UNIQUE

UNDERSTANDING GENES & CHROMOSOMES

TRIO-related neurodevelopmental disorder

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with TRIO-related neurodevelopmental disorder. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this condition.

What is TRIO-related neurodevelopmental disorder?

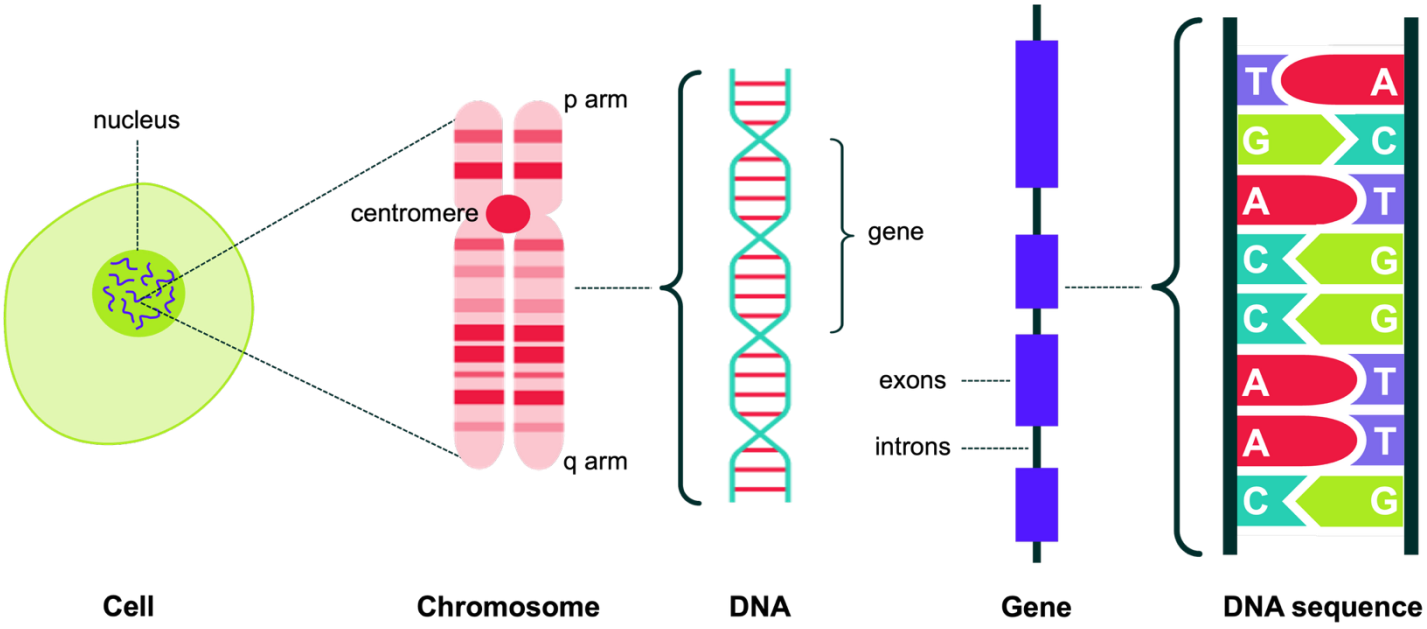
TRIO-related neurodevelopmental disorder, also referred to as TRIO-NDD, is a rare genetic condition associated with developmental delay, varying degrees of learning (intellectual) disability and distinctive physical features including a significantly smaller (microcephaly) or larger (macrocephaly) head than expected for their age and sex. As is usually common with genetic conditions, each person can be affected differently - even among affected members within the same family. Not everyone with TRIO-NDD will have all the possible features and each person with a certain feature won't necessarily be affected by it to the same level as other people with that feature.

TRIO-NDD is caused by certain changes (variants) in the TRIO gene or the loss (deletion) of part of the TRIO gene. The loss of the gene may occur as part of a larger deletion that affects the chromosome where the gene is located.

