What causes *SETD5*-related disorder?

When children are conceived the genetic material of each parent is copied in the egg and sperm that make a new child. The biological copying method is not perfect and occasionally random, rare changes can occur in the genetic code of children that are not present in the DNA of their parents. *SETD5*-related disorder occurs when one of these changes affects the *SETD5* gene in chromosome 3. These types of change happen naturally: they are not due to anything a parent did or did not do. No one is to blame when they occur and no one is at fault.

In most families the change in *SETD5* occurs out of the blue and is not inherited from one of the parents (*de novo*). In a minority of families, one parent may have the same genetic change as their child, but this is very rare.

Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. For *SETD5*-related disorder where parents do not carry the same genetic change as their child, the chance of having another affected child is little higher than for anyone else in the population. The chance is not zero, since occasionally a parent may carry the genetic change in their egg or sperm (this is called germline (gonadal) mosaicism). This means that parents who are not found to carry the change in the *SETD5* gene when their blood is tested, still have a very small chance of having another child with the condition.

If the genetic analysis of the parents of a child with *SETD5*-related disorder shows that they carry the same genetic change, the chance of it happening again is much higher and can be up to 50% (1 in 2). Each family situation is different and a clinical geneticist or genetic counsellor can give you specific advice for your family.

How common is *SETD5*-related disorder?

SETD5-related disorder is a rare condition and was identified for the first time in 2014. The first study into the condition identified changes (variants) in the *SETD5* gene as one of the more common genetic causes of intellectual disability with autism and behavioural concerns.

Can it be cured?

At present, there is no cure for this syndrome since the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means appropriate monitoring and treatment can be put in place.

Families say ...

"Our daughter made us see the world through different eyes. She is a gift to us." - 11 years
"Our son is very fond of electronics, seems to know a lot and gets excited to help others. He loves all special Olympics activities he participates in. Always excited to go and be part of the group. Always keeps us on our toes, very loving and loves to talk. One of the most special boys we have ever known." - 15 years
"Happy, non-verbal, very social. Very good social reading and loves people." - 13 years

Management recommendations

Children should be followed up by a general paediatrician who can oversee care so that development and behaviour can be monitored and the best help in the form of physiotherapy, occupational therapy, speech therapy and behavioural therapy can be given.
Consultation with specialists in cardiology, ophthalmology, neurology, orthopaedics and other medical specialties may be recommended.

Inform Network Support

Rare Chromosome Disorder Support Group

The Stables, Station Road West,
Oxted, Surrey, RH8, 9EE, UK,
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

www.facebook.com/groups/setd5families
www.facebook.com/groups/801819427421051
Simons Searchlight Community – /www.facebook.com/groups/SETD5/

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Unique

Understanding Chromosome & Gene Disorders

SETD5-related disorder/ 3p25.3 microdeletion syndrome

rarechromo.org

What is *SETD5*-related disorder?

The *SETD5* gene is located in the short 'p' arm of chromosome 3 in a region called 3p25.3. We have two copies of chromosome 3 in our cells, so we have two copies of the *SETD5* gene. *SETD5*-related disorder (also known as MRD23) occurs when one of the two copies of the *SETD5* gene does not function as expected. This can be due to specific changes (known as pathogenic variants) in the gene or the loss (deletion) of one copy of the gene.

SETD5 and 3p25.3 microdeletion syndrome

3p25.3 microdeletion syndrome is caused by deletion of a tiny part of one of the two chromosomes 3, involving band 3p25.3. When you study children with 3p25.3 microdeletion syndrome and those with changes in the *SETD5* gene, many of the features are similar. It is thought that the key features of 3p25.3 microdeletion syndrome are due to the loss of one of the two copies of *SETD5*.

Some children have a related genetic condition called 3pter-p25 deletion syndrome. This is similar to 3p25.3 microdeletion syndrome, but a larger part of the chromosome is missing so the deletion extends further towards the tip of chromosome 3. Children with 3pter-p25 deletion syndrome have similar features to *SETD5*-related disorder and 3p25.3 microdeletion syndrome but may have additional features due to the loss of extra genes in this region. See *Unique*'s guide to 3p25 deletions for more information

Frequent features

The most common features in children with *SETD5*-related disorder or 3p25.3 microdeletion syndrome are also found in many other genetic conditions that cause learning problems so children may not be easily diagnosed without genetic investigations. The first five features listed below are found in almost all children with these conditions. The other features may or may not be present.

