Understanding Chromosome & Gene Disorders

Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS) / *NR2F1* gene variants

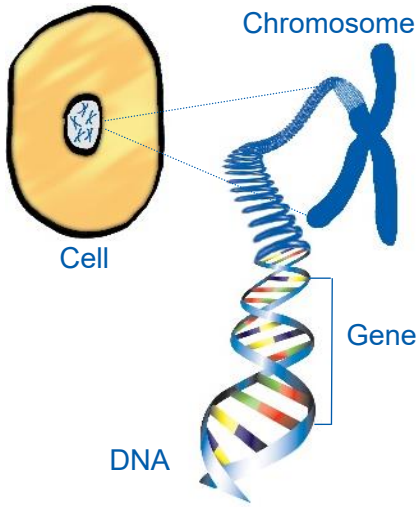
Image provided by the NR2F1 foundation

What is Bosch-Boonstra-Schaaf optic atrophy syndrome?

Bosch-Boonstra-Schaaf optic atrophy syndrome, also referred to as BBSOAS, is a rare genetic condition associated with visual impairment, development delay, seizures/epilepsy and intellectual disability. As is common with genetic conditions, each person is affected differently, not everyone with BBSOAS will have all of the possible features. Also, each person with a certain feature won't necessarily be affected by it to the same level as other people with that feature.

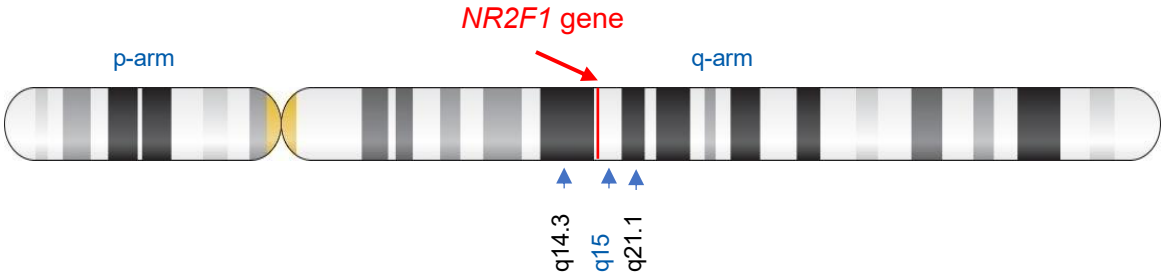
What causes BBSOAS?

Genes are instructions which have important roles in our function, growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies.



BBSOAS is caused by specific changes (known as pathogenic variants) to the DNA sequence of the *NR2F1* gene or the loss (also known as a deletion) of one copy of the *NR2F1* gene. *NR2F1* is an abbreviation of the gene's full name, Nuclear Receptor subfamily 2 group F member 1. The *NR2F1* gene is located in the long "q" arm of chromosome 5 in a region called 5q15 as shown in the image below.

Chromosome 5



We have two copies of chromosome 5 in our cells, so we also have two copies of the *NR2F1* gene. BBSOAS occurs when only one copy of the *NR2F1* gene is affected; the second copy is fully functional. This is known as autosomal dominant since all numbered chromosomes are called autosomes and genetic conditions that occur when only one copy of an autosomal gene is affected are known as dominant.

Unique publishes separate guides to Single Gene Disorders – Autosomal Dominant Inheritance and Deletions and Microdeletions.

Genetic Tests

An *NR2F1* gene sequence variant can be identified by a type of genetic test called sequencing (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS). An *NR2F1* deletion can also be identified by a sequencing test but is more commonly found using a different type of genetic test called a chromosome microarray (CMA, e.g. arrayCGH or SNParray).

Unique publishes separate guides to DNA sequencing, arrayCGH and SNParrays.

The *NR2F1* gene sequence is used to make the NR2F1 protein. This protein is important because it regulates many other genes, influencing the development of the brain and visual system.

