LEARNING ABOUT WILLIAMS SYNDROME

Children's HOSPITAL • ST. LOUIS
BJC HealthCare

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WILLIAMS SYNDROME

Williams syndrome (also known as Williams Beuren syndrome or WS) is a genetic condition that affects about one in 8,000 people. WS can affect many different organs as well as learning and development. This pamphlet is meant as an introduction to WS for families who have a child who has been newly diagnosed with WS.

WHAT ARE THE COMMON FEATURES OF WILLIAMS SYNDROME?

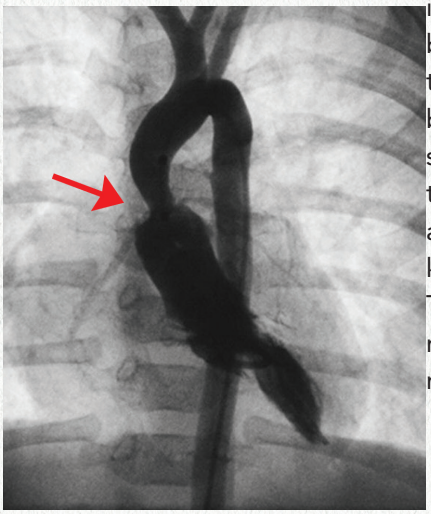
Each person with WS is unique, but there are many features that are more common in people with this syndrome. Having a combination of these features is what causes doctors to think about the diagnosis of WS.

FACIAL CHARACTERISTICS

Many children and adults with WS resemble each other, but they also look like other members of their family. Often those with WS have a wide mouth with full lips. They frequently have a broad tipped nose and puffiness around their eyes. Their eyes may have a pretty stellate (starlike) pattern to the iris (colored part of the eye). Curly hair is common.

HEART AND BLOOD VESSELS

Approximately 75 percent of people with WS have abnormalities in their blood vessels or heart structure. The most common blood vessel abnormality is called supravalvar aortic stenosis (SVAS). SVAS is a narrowing of the aorta, the large blood vessel that carries blood from the heart to the rest of the body. Other blood vessels can also have narrowings, such as the blood vessel from the heart to the lungs, called the pulmonary artery, or the blood vessels to the kidneys can also have narrowings. These narrowings are typically monitored by a cardiologist, and if necessary, treatment is available.



HORMONES

Increased levels of blood calcium (hypercalcemia) can be present in people with WS. This is most frequently a problem in infancy and usually improves over time. Greatly elevated calcium levels can cause irritability, loss of appetite and even seizures, so checking calcium levels is important. Because of the risk for high calcium levels, most people with WS should not take a multivitamin containing Vitamin D or eat a high-calcium diet. It is important that people with WS do not restrict the amount of calcium they get too much. Not getting enough calcium over a long period of time can lead to weaker bones.

People with WS can also have abnormalities of their thyroid function. The thyroid abnormalities can be transient and improve on their own, or can require treatment with medication. Because the thyroid hormones are very important for growth and development, thyroid function is checked on a regular basis throughout a person's life.

KIDNEYS

Those with WS have an increased risk for differences in the structure of their kidneys. They can also get high calcium levels in the urine (hypercalciuria), which can cause calcium deposits or stones in the kidney. People with WS can also have high blood pressure (hypertension). The doctor should check the level of calcium in the urine and blood pressure should be monitored on a regular basis.

EYES

Strabismus, a problem with eye muscle control that causes the eyes to have uncoordinated movement, or to turn in, is frequently found in people with WS. Farsightedness (hyperopia) is also common. Eye exams should be performed on a regular basis after age 1.

EARS

Ear infections are common in young children, and many children have ear tubes placed to help avoid fluid in the ears. Many people with WS have very sensitive hearing such that loud sounds may cause discomfort and anxiety. People with WS are also at risk for hearing loss over time, so hearing should be screened on a regular basis throughout childhood and adulthood.

CONNECTIVE TISSUE

People with WS frequently have differences in their connective tissue, the tissue that holds our bodies together. As a result, medical concerns such as hernias, scoliosis (curving of the spine), diverticulitis and loose joints are common. The joints can also develop tightness over time. Treatments are available to help with each of these concerns.

