Inform Network Support

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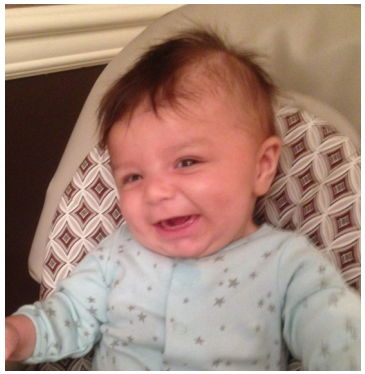
Understanding Chromosome & Gene Disorders

DeSanto-Shinawi syndrome/ WAC syndrome



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What is WAC syndrome?

WAC syndrome is a recently discovered disorder that occurs when one of a person's two copies of the *WAC* gene does not function normally. This can be caused by a spelling mistake (mutation) in the gene or by the loss of one copy of the gene (a deletion). Genes are made of a complex chemical called DNA and make up the "instruction manual" that tells the body how to grow, develop and function. Genes are arranged in organised structures called chromosomes. There are 23 pairs of chromosomes and we inherit one half of each pair from each parent, making a total of 46 chromosomes. The *WAC* gene is on chromosome 10 and codes for a protein that plays a role in different cellular and DNA processes, including processes important for brain development. WAC syndrome is also referred to as DeSanto-Shinawi syndrome (DESSH or DSS).

What is 10p12p11 deletion syndrome and how is it related to WAC syndrome?

Sometimes a deletion can occur that removes a large segment of DNA from a chromosome. Such deletions may remove a number of adjacent genes. One chromosome deletion that removes a single copy of the *WAC* gene along with neighbouring genes is the 10p12p11 deletion. For this reason, the 10p12p11 deletion syndrome has overlapping features with WAC syndrome.

To-date, 13 children have been described in the medical literature with 10p12p11 deletions. All have very similar clinical features, but none has an identical chromosome deletion. Broadly speaking, children with a 10p12p11 deletion have the same features as those with WAC syndrome. However, most of the children with a 10p12p11 deletion – especially those with larger deletions - tend to have additional problems, most likely due to the deletion of neighbouring genes included in the 10p12p11 deletion. Two genes that are sometimes included in this deletion and are suspected to contribute to additional features are *LYZL1* and *SVIL*. These genes are thought to play a role in the development of heart anomalies in children with larger deletions.

Websites and Facebook groups

https://www.dessh.org/ - The DESSH: DeSanto-Shinawi Syndrome Corporation non-profit community was created to help identify new patients, promote further research, and raise funds to aid in the treatment and cure of DESSH.

DESSH
DeSanto-Shinawi Syndrome

https://www.facebook.com/groups/dessh/ - Closed group for parents/relatives of patients. Approval required.

https://www.facebook.com/curedessh/?modal=admin_todo_tour

Publications

Abdelhedi *et al* (2016). A de novo 10p11.23-p12.1 deletion recapitulates the phenotype observed in WAC mutations and strengthens the role of WAC in intellectual disability and behavior disorders.Am J Med Genet A. 2016 Jul;170 (7):1912-7. PMID: 27119754

DeSanto *et al* (2015). WAC loss-of-function mutations cause a recognisable syndrome characterised by dysmorphic features, developmental delay and hypotonia and recapitulate 10p11.23 microdeletion syndrome. J Med Genet. Nov;52(11):754-61. PMID: 26264232

Lugtenberg *et al* (2016). De novo loss-of-function mutations in WAC cause a recognizable intellectual disability syndrome and learning deficits in Drosophila. Eur J Hum Genet. Aug;24(8):1145-53. PMID: 26757981

Mroczkowski *et al* (2014). Interstitial 10p11.23-p12.1 microdeletions associated with developmental delay, craniofacial abnormalities, and cryptorchidism. Am J Med Genet A. Oct;164A(10):2623-6. PMID:

25073539

Okamoto *et al* (2012). Deletion at chromosome 10p11.23-p12.1 defines characteristic phenotypes with marked midface retrusion.J Hum Genet. Mar;57(3):191-6.PMID:22258158

Shahdadpuri *et al* (2008). Pseudoarthrosis of the clavicle and copper beaten skull associated with chromosome 10p11.21p12.1 microdeletion. Am J Med Genet A. Jan 15;146A(2):233-7.