Genetic Test Results

An example result of a DNA sequencing test (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)), that can identify gene variants, is shown here for the *NR2F1* gene:

p.Glu104Gly (E104G) (GAG>GGG): c.311 A>G in exon 1 of the NR2F1 gene (NM_005654.4)

p.Glu104Gly (E104G)	Signifies the change to the protein: the amino acid glutamate (Glu) has been replaced by the amino acid glycine (Gly) at position 104 in the sequence of amino acids that make up the protein
GAG>GGG	signifies the gene sequence change; the A nucleotide has been replaced by a G nucleotide
c.311	signifies the base pair position of the change within the gene sequence (the position where the A nucleotide has been replaced by the G nucleotide)
exon 1	signifies which part of the gene has been altered, in this case exon 1
NR2F1 gene	signifies the gene that is affected
NM	denotes the reference sequence used.

The result of a chromosome microarray (CMA) test, that can identify deletions and duplications, is shown here for a microdeletion within band 5q15 between base pair (bp) numbers 92,594,997 and 93,569,402:

arr[hg19] 5q15 (92,594,997-93,569,402)x1 dn

arr	The analysis was by array (arr) comparative genomic hybridisation (cgh)
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new 'builds' of the genome are made, and the base pair numbers may be adjusted. This means base pair positions change depending on the assembly used
5q15	the chromosome involved is chromosome 5 and the position of the deletion is in band q15
92,594,997-93,569,402	the base pairs between 92,594,997 and 93,569,402 have been shown to be deleted. Take the first long number from the second and you get 974,405 (0.974Mb or 974kb). This is the number of base pairs that are deleted
x1	means there is one copy of these base pairs, not two – one on each chromosome 5 – as you would normally expect, so this a deletion
dn	means *de novo*. The biological parents' chromosomes have been checked and no deletion or other chromosome change has been found at position 5q15. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child mat here would mean that the deletion has been inherited from the mother; pat here would mean that it has been inherited from the father.

Unique publishes a separate guide to Interpreting Genetic Test Results.

BBSOAS can occur a number of ways through different changes in the *NR2F1* gene, they are explained in the table below:

Type of genetic change	Consequence	Example of genetic change in a genetics report (genotype)
Gene deletion	One entire copy of the *NR2F1* gene is missing.	chr5:92,594,000-93,569,000x1
Start codon variant	One copy of the *NR2F1* gene is not able to be used to make the protein.	c.2T>G; p.Met1?
Missense variant or non-frameshifting indel (DBD)	One amino acid (the building block of proteins) in the NR2F1 protein is replaced by another. Indel stands for insertion-deletion, meaning the addition or deletion of bases in the gene sequence. DBD stands for DNA-binding domain, a specific functional region of the NR2F1 protein.	c.425G>T; p.Arg142Lys
Missense variant or non-frameshifting indel (other)	One amino acid in the NR2F1 protein is replaced by another. 'Other' is used to describe a change outside of the DNA-binding domain (DBD) region of the protein.	c.661G>A; p.Glu221Lys
Nonsense variant	NR2F1 protein production is stopped and / or RNA (an intermediate molecule of protein production) is destroyed.	c.1050C>A; p.Cys350*
Frameshifting indel	The DNA coding sequence of the *NR2F1* gene is shifted by the addition or deletion of a base(s) (the building block of DNA) so an incorrect sequence of amino acids is used to produce the NR2F1 protein or protein translation is stopped and/or RNA is destroyed.	c.291delC; p.Tyr98Thrfs*21

What features and symptoms do people with BBSOAS have?

As is common with many genetic conditions, children and adults with BBSOAS can have a range of symptoms. As more children are diagnosed, and information is shared, the range of symptoms and features, abilities and difficulties and the likelihood of a child or adult having these features will become more clear.

Common features

Most children with BBSOAS have:

- Developmental delay
- Some degree of intellectual disability (ID) or learning difficulties (LD) ranging from mild to profound
- Visual impairment including:
  Damage to the nerve that sends signals from the eye to the brain (optic nerve atrophy)
  Underdeveloped optic nerve (optic nerve hypoplasia)
  Damage to the parts of the brain that process vision (cortical visual impairment (CVI))
  Reduced or absent tear production (aacrima)
  Involuntary eye movement (manifest latent nystagmus)
- Repetitive behaviour
- Autism spectrum disorder (ASD)
- Speech and language delay or are non-verbal
- Swallowing problems (oromotor dysfunction)
- Low muscle tone (hypotonia)
- Seizures/epilepsy, including infantile spams and seizures caused by a fever (febrile)
- Attention deficit hyperactivity disorder (ADHD)
- Hearing impairment