What causes TRIO-NDD?

Genes are instructions that have important roles in our 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. In people with genetic conditions, one or more of their genes don't instruct the body as we would expect, which can lead to changes in how their body works.

DNA is made up of building blocks called 'bases' or 'nucleotides'. There are four DNA bases which can be abbreviated to the letters A, C, G, and T. These DNA bases are paired up in the DNA structure into 'base-pairs'. The full sequence of our DNA is over three billion base-pairs long. There are changes in the DNA sequence (variants) present in everyone's genes. It is variants in our genes that make each one of us unique individuals.



TRIO-NDD is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called TRIO (TRIO is an abbreviation of the gene's full name, Trio Rho Guanine Nucleotide Exchange Factor). TRIO-NDD can also be caused by the partial loss of TRIO due to a chromosome deletion. The TRIO gene is located in the short 'p' arm of chromosome 5 in a region called 5p15.2 as shown in the image below.

We have two copies of chromosome 5 in our cells, so we also have two copies of the TRIO gene. TRIO-NDD occurs when only one copy of the TRIO 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 a separate guide to single gene disorders – autosomal dominant inheritance

Unique publishes a separate guide to deletions and microdeletions

The TRIO gene sequence is used to make the Triple function domain protein. This protein is important because it is involved in pathways that control cell production to support the growth of nerve cells for the development and maturation of the brain.

When the TRIO gene sequence is changed due to a variant, this could result in a gain of function (GoF) or a loss of function (LoF) of the TRIO protein. A gain of function variant in the TRIO gene means the resulting protein is too active, has a new role/function or is active at the wrong time/place. Individuals with a GoF variant tend to have more severe manifestations of TRIO-NDD. A loss of function variant in the TRIO gene results in a protein is not functional i.e. cannot do its job properly (or not made at all). Individuals with a LoF variant tend to have mild-moderate manifestations.

Genetic Tests

TRIO-NDD caused by gene sequence variants, can be identified by a type of genetic test called sequencing (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)). Gene deletions can also be identified by a sequencing test but are more commonly identified using a different type of genetic test, called a chromosome microarray (CMA, e.g. arrayCGH or SNParray).

Unique publishes separate guides to DNA sequencing

Genetic Test Results

The results of genetic (genomic) testing are likely to be given to you by your geneticist, a genetic counsellor or the clinician who ordered the test. Depending on the test that was carried out, someone with TRIO-NDD might have results that look like the following examples:

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 TRIO gene:

p.Arg1078Trp (R1078W) (CGG>TGG): c.3232 C>T in exon 19 of the TRIO gene (NM_007118.4)

p.Arg1078Trp (R1078W)	signifies the change to the protein: the amino acid arginine (Arg) has been replaced by the amino acid tryptophan (Trp) at position 1078 in the sequence of amino acids that make up the protein
CGG>TGG	signifies the gene sequence change; the C nucleotide has been replaced by a T nucleotide
c.3232	signifies the base pair position of the change within the gene sequence (the position where the C nucleotide has been replaced by the T nucleotide)
exon 19	signifies which part of the gene has been altered, in this case exon 19
TRIO gene	signifies the gene that is affected
NM	denotes the reference sequence used

The result of a chromosome microarray (CMA) test (e.g. arrayCGH or a SNParray), that can identify deletions and duplications, is shown here for a microdeletion within band 5p15.2:

arr[hg38] 5p15.2 (14,012,448-14,562,742)x1 dn

arr	The analysis was by array (arr) comparative genomic hybridisation (cgh)
hg38	Human Genome build 38. 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
5p15.2	the chromosome involved is chromosome 5 and the position of the deletion is in band p15.2
14,012,448-14,562,742	the base pairs between 14,012,448 and 14,562,742 have been shown to be deleted. Take the first long number from the second and you get 550,294 (0.550Mb or 550kb). 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 5p15.2. 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

What features and symptoms do people with TRIO-NDD have?

