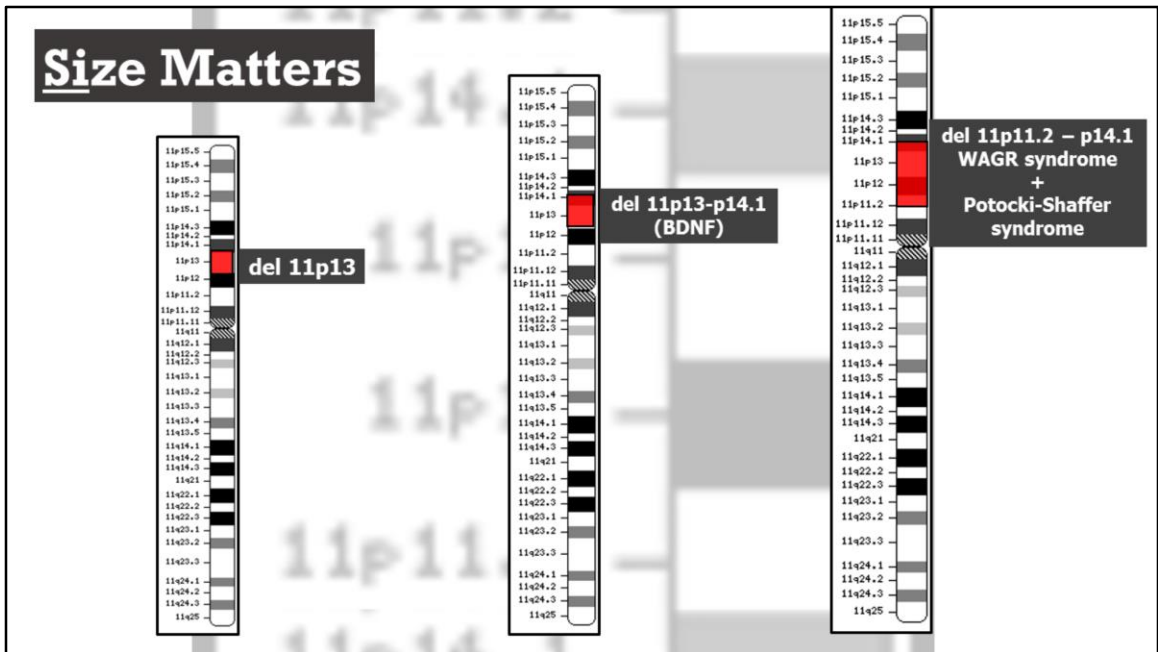
What is WAGR syndrome?

Rare
Contiguous
Deletion

Now. Let's get into the heart of this. I should mention that all of these slides feature actual patients with WAGR syndrome. The photos were contributed by parents who are members of the International WAGR Syndrome Association. This organization represents about 250 patients in more than 30 countries.

This adorable little girl is Maelynn. She's 3 years old, and lives in the Holland.

So WAGR syndrome is a rare, contiguous gene deletion disorder. How rare is it? The incidence is thought to be about 1 in 500,000 to 1 in 1 million. It is caused by a de novo, heterozygous deletion of genetic material on the short arm of Chromosome 11.



The genetic deletion involved in WAGR syndrome invariably encompasses the PAX6 and WT1 genes.

But the overall size of the deletion can vary dramatically from one patient to another – anywhere from 1 to 26 Megabase pairs.

Note the size of the red area on the left. This deletion is “classic” but it’s not necessarily typical. The deletion in the center is common to about 50% of patients with WAGR syndrome. As you can see, it extends to 11p14.1, which is the locus for a gene called BDNF, which Dr Han will be discussing in detail.

The deletion on the right extends toward the centromere, and is so large, it actually encompasses an additional syndrome.

So variations in both the size and position of the deletion are common, and this is probably why we see such a wide range of phenotypes.



This is Colton, who's 7 years old, and lives in Massachusetts.

The letters W-A-G-and R represent the "classic" clinical features, Wilms tumor, Aniridia, Genitourinary tract abnormalities and mental retardation – now referred to a Range of Developmental delays.

The problem with this acronym is that it implies a basis for clinical diagnosis. But there are patients with WAGR syndrome who do NOT have aniridia, and there are patients who have typical cognitive ability. They're not common, but the fact that they exist means that the absence of one of these features should not be used to exclude the diagnosis.



This is Evie and her parents. They live in Nevada. Evie is 12. This photo was taken at a Special Olympics Cinderella pageant, where Evie won Queen of her age bracket.

So how is WAGR syndrome diagnosed? With genetic testing of course, but routine karyotype analysis is not enough. Standard lymphocyte high resolution chromosome studies will detect larger deletions, but can easily miss smaller ones, or unusual mutations like mosaic deletions, insertional rearrangements, and translocations. So molecular cytogenetic testing is required, and involves these more sophisticated tests.