LEARNING ABILITIES

People with WS typically have intellectual disabilities in the mild to moderate disability range, although there are some individuals with intellect in the typical range and others who are more severely affected. Those with WS typically have a unique pattern of learning strengths and weaknesses. In general, vocabulary, skills requiring auditory (listening) abilities and long-term memory are strengths for people with WS. Spatial skills, such as reading maps, making comparisons, and drawing, are typically difficult for people with WS but may improve to some degree with age. Most children with WS require assistance in school and most adults with WS need help with certain aspects of their daily lives. They are usually not able to live independently.

PERSONALITY

Those diagnosed with WS are often described as friendly, outgoing and chatty and are highly motivated by social interactions. Many individuals with WS enjoy music.

WHAT CAUSES WILLIAMS SYNDROME?

WS is caused by a missing section of DNA on chromosome 7, called a deletion. To review, chromosomes are the packages for all of our genes. Most people have a total of 46 chromosomes, which come in 23 pairs. People have about 20,000 genes arranged along the chromosomes. Since we typically have two of each chromosome, we have two copies of each gene. Each gene is made up of DNA and is an instruction for the cell to make a protein that the body needs for growth, development or every day function. Individuals with WS have one copy of chromosome 7 that has all of the genes on it, and one copy of chromosome 7 that is typically missing 26 to 28 genes. The missing genes are responsible for the features that are part of WS. The missing section is usually 1.5 Mb (1.5 million base pairs, the units of DNA). The missing piece is called a "microdeletion," which means that it usually cannot be seen under the microscope without other special studies. Doctors and researchers are still learning which genes contribute to the characteristic personality and learning challenges for WS.

The elastin gene, abbreviated *ELN*, is missing in almost everyone with WS. This gene is responsible for the blood vessel narrowings seen in WS. Multiple other genes in the deletion are likely responsible for the social and developmental features of WS.

WHAT CAUSES THE DELETION?

In the vast majority of people with WS, the deletion was a random event that happened during the formation of the particular egg or the sperm that became that person. When parents produce eggs and sperm, genetic information has to be copied. Sometimes in the copying process, the pieces do not line up correctly and sections are left out (called a deletion). This happens prior to conception and is NOT caused by anything the mother or father did before or during the pregnancy. Many mothers especially worry that an event during the pregnancy caused WS to occur. It is important to specifically note that nothing a pregnant woman ate or drank, no medicines she took and no falls or other accidents that hoppened during the pregnancy caused WS to occur. In addition, WS has not been found to be associated with any specific behaviors or environmental exposures to the parents prior to pregnancy.

Some parents of children with WS have a difference in one chromosome 7 where the DNA is not in the usual order. This is called an inversion. The inversion causes no problems for the parent, but may make it more likely for that parent to have a child with WS. However, the likelihood a person with the inversion will have a child with WS is still very low (much less than one percent), and therefore doctors do not recommend that parents of children with WS (or any other family members with WS) be tested for the inversion.

WHAT IS THE CHANCE ANOTHER BABY WILL HAVE WILLIAMS SYNDROME?

If neither parent has WS, the chance that a future child will have WS is considered to be low, likely less than two percent. This chance is higher than for parents who have not had a child with WS. The chance is higher because a very small number of families have been reported who have more than one child with WS. This may be because one of the parents had more than one egg or sperm that had the deletion on chromosome 7 (called gonadal mosaicism). If a parent has features of WS, testing that parent may be recommended.

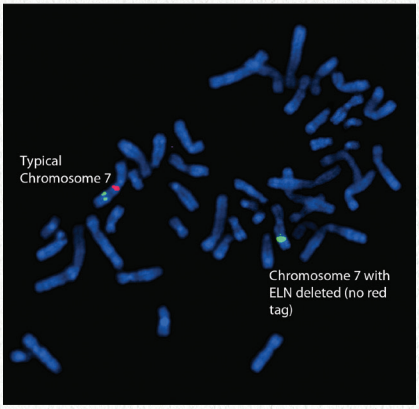
If either parent has WS, the likelihood that any future child would have WS is 50 percent. This is because whenever a parent has a child, the parent passes on half of their chromosomes to their child. When

a parent has WS, he or she can either pass on the chromosome 7 that has all of its genes, or he or she can pass on the chromosome 7 that has the deletion. While people with WS typically have normal fertility, they frequently do not have children because of their health and intellectual disabilities.

