



2020 IWSA Virtual WAGR Weekend Conference

The following are answers to questions submitted but not addressed (or answered) during the conference

Wilms Tumor Related Questions

Is Wilms tumor development inhibited as our children get older?

Wilms tumor is widely accepted as originating in embryonic/fetal kidney cells that have not yet developed (differentiated) into the mature cells of the kidney. The process of immature cells developing into the many, many different mature cells that are found in the fully developed kidney is nephrogenesis. In humans, nephrogenesis is usually completed before birth. However, during nephrogenesis a cell may sustain some molecular alteration that inhibits or delays its maturation. With additional alterations this cell may ultimately result in the development of nephrogenic rests (so named because an undifferentiated cell has halted or “rested” during the development process) or a Wilms tumor. The likelihood of this progression to a tumor decreases as children age.

The research on the mouse is very interesting and promising. With the deletion of IGF2 is there more possibility to develop Wilms tumor?

The IGF2 gene is an “imprinted” gene. This means that, unlike most genes, only one copy of the gene is active. In the case of IGF2, the copy of the gene inherited from the father (called the paternally-derived copy or the “paternal allele”) is the active gene; the copy inherited from the mother (the “maternally-derived allele”) is normally silent. Several types of IGF2 alterations have been observed in Wilms tumors, but the result of all these alterations is to turn the maternally-derived copy of IGF2 on. So instead of just one active copy of a gene that is important for fetal cell growth, there are two active copies. To the question: the part of the IGF2 gene that encodes the IGF2 protein is not deleted. Rather there are deletions in the DNA region that controls the imprinting of the

gene or other changes in the control region that, again, abnormally turn the maternally-derived IGF2 gene on.

There is a fetal overgrowth syndrome called Beckwith-Wiedemann Syndrome (BWS). Children with BWS have a germline alteration that turns the maternal copy of the gene "on". In addition to growth abnormalities, BWS children are predisposed to Wilms tumor and also other childhood tumors that arise from embryonal/fetal cells

Is there any evidence as our children age the size of their kidneys shrink?

Chronic kidney disease (in the form of FSGS, or Focal Segmental Glomerulosclerosis) is very common in older children and adults with WAGR syndrome. Atrophy (decreased size) of the kidneys is not typically associated with FSGS, though. Kidney atrophy should be evaluated thoroughly, as it can be caused by blockage of the arteries and other conditions that can lead to decreased function. Here's more info:

<https://www.kidney.org/atoz/content/what-kidney-atrophy#:~:text=This%20type%20of%20kidney%20atrophy%20is%20due%20to%20a%20lower.can%20lead%20to%20kidney%20disease.>

Has anyone on the panel experienced Pax 6 mutation and Wilms Tumor? I ask because my son does not have WT1 however, Pax 6 and Wilms Tumor.

It is conceivable that an individual with PAX6 mutation could develop Wilms tumor without having evidence of a mutation in the WT1 gene. After all, typical children without aniridia who develop Wilms tumor usually do not appear to have mutations in WT1. But the presence of Aniridia in a child with Wilms tumor would seem to raise the likelihood. It sounds like in your son's case, no evidence of a deletion or mutation in the WT1 gene has been found to date. However, genetic testing is a rapidly evolving field. Depending on the type of testing that has been done in the past, it is possible that more sensitive tests could examine his WT1 gene in more detail to detect a mutation. I would encourage you to discuss this with a geneticist. Additional testing could have clinically relevant results, as a diagnosis of WAGR syndrome would identify other conditions for which your son is at risk, allowing for early diagnosis and treatment. Here is more information: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5322952/>

Is there any data about children with WAGR who haven't developed Wilms tumor after the 7th birthday?

Data from the WAGR Syndrome Patient Registry indicates that development of Wilms tumor after age 7 is exceedingly rare. It has occurred, however. For this reason, some level of lifelong surveillance is recommended:

<https://wagr.org/about-wagr/what-is-wagr-syndrome/w-wilms-tumor-2/>

My son will be 8 on 12/31/20. I promised my son's Urologist Dr. Kryger I would find out what the protocol is after 8 in regard to urine/ultrasounds related to kidney performance and Wilms.

In several cases, Wilms tumor has been reported in individuals with WAGR syndrome up to age 25. For this reason, some form of monitoring should be continued throughout life. This surveillance may involve ultrasound examinations every 6 to 12 months, palpation of the abdomen during regular physical exams, and observing the individual for symptoms such as high blood pressure or blood in the

urine: <https://wagr.org/about-wagr/what-is-wagr-syndrome/w-wilms-tumor-2/>

Aniridia Related Questions

Should we be doing more daily eye lubricants for my son's eyes which have corneal opacity?