Sosoi *et al* (2015). Prenatal and postnatal findings in a **10**.6 Mb interstitial deletion at 10p11.22-p12.31.J Hum Genet. Apr;60(4):183-5. PMID: 25652353

Uehara *et al* (2018). Three patients with DeSanto-Shinawi syndrome: Further phenotypic delineation. Am J Med Genet A. 2018 Jun;176(6):1335-1340. PMID: 29663678

Vanegas *et al* (2018). DeSanto-Shinawi Syndrome: First Case in South America. Mol Syndromol. 2018 May;9(3):154-158. PMID: 29928181

Varvagiannis *et al* (2017). *WAC*-Related Intellectual Disability. PMID: 29190062

Wentzel *et al* (2011). Genomic and clinical characteristics of six patients with partially overlapping interstitial deletions at 10p12p11. Eur J Hum Genet. Sep;19(9):959-64. PMID: 21522184

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 (replication) is not perfect and occasionally random, rare changes (mutations) occur for the first time. Such changes, therefore, cannot be found in a child's parents. In all families that we know about so far, the DNA change in *WAC* occurred 'out of the blue' in this way (this is what you may hear a geneticist referring to as a *de novo* change).

Chromosome rearrangements affect children from all parts of the world and from all types of background. They also happen naturally in plants and animals. There is nothing that either parent did before, during or after pregnancy that caused the change. It is no one's fault.

Can it happen again?

Provided that neither parent is found to carry the same *WAC* gene mutation as their child, the chance of having another child with the same genetic change would be considered extremely low. Empirically, this risk would be considered less than 1%. The reason why there is some residual risk of recurrence is due to a rare phenomenon called 'gonadal mosaicism'. This is when a parent carries a genetic change, but it is limited to a small cluster of their egg or sperm cells. The genetic change would not, therefore, be detected in this parent's blood test. For specific advice about the chance of this happening again, it would be sensible to speak to a clinical geneticist or genetic counsellor. One presumed case of WAC syndrome as a result of gonadal mosaicism has been reported.

Most common features

Almost all children with WAC syndrome who have been identified to-date have:

- A mild degree of learning disability, although even individuals with the same *WAC* variant can be affected to a variable degree.
- Developmental delay.

Other typical features include:

- Low muscle tone (hypotonia) particularly affecting the mouth and throat area, resulting in poor articulation (dysarthria) and swallowing difficulties.
- Behavioural problems, including autism spectrum disorder, ADHD (attention deficit hyperactivity disorder), sleep disorders and anxiety.
- A characteristic facial appearance, typified by a square-shaped head;

deep-set, long eyes; a wide mouth; a broad chin; and minor ear anomalies. These features are not observed in all individuals and are not specific to WAC syndrome.

❝ My daughter has "typical" features seen in other children with DESSH, [although it is] hard to pinpoint exactly what they are. ❞ – WAC variant, 6 years

Development

Physical development

Almost all children experience a delay in meeting their motor development milestones, such as rolling, crawling and walking. The age at which children achieve independent walking ranges from 12 to 36 months. A developmental delay was universal among *Unique* members (3/3), with sitting achieved between 8 and 11months, and walking between 24 and 30 months.

❝ Despite being very clumsy and falling over a lot, she walks absolutely fine without any problems (she has a wide gait). She is very stoic and despite her tumbles is very tough and doesn't get upset or cry; she almost displays a determination not to show she is hurt (she seems to have a high pain tolerance) and refuses your fuss. ❞ – WAC variant, 6 years

Learning

The majority of children with WAC syndrome have a mild intellectual disability (ID) (a moderate to severe ID was observed in fewer than one in five children). Reported IQ values range from 44 to 98. Extensive psycho-cognitive evaluation of some of the children revealed relative difficulties in non-verbal skills and in sustaining attention and maintaining focus. Basic language skills and verbal memory skills are areas of relative strength.

