

## Why does SOX5-syndrome occur?

SOX5-syndrome mutations have an autosomal dominant and haploinsufficient pattern of inheritance. Autosomal dominant means that only one copy of the gene needs to be mutated/deleted for the person to be affected, with males and females equally likely to have the mutation. For most gene products quantity is not crucial, but for SOX5-syndrome mutations in the *SOX5* gene mean that not enough SOX5 TF is produced to maintain normal function. This is termed haploinsufficiency, meaning that both the copy of the gene inherited from the mother and the copy inherited from the father are required for normal development. Since the gene product of *SOX5* regulates the development of the nervous system, if there isn't enough SOX5 TF then the brain cannot develop to function 'normally'.

Almost all people with SOX5-syndrome are the only affected member of their family. This is because SOX5-syndrome is most often caused by *de novo* mutations. A *de novo* mutation means that the genetic change occurred as a "new event" in the sperm or the egg of the parent before fertilisation. These *de novo* mutations occur by chance and are not due to anything either parent did, or did not, do.

In a few instances the *SOX5* gene change is inherited from a mildly affected parent. Since *SOX5* is inherited in an autosomal dominant manner, someone with a change (mutation) in the *SOX5* gene has a 50% chance of passing the change on to any children they have. The severity of the symptoms caused by *SOX5* gene changes is variable, even within the same family, although we do not understand why.

## Families say ...

“ He is very affectionate and adorable but is sensitive to his surroundings. He has been diagnosed with ASD and ADHD is a possibility. Now we know what his needs are and we try to cater to them as best as we can. Adopting a calm and understanding parenting style means his behaviour is entirely manageable. I love seeing him grow and develop his personality. ”

## Management options might include:

- Feeding management if necessary e.g. tube feeding as a baby.
- An EEG (measurement of the brain's electrical activity) if seizures are suspected.
- Eye examination e.g. check if glasses are needed.
- Brain imaging with MRI e.g. if a child has seizures or limb weakness.
- Follow up by a developmental paediatrician.
- Physiotherapy and speech and language therapy.
- Clinical genetics referral (to help interpret genetic test results, advice about future pregnancy etc.)
- An assessment to identify the most appropriate schooling for the child with SOX5-syndrome.

## Families say ...

“ He is prone to constipation. Taking fibre supplements has been life-changing. He used to wake up throughout the night and cry; however, since correcting the constipation, he wakes up less than a quarter of the time that he used to. I think he was just in pain. ”

## Inform Network Support



### Rare Chromosome Disorder Support Group

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Understanding Chromosome & Gene Disorders

## SOX5-syndrome/Lamb-Shaffer syndrome/ 12p12 deletions (including SOX5)



## What is SOX5-syndrome?

SOX5-syndrome is a neurodevelopmental disorder that is caused by a change in the *SOX5* gene, located on the short (p) arm of chromosome 12 at position 12.1 (12p12.1).

SOX5 syndrome, also known as Lamb-Shaffer syndrome (LAMSHF), is associated with intellectual disability (learning problems) and developmental delay (meeting developmental milestones such as walking later than expected). Being a relatively newly discovered syndrome, the information we have on the features associated with SOX5-syndrome may not be fully complete.

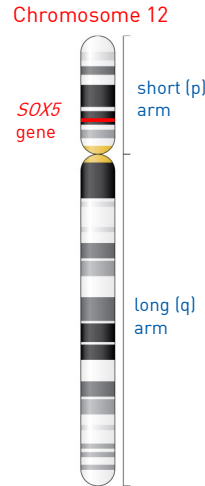
## What causes SOX5-syndrome?



The human body is made up of billions of cells. These cells are important for carrying out different functions in the body as well as housing the vital “instructions” that enable our body to work properly, contained within the DNA that make up our genes. Each person has several thousand genes, one copy inherited from their father and one

copy inherited from their mother, grouped along thread-like structures called chromosomes, which are packaged to fit inside our cells.

SOX5-syndrome happens when one of a person's two copies of the *SOX5* gene doesn't function as it should. SOX5-syndrome can be caused by changes (mutations) in the *SOX5* gene, which stop the gene from working properly. It can also be caused by loss of one copy of the section of chromosome 12 that contains the *SOX5* gene (a deletion), meaning there is only one copy of the gene. Some of these chromosome deletions contain only the *SOX5* gene; some contain additional genes.



## How do changes in the *SOX5* gene cause the symptoms?

The *SOX5* gene is thought to give an important instruction for brain development. This is why alterations in the *SOX5* gene are mainly associated with a neurodevelopmental disorder and people with SOX5-syndrome often display behavioural problems, speech delay and intellectual disability.

The *SOX5* gene codes for a transcription factor (TF). TFs regulate when a gene is switched on or off. The SOX5 TF is involved with embryonic development and the development of the nervous system (brain). So, if not enough SOX5 TFs are made or if they are non-functional, this affects the normal development of the nervous system.

## What are the chances of a couple having another child with SOX5-syndrome?

Provided that neither parent is found to have the same genetic change affecting *SOX5*, then the chances of having another affected child are very low. The chance is not zero as there is a small possibility that one parent may carry the genetic change in their sperm or eggs alone (gonadal mosaicism). More details can be obtained from your Clinical Genetics department.

## Can it be cured/what treatment is there?

There is no specific treatment for SOX5-syndrome. Treatment should be in a multidisciplinary setting with input from an appropriate paediatrician.

### Most common features

SOX5-syndrome causes a variety of features, sometimes including:

- Speech delay
- Intellectual disability
- Developmental delay
- Behavioural concerns
- Low muscle tone and strength (hypotonia)
- Feeding problems early in life

### Other possible features

- Epilepsy (fits)
- Strabismus (a squint)
- Spinal curvature

## Development

### ■ Growth

Babies with SOX5-syndrome are generally of average birth weight and height in childhood lies within the average range. Some children may have a mild to moderate short stature and mild microcephaly (small head). Where head circumference is reduced, it is likely not to be noticeable to a casual observer. Some children with SOX5-syndrome have had problems with feeding early in life.

### ■ Sitting, walking & moving

All children had some degree of delayed motor development and children may feel floppy due to low muscle tone and strength. Most learned to walk independently at two to three years.

### ■ Speech

Speech is often the most affected area and a minority of children with SOX5-syndrome do not develop speech. All but one child had a delay in speaking, with first words spoken between 18 months and 4 years.

### ■ Learning

All children we know of who are of school age have required some help with learning.

### ■ Behaviour

Some children with SOX5-syndrome have been diagnosed as autistic or as having attention deficit hyperactivity disorder (ADHD). Aggressive behaviour has been described in some children.

## Medical concerns

■ Occasionally, SOX5-syndrome may be associated with epilepsy (fits). Some children with SOX5-syndrome may have a squint. Children may have minor anomalies of the hands and feet. A few children have a curvature of the spine. Internal organ malformations (e.g. a hole in the heart) are generally not seen in SOX5-syndrome.

## Families say ...

“ Struggles with fine motor skills like eating with utensils or an appropriate grip when colouring. He learns best when things are explained step by step. ”