

Inform Network Support



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Websites and Facebook groups

There are currently two websites and groups for families:

Information website 'Bohring-Opitz Syndrome – A Worldwide Exchange of Information and Awareness' with 'Bohring-Opitz Support Group' (established 2011):

<https://bohring-opitz.org> | <https://www.facebook.com/groups/okketje/>

'Bohring-Opitz Syndrome Foundation' with 'Bohring-Opitz Connection Group' (established 2015):

<https://bos-foundation.org> | <https://www.facebook.com/groups/BohringOpitz/>

There is an active international community of families keen to hear from new families affected by BOS. Links to medical literature can also be found on the websites above.

Facebook groups in other languages/countries:

Italy: <https://www.facebook.com/groups/1570558623230939/?fref=ts>

France: <https://www.facebook.com/Syndrome-de-Bohring-Opitz-France-468556996637745/>

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.

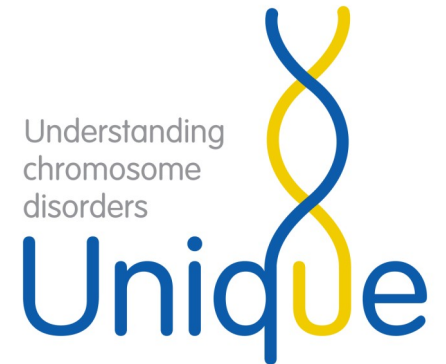
This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This booklet was compiled by Dr Joanna Kennedy, Academic Paediatric Trainee, Severn Deanery and reviewed by Professor Ruth Newbury-Ecob, MB ChB, MD, FRCP, FRCPCH, Consultant Clinical Geneticist, Department of Clinical Genetics, University Hospitals Bristol NHS Foundation Trust.

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Bohring-Opitz Syndrome (BOS)



What is Bohring-Opitz Syndrome (BOS)?

Bohring-Opitz Syndrome is a rare genetic condition that results from 'spelling mistakes' (aka mutations) in genes. The syndrome is named Bohring-Opitz after the two doctors who published a paper describing some of the early cases. Individuals with BOS have a wide range of symptoms. Some of these symptoms are found in all individuals with BOS and some are found in some cases but not all. Some of the more common symptoms include severe learning difficulties, a characteristic posture with bending at the elbows and wrists, a red birth mark on the forehead, prominent eyes and feeding difficulties.

What are genes and chromosomes?

We all have an 'instruction manual' made up of 23 chromosomes which is present in almost all of our cells. This tells cells how to behave from the moment of conception onwards. We inherit two copies of the 'instruction manual', one from our mothers and one from our fathers which means each person has 46 chromosomes. The chromosomes are made up of DNA which is like a string of letters that use a 4 letter code (G, A, T, C). Some of this code has instructions for cells to make proteins. The parts of the chromosomes that do this are called genes.

What genetic changes cause BOS?

When BOS was first described no one knew what genetic changes caused BOS and children were diagnosed based on their symptoms alone. Since then there have been major advances in our ability to look for genetic changes. In 2011 a group of researchers found that more than half of the children they tested with a clinical diagnosis of BOS had a mutation in a gene called ASXL1 (located on the long arm (q) of chromosome 20 within band 20q11.21). Because this change was not found in all children there may be other genetic causes of BOS.

What does the ASXL1 gene/protein do?

The ASXL1 protein (made from the ASXL1 gene) is involved in controlling the production of proteins from other genes. It can increase the production of some proteins and decrease the production of others. Because the protein is involved in controlling the expression of many other genes the syndrome can cause changes in many different parts of the body.

We do not yet know all the functions of the ASXL1 gene/protein. Our knowledge of ASXL1 and its functions and our knowledge about other genetic causes of BOS will improve over the years with further research.

Why did this happen and could it happen again?

