Understanding Chromosome & Gene Disorders

SOX11 syndrome

(Sox11 variants and 2p25.2 deletions)

rarechromo.org

This leaflet is based upon what is known about SOX11 syndrome (2021), from a small group of affected individuals. There are many gaps in knowledge and with time, and further research, further information will become available.

What is SOX11 syndrome?

"Syndrome" is a medical term which means a combination of symptoms and physical features which are found together in a person and are all due to the same underlying cause. Not every person with the syndrome will have identical combinations of symptoms and physical features, but there will be shared features.

SOX11 syndrome is the medical term used to describe the medical condition which affects a person who has a change in one of the two copies of their SOX11 gene. This change can be a deletion of the part of chromosome 2 which contains the SOX11 gene, known as a chromosome 2p25.2 deletion, or a change to the SOX11 gene sequence, known as a single nucleotide variant (SNV).

People with SOX11 syndrome have combinations of slowness in reaching developmental milestones, learning difficulties and neurological conditions such as autism.

How common is SOX11 syndrome?

SOX11 syndrome was only recognised in 2016 when the first research paper describing a group of affected children was published. It is a very rare condition with only very few known affected people. Recently, researchers at the University of Sheffield identified around 50 people worldwide with either changes to the SOX11 gene or chromosome deletions affecting SOX11. There are likely more people with this syndrome who have yet to be identified, but this gives an idea of how uncommon the condition is.

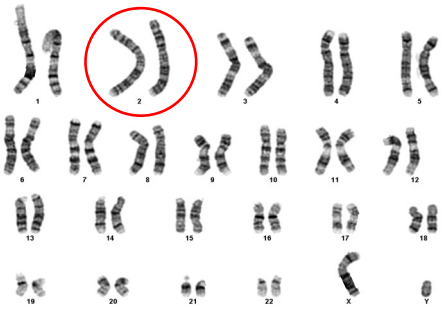
What are genes and proteins?

Genes are the instructions that tell our bodies how to develop and function. We all have about 20 000 genes. Our genes are arranged in pairs, one of each pair is inherited from our mother and the other is inherited from our father. Genes are biological instructions and are made of a biological alphabet that contains four letters (A, C, T, G). This is called the genetic code. Long combinations of these biological letters code for detailed instructions (genes) on how to make proteins.

Proteins carry out specific tasks in our bodies and are used to make our cells, tissues and organs. Changes to gene 'letters' can alter the function of the protein they produce, or even stop it working altogether. However, when we think how much variety there is in people (for example height, eye colour, voice, etc.) we can appreciate that the genetic code of each person varies a great deal. Because of this, it can be difficult sometimes to work out if a change to the lettering of a gene will cause a medical condition or if the change is just part of the natural variation we see from one person to the next.

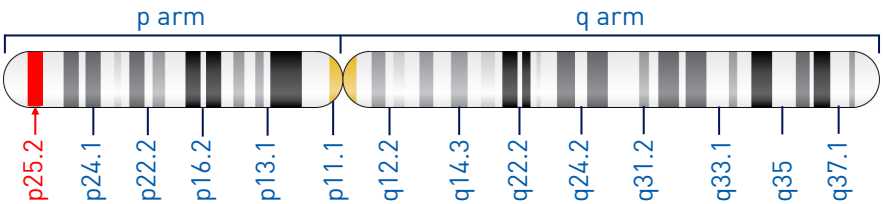
What are chromosomes?

Chromosomes are the structures which contain our genes. We have 46 chromosomes in each cell. These are arranged in pairs (as shown in the image opposite), from pair number 1 (the longest) to pair number 22 (the shortest) and two X chromosomes in a genetic female and an X and a Y in a genetic male. If a piece of chromosome is missing it is called a deletion. If a deletion removes a gene, or part of a gene which gives an important instruction for development it can cause a medical condition. SOX11 syndrome can be caused by a deletion called a 2p25.2 deletion. The number 2 denotes chromosome 2, p denotes the short arm of chromosome 2 and 25.2 refers to a more precise position on the chromosome which is missing the piece of genetic material as shown in the image below.



Chromosome pairs 1-22, X and Y (genetic male).
Chromosome 2 pair circled in red.

Chromosome 2



How do doctors find changes in genes?

Our genetic code can be read by a test called sequencing. There are two main types of this test that are used to identify changes in the sequence of gene lettering. One is called exome sequencing, this reads the code of all of our genes. The other is called genome sequencing, which reads the code of our entire genome, which includes all 20 000 genes and the parts of the genetic code that control the activity of genes.

Once a change to the lettering of a gene is identified it is looked at in great detail and doctors and genetics laboratory staff try to work out if it is likely to be causing a person's symptoms or not. For example, if a computer program identifies that the genetic change is likely to stop the gene and its protein from working properly this would indicate that the gene change might be causing symptoms. On the other hand, if the genetic change is found in lots of unaffected people then it would indicate that this genetic change is just a natural variation in the genetic code.