As is common with many genetic conditions, children and adults with TRIO-NDD can have a range of features and symptoms. As more people are diagnosed, and information is shared, the range of features, and the likelihood of a child or adult having these features, will become clearer.

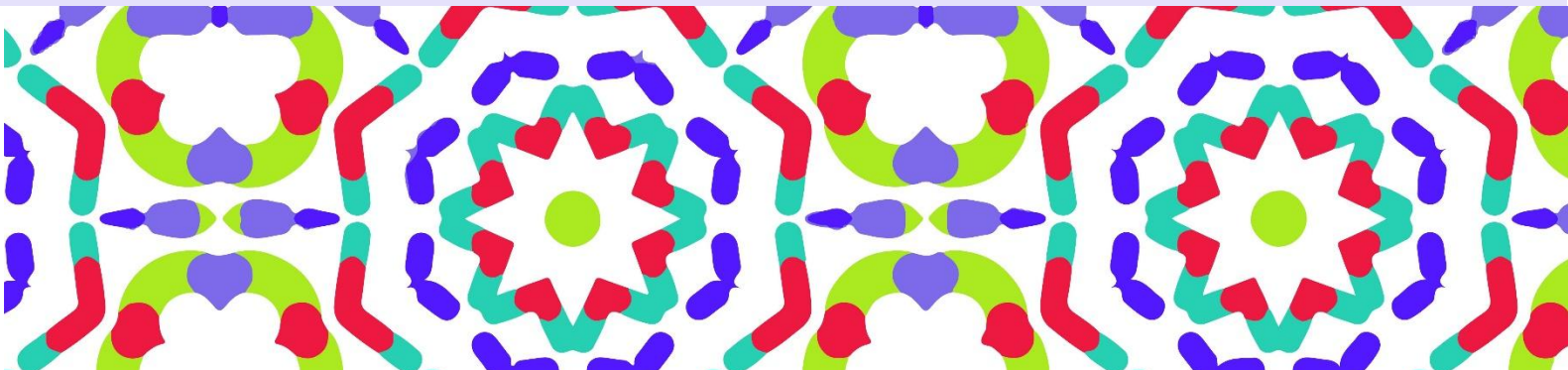
Common features

Most children with TRIO-NDD have:

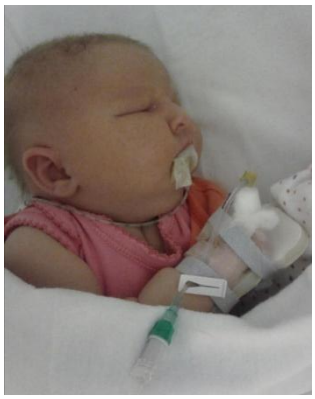
- Some degree of developmental delay, ranging from mild to severe in GoF and mild to moderate in LoF
- Some degree of intellectual disability (ID) or learning difficulties (LD), ranging from mild to moderate
- Speech and language delay/non-verbal
- Feeding difficulties
- Behavioural differences
- Large head size (macrocephaly) is usually observed in GoF
- Small head size (microcephaly) is usually observed in LoF
- Growth delay
- Short stature

Other possible features include:

- Gastro-oesophageal reflux (GERD/GORD)
- Constipation
- Skeletal anomaly e.g. scoliosis
- Seizures
- Heart conditions
- Brain anomalies and brain MRI anomalies
- Anomalies of the hands and feet
- Dental issues
- Eye conditions
- Recurrent infections
- Urinary incontinence
- Brisk reflexes
- Nipple anomalies
- Cleft lip
- Profound neonatal anaemia
- Specific areas of the skin being underdeveloped (cutis aplasia)



Pregnancy and birth



While most pregnancies are unremarkable and proceed without complication, occasional concerns during pregnancy have been reported, often following mid-pregnancy anomaly scans. Where a cause for concern was noted, most often parents reported slow growth in the womb (intrauterine growth retardation, IUGR) and anomalies of the kidneys (hydronephrosis).

