GenIDA

UNIQUE
UNDERSTANDING GENES & CHROMOSOMES

# White-Sutton syndrome (WHSUS)
# (POGZ-related syndrome)

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with White-Sutton syndrome. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this condition.

## What is White-Sutton syndrome?

White-Sutton syndrome (WSHUS), also referred to as *POGZ*-related syndrome, is a rare genetic condition characterised by varying degrees of learning (intellectual) disability, developmental delay (particularly affecting speech and language development), low muscle tone (hypotonia) and behavioural differences. Additional other features associated with WHSUS include a tendency to be overweight, eye anomalies, feeding difficulties, cyclic vomiting and sleep concerns. As is common with genetic conditions, each person can be affected differently - even among affected members within the same family. Not everyone with WHSUS will have all the possible features and each person with a certain feature won't necessarily be affected by it to the same degree as other people with that feature.

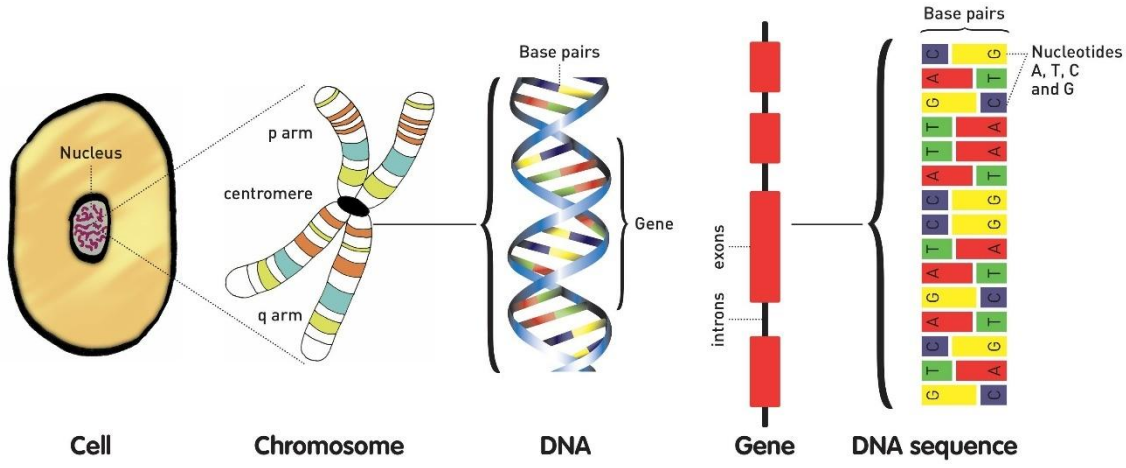
WHSUS is caused by a change (variant) in the *POGZ* gene or very rarely the loss (deletion) of one copy of the *POGZ* gene. The type of variant may affect the features an individual experiences.

*Unique* publishes a separate guide to deletions and microdeletions.

## What causes WHSUS?

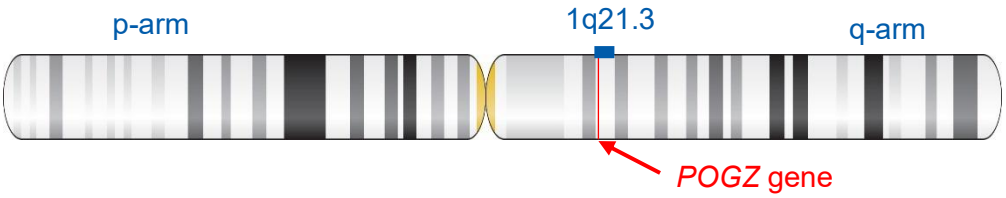
Genes are instructions that have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies. In people with genetic conditions, one or more of their genes don't instruct the body as we would expect, which can lead to changes in how their body works.

DNA is made up of building blocks called 'bases' or 'nucleotides'. There are four DNA bases which can be abbreviated to the letters A, C, G, and T. These DNA bases are paired up in the DNA structure into 'base-pairs'. The full sequence of our DNA is over three billion base-pairs long.




WHSUS is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called *POGZ* (*POGZ* is an abbreviation of the gene's full name, pogo transposable element derived with ZNF domain). The *POGZ* gene is located in the long 'q' arm of chromosome 1 in a region called 21.3 as shown in the image on the next page.