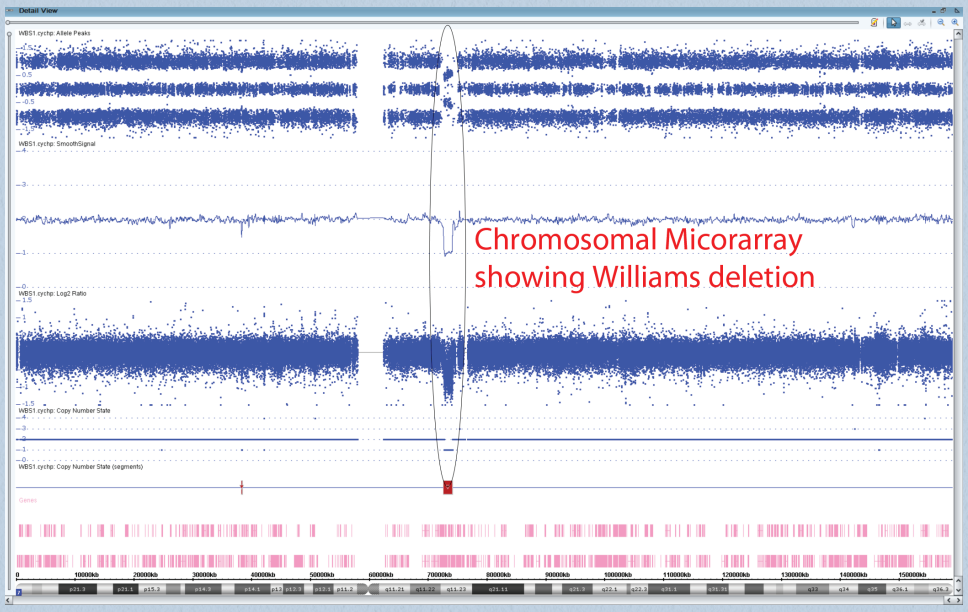
HOW IS WILLIAMS SYNDROME DIAGNOSED?

Clinical Diagnosis: WS was originally diagnosed based on clinical features, meaning that doctors familiar with the condition would recognize a set of different symptoms in a person and then tell the family that the child had the syndrome. Doctors who are very familiar with WS are very accurate at diagnosing the condition in most people. However, people with unusual features or more/less severe problems than a typical person with WS may be missed or misdiagnosed.

Fluorescence in situ hybridization (FISH): The FISH test was developed in the laboratory to detect small missing sections of DNA that cannot be seen under the microscope. FISH is performed on a small sample of blood. Cells are removed from the blood, and glowing tags that attach in specific places, including one that attaches at the *ELN* gene on chromosome 7, are added to the cells. The cells are then examined under the microscope, and the glowing tags are counted. If a glowing tag is missing, then the person is missing the genes in the area where the tag attaches. The WS FISH is able to determine the presence or the absence of the *ELN* gene. Anyone who is missing the *ELN* gene is diagnosed with WS. FISH cannot determine the size of the missing piece. Most people with WS have a very similarly sized deletion. However, there are a small number of people with WS who have a much larger deletion or a much smaller deletion. As long as *ELN* is in the deletion, the FISH testing would indicate the person being tested has WS. The FISH testing cannot detect when more genes than usual are deleted (which can result in more significant issues including seizures) or when less genes than usual are deleted (which may result in more mild issues).



FISH testing is considered "standard of care" and therefore typically covered by insurance. FISH testing for WS is specific for WS, which means that a person does not get information about any other genes or chromosomes from the FISH. FISH results are available very quickly, usually within two-to-three days.