The majority of pregnancies go to term, but a few babies are born prematurely. Some babies show some signs of difficulty at birth, related to difficulties with feeding and/or jaundice. Birth weights are usually average.

> ***"When our daughter was born weighing 9lb 13oz we were thrilled to have a second daughter in our family. But something wasn't right. She had difficulty feeding, which made her throw up her feeds, so she was put on a feeding tube. She also had difficulty breathing which the doctors thought was due to a narrow nostril and on top of all this she had an infection so was put on antibiotics through a drip.***
> ***She managed to have her first bottle a few days later and managed to feed slowly. So she was able to come home."***

Appearance

Certain facial features are found more often in children with TRIO-NDD than in other children. These features may mean that you see unexpected similarities between your child and others with TRIO-NDD. The most common characteristic features include up-slanting eyes; a long and narrow nose (tubular nose); a bulbous nose; facial asymmetry; large protruding ears; and a smaller than average lower jaw (micrognathia) and/or the lower jaw being set further back (retrognathia).

9 months 7 years 13 years

Development

Gross and fine motor skills

Developmental delay has been reported in all children with TRIO-NDD so far [2025]. The degree of delay ranges from mild to moderate in TRIO-NDD with loss of function and moderate to severe in TRIO-NDD with gain of function. 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, with some children acquiring mobility and other skills around the same age as "typical" children and others showing more obvious delay. Low muscle tone (hypotonia) is common and may affect mobility. Some children may have an unusual gait when walking because of stiffness, or balance issues (known as ataxia). 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).

"Before her diagnosis we noticed she had trouble gaining weight and not achieving her milestones, speech, her fine motor skills and other problems compared to her older sister and it made us worried. She never learnt to crawl before walking, only shuffled on the floor. She started to walk when she was 14 months old and was toilet trained by 3 years old."

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Intellectual development and learning

It is likely that all children with gain of function TRIO-NDD and most children with loss of function TRIO-NDD have intellectual disability (ID) or learning difficulties. ID ranges from mild to severe but is usually in the mild range for loss of function TRIO-NDD and in the severe range for gain of function TRIO-NDD. 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 TRIO-NDD typically experience some degree of speech and language delay and many 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. Many parents believe that their child can understand a lot more than they can express.

An assessment by a speech therapist should be able to identify your child's specific difficulties, allowing regular therapy sessions tailored to your 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 some to communicate their thoughts and needs well.

"[When she was two] we taught our daughter some Makaton as she couldn't communicate with us without hurting herself by head banging etc.. She started talking and putting words together when she was 5 years old."

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. Some babies also suffer from gastro-oesophageal reflux (GERD/GORD) (in which feeds return readily up the food passage), which may require treatment, including careful positioning for feeds, medication, nutritional supplements or, in some cases, insertion of a nasogastric tube (NGT) or percutaneous endoscopic gastrostomy tube (PEG/G-tube). 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.

> ***She had a false positive sweat test [for cystic fibrosis], which led to her having a dietitian who prescribed her high calorie milkshakes and a high calorie diet and physio. After a year of this she was at a normal weight."***

Unique publishes a separate guide to Feeding

Growth and stature

Many children with gain of function TRIO-NDD and some children with loss of function TRIO-NDD described in the medical literature so far [2025] are noted as having short stature and poor weight gain. Most of these children also have larger (associated with gain of function variants) or smaller (associated with loss of function variants) than expected head size (macrocephaly/microcephaly). Beyond infancy, height and weight is variable but tends to remain below average.