### Chromosome 1




We have two copies of chromosome 1 in our cells, so we also have two copies of the *POGZ* gene. WHSUS occurs when only one copy of the *POGZ* gene is affected; the second copy is fully functional. This is known as autosomal dominant since all numbered chromosomes are called autosomes and genetic conditions that occur when only one copy of an autosomal gene is affected are known as dominant. *Unique* publishes a separate guide to single gene disorders – autosomal dominant inheritance.

The *POGZ gene* sequence is used to make the POGZ protein. The POGZ protein is thought to be important to brain development due to its role in regulating the expression of other genes.

## Genetic Tests

WHSUS is caused by gene sequence variants, which can be identified by a type of genetic test called sequencing (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)). Gene deletions can also be identified by a sequencing test but are more commonly found using a different type of genetic test called a chromosome microarray (CMA, e.g. arrayCGH or SNParray).

*Unique* publishes separate guides to DNA sequencing, arrayCGH and SNParrays.

## Genetic Tests

The results of genetic (genomic) testing are likely to be given to you by your geneticist, a genetic counsellor or the clinician who ordered the test. An example result of a DNA sequencing test (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)), that can identify gene variants, is shown here for the *POGZ* gene:

### p.(Arg495Ter) POGZ c.1483C>T (NM_.....)

| | |
|---|---|
| p.Arg495Ter | Signifies the change to the protein: the amino acid arginine (Arg) has been converted to a stop of protein formation (signified by Ter) at position 495 in the sequence of amino acids that make up the protein. |
| C>T | signifies the gene sequence change; the C nucleotide has been replaced by a T nucleotide |
| c.1483 | signifies the base pair position of the change within the gene sequence (the position where the C nucleotide has been replaced by the T nucleotide) |
| POGZ | signifies the gene that is affected |
| NM | denotes the reference sequence used e.g. NM_001194937.1 |

*Unique* publishes a separate guide to Interpreting Genetic Test Results.

## What features and symptoms do people with WHSUS have?

As is common with many genetic conditions, children and adults with WHSUS can have a range of features and symptoms. As more people are diagnosed, and information is shared, the range of features, and the likelihood of a child or adult having these features, will become clearer.

## Common features

### Most children with WHSUS have:

- Some degree of intellectual disability (ID) or learning difficulties (LD) ranging from mild to severe
- Speech and language delay/non-verbal
- Some degree of developmental delay
- Low muscle tone (hypotonia)
- Behavioural differences
- Sleep issues
- Feeding difficulties
- Gastro-oesophageal reflux (GERD/GORD)
- Constipation
- Eye/vision anomaly
- Cyclic vomiting
- Small head size (microcephaly)
- Tendency towards being overweight
- Dental issues

### Other possible features include:

- Seizures
- Hearing loss
- Sleep apnoea
- Congenital diaphragmatic hernia
- Other GI concerns
- Skeletal anomaly, including minor anomalies of the hands and feet
- Cleft lip or palate or other palate anomalies
- Anomalies of the kidneys and genitals (urogenital anomalies)
- Frequent respiratory infections
- Skin condition
- Heart condition

## Pregnancy & Birth

While some pregnancies are unremarkable and proceed without complication, for others concerns during pregnancy have been reported, sometimes following mid-pregnancy anomaly scans. Where a cause for concern was noted, most often parents reported slow growth in the womb (intrauterine growth retardation IUGR) and reduced fetal movements.

For some, concerns were raised in the newborn period, including difficulties with feeding and low muscle tone (see Feeding and Development).

## Appearance

Certain facial features are observed more often in children with WHSUS than in other children. These features are of no medical or even cosmetic consequence, but may mean that you see unexpected similarities between your child and others with WHSUS. Features vary and may be subtle but include a high and broad forehead; wide-set, down-slanting eyes; an upper jaw, cheekbones and eye sockets that have not grown as much as the rest of the face (midface hypoplasia); a short space between the nose and upper lip; a downturned mouth with a thin upper lip; and low-set ears.

## Development

### Gross and fine motor skills

Developmental delay has been reported in most children with WHSUS so far (2024). Developmental "milestones", including rolling, sitting, walking, playing with toys, using cutlery, using zips and buttons, and toilet training, are often delayed, although there is a wide range of eventual ability, with some children acquiring mobility and other skills around the same age as "typical" children and others showing more obvious delay. Most children start to walk independently sometime between the age of 12 months and six years. Some children may have an unusual gait when walking or find coordination difficult.

Delays in motor skills are often linked to low muscle tone (hypotonia), which is very common in those with WHSUS and may be the first sign to raise concerns with doctors.