Chromosomal Microarray (CMA) also called comparative genomic hybridization (CGH): CMA has been available clinically since 2005, but has greatly improved over time. CMA also uses a small sample of blood. DNA is collected from the blood and is compared to normal DNA. Computer software is then able to determine if there are any small pieces of DNA that are missing (a deletion) or extra (a duplication). CMA has the potential to determine the exact size of the missing piece in a person with WS, and therefore exactly which genes are deleted. Because CMA analyzes all of the chromosomes, it can also tell if there are other missing or extra sections of DNA on any other chromosome. Deletions or duplications on other chromosomes are not related to WS, but have the potential to explain unusual features in a person with WS or if a person with WS has more severe learning problems than is typical.

It is important to understand that knowing the exact genes that are missing in a person with WS does NOT mean that you can predict their

medical future or educational challenges. Most people with WS are missing the exact same genes and yet there is still significant variability from one person to another. CMA is more expensive than FISH and may not always be covered by insurance. In addition, CMA results frequently take three-to-four weeks, so it is a less helpful test when finding an answer is urgent.

HOW DOES WILLIAMS SYNDROME AFFECT PEOPLE THROUGHOUT THEIR LIVES?

INFANCY

Many children with WS are diagnosed as babies because of their heart and blood vessel issues, developmental concerns or characteristic facial features. Babies with WS are frequently small at birth and may continue to grow slowly. Special growth charts developed just for WS should be used to plot the growth of children with WS. Babies may have difficulties with feeding, such as being slower to eat or eating smaller amounts. Many babies have frequent spit-ups. Colic and irritability are common in infancy, but usually start to improve by 10 months of age. Transitioning to baby foods or to thicker/different textured foods can be difficult for some babies. Constipation is a common concern and should be managed carefully with diet and sometimes medications due the increased risk for rectal prolapse and diverticulitis in those with WS. Sleeping is often challenging, with frequent wake-ups. Blood vessel narrowings can change more quickly in infancy and may need to be followed more closely.

Babies with WS are frequently very social. However, infancy can be a challenging time for families of babies with WS because of the feeding struggles, sleep issues and irritability. This improves over time! Please use all the resources you have available to you during this period, including grandparents and friends. Let your doctor know if you need any additional assistance. Babies should receive therapy services, especially physical and occupational therapy to help with strengthening muscles and learning fine motor skills. Speech/feeding therapy may also be considered for babies with difficulties feeding.

PRESCHOOL

Toddlers with WS frequently have delays in meeting their milestones, such as walking and talking. While speech may be slow to develop,

it becomes a relative strength. Constipation and sleep problems can continue to be an issue in toddlers. Toddlers in general (and especially with WS) can be very picky eaters, but attempts to try new healthy foods should be made on a regular basis.

At the age of 3, therapies transition into the school district, and in most cases are provided through pre-school programs. At this age, most children with WS continue to need physical, occupational and speech therapy. Balance and fine motor skills like learning to write or cut with scissors may be areas requiring additional work.

SCHOOL AGE

During the school-age years, the heart and blood vessel issues are often more stable. Anxiety is common in school-aged children with WS. The anxiety may be be related to something specific, such as blood draws or storms, or it may be more generalized. Difficulties with concentration and focusing frequently become more apparent as children start school. Many children with WS have areas of special interest, topics that they love to learn or read about. Children with WS typically require an Individualized Educational Program (IEP),

which provides support and assistance in their education. Children with WS often greatly enjoy school, especially the social aspects of school, but may need assistance with developing relationships with their peers.

Scoliosis is another common medical issue in WS and can worsen during growth spurts. Puberty is frequently early, although not usually early enough to be a medical problem. Because children with WS tend to be very friendly, it is important for parents to discuss safe touches with their child in a developmentally appropriate way.

ADULT

The transition out of high school can be difficult for some young adults with WS as much of their social life and their services are dependent on their school. Adults with WS, like most people, seem to be happiest when they feel productive and purposeful. It is important to continue to find social outlets for adults with WS, such as church or community groups, Special Olympics and volunteering. Jobs in supportive environments are also beneficial.