Other possible features include:

- Mild and inconsistent facial features
- Thin bundle of nerve fibres (corpus callosum) that connect the two hemispheres of the brain

The clinical features of BBSOAS are variable, and not everyone with BBSOAS will have all of these features. Also, the severity of the condition varies from one individual to the next. Individuals with sequence changes in the DNA-binding domain (DBD) of the gene have somewhat more severe symptoms and features compared to those with whole-gene deletions. This is most likely because protein function has been altered as opposed to being lost.

Development

Gross and fine motor skills

Developmental delay has been reported in most children with BBSOAS so far. The degree of delay ranges from mild to profound. Developmental "milestones", including rolling, sitting, walking, playing with toys, using cutlery, using zips and buttons, and toilet training, are often delayed, although there is a wide range of eventual ability. Low muscle tone (hypotonia) is common and may affect mobility. Some children may have an unusual gait (ataxia) when walking or balance issues. For some, independent walking may not be achieved. Many benefit from early intervention with treatments or therapies such as orthotics e.g. insoles, braces, splints and callipers; occupational therapy (OT); and physiotherapy (PT).

Unique publishes separate guides to Therapies.

Intellectual development and learning

Most children with BBSOAS have intellectual disability (ID) or learning difficulties. ID ranges from mild to profound but is usually in the moderate range and most children have needed additional support with their learning. Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended.

Unique publishes separate guides to Education and Further Education, Training and Work.

Speech and language

Children with BBSOAS typically experience some degree of speech and language delay and some may find it difficult to co-ordinate movement of their lips, jaw and tongue to make the right sounds (apraxia of speech). The eventual range of achievement is broad, but some may remain non-verbal. Those who do develop speech may achieve single words, short phrases or basic sentences and some go on to develop conversational skills and a broad vocabulary.

An assessment by a speech therapist should be able to identify each child's specific difficulties, allowing regular therapy sessions tailored to each child's specific areas of need. Where individuals have no speech or very few words, Augmentative and Alternative Communication (AAC) methods, including pointing, pictograms, gestures, facial expression and simplified sign language and high-tech communication systems (aided communication) have enabled many to communicate their thoughts and needs well.

Unique publishes a separate guide to Communication.

Feeding

Feeding issues in the new-born period are common. Low muscle tone may contribute to difficulties with swallowing and some babies will suck weakly and may need high energy milks to encourage weight gain. Other issues that have been reported include aspiration (where fluid, food or saliva enters the airway or lungs). Some children have benefited from attending a feeding clinic where an assessment can be made, and advice to help treat any eating and drinking difficulties provided.

Unique publishes a separate guide to Feeding.

"From 3 months of age he would get repeated chest infections and would become really unwell, it wasn't until the age of 1 year old that tests were carried out and we found out he had an unsafe swallow. It was at this point he was then fed via an NG tube until he had PEG surgery at around 2 years of age then a year later, a mic key button. Over time his swallow has improved and he is able to have food and liquid orally, although not yet enough to fully sustain him without the button." Age 5½ years

Behaviour

Children with BBSOAS typically tend to have behaviour in keeping with their overall degree of developmental delay, and most have a happy disposition. Some children have an autism spectrum disorder (ASD) diagnosis or traits. Other behaviours including attention deficit hyperactivity disorder (ADHD) have also been reported. Some children also have sleep problems. Children usually benefit from consistent routines, boundaries, rewards and other behaviour management techniques. Efforts to take into account and introduce strategies to tackle communication and other difficulties can also be beneficial.

Unique publishes separate guides to Challenging Behaviour and Sleep.

Puberty

There is limited information available about puberty in children with BBSOAS. Some families of children with chromosome disorders and behavioural or learning difficulties can be particularly concerned at their daughter's ability to cope with menstruation, and for some discussing menstrual regulation options with a paediatrician may be beneficial.

Unique publishes a separate guide to Puberty.

Medical concerns

The following medical concerns have been found in children with BBSOAS. They are not found in all children so not all children with BBSOAS will be affected.