Extremely loose (hyper-mobile) joints (elbows, wrists, knees, hips), have been reported rarely, which mean babies and children can move their limbs into positions others find impossible (GenIDA dataset). While this may cause no problems, hyper-mobility may cause or contribute to gross motor developmental delay, and is sometimes associated with pain and stiffness in the joints and muscles, joints that dislocate (come out of position) easily, and injuries including sprains.

Many benefit from early intervention with treatments or therapies such as orthotics e.g. insoles, braces, splints and callipers; occupational therapy (OT); and physiotherapy (PT).

A few children have a degree of hip dysplasia (GenIDA dataset), in which the hip joints are easily dislocated. This may be apparent at birth or develop later. In either case it is treated with splinting and, if necessary, immobilisation in plaster and possibly surgery.

"All milestones missed, gross motor skills delayed, didn't roll until 10 months and sat up at 15 months. Walked independently at 2 years but now at 4 years his walk is still rather unsteady. He can run but doesn't jump. Hypotonia is his most significant symptom meaning all his gross motor skills were delayed, and that subsequently has been affecting his fine motor skills. It affected feeding as well."

"Smiled at 2 months, rolled at 5 months, sat at 6 months, crawled at 9 months, walked at 15 months, talked at 18 months, toilet trained at 2.5 years, read at 4 years, writing at 5 yearrs."

"Persistent hypotonia in the hands. Fine motor skills still problematic." 11 years

"Independent but monitored due to difficulty in properly performing personal care." 20 years

"He is relatively independent, but thinks he can't do things. In the morning, he wants me to help him get dressed, even though he can do it. In the evening, I have to help him brush his teeth, even though he can do that on his own too." – 8 years

"Does a lot of things on her own." 15 years

"Can't close buttons. Can close zippers if they work well." 9 years

"At 11 years old, almost independent."

*Unique* publishes separate guides to Therapies and Toilet training and continence.

## Intellectual development and learning

Almost all children with WHSUS we know about so far have intellectual disability (ID) and/or learning difficulties. ID ranges from mild to profound. Many children have needed additional support with their learning. Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended.

"We are unsure of how he is going to do with regards to his learning abilities, this will be tested when he starts school."

"Has mild ID. Her writing is large and takes time because of dyspraxia. Drama is something she loves. She did not have a statement of special needs until she went to mainstream school. At school was bullied. Managed in mainstream but moved school in year 10. The gap widened and she moved to an MLD school in year 11. At 35 years still at college. Needs social skills."

"Need support to progress in tasks that he finds difficult (writing, reading)." 14 years

"Specialised support at school. Six hours per week with a specialised teacher, measures will be put in place for exams, such as dictating answers to an adult because writing takes up a lot of time." 9 years

*Unique* publishes separate guides to Education and Further education, training and work.

## Speech and language

Almost all children with WHSUS typically experience some degree of speech and language delay, which is often more pronounced than motor delays. The eventual range of achievement is broad, but a few may remain non-verbal after the age of six. Those who do develop speech may achieve single words, short phrases or basic sentences and some go on to develop conversational skills and a broad vocabulary, although there may be difficulties with articulation. Many parents believe that their child can understand a lot more than they can express.

An assessment by a speech therapist should be able to identify your child's specific difficulties, allowing regular therapy sessions tailored to your child's specific areas of need. Where individuals have no speech or very few words, Augmentative and Alternative Communication (AAC) methods, including pointing, pictograms, gestures, facial expression and simplified sign language and high-tech communication systems (aided communication) can enable communication of thoughts and needs.

"Started to say intelligible words at 2 years. She would wait for people to ask. Autism tendencies have affected her, [but as an adult] she likes to talk to those who are understanding and include her."

"At almost 4 years, he is bi-lingual now, speaks two languages fluently. He has a very clear speech, he's a chatterbox."

"Inhibited when he is not confident. Speaks minimally during medical appointments etc. whereas he can speak a lot at home or in a situation of trust." 16 years

*Unique* publishes a separate guide to Communication.

## Feeding

Feeding issues in the new-born period are common. Low muscle tone may contribute to difficulties with swallowing and some babies will suck weakly. Some babies also suffer from gastro-oesophageal reflux (GERD/GORD) (in which feeds return readily up the food passage), which may require treatment, including careful positioning for feeds, medication, nutritional supplements or, in some cases, insertion of a nasogastric tube (NGT) or percutaneous endoscopic gastrostomy tube (PEG/G-tube). Other issues that have been reported include problems with chewing or swallowing and food aversion. Children may also overeat, leading to a tendency towards being overweight.