In most cases BOS is caused by a genetic change or mutation in the ASXL1 gene which occurred in the formation of the egg or sperm from which the child was conceived, but not inherited from either parent so the risk of having another child with the condition is very low. This is called a new or de novo mutation. Very occasionally a change in ASXL1 can be found in some of the cells of the mum or dad, this is called 'mosaicism' and can lead to further children having the condition. Some children with BOS do not have a mutation in ASXL1. It is likely they have a mutation in another related gene but as a scientific community we are still working out what the other causes are. Recently a few children with a clinical diagnosis of BOS have been found to have mutations in both copies of a gene called KLHL7 (chromosome 7p15.3, publication planned). These families would be at a higher risk of having further children with similar symptoms. For these reason genetic counselling is recommended for families wanting to have further children. Whatever the inheritance, it is important to emphasize that this is nobody's fault.

Medical/Educational Guidance Summary

- Children should be under the care of a general or community paediatrician to monitor their health and development.
- Input from the neurology/neurodevelopment teams may also be required.
- Health visitors and community nurses play an important role in caring for individuals with BOS.
- Monitoring weight gain in infancy is important. Feeding difficulties and reflux are common and may need significant medical support.
- Assessment to check for a cleft palate should be made.
- Constipation is a common feature and may need medical management.
- An assessment of special educational needs should be carried out so that extra help can be put in place at school.
- Early input from a speech and language therapist is important.
- Early input from a physiotherapist and from occupational therapy is important.
- Structural heart problems and intermittent bradycardia is common and we would suggest that a cardiology review should be considered for all children. An ECG should be performed.
- Vision should be assessed, short-sightedness is seen in most children and is often severe. Retinal abnormalities and cortical visual impairments are seen in some children. Strabismus is common.
- Recurrent infections are common and may require further investigations. Urinary tract infections (UTIs) should be checked for and if recurrent, a renal USS (jelly scan looking at the kidneys) should be performed.
- Individuals with BOS are at a theoretical increased risk of cancer. They should have regular screening up to the age of 8 years to monitor for Wilms tumour.
- Sleep disturbance may improve with melatonin.
- Sleep apnoea can be a significant problem and may need investigation and management.
- As there is a high level of disability and a high rate of infant mortality input from paediatric palliative care teams is entirely appropriate.

Families say ...

“ Receiving a diagnosis of BOS can be very difficult. We have found that the best source of information is other parents. The Parent Support Group is a great way to exchange information with other families. Another way to connect with families is to attend our annual BOS Meet-Up. ” Taylor Gurganus, Bohring-Opitz Syndrome Foundation, Inc., www.bos-foundation.org

In addition some children have episodes of slow heart rate (aka bradycardia). As more children are diagnosed we will learn more about the frequency and types of heart problems individuals with BOS have.

■ Sleep

Some children have difficulty sleeping. This includes difficulty establishing sleep and frequent waking. Some children take medication called melatonin to help with this. This is not helpful for all children but may be tried if children have severe difficulties sleeping.

Some people with BOS have sleep apnoea. This is when there are prolonged pauses in breathing or very shallow breathing that result from a floppy airway. After a period of not breathing, individuals often gasp or snore loudly. If you think your child has sleep apnoea, it is important to let your doctor know. Investigative sleep studies can be carried out and sleep devices can be used if your child is identified as having sleep apnoea.

■ Kidneys

A small minority of children have abnormalities of the kidney, this includes a dilated tract from the kidney to the bladder that can make urine infections more likely.

■ Cancer

The ASXL1 gene which contains a mistake in most cases of BOS is associated with blood cancers. In most cases of cancer the mistake has occurred after birth and is thus present in only some of the cells. We suspect this means that individuals with BOS are at a slightly higher risk of developing cancer. A small number of children with BOS have been found to have a cancer of the kidney (known as Wilms tumour). Because of the likely increased risk of Wilms tumour, screening in the form of an ultrasound scan (jelly scan) of the stomach every 3 to 4 months until the age of 8 years is recommended. One child with BOS developed a brain cancer called medulloblastoma. We would recommend that if children have symptoms that could suggest malignancy there should be higher level of suspicion than for individuals that do not have BOS. It is important to note that the vast majority of individuals with BOS have not developed cancer and there have been no reported cases of blood cancer to date.