❝ He appears to have an amazing memory. As an 8-year-old, now that he can talk more, he appears to have memories from nursery when he was three-years-old – we find this surprising as he did not talk then and appeared to have very limited understanding. ❞ – WAC variant, 8 years

❝ When our daughter was ~12-months-old, we had no idea whether she'd be able to walk or talk. She's now five-years-old and attends mainstream school with 1:1 support and doesn't stop talking. She never ceases to amaze us and, whilst her learning is an issue - particularly Maths - she holds her own and tries very hard; she has a very determined spirit, often to the point of being belligerent. She has a fantastic memory which means she's very good at reading, as it's predominantly from recall rather than logically working through a word using phonics.

Now that she's in her second term in Year 1, we are starting to see more and

Families say ...

❝ He is mischievous in the best sense of the word! His antics are meant to make those around him laugh. He hides toys and asks where they are, only to reveal he knew the whole time. We will ask him to repeat "I love Mom" and he says: "I love Hope" (Hope is the neighbour's dog). Then he'll gives a big giggle before repeating "I love Mom". He has a little sister that he loves to pieces. He enjoys giving her hugs and doing what he can to make her laugh too! ❞ – WAC variant, 3 years

❝ She's an extremely loving and endearing little girl who loves to help and please. ❞ – WAC variant, 6 years

❝ He says the funniest things sometimes – he is quirky, and he makes us laugh. We have to be inventive about play to keep him occupied and sometimes our daughter joins in – we play together a lot as a family. He has a real sense of humour – as he can now understand more, he is laughing at things he sees on the television. It is lovely to hear. ❞ – WAC variant, 8 years

Hirsutism

In some children, excessive hairiness on parts of the body where normally hair is absent or minimal has been observed, including two of three children in the *Unique* series.

Other birth anomalies

A wide range of congenital anomalies have been described, but none of them have been found recurrently in children with WAC syndrome. Reports include: kidney anomalies; occlusion of the tear duct; an abnormality of the windpipe (trachea); hip dysplasia; hearing loss; anomalies of the feet and hands; hypogammaglobulinemia associated with recurrent infections; leukopenia and thrombocytopenia; and diaphragmatic hernia (the sheet of muscle between the abdomen and the chest is not complete, allowing organs from the abdomen to be displaced into the chest).

Children with 10p12p11 deletions that include *WAC* as well as neighbouring genes tend to have more medical concerns than children with changes confined to the *WAC* gene alone. Heart abnormalities in particular seem to be more frequently observed in children with 10p12p11 deletions.

Management recommendations

At diagnosis:

- Feeding management, where necessary
- EEG, if seizures are suspected
- Eye check
- Treatment of constipation, where necessary
- Evaluation of swallowing problems, where necessary

After diagnosis:

- Long-term follow up by a developmental paediatrician
- Speech and language support
- Physiotherapy and occupational therapy, as needed
- Regular eye sight checks

more the learning disparity between her and her peers. We suspect this will only widen as time goes on and other parents of children with DSS on the DSS Facebook support group have confirmed this. She absolutely loves going to school and takes it all in her stride. She is popular and outgoing in school. ” – WAC variant, 6 years

Behaviour

A variety of behavioural problems are known to be part of WAC syndrome. ADHD, autism, anxiety, sleep disturbances and aggression have been reported in one or more children.

“ He was tested for autism but doesn't have all the features. His autistic features relate to his strong need for rigid routines, quirky habits and preoccupations, but he likes social interaction. When it comes to sleep, he needs a set routine and a longer time to settle. He doesn't like to be left alone to sleep; he can semi-wake up and be very irritated and agitated and doesn't sleep through the night unless someone lies next to him. We have had help from sleep practitioners. ” – WAC variant, 8 years

Speech

A delay in language development is observed in almost all children with WAC syndrome. The age at which children speak their first words ranges from 14 months to five years. A similar pattern was seen in *Unique* children. Only a small minority of children remain non-verbal. Due to low muscle tone around the mouth and throat, some children have problems with articulation (dysarthria). At an older age, most children can speak in full sentences.

“ Speech is the area that he is most delayed in. At six-years-old it was reported that he had severe language delay and severe speech sound disorder with possible verbal dyspraxia. We all learned Makaton to help him; he doesn’t use it anymore but it’s quite handy for silent family communication!! His NHS speech and language therapist recommended ‘Talk Tools’. We had to pay for this privately; however, we do feel that this really helped him. ” – WAC variant, 8 years

“ Her speech development is ~12-18 months behind and her sentence structure can still be clunky. ” – WAC variant, 6 years

Fine motor skills

Development of hand use and hand-eye coordination are impaired in children with WAC syndrome. Children usually benefit from physiotherapy and occupational therapy.