When a gene change is identified as causing specific symptoms, it is called a pathogenic variant, when professionals are unsure whether the change could be causing these symptoms, it is named a variant of uncertain significance (also known as a VOUS or VUS).

It is routine practice to sequence the genes of the parents of a child who has a genetic change. If the sequencing shows that the genetic change has been inherited from an unaffected parent, then this normally suggests that the genetic change is a natural gene variant found in that family, and is not causing the difficulties their child is experiencing. However, if the genetic change has not been inherited from either parent, then this suggests that it could be causing the child's symptoms. If a genetic variant is not inherited, it is known as de novo.

Pieces of missing chromosomes can be identified using a test called a microarray, which is also known as comparative genomic hybridization or aCGH. This type of test can detect very small pieces of missing chromosome known as deletions, microdeletions or copy number variants (since a single copy of a piece of chromosome is now present instead of two copies). Again, sophisticated computer programs need to be used to work out if the chromosome change is possibly causing a medical condition or is just a natural chromosome variation.

What is the SOX11 gene?

The SOX11 gene provides the instructions necessary to make a protein called a transcription factor. This type of protein switches other genes on and off during development and is particularly important in the brain. The activity of this protein makes sure that the correct genes (instructions) are active during brain development so that the brain forms as expected.

In the developing brain (when the baby's brain is growing in the womb), SOX11 helps control the production of brain cells (neurons). SOX11 stimulates cells to divide to produce more cells, and so increase the number of neurons. SOX11 also helps guide brain cells to the correct parts of the brain for their appropriate and specific function. We need two working copies of the SOX11 gene for our brains to develop as expected, so a deletion or change to the sequence of one of the two SOX11 genes causes SOX11 syndrome.

Why has this happened?

In most people with SOX11 syndrome, the gene change or chromosome deletion has happened for the first time in them and has not been inherited from either of their parents (de novo).

Nothing that either parent did, or did not do, caused this to happen. There are no known drugs, environmental or occupational factors which cause SOX11 gene changes. It is no one's fault.

Could this happen again?

If neither parent is found to have this chromosomal or gene change, it is unlikely that they will have another child with SOX11 syndrome. Very rarely, parents are identified as having unaffected chromosomes by a blood test, but a few of their egg or sperm cells carry the genetic change. This is called germline (or gonadal) mosaicism and it means that such parents can have more than one child with the same chromosome/gene disorder. If they wish, parents can discuss their specific recurrence risks with a genetic counsellor at their local Clinical Genetics department (your GP can refer you).

What are the most likely features of SOX11 syndrome?

There is a lot of variability in the symptoms people with SOX11 syndrome have. It is not fully understood why symptoms are so variable.

People with SOX11 syndrome can have combinations of:

- **Delayed motor development**
  (sitting and walking)
- **Cleft lip and palate**
- **Delayed speech development**
- **Epileptic seizures**
  (altered electrical activity in the brain)
- **Intellectual disability**
  (children will need extra help at school or may attend a special school)
- **Autism**
  (an unusual pattern of behaviour with impaired social interaction)
- **Alterations to brain structure**
  (detected by a brain scan called an MRI)
- **Delayed onset of puberty**
  (due to reduction in production of hormones that trigger puberty)
- **Alterations to kidney structure**
  (without apparent effect on kidney function)
- **Very mild unusual physical appearance**
  (likely only to be noticeable by a trained professional)
- **Eye anomaly**
- **Hearing anomaly**
- **Underdeveloped fifth toenail**

Appearance

People with SOX11 syndrome have subtle, but characteristic alterations to their facial appearance. This would not be noticeable to a lay person, but is likely to be identified by a specialist doctor. However, this facial appearance would not in itself be sufficient to make a diagnosis of SOX11 syndrome, which would need to be confirmed by a genetic test.

Growth

People with SOX11 syndrome tend to be within the average range for height, but towards the lower end of average. People with SOX11 syndrome tend to be of low weight, sometimes even below average weight.

Sitting and moving (Gross motor skills)

All people with SOX11 syndrome have some difficulties with gross motor skills. Many babies with SOX11 syndrome are floppy at birth, this is known as hypotonia. It is difficult to provide a lot of information regarding gross motor skills since so few people have been diagnosed and fully assessed, but delayed walking is common. About 50% of children with SOX11 syndrome are thought to achieve independent walking by 30 months. More research is needed to define the full range of movement abilities in individuals with SOX11 syndrome.

Communication abilities

Children with SOX11 syndrome have markedly affected communication abilities. Most have only a few or no spoken words by the age of 5 - 10 years. Further research is needed to be able to produce detailed information on the communication abilities of people with SOX11 syndrome at older ages.

Hearing

There seems to be an increased chance of both conductive (when sounds do not reach the inner ear) and sensorineural (when the inner ear or nerves are affected) deafness in people with SOX11 syndrome.

