What is White Sutton Syndrome?

White Sutton Syndrome (WHSUS) is a condition characterized by autism and developmental delay and/or intellectual disability, as well as a characteristic facial profile. Children may also have speech and language delay, motor difficulties, vision problems, hearing loss, seizures, gastrointestinal problems, obesity, anxiety, and attentional problems.

What causes White Sutton Syndrome?

In order to understand what causes WHSUS, we will review some genetic concepts. Our bodies are made up of billions of cells. Each cell carries a copy of our genetic code, or DNA, that has the instruction for how to cells grow, develop, and function properly. A change in the genetic code can sometimes cause problems by interfering with the body's ability to function normally and can lead to physical and/or developmental difficulties.

WHSUS occurs when one of the two copies of the POGZ gene has lost its normal function. This can be caused by a change in the gene that is like a spelling mistake. Sometimes, the spelling mistake occurs as a "de novo" change, which means it first appears in the individual with the condition for the first time in the family, and that it was not inherited. While this mistake in the gene could theoretically be inherited from a parent, all known cases of WHSUS are de novo. Almost all POGZ changes documented in medical literature are also

"nonsense" genetic changes that result in the gene stopping production of the protein it is supposed to make, resulting in WHSUS patients' genes only manufacturing half the normal amount of POGZ protein.

The POGZ gene is important in the normal development and function of the brain. It is likely that this is why WHSUS is primarily associated with developmental delay, intellectual disability, and autism or related behavioral problems.

How many individuals have this condition?
Approximately 50 individuals have been reported in the medical literature, although with the increasing use of the latest genetic sequencing technology it is expected that many more people will be diagnosed over the next few years.

White Sutton Syndrome is associated with the following features, although no one individual will necessarily have all of the features:

- Developmental delay and/or intellectual disability
- Speech and language delay
- Autism and/or autistic features
- Other behavioral challenges
- Seizures
- Distinct facial features
- Low muscle tone
- Hearing loss
- Vision problems

- Gastrointestinal problems
- Obesity
- Sleep problems
- Migraines and episodes of severe vomiting

Appearance
Individuals with WHSUS have a characteristic facial appearance, including wide-set eyes, a pointed chin, rotated ears, a broad nose, and a full lower lip. Some children also have differences in the hands, including a fusion of two or more fingers or a shortening of the fingers. These features tend to vary between individuals.

Medical Concerns

Growth:
Birth weight and length tend to be in the normal range, but in one study 4 of 5 (80%) individuals were short for their age. In two studies 13 of 29 (45%) individuals had small head size. Thirteen of 25 (52%) individuals were overweight.

Muscle tone:
In two studies 10 of 11 (91%) individuals had low muscle tone (hypotonia), which can result in delayed developmental milestones such as sitting and walking.

Motor skills:

Twenty-two of 25 (88%) individuals had delayed motor development.

Seizures:
Two individuals were reported to have seizures.

Gastrointestinal:
Four of 5 (80%) individuals had gastrointestinal problems, including gastroesophageal reflux and/or constipation. Ten of 25 (40%) individuals had feeding problems, including problems with chewing and swallowing and aversion to solid foods.

Sleep:
One study reported that sleeping problems were frequently observed, and two individuals were specifically reported to have sleep apnea.

Eyes, eyesight, and hearing:
In two studies 19 of 24 (79%) had vision problems, including crossed eyes, nearsightedness, farsightedness, and astigmatism. One individual had cortical visual impairment, where impaired vision is due to abnormalities in the brain rather than the eyes. Three of 5 (60%) individuals had hearing loss, due to damage to the inner ear or to the nerve pathways from the inner ear to the brain.

Immune system:
Two individuals were reported to have repeated infections.

Development and Behavior

Sitting and walking:
Children with WHSUS usually show delay in sitting and walking, with 10 of 25 (40%) children walking at or after 2 years of age.

Speech:
Almost all children have speech delay. Children are often late to start talking an may have limited vocabulary. One child had no speech at the age of 8 years.

Learning:
While all children with WHSUS have shown some level of intellectual disability, there is no one-size-fits-all educational plan. Each child should be evaluated by a psychologist (or other professional) to determine their strengths and weaknesses and develop an individualized educational plan.