■ Prognosis

Very sadly quite a few children with BOS pass away in infancy. Reports suggest about 40% of children die in infancy. This is most often because of severe infection. Some children are reported to have passed away from problems with breathing and heart problems. We are hopeful that our increasing knowledge of BOS will enable us all to provide better care for individuals affected that may reduce the number of children that pass away in infancy. Children that survive beyond infancy tend to find that some of their issues, like feeding difficulties, improve and the number of children that pass away after infancy seems to be much lower.

■ Personality

Many children with BOS are noted to be happy and sociable.

Families say ...

“ Many may see her as imperfect...but in our eyes she is truly extraordinary. She has given us the gift of the most pure, unconditional love, she has refined our sense of humour with her curiosity and mischievous tricks, she has taught us compassion, and shown us the great beauty in the world’s smallest things which we now treasure. ”

Sheri M. Bermejo, Bohring-Opitz support group, <https://bohring-opitz.org/>

What features and symptoms do people with BOS have?

People with BOS have a lot of overlapping features.

■ Feeding Difficulties and Constipation

The majority of babies have problems with feeding including severe reflux/vomiting. Some need early tube feeding for a period of time because of these difficulties and some benefit from medications to help control reflux. If reflux is severe, a feeding tube can be inserted in to the stomach (aka PEG, aka Gastrostomy). As children get older the feeding issues improve and the reflux/vomiting resolves although a small number of children still occasionally vomit or gag. Many children have problems with constipation which may need to be medically managed.

■ Developmental Delay

All children identified with BOS have developmental delay. This means that they are delayed in reaching milestones like sitting and walking and have learning difficulties. The severity of developmental delay varies between children but tends to be severe or profound. Many babies are noted to be more floppy than other children of the same age (this is known as hypotonia) and some have a floppy trunk but stiffer arms and legs. All children with BOS develop differently. All make some developmental progress. Some children are able to sit and stand and a few develop the ability to walk. Children require the help of physiotherapy and occupational therapy to help them achieve their full potential. Therapists can supply children with equipment like wheelchairs and walking frames and will suggest and perform exercises and stretches to prevent the development of muscular problems and spinal curvature.

■ Posture

Individuals with BOS are noted to hold their arms in an unusual posture. Their shoulders are often rotated inwards, their elbows, wrists and fingers are often bent and their hands are often turned towards the little finger. ‘Fixed contractures’ where the arms are unable to straighten can develop and stretching under the guidance of a physiotherapist can help to minimise this.

■ Facial features

Children with BOS all look different but there are some features that they have in common. These include a red birth mark on the forehead, eyes that are wide apart and prominent, and large arching eyebrows that can be quite bushy. Common features in the mouth include a narrow and high palate, thick gums and unusually shaped teeth. Some children have ‘retrognathia’ or ‘micrognathia’, this is when the jaw is set back or very small. Children often have more hair than most children. Physical features can help doctors identify other individuals with the syndrome.

This leaflet is designed to help families and healthcare professionals looking after people affected by Bohring-Opitz Syndrome. It contains information about the causes of Bohring-Opitz Syndrome, the ways in which it can affect people and suggestions about the help and management that can benefit people with the syndrome. It also contains information about support groups that families can access. The information in this guide is drawn from clinical experience and cases published in the medical literature. Further publications are planned.

■ Cleft Lip/Palate

A minority of children have a cleft lip and/or palate. This is when the top lip and/or roof of the mouth fail to form properly. This can cause difficulty with feeding and can be surgically corrected.

■ Eye features

Some individuals with BOS have droopy eyelids, this is called ptosis (with a silent p). Some have eyes that look in different directions which means the eyes have difficulty focussing together, this is called strabismus (or more commonly 'cross-eyed' or 'squint') and is normal in new-born babies but should have resolved by 6 months. It is important to pick this up as it is correctable but can cause damaged vision in one eye if not corrected. Most children have poor vision so this should be tested, it is mostly due to short sightedness which is often quite severe and correctable with glasses. A few children have 'cortical visual impairment', which means their brain has difficulty processing images. Some children have problems with their retina, which is the part of the eye that detects light. A small number of children have problems with the front part of the eye (aka anterior chamber), this can include increased pressure (aka Glaucoma).