Brain anomalies

Most children have a structural brain anomaly, which can be detected by an MRI (magnetic resonance imaging) or a CT (computerised tomography) scan of their brain. The changes seen vary but include abnormalities of the visual system (damage to or malformation of the optic nerve (optic nerve atrophy); thinning of the part of the brain where the optic nerves cross (optic chiasm thinning)); changes in brain organization (nerve cells that do not migrate as expected during brain development (bilateral periventricular heterotopia); malformed ridges on the outer layer of the brain (abnormal gyration); thinning of the connection between the two halves of the brain (corpus callosum thinning); and reductions in white matter), (Bertacchi 2022).

Seizures

Frequently children with BBSOAS experience some form of seizure (a sudden and unexpected change in the electrical activity in the brain). Depending on the part(s) of the brain affected, symptoms vary, but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Age of onset can vary considerably, and seizures may only occur once or more regularly. More than one type of seizure may be present in the same individual. Electroencephalograph (EEG) and video telemetry (video EEG) are medical tests that can be used to measure and record the electrical activity of the brain and are tools that, when used alongside other tests, can help diagnose the type of seizure experienced.

When a child has a seizure for the first time, it is important to remove nearby hazards so they can't hurt themselves, and contact a medical professional.

Seizure types reported so far include:
Febrile seizure: Episodes only occur when the child or adult has a high temperature.
Absence seizure: A change in behaviour as if the child or adult 'switches off', sometimes with staring, eyelid flickering or lip smacking. Absences are very brief often lasting less than half a minute.
Atypical absence seizure: A child or adult may appear confused and unresponsive for minutes (very different from a typical absence seizure).

Infantile spasm: Type of seizure usually occurring in clusters in babies between 3-10 months. Seen most often when a baby wakes and may be obvious or subtle.
Generalised tonic clonic seizure: At the onset of a seizure, the abnormal electrical activity involves both sides of the brain. The seizure involves a phase of stiffening followed by jerking.
Myoclonic generalised seizure: Involving jerky or shock-like contraction of different muscles anywhere in the body but usually the arms or legs. Each myoclonic seizure lasts for a fraction of a second or a second at most.
Myotonic seizure: Seizure involving stiffening of the muscles.
Myoclonic-atonic Seizure involving jerky or shock-like contraction of muscles, followed by a loss of tone so someone standing up falls to the ground.

■ Eyes and eyesight

Eye anomalies and difficulties with vision are common in children with BBSOAS. A wide range of conditions have been reported and an individual may have more than one vision or eye-related concern.

Optic nerve atrophy: damage to the nerve that relays messages from the eyes to the brain
Pale/small optic disc: the place where nerve fibres exit the eye is small and pale
Cortical visual impairment: the parts of the brain that process vision do not function as expected
Amblyopia: when one eye is weaker than the other, which can occur for various reasons. If the stronger eye is favoured, the weaker eye can become a 'lazy eye'. Treatment involves glasses or wearing a patch over the stronger eye to encourage use of the weaker eye.
Strabismus: also known as a squint, when eyes do not align properly with each other.
Nystagmus: involuntary, rapid and uncontrollable eye movements.
Alacrima: reduced or absent tear production.
Myopia: short/near-sightedness.
Hypermetropia: long/far-sightedness.

■ Hearing

Some children have a hearing impairment, but hearing is unaffected in other children and hearing tests at birth may give a clear response. A hearing loss may be conductive, where sound is unable to travel effectively to the inner ear; sensorineural, where there are problems with the inner ear, sometimes with the cochlea or auditory nerve (the nerve that sends signals to the brain about sound); or a combination of both conductive and sensorineural.

Many types of hearing loss can be managed by using hearing aids. As children are at risk of speech delay, parental concerns should be acted on early and home- or school-based therapy provided.

Some children experience "glue ear", where fluid builds up behind the ear drum, which may be made worse by unusually narrow external ear canals and excess wax in the ear canal. Glue ear is a type of conductive hearing loss and is typically treated by inserting aeration tubes (grommets) into the eardrum. This surgical operation may need to be repeated. Improved hearing may not be achieved with aeration of the space behind the eardrum (middle ear) and hearing aids may help as a temporary or longer-lasting measure, although this appears to be uncommon.