Lubrication helps prevent opacity. Once it is there only surgery helps unless the surface over the opacity is breaking down in which case lubrication helps.

Would stem cell procedures for the eye be considered for a person who already takes anti-rejection medication?

Interesting question, I think it would depend on what medications as some are used for different things.

I was wondering if Dr. Levin recommends eye lubrication as a preventative measure even for a child that isn't having major eye issues yet?

Absolutely. I have all my patients on artificial tears 3-4 times daily.

What is the success of K-pro in (Aniridia) WAGR patients?

Very low

What is the cataract/glaucoma incidence rate in WAGR?

Glaucoma approximately 50%. Cataracts incidence rate is higher but many are minimal and surgery can be avoided.

Has anyone used artificial tear drops and if so, can you recommend a brand?

It's recommended to use preservative free artificial tears. The most common OTC brands that can be used are Systane, Refresh, and Theratears. The preservative free tears will be in single use containers.

My daughter's eyes never had tears and we use her eye drops up to 10x a day due to her eyes always being very dry and crusty. Is this quite normal to still have the dry eyes with the drops, she's 11 in October?

Sometimes it is very difficult to keep some kids from getting dry. In these cases, using more viscous tears or ointments may help. Also consider punctal plugs in the draining holes in the eye lids to keep tears and drops from draining out.

How important are sunglasses for a child with WAGR (aniridia) plus Peters Anomaly or glasses with no script for protection?

Sunglasses are more for comfort than protection. If they help symptoms then wear them. Otherwise, consider them optional. Protective glasses are more important if there is one good eye and one bad eye as they protect the good eye from an accidental injury.

Genetics Related Questions

Is there a value to full genome mapping as opposed to just exome?

Whole exome sequencing looks at deletions within genes (which are made up of exons) whereas whole genome sequencing looks at both genes and the regions between genes. The challenge with both is the interpretation of the data. Each time a test like this is run, the ordering medical care provider makes a list of clinical features that the patient has and the data is sorted looking for genetic changes that relate to these features. What we know about genetic changes and how they relate to specific clinical features is

constantly improving so some clinical testing laboratories will offer to re-analyze results over time as the database improves.

If we wanted to pursue genetic testing to add to the registry, is there a basic/standard testing you would recommend, or would different researchers require different tests?

Genetic testing results of any type can be very helpful and can be uploaded to the WAGR Syndrome Patient Registry. In terms of research, investigators who wish to study genotype/phenotype correlation (comparison of an individual's genetic makeup to their physical characteristics and medical conditions) could use the tests that have already been done or could choose to offer a specific type of testing to participants.

Is a whole genome SNP microarray an adequate genetic test for WAGR?

A SNP microarray looks for large deletions (missing parts) and duplications (additional parts) of chromosomes. Depending on the size of the deletion, an array may be able to detect the deletion. Smaller deletions or mutations in specific genes in the WAGR region would not be detected by array.

Speech Related Question

How long does speech and language delays usually last?

Language delay in children with WAGR syndrome is highly variable. Most kids with WAGR syndrome have some degree of delay. The cause of the delay may be attributed to cognitive impairment, but it's important to be aware that most individuals with WAGR syndrome also have auditory processing disorder (APD). APD can be addressed with fairly simple measures by both parents and teachers. Most children with WAGR syndrome will learn to speak eventually, but some do not. Early intervention services, including sign language and speech therapy can be very helpful. These services should not focus solely on producing speech, however. For those with significant speech delay, alternative forms of communication such as assistive speech devices can make a big difference in quality of life.

BDNF Related Question

Have you seen any of the possible symptoms seen in BDNF absence in patients without BDNF absence? It seems that our daughter experiences lower pain, heat, cold and has a bigger appetite than other children. My daughter does have BDNF but absence of WT1 and Pax6.

I think that it is possible that there are other genetic regions on chromosome 11 that could have an impact on how BDNF functions even if BDNF is not directly affected. I recognize the name of this child and recall that the family may have sent me the genetic report of the child a number of years ago but since they did not actually enroll in a study, all I have are email records and I can't locate the specific genetic report. If they wish to send it to me again, I would be happy to review to see if there's a possible explanation for the symptoms.