- Developmental delay
- Language delay and/or stammer
- Intellectual disability
- Behavioural concerns and/or ASD
- Small head (microcephaly)
- Poor feeding and slow growth
- Bowel or other gastrointestinal problems
- Characteristic facial features
- Heart conditions
- Hearing problems
- Eye and vision anomalies including ptosis
- Curvature of the spine or other orthopaedic concerns
- Seizures
- Hypotonia (low muscle tone)

Development

Appearance

Children may share common characteristic facial features. The most common include a triangular-shaped face, prominent eyebrows that meet or nearly meet (synophrys), a nose with a wide base and tip, a long and smooth philtrum (the region that connects the nose to the upper lip), a thin upper lip and low-set or unusual ears. Some children have teeth anomalies.

Growth

Babies may be small at birth and a minority have a small head (microcephaly). While many remain small and are short as children, some are of average height.

Feeding

Feeding difficulties in the new-born period are common. Typically, babies suck weakly and some need high energy milks to encourage weight gain. Some babies readily bring feeds back up (gastro oesophageal reflux) and need careful positioning for feeding and while sleeping. Some babies are helped by medicines for reflux. Occasionally surgery is helpful to improve the effectiveness of the valve between the stomach and the food pipe (a fundoplication). Some babies need to be fed temporarily through a tube direct into the stomach (gastrostomy). Older children typically have chewing difficulties. Rarely, anomalies of the roof of the mouth (palate) may contribute to feeding issues in infants. Some children may have low sugar levels in the blood (hypoglycemia) that need monitoring, but there are no scientific data on the frequency of this condition yet.

Sitting, moving, walking

Babies are usually quite late to become mobile. Low muscle tone may underlie some of these mobility difficulties. Some children have an unsteady gait (instability whilst walking) which can affect their mobility. With the help of standing and walking aids, some children learn to walk and eventually to swim, run and dance but for others this is not possible.

Speech and communication

Children typically experience delay in speech and communication. The eventual range of achievement is very broad, from a few children who have a large vocabulary to others who use signing, gestures and vocal noises to express their needs.

Intellectual development (ID) and learning

While many children need considerable support with learning and most have a diagnosis of developmental delay and/or ID, children and adults with only mild or no ID have been reported.

Behaviour

As a group, children appear to have a happy disposition. There are reports of autistic tendencies and hyperactivity at school age and some have a diagnosis of ASD and/or ADHD. Some children have obsessive compulsive disorder (OCD) and experience obsessive thoughts or behaviours. These behaviours can sometimes be controlled with medication, but others may continue to have quite challenging behaviour requiring specialist advice and support.

Medical concerns

Heart conditions

Around one baby in three is born with a heart anomaly, typically an atrioventricular septal defect (AVSD). This is a group of conditions affecting the development of the walls between the two upper and the two lower chambers of the heart (the atria and ventricles) and the valves that control the blood flow between them. Many babies will need open heart surgery but *Unique*'s experience is that they thrive afterwards.

Seizures

Some children are known to experience seizures, although these may be rare or occasional.

Eye and vision anomalies

In *Unique*'s experience, many babies and children have an eye anomaly or problems with vision. These include a squint (strabismus), involuntary eye movements (nystagmus) and long-sightedness (hypermetropia) or short-sightedness (myopia). Many of these eyesight differences can be corrected with surgery (such as strabismus) or glasses (such as long- or short-sightedness). Some children are unable to open the upper eyelid(s) fully (ptosis). Ptosis can affect one or both eyes. In more severe cases when vision is affected, ptosis can be corrected with surgery to hold the eyelid up.

Hearing

Hearing impairment, either temporary or permanent, can affect children. Hearing issues may also impact speech and language development and concerns should be acted on early.

Extra fingers and/ or toes (polydactyly)

The presence of extra fingers or toes at birth is described in one in four children, but these can be removed and do not usually cause any long-term problems.

Genitals

Some boys have hypospadias, where the hole usually at the end of the penis is on the underside, and some are born with undescended testicles (cryptorchidism). Both conditions may need no treatment but if they do, they can usually be corrected with straightforward surgery. Some children have an inguinal hernia (bulge in the groin area due to weakened muscle) which can be treated with routine surgery.

Skeletal/spinal anomalies

Some children have an abnormal curvature of the spine. The severity and type of curvature varies as will the type of treatment required. A small number of children have also been reported to have fragile bones.