Children may benefit from attending a feeding clinic where an assessment can be made, and advice to help treat any eating and drinking difficulties provided.

“Never latched on. Low muscle tone affected sucking, meant bottle feeding was taking a long time, and generally we had a very difficult process of introducing solids.”

“Nausea, only eats 3-4 spoons of puree, main diet is infant formula.” 20 months

“Does not eat foods containing strings: green beans, pineapple, spinach, stringy meat.” 6 years

“Major swallowing disorder (choking causing repeated pneumonia).” 37 years

*Unique* publishes a separate guide to Feeding.

## Growth and stature

While some babies are recorded as having intrauterine growth restriction (IUGR) and are small at birth, most babies have birth weight, length and head circumference measurements within the “normal” range.

Beyond infancy, height and weight is variable but some children with WHSUS described so far (2024) are noted as having a short stature and/or a tendency to be overweight. A head size that is smaller than expected (microcephaly) is also common.

“She has weight issues, is 4'11" in height.”

“Obesity causes mobility problems.” 16 years

## Behaviour

Children with WHSUS have been described by their parents as happy, charming, loving and caring.

Parents often highlighted the anxiety experienced by their children as a key concern. Some children may exhibit disruptive behaviours that can be challenging. Other behaviours including attention deficit hyperactivity disorder (ADHD), phobias, impulsivity, obsessive behaviours, shyness around unfamiliar people and aggressive behaviours have also been reported. Around half of children have an autism spectrum disorder (ASD) diagnosis or traits.

Where a parent believes that their child may have a specific disorder - such as anxiety, an ASD or ADHD - they should consult their general practitioner/ paediatrician who can refer then to a behavioural or clinical psychologist to undergo assessment. There is not a ‘medical test’ that can diagnose autism, but children undergo an autism-specific behavioural evaluation, usually carried out by a specially trained physician and psychologist. The evaluation may be multidisciplinary and include a speech and language therapist as well as an occupational therapist. It is also tailored to the age of the child. Depending on the outcome, further evaluation by a specialist, such as a developmental paediatrician, neurologist, psychiatrist or psychologist, may be offered.

Children may be prescribed medical and behavioural therapies to help with specific disorders following diagnosis. An occupational therapist may be able to help with some behavioural issues by giving your child tools to deal with their sensitivities, if need be. Joining a social skills group may help a child with social difficulties to learn and practise important social skills. A parenting course for autism may also help parents to learn behaviour management skills and help to encourage communication and cooperative behaviour in their child, to strengthen their emotional wellbeing.

“[Diagnosed with] autism at 6 years. Trust is an issue with people. Autism tendencies have affected her; she likes to talk to those who are understanding and include her. She is a very giving and caring person. No ADHD or aggressive behaviours. Has sleep concerns.”

“At almost 4 years, anxiety developing recently. Sensitivity to noises, fear of sudden noises, large settings. He is a very happy child, brings so much joy and laughter to our life. He’s very charming and sociable. He loves people and people love him. He attracts a lot of attention with his happy,

chatty demeanor. But, this applies to one to one situations or small groups of people. In bigger settings (nursery), he gets anxious and overwhelmed."

"He speaks very easily with adults but has much more difficulty integrating with children his age. However, since he started school, each year we have noticed an improvement. Currently, in class things are going relatively well. He has certain phobias e.g. fear of people on crutches, in wheelchairs. He will not necessarily tell us directly but will do everything to avoid having to go next to someone in a wheelchair. He does not like his name to be written on his clothes or on a cup. On birthdays, when the children's names are written on the cups, he will not drink anything all day, but he will not say why, he will just say that he is not thirsty!" 9 years

"Has no filter towards the people he meets: approaches strangers, touches them, takes their things to play with." 7 years

"No behavioural problems noticed. Cognition is very delayed in all areas as he is nonverbal/mobile." 9 years

Parents often report sleep concerns which can have a significant impact on the whole family, including difficulty falling asleep, frequent night wakings, night terrors and sleepwalking. Some experience episodes of sleep apnoea, when there is an abnormal breathing pattern during sleep. An evaluation for sleep disorders and/or sleep apnoea may be suggested and a sleep study considered.

"At night, he wakes up a lot. He can't fall back asleep without me there. He also calls if he needs to go to the bathroom. He's afraid to get up by himself." 8 years

"She doesn't get up at night, sleeps early." 20 years

"Undergoing examinations, possibility of sleep apnoea, snoring, agitation." 7 years

*Unique* publishes separate guides to Challenging Behaviour and Sleep.