It's especially important for the diagnosis of WAGR syndrome to be accurate and timely, because surveillance for Wilms tumor should begin soon after birth. Wilms tumor is highly treatable in early stages, but complication rates increase and survival rates decrease the later the stage.

One word about CANDIDATES for referral for genetic testing:

The obvious candidate is the newborn with sporadic aniridia.

But less obvious candidates include

The older child or even adult with sporadic aniridia who has not previously had

genetic testing. **Remember:** Just because an older child has not had Wilms tumor, or the patient has a normal IQ does NOT rule out the possibility of the syndrome. This is very important, because in addition to Wilms tumor, there are other conditions associated with the syndrome that can occur later in life. But you need to know that the patient has WAGR in order to be on the lookout for those.



This is 12 year old Kadina and her father Marc at a Father-Daughter dance near their home in Illinois. Mark has written a wonderful book about the special bond between the two of them, called “Through My Daughter’s Eyes.”

You are probably all aware of the classic features of WAGR syndrome, so I won’t spend a lot of time on them. Wilms tumor is a malignant tumor of the kidney that is eventually found in approximately 50% of children with WAGR, and it’s the Number 1 Reason to insure that the syndrome is recognized soon after birth.

Wilms tumor most often appears before age 3, but it has **occurred in some patients with WAGR syndrome as late as age 25.** For this reason, we suggest that some level of surveillance continue throughout life. Ultrasounds are noninvasive and continuing these at 6 to 12 month intervals seems reasonable.

Aniridia

When it comes to Aniridia, there’s some question about whether there are differences in the onset, type or rate of ocular complications in patients with WAGR syndrome versus those with isolated aniridia. Until those questions are resolved, the main difference is that patients with WAGR may take longer to learn to cooperate

with an ophthalmic exam, and so may require exams under anesthesia for a longer time due.

Genitourinary Abnormalities


The genitourinary anomalies of WAGR syndrome are probably a little beyond your scope of practice, so I won't go into great depth here.

These anomalies are well-documented in males, about 60% of whom will have cryptorchidism and/or hypospadias. Genital anomalies are also present in females, possibly at about the same rate as males, but since they involve the ovaries, uterus or vagina they require specific imaging. This is important, because girls with WAGR and abnormal or streak ovaries are at risk for Gonadoblastoma and dysgerminomas.

Mental Retardation → “Range of developmental delay”

Mild to moderate cognitive impairment is very common in WAGR syndrome. The average IQ is 50 to 70, with a few individuals functioning below that and a few well above it.

Early intervention and special education services are necessary when a child has a sensory impairment, but they are especially critical when a child is at risk for intellectual disability. These services maximize development and improve long-term function.



Cardiopulmonary

Cardiomyopathy
Congestive heart failure

Tracheomalacia
Bronchomalacia
Laryngomalacia

- Asthma
- Recurrent pneumonia
- Patent foramen ovale
- Patent ductus
- Hypertension
- Valvular hypoplasia
- Atrial septal defect
- Tetrology of fallot

This is Aydin. She's 7 years old and lives in Oregon. Aydin dreamed of becoming a singer, so the Make-A-Wish organization made that dream come true and made her a Rock Star for a day.

The conditions associated with WAGR syndrome go far beyond the W-A-G- and the R. I'll do a quick review of systems and just highlight some of these.

Cardiomyopathy can occur as a long term complication of treatment for Wilms tumor with a drug Adriamycin. This drug can cause late-onset congestive heart failure which can take many years to manifest. Lifelong periodic testing is required, and if it does occur, treatment with ACE inhibitor drugs has been shown to slow its progression.



Head, Eyes, Ears, Nose, Throat

Obstructive sleep apnea

Hearing impairment:

sensorineural hearing loss 5%

Abnormal auditory brainstem response 50%

Auditory processing deficits in 92%

Low set ears

Pinna abnormalities

Cleft/high/narrow palate

Severe dental malocclusion
delayed loss of primary teeth

Micrognathia

Narrowing of pharynx

This is Lucienne. She's 15 years old, and lives in the Netherlands. In this photo she's just won a blue ribbon in a horseback riding competition.

Sleep apnea occurs in both youngsters and older children and adults with WAGR syndrome, and may be caused by a variety of different abnormalities of the airways.

CPAP, or Continuous Positive Airway Pressure can be used to maintain oxygen levels while sleeping, and tonsillectomy/adenoidectomy may also be helpful.

As you know –hearing impairment in a child who is already visually impaired can be devastating to development. So early identification of hearing problems is critical.