Behavior and Cognitive Related Questions

Has there been any investigation into the relation in decrease in cognitive ability and brain development into correlation with having ADHD and difficulty with long-term memory retention?

I am not aware of any research on this in WAGR syndrome. Diagnoses of intellectual disability, ADD/ADHD, Autism, Sensory Processing Disorder (SPD), and Auditory Processing Disorder (APD) are very common in WAGR syndrome. Each of these diagnoses can have a negative impact on learning and memory. Early Intervention services, special education, and targeted therapies can help lessen their impact.

My son has a lot of repetitive behaviors and speech. Is it a good idea to try and stop it? If so, what's the best way to do it?

Repetitive behaviors and speech may be related to anxiety, Obsessive-Compulsive Disorder, Autism, or other conditions. Since the treatment for each of these conditions is different, it's important to find out the cause in your son's case. Talk with his doctor about options for evaluation.

My daughter is 2 and displaying some autistic-like behaviors. Family members have voiced concerns. She is also completely blind in her left eye with very limited vision in her right eye. (bilateral Peters anomaly and left micro). I am curious about the differences in actual autism vs simply visual impairment behaviors and how to respond to family members.

Vision impairment, intellectual disability, Sensory Processing Disability, Auditory Processing Disorder, Anxiety Disorder, and other conditions associated with WAGR syndrome can all cause behaviors that look like Autism. For example, children with autism often don't make eye contact with others as much or in the same ways as typical children. The same is true of children with vision impairment. It's important not to assume the cause of concerning behaviors, though. If one of these conditions is present in addition to vision impairment, early diagnosis and appropriate treatment or therapy can make a big difference.

As far as how to respond to the concerns of family members, that can be tough. It may help to remind them that WAGR syndrome is a very rare disorder, but you are becoming more of an expert on it every day!

My son suffers badly from sensory processing issues, needing to chew, bite, and over stimulate. Could medication help with the need to chew, bite and over stimulate? I did hear some drug trials were happening to soften the effects of bdnf, any update on this?

These behaviors are often referred to as sensory seeking behavior. Although exploring objects with our mouths is a normal developmental behavior, those with sensory processing issues will continue to self-soothe/self-regulate. It can be caused by a child being either under or over stimulated. For children with sensory needs, oral sensory input can play a particularly important role. Short for self-stimulation, stimming is one way that individuals with sensory issues organize themselves and manage all of the extra sensory information bombarding their systems. Stimming is typically anything repetitive, such as flapping one's hands, rocking back and forth, spinning things, repeating certain words, chewing, etc. Although there are not any current medications recommended to treat or diminish these behaviors, there are some recommended steps one can take to manage it. The first recommendation is to consult with your child's pediatrician about seeing an occupational therapist. They can help you identify a pattern or triggers to these behaviors and help to develop an interventional strategy. It may also be beneficial to explore different textured toys that are meant for oral-sensory stimulation. There are different options when selecting sensory chew toys, with them coming in different sizes, textures, and colors. A few recommended websites for purchasing can be provided if requested.

Miscellaneous Questions

Has Covid taken the lives of any of our kids?

I am aware of one individual with WAGR syndrome who has tested positive for COVID-19 and recovered. There is evidence that children/adults with intellectual disabilities are at increased risk for contracting the virus, and also more likely to die from it:

<https://www.npr.org/2020/06/09/872401607/covid-19-infections-and-deaths-are-higher-among-those-with-intellectual-disabili>

How often should WAGR patients be screened and up to what age should they go for screening?

Here's a checklist:

<https://wagr.org/for-parents/medical-care-for-your-child-with-wagr-syndrome-a-checklist-for-parents/>

How many living adults are there with WAGR syndrome?

Here's more information:

<https://wagr.org/about-wagr/what-is-wagr-syndrome/associated-conditions/longevity-in-wagr-syndrome/>

Are you doing any live studies currently with WAGR individuals?

Yes. The IWSA WAGR Syndrome Patient Registry is an ongoing research study. Participating in this study involves simply completing an online (or paper copy) questionnaire. There is also a portal for researchers. Click here for more information:

<http://www.cordsconnect.sanfordresearch.org>

How many WAGR kids end up getting pancreatitis? And how can you tell?