> ***At 5 years old she was 3ft 11inches and at 13 years old she is 5ft 4inches."***

Behaviour

Children with TRIO-NDD typically tend to have behaviour in keeping with their overall degree of developmental delay, and most have a happy disposition with parents describing their children as happy, free-spirited, joyful and caring. Many children have an autism spectrum disorder (ASD) diagnosis or traits. Other behaviours including attention deficit hyperactivity disorder (ADHD), stereotypies (repetitive, often rhythmic, movements, postures, or vocalisations that don't seem to have a clear purpose), self-harming, aggressive behaviours and obsessive compulsive disorder (OCD) have also been reported. Some also have sleep problems.

Management strategies should focus on addressing the root causes of challenging behaviours - such as providing sensory supports, using strategies to manage anxiety, and creating structured environments to help with attention - while nurturing the child's inherently friendly and sociable personality. Efforts to take into account and introduce strategies to tackle communication and other difficulties can also be beneficial.

Our daughter absolutely loves water. That's why the doctors thought she had Angelman syndrome. She is so caring and thoughtful and will always help someone who is in need. She always has a smile on her face and that smile spreads to everyone around her."

Unique publishes separate guides to Challenging Behaviour and Sleep

Puberty

There is limited information available about puberty in children with TRIO-NDD. We do know that most boys and girls appeared to go through puberty as expected. 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.

She started her periods when she was 12 years old. She has managed this very well as she has an older sister who went through it all before she did and she knew the ins and outs of having a period. Her school were also very supportive about this and explained things to her as well. She has heavy periods but isn't on any medication to stop her periods as she copes with it. The only thing we have noticed is her emotions and behaviours are heightened when she's on her period and she's more sensitive, so we have to be more mindful. She does tend to get more aggressive with her behaviours during this time. She uses period pants as they are an easier and a comfortable option as well as being familiar to her when she is on her period. Using any other methods of sanitary wear would cause sensory issues. She also needs extra help to look after herself during this time e.g. showering and self-care to make sure she's looking after herself, as well as pain management."

Unique publishes a separate guide to Puberty

Adulthood

"Working at a day service charity shop."

Experiences of adulthood are likely to vary considerably and will depend on many factors. These include the level of any LD/ID, possible on-going medical concerns and improvements in early intervention and therapies/treatments.

Adults with TRIO-NDD have varying levels of independence. A few have gone on to have families of their own and manage to run their own households and work. Most continue to live with their parents or in supported settings such as a group/residential care home, with caregivers who can provide support. A few may live independently but require some support from family or friends with certain tasks. Levels of employment and the nature of employment varies but some do undertake some form of paid or unpaid employment.

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Medical concerns

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

Brain

Most children with TRIO-NDD have a larger than expected head size (macrocephaly) or a smaller than expected head size (microcephaly) for age.

Some children also have a structural brain anomaly, which can be detected by MRI (magnetic resonance imaging) or a CT (computerised tomography) scan of their brain. The changes seen vary but include:

- Enlarged fluid-filled cavities in the brain (dilated ventricles/ventriculomegaly)
- A build-up of fluid within the brain (hydrocephalus)
- Underdevelopment (hypoplasia) or partial/complete absence (agenesis) of the white matter connecting the two halves of the brain (corpus callosum and anterior commissure)
- Delayed myelin maturation
- Chiari I malformation (where the lower part of the brain pushes down into the spinal canal)
- Enlarged occipital horns (colpocephaly)
- A rare viral disease that damages white matter (progressive leukoencephalopathy)
- Absence of grooves and folds (lissencephaly)
- Cysts in between the hemispheres of the brain (interhemispheric cysts)

Some children may also exhibit other neurological symptoms such as tremors, sustained or repetitive muscle contractions (dystonia) and/or damage of the myelin sheath of neurons (demyelinating peripheral neuropathy).

Seizures

Some children with TRIO-NDD 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, while seizures may be isolated to a single incident or occur 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.

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 medical treatment. A group of medicines called benzodiazepines are reported as the best medication for seizure control. If your 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 in individuals with SLC6A1-related NDD include:

Febrile seizure Episodes only occur when the child has a high temperature.