## Puberty

There is limited information available about puberty in children with WHSUS. Some families of children with chromosome disorders and behavioural or learning difficulties can be particularly concerned with their daughter's ability to cope with menstruation, and for some discussing menstrual regulation options with a paediatrician may be beneficial.

"At puberty started gaining weight, unusually on upper arms. From elbows downwards, normal sized arms. [She also developed] Hidradenitis Suppurativa (HS) (a skin condition).."

*Unique* publishes a separate guide to Puberty.

## Adulthood

Experiences of adulthood are likely to vary considerably and will depend on many factors. These include the level of any LD/ID, possible on-going medical concerns and improvements in early intervention and therapies/treatments.

Adults with WHSUS have varying levels of independence. We know a few adults have gone on to work, manage their own care and have families of their own. Others continue to live with their parents or in supported settings such as a group/residential care home, with caregivers who can provide support.

*Unique* publishes a separate guide to Transition.

"At 35 years she is still at college. She is very special, kind, thoughtful and caring of others. She will speak her mind and stand up for things that are not kind. Needs social skills. She can get anxious, likes sameness. She is living in supported living and needs support with personal skills, budgeting and cooking. I feel her supportive living could be more supportive. She pays for a PA, who she has known for several years, for 3 hours/week and short breaks. She stills sees ENT and had a squint in one eye as a child and vision impairment (longsighted in right eye). Now has normal vision."

## Medical concerns

The following medical concerns have been found in children with WHSUS. They are not found in all children so not all children with WHSUS will be affected.

### ■ Eyes and sight

Problems with eyes and vision are common in children with WHSUS. A wide range of conditions have been reported and an individual may have more than one vision or eye-related concern.

Known concerns include short or long-sightedness (myopia or hypermetropia), which can usually be corrected by glasses; a slight alteration in eye shape that can lead to blurry vision (astigmatism); a squint (strabismus), where one eye or both turns inward, outward, up or down, which may be treated with patching, glasses, exercises or surgical correction; droopy upper eyelids (ptosis); uncontrolled eye movements (nystagmus); underdevelopment (hypoplasia) of the optic nerve; and retinal dystrophy (a range of chronic and progressive eye conditions affecting vision).

### ■ Head & Brain

An unusually small head (microcephaly) is relatively common and for some the back of the head may be flattened (brachycephaly).

While not a consistent feature of WHSUS, up to two thirds (2 in 3) children have been found to have a structural brain anomaly, which can be detected by MRI (magnetic resonance imaging) or a CT (computerised tomography) scan of their brain. The changes seen vary but include a brain malformation affecting the cerebellar (cerebellar dysgenesis), thinning of the white matter connecting the two halves of the brain (corpus callosum), and a Dandy-Walker malformation (where an area at the back of the brain (cerebellum) that controls movement and balance does not develop properly).

"MRI and brain scan. Normal results." 8 years

"MRI. Cerebellar abnormality." 6 years

### ■ Severe vomiting & migraines

Vomiting is relatively common, especially in younger children, with some experiencing recurring episodes that may be cyclical in nature. Vomiting tends to become less frequent or even resolve with age. Anecdotally, some parents have testified that the nausea and vomiting their child experiences responds well to therapies for "abdominal migraines".

"Vomiting started around the age of two [and] lasted about 2 days. The first times the vomiting occurred, we stayed at home to treat [him]. Then, after talking to our paediatrician, we went to the hospital each time at the first signs of stomach problems. At the hospital, the doctors gave him an IV to rehydrate him. Thanks to the IV, the vomiting generally stopped after 3-4 hours. From the age of 2 to about 5-6 years, this vomiting always happened in the morning when he woke up. For about 2 years, it has been a little more random [and] starts more at the end of the day. However, for the past two years, the vomiting has been much less frequent, about twice a year compared to 8-10 times a year. However, he has had stomach aches and migraines more often for about two years." 9 years

"Gastric migraines since the age of three, more episodic now that she is 23 because she is on medication continuously." 25 years

### ■ Constipation

Constipation has been reported among children with WHSUS and can be related to low muscle tone, little exercise, a low-bulk diet and small fluid intake, among other reasons that are not fully understood. It is important that possible causes are discussed with a health visitor or doctor, who may recommend adapting diet or giving stool softeners or laxatives. Some children have benefitted from enemas when symptoms were particularly severe.