Sensorineural hearing loss and abnormalities in auditory brainstem response occur at about the same rate in patients with WAGR syndrome and patients with isolated aniridia --- about 5% and 50%.

But auditory processing deficits are found in 92% of patients with WAGR.

We don't know why there such a high rate of APD in patients with WAGR syndrome,

but this finding really emphasizes the importance of recognizing any type of hearing impairment early on, and targeting interventions for it.

Neurologic

Epilepsy

Idiopathic intracranial hypertension

Cerebellar hypoplasia

Periventricular nodular heterotopias

Agenesis of the corpus Callosum

Hypertonia/Hypotonia

Cerebral palsy

Enlarged ventricles

Pineal hypoplasia

**Hypoplasia/agenesis:
Olfactory bulb (CNI)
Abducens (CNVI)**

Hypoalgesia




This is Triston. He's 11 years old and lives in California. As you can see, he believes that a bad day fishing is better than a good day doing anything else.

Some of the big news in neurologic findings in WAGR syndrome parallels those in patients with isolated aniridia, including smaller pineal volumes, decreased melatonin production and increased sleep disturbance, as well as small or absent olfactory bulb or abducens nerve.

But one I'd like to point out one finding to you that's exclusive to WAGR syndrome: Hypoalgesia --- or impaired pain perception. You remember that about 50% of patients with WAGR syndrome are deleted for the BDNF gene? This gene is important to nociception. These patients are capable of feeling pain, but have a decreased response to it.

This is important for you because these patients may not have obvious pain when they have an injury or illness – so if they have a corneal abrasion, for example, they may have tearing and redness, but otherwise seem just fine. Same for an extremely high Intraocular Pressure. So don't be fooled. In these patients you may need to instruct parents to watch for symptoms other than pain.



Musculoskeletal

Hypertense Achilles

- Short stature
- Hyper/Hypotonia
- Talipes
- Hemihypertrophy
- Polydactyly
- Syndactyly
- Clinodactyly
- Scoliosis
- Kyphosis
- Metatarsus adductus
- Brachycephaly
- Multiple Hereditary Exostoses

This is Dylan, he's 13 years old and lives in Tennessee. In this photo, you can see Dylan wearing casts on both legs - he was 3 weeks postop. And yet here he is on his bike! This is a good example of impaired pain perception.

Toe walking and Hypertense Achilles are extremely common in WAGR syndrome, and may be severe enough to require orthotics, or serial casting, or like Dylan here, surgical lengthening of the tendons.



This is Alex. He's 20 years old and lives in New Mexico. He has played golf since he was 3, and earned his Varsity letter playing for his high school team.

The NIH study found that while many children with WAGR syndrome have a diagnosis of autism, overall they do not meet the criteria for "true" autism. Their behaviors appear to be more the result of auditory and sensory processing deficits and visual and cognitive impairment.

But a diagnosis of Autism may fit well enough to be very helpful in terms of opening the door to services and behavioral therapies that might not otherwise be available.

Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder are very common in kids with WAGR. As you've probably discovered in other young patients, medication can be effective, but finding the right drug and right dose is usually a long process of trial and error. To complicate this, many of the drugs currently used for ADD/ADHD should be used with caution in patients with glaucoma.

So it's very helpful when the ophthalmologist can work closely in this process with

the pediatrician and the parents.