“ Being able to share and celebrate unmeasurable achievements of my son with fellow families, without explaining what these little milestones mean to me, is a tremendous gift and confirmation that creating the Bohring-Opitz Syndrome support group was one of the best things I ever did.”

Sünne van Gemert-Godbersen
Bohring-Opitz support group
<https://bohring-opitz.org>



■ Speech and Language

Children are also often very delayed in their ability to speak. Many children do not learn any spoken language but do communicate their feelings through expressions and noises. A small number of children do learn some language. For some children it has been noted that their understanding is better than their ability to speak. Speech and language therapists can help by supporting feeding and assessing communication skills. They can help with speech development and introduce communication devices. They can also help to ensure that whatever your child's ability, they are supported in achieving their full communication potential.

■ Seizures

About half of people with BOS experience problems with seizures. These can be 'generalised tonic clonic seizures' which means that the whole body is involved and, when seizing, alternate stiffening and shaking is seen. Some children have absence seizures when they become vacant and unresponsive for a short period of time. Seizures can cause a lot of worry for families and can be frightening to observe but in the majority of cases they self-resolve, or resolve with minor medical treatment and do not cause permanent problems. If you child has a seizure for the first time make sure you remove

nearby danger so they can't hurt themselves and call for an ambulance. Individuals with seizures may have investigations to check the activity of the brain and to rule out any reversible causes. This may include an 'EEG' (electroencephalogram) that looks at the electrical activity in the brain. This is done by attaching stickers, that are attached to wires, to the scalp. Children with BOS who get seizures often show some abnormalities on an EEG.

■ Infections

A number of children are reported to have frequent infections and often children are more severely affected and take longer to recover from infections than other children. These are typically chest infections, urinary infections and ear infections, all of which commonly occur in childhood but occur more in some children with BOS. There are several reasons why this may be the case. Children with BOS often vomit when they are younger and this can lead to chest infections if material from the stomach enters the lungs (aka aspiration). Sometimes structural differences can lead to increased infections, for instance some children have been noted to have small ear canals which can make ear infections more likely. Increased numbers of infections can also result from problems with the immune system. If your child has more infections than would be expected for their age, or if their infections are of greater severity than would be expected, this would be something to discuss with your doctor who may wish to arrange further investigations. It is important to note that young children normally have frequent mild colds and often get ear infections. Generally, extra investigations are only carried out if the infections are abnormal in type or severity.

■ Head size and brain

Most children with BOS have a smaller head than other children of the same age. They can also have unusual findings on brain scans. A common finding is a small or absent 'corpus callosum' which is part of the brain that connects the right and left sides of the brain. This is relatively rare and as a medical community we do not fully understand how this affects individuals. Some people with an undeveloped or absent corpus callosum, and otherwise normal brains, have only mild learning difficulties and social issues; others have more severe learning difficulties. Some children have changes in their cerebellum, which is the part of the brain that co-ordinates movement. Some have changes to the brain stem, which controls movement and feeling in the face and contributes to activities like eating and sleeping and the control of heart rate and breathing.

■ Heart

Many individuals with BOS have a problem with their heart. We do not know exactly what proportion of individuals will have a heart defect, but it is likely to be around a third to a half. Reported anomalies include septal defects (holes between the left and right side of the heart) patent ductus arteriosus (the continued presence of a connection between the circulation to the lungs and the circulation to the rest of the body that is normally present before birth but usually closes soon after birth), pulmonary stenosis (a narrowing of the vessel that takes blood from the heart to the lungs and hypertrophy (thickening) of heart muscle. A minority of children have required heart surgery. If your child has not had their heart checked this is something to discuss with the doctors looking after your child who may wish to arrange further investigations. Such investigations may include an ultrasound scan of the heart called an ECHO (aka echocardiogram) to make sure your child does not have any problems with their heart.