## ■ Hearing

Some children have a hearing impairment. Hearing loss may be conductive, where sound is unable to travel effectively to the inner ear; sensorineural, where there are problems with the inner ear, sometimes with the cochlea or auditory nerve (the nerve that sends signals to the brain about sound); or a combination of both conductive and sensorineural hearing loss. Many types of hearing loss can be managed by using hearing aids.

Children may be affected by “glue ear”, where fluid builds up behind the ear drum, which may be made worse by unusually narrow external ear canals and excess wax in the ear canal. Glue ear is a type of conductive hearing loss and is typically treated by inserting aeration tubes (grommets) into the eardrum. This surgical operation may need to be repeated. Improved hearing may not be achieved with aeration of the space behind the eardrum (middle ear) and hearing aids may help as a temporary or longer-lasting measure, although this appears to be uncommon. As children are at risk of speech delay, parental concerns should be acted on early and home- or school-based therapy provided.

*Unique* publishes a separate guide to Hearing.

## ■ Teeth

Dental concerns are very common in children with chromosome disorders. A number of issues have been described by parents including unusual dental development such as widely-spaced teeth and frequent dental caries (cavities). A high standard of dental care is important to minimise damage by decay and erosion.

Unique publishes separate guides to Looking after your child’s teeth and Teeth: common concerns.

## ■ Seizures

About 1 in 5 (20 per cent) of children with WHSUS experience some form of seizure (a sudden and unexpected change in the electrical activity in the brain). Depending on the part(s) of the brain affected, symptoms vary, but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Age of onset varies but is typically between one and four years. Electroencephalograph (EEG) and video telemetry (video EEG) are medical tests that can be used to measure and record the electrical activity of the brain and are tools that, when used alongside other tests, can help diagnose the type of seizure experienced.

Seizures can cause a lot of worry for families and can be frightening to observe but are generally well controlled with medical treatment. If your child has a seizure for the first time, it is important to remove nearby hazards so they can’t hurt themselves and contact a medical professional.

## ■ Heart

A heart condition(s) has been found in around 1 in 8 (12.5%) of people reported so far with WHSUS. A study by Duan et al. (2023) found that the incidence of a heart condition that is present from birth (congenital heart disease) is significantly higher in people with a *POGZ* variant than in the general population, suggesting it is a relatively uncommon feature of WHSUS.

The type of heart condition is variable but include anomalies affecting the size and structure of the heart muscle and valves, most often an ASD (atrial septal defect - a hole between the top two chambers of the heart). Other conditions reported include a change in one of the heart valves (a bicuspid aortic valve) and PFO (persistent foramen ovale - an opening between the two upper chambers of the heart does not close in the first year of life, as would normally be expected).

In children for whom heart problems are suspected, these can be diagnosed using tests like an electrocardiogram (ECG) (recording the electrical activity of the heart), echocardiogram (ultrasound scan of the heart), or chest X-ray. Some of these conditions are relatively minor and resolve naturally in time. Medical treatment may be necessary for others, and some may require surgery.

## ■ Spine

Occasionally, a spinal curvature has been reported (GenIDA dataset), either a sideways curve of the spine (scoliosis), a rounding of the upper back (kyphosis) or kyphoscoliosis (a combination of kyphosis and scoliosis). The curvature can be treated with physiotherapy and exercises, or a support brace or surgery may be needed.

## ■ Hernias

A few babies are born with a hernia, where an organ or fatty tissue pushes through a weak spot in a surrounding muscle or tissue. These include instances of congenital diaphragmatic hernia (CDH) (where the muscle that separates the chest cavity from the abdominal cavity is affected). Hernias may heal naturally without the need for treatment, but in the majority of cases surgical repair was required.

## ■ Palate

Anomalies of the palate (roof of the mouth), ranging from those that may be invisible to the casual onlooker such as a high/arched palate to more obvious conditions such as a cleft palate, have been reported. Anomalies of the palate, particularly clefting, can cause difficulties in feeding, hearing, teething and speech production. As well as helping aesthetically, surgical repair eases these problems and may even eliminate them altogether.

## ■ Kidney and urinary tract

Occasionally babies are born with anomalies of the kidneys and/or urinary tract. These include kidneys that did not develop properly during pregnancy (dysplastic kidneys), meaning they may be a different shape or size than is usual. They often also have fluid-filled sacs called cysts which prevent the kidney from working normally. Other anomalies include babies born with an enlarged kidney(s) (hydronephrosis) due to a build-up of urine inside, and duplex kidney, where one or both kidneys have two ureter tubes to drain urine rather than a single tube, which can increase the risk of UTIs. Urinary tract infections (UTIs) are relatively common and may need to be treated with antibiotics. Repeated urinary infections may require preventive treatment with antibiotics.