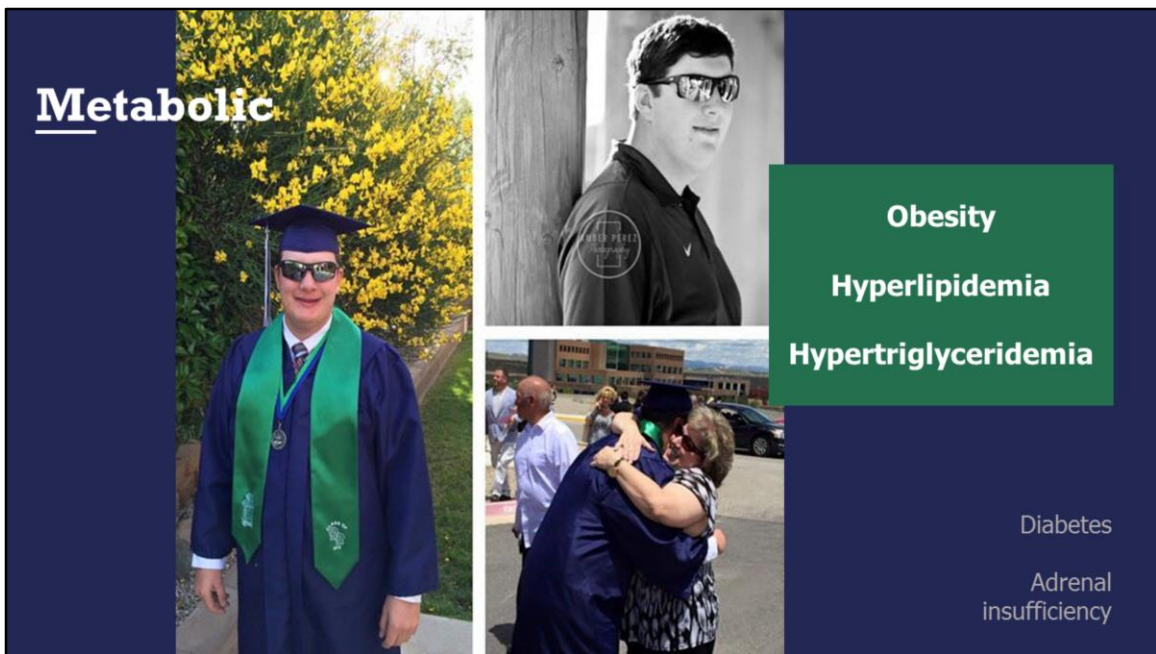


This young man is Braxton. He's 16 years old, and lives in my home state of Texas, where American football is KING. Braxton is a beloved member of his high school football team, even though he doesn't actually play. In fact, his enthusiasm and support for his teammates is so important to them, he was named their MVP -- their Most Valuable Player.

The most well-known renal issue in WAGR syndrome is Wilms tumor, but in recent years late onset nephropathy has become just as important – because just like Wilms tumor, it's a life-threatening condition that's amenable to treatment, but **ONLY IF** it is diagnosed and treated in a timely fashion.

This nephropathy affects more than 60% of patients over the age of 12, and is caused by a progressive lesion called Focal Segmental Glomerulosclerosis, or FSGS. Without treatment it can result in end-stage renal failure requiring either dialysis or transplant.

Aggressive treatment with ACE inhibitor drugs has been shown to slow progression of the disease, in some cases for many years.



This is Alex, who is 21 years old and lives in New Mexico. Alex is currently attending a special services university program, where he plans to earn an Associate's degree.

Dr Han will be speaking about Obesity and the BDNF gene so I won't go into these.

I will focus on hyperlipidemia in these patients. The big issue here is that patients with WAGR syndrome often have elevated triglycerides. When the level is extremely elevated they may have chronic pancreatitis as a result.

But these patients – those who have WAGR and hypertriglyceridemia - are also at risk for acute pancreatitis when they're given the anesthesia medication propofol. Since these patients often undergo many, many diagnostic and treatment procedures under anesthesia, this is a very significant risk for them.

So you'll want to be aware of this when scheduling patients with WAGR for exams under anesthesia, or when performing any procedure that requires general anesthesia.

Gastrointestinal

Diaphragmatic hernia

Inguinal hernia

Gastroesophageal reflux (GERD)

Biliary atresia

Fatty liver

Pyloric stenosis

Intestinal polypsis

Cholelithiasis

Gallbladder Cholesterosis

Situs inversus

Situs ambiguous
(Heterotaxia)

Intestinal malrotation

Chronic constipation



This is Alyvia. She's 15 years old and lives in California. Alyvia started high school this year, and just found out she made the school's Cheerleading team.

One condition that is extremely common is chronic constipation. To be honest, we tend to just treat it symptomatically, even though many patients struggle with it all their lives. But our patient Registry has uncovered cases of situs inversus, situs ambiguous, and intestinal malrotation. The possibility that there's a genetic basis for these defects is really intriguing, and exploring this could lead to more definitive treatment.



So in conclusion, remember your 3-month old patient, the one newly diagnosed with WAGR syndrome?

Her first few years of life may well look a lot like this. Numerous hospitalizations, a variety of procedures and surgeries, and a growing list of additional diagnoses.

This is a picture that challenges clinicians, and strikes fear in the hearts of parents. It's a picture that suggests a long, hard climb, with very little hope for the future.

But now you know that - eventually - this patient can grow up to look like... this....



This is Amy. When she was 17 years old, her dedication to insuring access to school sports for herself and for other kids with special needs got the attention of the White House. She was invited to meet the President of the United States, and he personally thanked her for her efforts.

Now, it's true that the view from the top of the mountain of WAGR syndrome does not always look exactly like this.

But doesn't it make a difference - just knowing that it CAN? That is what I most wanted to give you today. Not just a long list of diagnoses and clinical does and don'ts. But a sense of **hope**.

The knowledge that it is possible, despite many challenges - including the challenge of intellectual disability – to live a life that is happy, fulfilling and purposeful. Because with great medical care and high expectations, it is. These kids are proof of that. Thank you.



**Thank You
from the families of the
International WAGR Syndrome Association**