Unique publishes a separate guide to Hearing.

How common is BBSOAS?

BBSOAS is extremely rare. Currently about 300 individuals with an *NR2F1* gene variant have been reported in the medical literature. It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

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 is not perfect, and random changes occur in the genetic code of all children, that are not seen in the DNA of their parents. This happens naturally and is not due to the parents' diet, environment or lifestyle. Most of these DNA changes have no obvious effect. But in rare instances these random DNA changes can lead to health issues or affect development. When such a random change disrupts the function of the *NR2F1* gene then a child will have BBSOAS. In most people identified so far with BBSOAS, the genetic change was a random (also known as "*de novo*") change, meaning the change occurred for the first time in that family in the affected individual. Very rarely, one parent may have a chromosomal rearrangement that led to BBSOAS in their child, or one parent may have the same change (or variant) in some of their egg or sperm cells and pass it on to their child (this is known as germline mosaicism). However, it is important to recognize that no one should be blamed for variants in their DNA and no parent is at fault when a new DNA change occurs in their child.

Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. In almost everyone reported with BBSOAS so far (2024) the genetic alteration has been found to be *de novo* (dn), which means neither parent was found to have the same *NR2F1* gene change as their child, and neither parent was found to have a chromosomal rearrangement that might have resulted in an *NR2F1* deletion in their child. Therefore, the chance of having another child with BBSOAS is usually less than 1%.

One reason why there is some residual chance of recurrence is due to the rare phenomenon called germline mosaicism that was mentioned above. This is when a parent carries a genetic change, but it is limited to some of their egg or sperm cells. The genetic change would not, therefore, be detected in the parents' blood tests.

Unique publishes a short general guide to mosaicism.

A clinical geneticist or genetic counsellor can provide specific advice for each family about the chance of having further children with BBSOAS.

Unique publishes separate guides to Planning Your Next Child, Prenatal Genetic Testing and Diagnosis, A Clinical Genetics Appointment and Supporting Siblings of Children with a Rare Genetic Condition.

Can BBSOAS be cured?

There is no cure for BBSOAS since the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and interventions can be put in place.

Management recommendations

Children with BBSOAS should be under the care of a multidisciplinary team. The team should include a geneticist and paediatrician who can oversee care so that development and behaviour can be monitored, and the best help given in the form of physiotherapy, occupational therapy, speech therapy and, if needed, vision therapy and behavioural therapy. Individuals may have evaluations with neurology, respiratory, ophthalmology, audiology, and gastroenterology specialists.

Is there any research into new treatments for BBSOAS?

The genetic change causing BBSOAS affects development of the brain and other parts of the body before birth. Therefore, a complete cure is unlikely, even in the future, since the brain has already formed by the time a diagnosis is made. However, research into improved treatments and management for various features of BBSOAS, like optic atrophy and cortical visual impairment (CVI), is ongoing. The NR2F1 Foundation, a charity with the mission to empower families and individuals living with rare *NR2F1* variants, is partnering with leading *NR2F1* scientists in the hope of identifying treatments in the future.

Families say ...

"When we received the diagnosis of BBSOAS for our daughter we felt absolutely lost and hopeless. Then we found the NR2F1 Foundation and realised we were not alone. They are doing great work to further the understanding of BBSOAS."

Sources

The information in this booklet is drawn from the published medical literature, information from the NR2F1 Foundation and Unique members. In 2024, Unique had 6 members with BBSOAS.

The first-named author and publication date for articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed (https://pubmed.ncbi.nlm.nih.gov/). You can obtain free access articles from Unique.

References

Published papers on NR2F1 can be found on the NR2F1 Foundation website.

Inform Network Support

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Join Unique for family links, information and support.
https://rarechromo.org/join-us/

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!

Websites, Facebook groups and other links:
www.nr2f1.org
BBSOAS Parents Only Facebook Group
NR2F1 Facebook Group

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 guide was compiled by Jennifer Coughlin, NR2F1 foundation President and Unique (AP) and reviewed by Dr Sarah Poliquin, PhD, COMBINEDBrain, Brentwood, TN, USA.

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