## ■ Genitals

Minor anomalies of the genitals in boys have been reported occasionally, including undescended testes (cryptorchidism), a very small penis (micropenis) and underdeveloped (hypoplastic) testes or scrotum. Many of these anomalies can also be seen in children without WHSUS and are not of major concern. If necessary, cryptorchidism can be corrected with surgery to bring the testicles down (orchidopexy).

## ■ Skin

Some children are known to have a skin condition such as eczema, where the skin becomes red, itchy and inflamed. Your doctor should be able to recommend self-care techniques, emollients and other treatments that may help to relieve symptoms.

## How common is WHSUS?

It is difficult to say. Currently (2025) over 100 individuals with WHSUS have been reported. It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

## Why did this happen?

When children are conceived, their parents' genetic material (DNA) is copied in the egg and sperm that makes a new child. The biological copying method is not perfect, and random changes occur in the genetic code of all children, that are not seen in the DNA of their parents. This happens naturally and is not due to the parents' diet, environment or lifestyle. Most of these DNA changes have no obvious effect. But in rare instances these random DNA changes can lead to health issues or affect development. When such a random change disrupts the function of the *POGZ* gene then a child will have WHSUS. In most people identified so far (2024) with WHSUS, the genetic change was a random (or "*de novo*") change, meaning the change occurred for the first time in that family in the affected individual. Occasionally, one mildly affected parent may have a chromosomal rearrangement that led to WHSUS in their child, or one parent may have the same change (or variant) in some of their egg or sperm cells and pass it on to their child (this is known as germline mosaicism). However, it is important to recognize that no one should be blamed for variants in their DNA and no parent is at fault when a new DNA change occurs in their child.

## Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. In almost everyone reported with WHSUS so far (2024) the genetic alteration has been found to be *de novo* (dn), which means neither parent was found to have the same *POGZ* gene change as their child. Therefore, the chance of having another child with WHSUS is usually less than 1%.

One reason why there is some residual chance of recurrence is due to the rare phenomenon called germline mosaicism that was mentioned above. This is when a parent carries a genetic change, but it is limited to some of their egg or sperm cells. The genetic change would not, therefore, be detected in the parents' blood tests.

*Unique* publishes a short general guide to mosaicism.

In families where the *POGZ* variant has been inherited from a parent, the possibility of having another child - either a girl or a boy - with WHSUS rises to 50 per cent (I in 2) in each pregnancy. However, the effect on the child's development, health and behaviour cannot be reliably predicted. Your genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a *POGZ* variant goes on to have children of their own, the chances of passing on the variant to their child are 50 per cent (1 in 2) in each pregnancy. Your child's ability to look after their own child is very likely to be closely related to their own learning ability and behaviour.

A clinical geneticist or genetic counsellor can provide specific advice for each family about the chance of having further children with WHSUS. *Unique* publishes separate guides to Planning your next child, Prenatal genetic testing and diagnosis, A clinical genetics appointment and Supporting siblings of children with a rare genetic condition.

## Can WHSUS be cured?

There is no cure for WHSUS since the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and interventions can be put in place.

## Management recommendations

### Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of WHSUS that are present in the child or adult who has been diagnosed with this genetic condition should be carried out. This can determine which of the features of WHSUS are present and how severe they are.

### Supportive care

Children with WHSUS are likely to be under the care of a multidisciplinary team, but the management varies based on the needs of each child. The team should include a community or hospital paediatrician who can oversee care; monitor growth, development and behaviour; and link in with affiliated services.

How a person with WHSUS is supported can require a co-ordinated care team of specialists, which may include:

**Paediatrician** – a doctor who specialises in the physical, mental and social health of children from birth to young adulthood.

**Gastroenterologist** – a doctor who specialises in conditions affecting the stomach and intestines.

**Ophthalmologist** – a doctor who specialises in conditions affecting the eyes.

**Audiologist** – a health care professional who diagnoses, treats and helps manage a condition that involves hearing or balance.

**Neurologist** – a doctor who specialises in conditions of the brain, spinal cord and nervous system.

**Cardiologist** – a doctor who specialises in heart conditions.

**Urologist** – a doctor who specialises in diagnosing and treating conditions affecting the urinary system.

**Nephrologist** – a doctor who specialises in conditions affecting the kidneys.

**Psychiatrist** – a doctor who specialises in mental health.

**Occupational therapist (OT)** – a health care professional who uses activities to aid self-management of a condition and can provide equipment.