Growth

Babies with WAC syndrome are usually born at a normal birth weight and

continue to grow at the expected rate. Some children have problems maintaining their weight within a normal range, while some instances of children who are overweight have been reported.

❝ If anything, trying to control food intake is an issue." – WAC variant, 6 years

Medical concerns

Low muscle tone

Low muscle tone (hypotonia) is obvious in around half to three quarters of children and may persist throughout childhood, including in two of the three children in the *Unique* series. The condition is particularly severe around the mouth and throat area, resulting in poor pronunciation and swallowing difficulties.

Feeding difficulties

Feeding difficulties in the neonatal period have been reported, including gastroesophageal reflux disease (GERD). For some babies who are more severely affected, temporary feeding by nasogastric tube may be necessary.

❝ He was unable to breastfeed; he had difficulty 'latching' on. We switched to bottle-feeding at two weeks, but he also struggled with this - milk would pour out of his mouth as he fed. He took Gaviscon for a while for reflux when he was about three years of age. He also had lots of unexplained vomiting. He was prone to choking once he started eating solids and at 8 years, he still tends to eat with his mouth open. ❞ – WAC variant, 8 years

Constipation

Constipation has been observed in several children with WAC syndrome. Treatment options include stool softeners or laxatives. Some children may benefit from enemas if symptoms are particularly severe.

❝ Even when he was a baby and only having formula milk, his poos were solid and you could empty them from the nappy into the toilet. He became constipated soon after being weaned and has been on various medications to help. At one point he ended up with severe constipation and has been on medication for a few years - just trying to wean him off now at 8 years.❞ – WAC variant, 8 years

❝ My daughter suffered from constipation - particularly as a baby - and often required a laxative. This was attributed to gluten intolerance. It hasn't been an issue since she was three-years-old. ❞ – WAC variant, 6 years

Seizures

Several children are known to have epilepsy, including two in the *Unique* series. An EEG should be undertaken if seizures are suspected. Cases of tonic-clonic seizures, absence episodes and febrile convulsions have been reported.

❝ He has had "eye rolling events" (reported as "afebrile paroxysmal events with eye rolling"). He also experienced one episode of tonic-clonic seizures when he was unwell. ❞ – WAC variant, 8 years

❝ She has West Syndrome [a type of epilepsy syndrome that is characterised by epileptic/infantile spasms, abnormal brain wave patterns (hypsarrhythmia) and intellectual disability]. ❞ – WAC variant, 6 years

Eyes & eyesight

A wide range of eye and eyesight problems have been reported. These include but are not limited to: unexplained reduced vision or cortical visual impairment (an inability of the brain to interpret what the eyes can see), long -sightedness and strabismus (a squint).

❝ He can very easily roll his eyes until you can only see the white part. He seems to do this purposefully. We have also noticed that he can tolerate really bright light without blinking or turning away. Not sure why this is but his eyes were checked regularly, and he has no issues that we know of. ❞ – WAC variant, 8 years

❝ She has very good eyesight. ❞ – WAC variant, 6 years

Recurrent respiratory infections

Recurrent respiratory infections have been reported in almost half of children in the medical literature, most frequently in childhood. Cases of asthma and an abnormal breathing pattern have also been observed.

❝ Her chest is her Achilles' Heel; she develops a viral wheeze with every cold. ❞ – WAC variant, 6 years

Neuroimaging anomalies

Some children have non-specific anomalies of the brain, of which an enlargement of the fluid-filled ventricles in the brain is the most frequently reported. This may interfere with the body's ability to drain cerebrospinal fluid from the brain resulting in hydrocephalus - a build-up of fluid within the brain. Ventriculomegaly and prominence/enlargement of subarachnoid spaces have each been reported on a few occasions. Other findings include asymmetry of the hemispheres of the brain.

❝ An MRI at 10 months revealed white "bright spot" areas [changes to the white matter in the brain]. A follow up MRI 12 months later revealed that the white areas were no longer present. ❞ – WAC variant, 6 years