We're not sure of the percentage of pancreatitis in individuals with WAGR syndrome. Both acute and chronic pancreatitis can occur. The risk appears to be increased in individuals who have hyperlipidemia (high blood cholesterol) and receive a medication called Propofol. Propofol is commonly used in general anesthesia. For this reason, it's important to discuss the risk with your child's doctor whenever they must undergo a procedure involving general anesthesia. Here's more information:

<https://wagr.org/about-wagr/what-is-wagr-syndrome/associated-conditions/pancreatitis/>

My son has a lot of bronchospasm. Is this associated with WAGR?

Bronchospasm (constriction of the muscles in the walls of the bronchioles) usually occurs in asthma, or in allergic conditions. Asthma does not appear to be more common in children with WAGR syndrome than in typical children. However, respiratory infections such as pneumonia are more common, particularly in very young children. Assessment by a pulmonologist (a doctor who specializes in diagnosis and treatment of diseases of the lungs) may be helpful.

Is scoliosis related to the syndrome?

Scoliosis is more common in individuals with WAGR syndrome than in typical people.

My son was born with ambiguous genitalia. He has diverticula at the back of his bladder since birth. During the last ultrasound, they saw sludge in his bladder. At a follow up ultrasound, the sludge was gone. Is there anything important to share with his urologist concerning the debris?

If he is not having recurring urinary tract infections then watchful waiting is probably fine but if he has recurrent UTIs, then making sure that he doesn't have a Mullerian duct remnant would be advisable.

My daughter has had large tumors/cysts removed from ovaries, pancreas and liver. We have had genetic testing done twice and our geneticists haven't found any reason why do you have any idea? She currently has 8+ cysts swiss cheesed throughout the liver. They think it may be caused by birth control pills. Will do another MRI scan in 8 weeks to see if they have decreased at all after stopping taking the birth control pills. Any comments?

Tumors are generally solid while cysts tend to be fluid filled – so was it a combination of both? The estrogen component of birth control pills can increase the risk for hepatic adenomas but generally suppress cyst formation in the ovaries. Pancreas cysts can be associated with genetic syndromes (but it sounds like they checked for that and ruled out), but they can also form after chronic or acute pancreatitis. If the patient has obesity, the risk of cysts in all 3 of the organs described can increase so that might be common link. Does the patient have obesity?

What was the brand of plate and silverware within Dr. Han's presentation?

Sammons Preston- sold through Performance Health offers a large assortment of assistive equipment for daily living, including for eating. However, this equipment is also frequently sold on Amazon: The two links below are for the utensils. You can also visit Amazon, and type: "offset silverware."

https://www.amazon.com/Piece-Super-Easy-Grip-Flatware/dp/B07GVP1VJB/ref=sr_1_3?dchild=1&keywords=adaptive+spoon+with+strap&qid=1596712759&sr=8-3

https://www.amazon.com/Sammons-Built-Up-Stainless-Steel-Easy-Hold-Removable/dp/B0745J8X81/ref=sr_1_1_sspa?dchild=1&keywords=adaptive+spoon&qid=1596712721&sr=8-1-spons&psc=1&spLa=ZW5jcnlwdGVkUXVhbGlmaWVyPUEFRUFpEUEYzWTFBNEkmZW5jcnlwdGVkSWQ9QTA3Nzg5MjlyNEQxWUU5NTNBVTNTJmVuY3J5cHRIZEFkSWQ9QTAzOTg4MzczVEIDRE1QVzJPVFUxJndpZGdldE5hbWU9c3BfYXRmJmFjdGlvbj1jbGlja1JIZGlyZWN0JmRvTm90TG9nQ2xpY2s9dHJ1ZQ==

The link for the spillproof scoop plate is:

https://www.amazon.com/Providence-Spillproof-Scoop-Plate-White/dp/B01AO9K4RU/ref=sr_1_3?dchild=1&keywords=adaptive+plate&qid=1596712984&sr=8-3

I'm a WAGR researcher living in Japan. Please tell us about the current state of early childcare and inclusive education for WAGR children in your country.

In the U.S., this answer varies from state to state. Each state must comply with a federal law, Individuals with Disabilities Education Act. However, states may use different models for deciding if your child is eligible. That's why a learning difference that qualifies as a "specific learning disability" in one state may not in another.

Here is a link that gives some state specific examples of inclusion programs:

<https://ectacenter.org/topics/inclusion/stateexamples.asp>

Below is also a link to the U.S. Department of Health and Human Services U.S. Department of Education's Policy Statement on Inclusion of Children With Disabilities in Early Childhood Programs:

https://journals.lww.com/iyjournal/fulltext/2016/01000/Policy_Statement_on_Inclusion_of_Children_With.2.aspx