**Physiotherapist (PT)** – a health care professional who uses exercise, movement, manual therapy, education and advice to help with the body's strength and mobility.

**Speech and language therapist (SALT)** – a health care professional who helps with speech, language communication and sometimes feeding/swallowing difficulties.

**Specialist nurses and/or other healthcare professionals** may need to systematically and comprehensively plan a child or adult's treatment.

### Treatments and therapies

Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended. An individualized education plan (IEP) in the US, education, health and care plan (EHCP) in the UK, or equivalent document in other countries, may be issued after a child has undergone an assessment, to help ensure that the educational, health and social provisions deemed necessary to support the child's needs are delivered.

Treatment will depend on the specific features and symptoms experienced by the person with WHSUS but may include:

- **Physiotherapy (PT)** Helps people affected by injury, illness or disability through movement and exercise, manual therapy, education and advice. Can also provide advice on pain management.

- **Occupational Therapy (OT)** A health professional who promotes health and wellbeing through the use of particular activities as an aid to self-management of a condition. OTs can help individuals with genetic conditions to develop gross and fine motor skills and provide equipment.
- **Speech and Language Therapy (SALT)** Helps address speech, language and communication difficulties.
- **Behavioural Therapies** Children may benefit from early access to advice and therapies to help with behavioural differences.
- **Medications** Such as anti-seizure medicines to help treat and prevent seizures and standardised treatments for cyclic vomiting and reflux.
- **Regular dental check-ups** To maintain a high standard of dental care.
- **Diet** A high-fibre diet or stool softeners and/or laxatives may be recommended to help relieve constipation.

### Surveillance

Surveillance options to monitor an individual's existing symptoms, how they respond to care and treatment, and whether any new symptoms emerge over time include:

- Monitor developmental progress
- Monitor educational needs
- Monitor behavioural needs
- Monitor height and weight
- Monitor for vomiting and constipation
- Examination by an ophthalmologist
- Examination by an audiologist
- Consider need for a sleep study
- Consider a cardiac review
- Consider a neurologic review (including MRI and EEG, if indicated by seizures)
- Consider a genitourinary review

## Research into new treatments for WHSUS

The genetic change causing WHSUS affects development of the brain and other parts of the body before birth. Therefore, a complete cure is unlikely, even in the future, since the brain has already formed by the time a diagnosis is made. However, research into improved treatments and management for various features of WHSUS, like ASD, is ongoing. In addition, although WHSUS is a relatively rare condition, the POGZ gene is the subject of research, which may identify further potential treatments.

Details of clinical trials related to a particular condition or gene can be found at ClinicalTrials.gov and EU Clinical Trials Register.

## Sources

The information in this booklet is drawn from the published medical literature, information from Unique members and information shared by 38 families in response to an online GenIDA questionnaire (https://genida.unistra.fr/). In 2024, Unique had 11 member families with WHSUS. The first-named author and publication date for articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed (https://pubmed.ncbi.nlm.nih.gov/). You can obtain most articles from Unique.

## References

*Assia Batzir N, White J, Sutton VR (2021) White-Sutton Syndrome. GeneReviews® [Internet]. Link to article

*Murch O *et al* (2022) Further delineation of the clinical spectrum of White-Sutton syndrome: 12 new individuals and a review of the literature. Eur J Hum Genet 30 (1): 95-100. Link to article

*Duan J *et al* (2023 White-Sutton syndrome and congenital heart disease: case report and literature review. BMC Pediatr., 23(1): 158. Link to article

Note: an asterisk indicates articles which are “open access” and available to everyone at https://pubmed.ncbi.nlm.nih.gov

### Websites, Facebook groups and other links:

White Sutton Syndrome Foundation Non-Profit Group www.whitesutton.org

White Sutton Syndrome Foundation Facebook Page www.facebook.com/WhiteSuttonSyndrome/

White Sutton Syndrome Parents Private Facebook Group

www.facebook.com/groups/WHSUSParents

POGZ Related Disorder / White Sutton Syndrome Facebook Group

www.facebook.com/groups/532193070301998/

POGZ: Simons VIP Connect Community Simons VIP Connect Facebook Group for POGZ Families

www.facebook.com/groups/POGZgene/

# Inform Network Support

Rare Chromosome Disorder Support Group
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Tel: +44(0)1883 723356
info@rarechromo.org I www.rarechromo.org

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GenIDA

This guide was produced in collaboration with GenIDA (www.genida.eu/home)

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.

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