Eyesight

People with SOX11 syndrome have an increased chance of developing eye anomalies. In some individuals, the entire eye is smaller than it should be, this is known as microophthalmia. An altered shape to the iris (known as a coloboma) and thinning of the optic nerve have also been described. Impaired eye movements (known as oculo motor apraxia) can also occur. Some people with Sox11 syndrome are farsighted, have a squint or ptosis (droopy upper eyelids).

Education and learning

Based upon the information we have so far (2021), it seems that people with SOX11 syndrome will need additional help with education and schooling. Most children identified so far benefit from the additional support provided by a special educational needs school.

Further research to collect detailed information on the strengths and weaknesses in learning of people with SOX11 syndrome is needed.

There is little information on the level of independence of adults with SOX11 syndrome. It is likely that an adult with SOX11 syndrome will not be able to live completely independently. For example, they may need to live in sheltered housing.

Therapies

People with SOX11 syndrome would benefit from multidisciplinary care. Standard therapies would be speech and language (to help with communication), physiotherapy (to help with motor development) and occupational therapy (to help with adaptations in the home). This could be delivered via a child development clinic or community paediatrics.

An assessment by a specialist eye doctor should be considered. Some of the eye anomalies that can occur in individuals with SOX11 syndrome would only be detected by specialised tests.

An assessment by a specialist hormone doctor (Endocrine specialist) should be considered. Some adolescents with SOX11 syndrome do not produce the hormones required to trigger puberty. They may need blood tests to confirm this and hormone replacement treatment may be recommended.

An assessment by a Paediatric Neurology doctor may be considered if the child with SOX11 syndrome has mobility difficulties or significant clumsiness. A brain scan might be suggested, since an alteration to the structure of the brain might be identified to explain these symptoms.

An ultrasound scan of the kidneys, to check there is no structural alteration, could be done. This is a painless jelly scan, similar to what is done to scan a baby in the womb. It is unlikely that any alteration to kidney structure in SOX11 syndrome would need treatment.

Chromosome 2p25.2 deletion

The symptoms outlined in this guide are those for people with changes in the lettering of the SOX11 gene. There seems to be a lot of similarities between the symptoms in people with deletions of chromosome 2p25.2 (which contains SOX11) and people with changes to the lettering of the SOX11 gene. Based on our current understanding we would suggest that people with 2p25.2 deletions that include the SOX11 gene have the same medical care as people with changes to the lettering of the SOX11 gene.

Link between SOX11 and "Coffin-Siris Syndrome"

Coffin-Siris syndrome was named after the two doctors who first described it. People with Coffin-Siris syndrome have a distinctive facial appearance and other features such as small nails on their 5th fingers. Some people with SOX11 syndrome are said to have Coffin-Siris syndrome based upon their physical appearance. But many people with SOX11 syndrome do not have features of Coffin-Siris syndrome. It seems that SOX11 syndrome is a distinct condition from Coffin-Siris syndrome, but with many common symptoms and issues.

Families say ...

“ She is currently 2 years and 11 months. She has a very laid back nature, and is extremely sociable. She has a good imagination, and is very playful.

Although slightly delayed, her speech is vastly improving, and she can now communicate her needs effectively. She is seeing a speech and language therapist who is investigating her continuous dribbling, with the possible cause being muscle control.

She is currently attending nursery and her EYFS (early years foundation stage) scores are within the typically developing range. Potty training is still an ongoing challenge, with occasional mistakes of one accident per day. However her ability to entertain through singing and dancing is a constant joy, heightened by her love for dressing up! ”

“ He is 3 ½ now but his genetic investigations started when he was 7 months old following a diagnosis of hypotonia and feeding difficulties. He had no problems with purees or solid food as a baby, but had trouble swallowing milk as it made him cough. Whole exome sequencing identified a de novo variation of the SOX11 gene.

In terms of physical appearance, he has mild dysmorphic features such as low set ears and hooded eyelids. He also has very small nails on his fifth toenails which is a feature of SOX11 syndrome.

In terms of physical development, he crawled on all fours at 12 months, started walking at 22 months, and although he still has gross motor delays he is developing well.

He is very sociable, sometimes overly sociable! He enjoys nursery, which he attends 4 days a week, and although he has significant speech and language delay, he communicates well and is keen to do so. His receptive language is much better than his expressive, as he understands a lot and has a wide vocabulary but he struggles to articulate a number of consonant sounds. ”

Inform Network Support

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Understanding Chromosome & Gene Disorders

Join Unique for family links, information and support

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at http://www.rarechromo.org/donate Please help us to help you!

Facebook groups

Sox11 specific group: https://www.facebook.com/groups/sox11

There are also numerous Coffin-Siris syndrome groups in different countries. (Coffin-Siris syndrome is the name given to a syndrome currently thought to be caused by changes to a number of different genes.

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Sir Halley Stewart Trust

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

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. This booklet was written and updated by Dr Alisdair McNeill, Senior Clinical Lecturer in Neurogenetics (University of Sheffield) and consultant in clinical genetics (Sheffield Children's Hospital).

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