All adults should try to eat healthy foods, especially fruits and vegetables, and get regular exercise, and that is certainly true for adults with WS. Adults with WS have an increased risk for obesity and obesity-related health risks such as diabetes and high cholesterol and should be screened for these concerns. Skin and hair may show signs of premature aging, such as early graying or wrinkles.

AFTER THE DIAGNOSIS OF WILLIAMS SYNDROME: WHAT SHOULD WE DO NOW?

Most children with WS are happy, healthy kids. However, they are at risk for additional medical concerns, most of which are treatable. Consequently, after the diagnosis is made, it is important for your child to have the following evaluations:

1. **Echocardiogram (heart ultrasound) and EKG (heart rhythm test):** An echocardiogram is performed to look at the structure of the heart and to check the blood vessels around the heart and lungs for any narrowings. An EKG is performed to check the rhythm of the heart. A cardiologist (heart doctor) will review the tests and discuss any findings with you.

2. **Kidney (renal) and bladder ultrasound:** An ultrasound is performed to look at the structure of the kidneys and bladder and to look for any calcium deposits in the kidney or bladder. Dopplers, a study of blood flow in the kidneys, may also be performed.
3. **Blood calcium levels:** A blood test to check the calcium.
4. **Urine calcium levels:** A urine test to check the amount of calcium in the urine.
5. **Urinalysis:** The urine sample is also checked for blood, protein and infections, signs that the kidneys are not working well.
6. **Thyroid function tests:** Thyroid stimulating hormone (TSH) and Free T4 (FT4) are checked in the blood to make sure the thyroid is functioning normally.
7. **Eye exam:** An exam by a pediatric ophthalmologist is recommended to check vision and eye muscle control.
8. **Audiology (hearing test):** A hearing test is recommended if your child is 1 year or older. This can be done sooner if you have specific concerns about your child's hearing.

9. **Monitor growth:** Height, weight, and head size should be graphed on a growth chart specific for children with WS. These are available online through the Williams Syndrome Association website (williams-syndrome.org).

10. **Blood pressure:** Many children with WS have high blood pressure, but blood pressure readings can also be used to detect narrowing at different points along the blood vessel tree. Consequently, your child's pediatrician should check the blood pressure in both arms and the cardiologist should check all four limbs.

11. **Developmental evaluation:** Your child should have an evaluation to see if any assistance is needed with learning and development. If your child is less than 3, he or she automatically qualifies for the early childhood intervention program in your area. If your child is older than 3, the school district in your area can typically perform the evaluation. A developmental evaluation can also be performed by a developmental pediatrician, or in some cases, a psychologist or psychiatrist.

    Children with WS typically qualify for:

    - Speech therapy for talking (some speech therapists also focus on feeding issues).
    - Occupational therapy for fine motor skills and activities of daily living (some OTs also focus on feeding).
    - Physical therapy for gross motor skills (like walking and climbing) and maintaining range of motion in the joints.

    Depending on your location and your child's abilities, music therapy, developmental therapy (working on cognitive thinking skills), aqua therapy (essentially physical therapy in the water) and horse therapy may also be available.

12. **Make sure you take care of yourself:** (this is not a medical evaluation for your child, but is just as important!). Getting a new diagnosis for your child, especially one that has lifelong medical and learning concerns, can be very overwhelming and frightening. Many parents find this time to be very difficult as they adjust to a new set of worries and future possibilities for their child. The Williams Syndrome Association is a great resource for families

to go to learn more information and to meet other parents of a child with WS. Family members, clergy and friends can also be helpful for you to talk to as you are coping with the diagnosis.

13. **Genetic counseling:** Meet with a genetic counselor and/or geneticist familiar with WS to ask any and all the questions you can think of. As with any child, there is no way to predict the future for your child with WS. The geneticist and genetic counselor can give you an idea about what typically happens as children with WS get older and can help you determine if additional tests or treatments are needed to help keep your child healthy. Information about WS changes with time as researchers learn more about the condition. Your doctor can talk with you about how those changes may impact your child's health.

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