Behavior:
In one study, 11 of 25 (44%) individuals who were characterized as having autism or autistic features. Related problems include anxiety and attention deficit hyperactivity disorder (ADHD).

Is there a medicine for White Sutton Syndrome?

There are no medicines or treatments specifically for WHSUS. Nor are there any known medications or immunizations that should be avoided. However, knowing this diagnosis means that appropriate monitoring and therapies can be put in place for your child.

Management Recommendations

Following the initial diagnosis, a comprehensive physical and neurologic examination, genetics consultation, and developmental/behavioral evaluation should be completed if they have not already been done. Children with WHSUS should be followed by a developmental pediatrician, neurologist, or psychologist, particularly one who is familiar with children with developmental challenges and behavioral problems to oversee the care and implementation of appropriate therapies (e.g. physical therapy, occupational therapy, speech therapy, behavioral therapy) and individualized education plans. Enrollment in early intervention programs and receiving proper therapies is essential to maximize the child's neurodevelopment potential.

Why did this happen?

WHSUS is an autosomal dominant condition, which means that an individual has the condition when only one of the two copies of the POGZ gene is altered. The process of copying the genetic material (DNA) when a child is conceived is not

perfect, and occasionally a random change may occur in the sperm or egg that made the child that is not found in either parent. This type of change is not inherited and is referred to as a de novo (new) change. To date, the POGZ genetic changes found in all individuals with WHSUS are de novo, as the parents who have been genetically tested have not been found to carry the POGZ gene change present in their child. It is important to remember that nothing you did or did not do before or during the pregnancy caused this to happen. No environmental, dietary or other factors are known to cause a change in the POGZ gene. This genetic change occurred spontaneously and could not have been predicted or prevented.

Can it happen again?

If neither parent is found to carry their child's POGZ gene change, the chance of having another child with WHSUS is very low (<1%), but remains higher than that of the general population. This is because of the very small chance that more of the mother's egg cells or more of the father's sperm cells carry the change in the POGZ gene. This has not been reported in the medical literature for WHSUS, but remains a possibility. If the same POGZ gene change is found in either parent, the chance of having another child with WHSUS is much higher. Each family situation is different. Your clinical geneticist/genetic counselor can give you specific advice on the chance for this to happen again in your family.

Support Resources

- White Sutton Syndrome Foundation *Non-Profit Group* https://www.whitesutton.org
- White Sutton Syndrome Foundation *Facebook Page* https://www.facebook.com/WhiteSuttonSyndrome/
- POGZ Related Disorder/White Sutton Syndrome *Private Facebook Group* https://www.facebook.com/groups/532193070301998/
- POGZ: Simons VIP Connect Community *Simons VIP Connect Facebook Group for POGZ Families* https://www.facebook.com/groups/POGZgene/

Sources and References

The information in this brochure is drawn from what is known about approximately 50 individuals with White Sutton Syndrome from the medical literature. Articles used include:

- Iossifov *et al.* 2012 - De novo gene disruptions in children on the autistic spectrum.
- De Rubeis *et al.* 2014 - Synaptic, transcriptional and chromatin genes disrupted in autism
- Deciphering Developmental Disorders Study Group 2015 - Large-scale discovery of novel genetic causes of developmental disorders

- Ye *et al.* 2015 - De novo POGZ mutations are associated with neurodevelopmental disorders and microcephaly.
- White *et al.* 2016 - POGZ truncating alleles cause syndromic intellectual disability.
- Tan *et al.* 2016 - A novel de novo POGZ mutation in a patient with intellectual disability.
- Stessman *et al.* 2016 - Disruption of POGZ is associated with intellectual disability and autism spectrum disorders.
- Matsumara *et al.* 2016 - De novo POGZ mutations in sporadic autism disrupt the DNA-binding activity of POGZ.
- Wang *et al.* 2016 - De novo genic mutations among a Chinese autism spectrum disorder cohort.
- Stessman *et al.* 2017 - Targeted sequencing identifies 91 neurodevelopmental-disorder risk genes with autism and developmental disability biases.
- Deciphering Developmental Disorders Study Group 2017 - Prevalence and architecture of de novo mutations in developmental disorders.

The first-named author and year of publication are provided to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nigh.gov/pubmed)

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis,

management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change.