Absence seizure A change in behaviour as if the child 'switches off', sometimes with staring, eyelid flickering or lip smacking. Absences are very brief often lasting less than half a minute.

Atypical absence seizure The child may appear confused and unresponsive for minutes (very different from a typical absence seizure).

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.

Nocturnal Episodes occur when the child is sleeping.

Refractory seizures These occur when medicines have little or no impact on controlling the episodes.

Constipation

Constipation is common among children with TRIO-NDD and can be related to low muscle tone, little exercise, a low-bulk diet and small fluid intake, among other reasons that are not fully understood. It is important that possible causes are discussed with a health visitor or doctor, who may recommend adapting diet or giving stool softeners or laxatives. Some children have benefitted from enemas when symptoms were particularly severe.

Gastrointestinal

As well as constipation, some families have reported other gastrointestinal issues in their children. Known concerns include episodes of vomiting which some children may experience. A few children may also experience the intestines not rotating properly which requires surgery (intestinal malrotation) and/or an overabundance of white blood cells in the oesophagus (eosinophilic oesophagitis).

Hands and feet

Children with TRIO-NDD occasionally have anomalies of the hands and feet. Most common among these are fingers or toes that curve inwards (clinodactyly); unusually short fingers and toes (brachydactyly); fused fingers and toes (syndactyly); and broad or wide middle knuckles of the fingers (proximal interphalangeal joints). A less common observation seen in children is a closer positioning of the thumb to the palm and wrist (proximally placed thumb). Some children are only mildly affected, and any condition will not require treatment. Others may benefit from massage, orthotics and physiotherapy. Treatment is tailored to the individual child, and in some cases surgical correction will best enhance eventual mobility.

Spine

Some babies are born with or develop a spinal curvature, either a sideways curve of the spine (scoliosis), a rounding of the upper back (kyphosis) or kyphoscoliosis (a combination of kyphosis and scoliosis). The curvature can be treated with physiotherapy and exercises, or a support brace or surgery may be needed. A sacral dimple (dimple or hole in the skin just above the crease between the buttocks) is also sometimes seen. The dimple may be shallow so you can see the base, but stools can collect there before your child is toilet-trained, so keeping it clean and protected is important. A sacral dimple may be deep and even connect to the spinal canal or the colon. If there is any concern about this, your baby's spine will be imaged, usually with ultrasound or an MRI scan.

Other musculoskeletal conditions

A few children may also experience other musculoskeletal concerns such as a funnel chest or sunken chest (pectus excavatum), which may affect the heart and lungs over time.

Teeth

Dental concerns are very common in children with chromosome disorders. A number of issues have been described by parents including unusual dental development like larger or smaller than average teeth (macrodontia/microdontia); an unusual size of the jaw, leading to overcrowding or widely-spaced teeth; feeding

difficulties and delayed eating and chewing activity; missing teeth also known as hypodontia/oligodontia (this condition is certainly not specific to TRIO-NDD and is seen in many others); eruption of teeth earlier or later than expected; and issues with the enamel of the teeth. A high standard of dental care is important to minimise damage by decay and erosion (by grinding). Children and adults may also benefit from specialist hospital dental services and may require treatment under general anaesthetic.

Unique publishes separate guides to Looking after your child's teeth and Teeth: common concerns

Eyes and sight

Problems with eyes and vision are uncommon in children with TRIO-NDD. A wide range of conditions have been reported in individuals with loss of function variants, and an individual may have more than one vision or eye-related concern. Known concerns include damage to the optic nerve (optic atrophy), which can lead to permanent blindness; a squint (strabismus) where one eye or both turns inward, outward, up or down, which may be treated with patching, glasses, exercises or surgical correction; blocked tear ducts (nasolacrimal duct obstruction); and problems affecting the central part of the retina in both eyes (bilateral macular pathway dysfunction).

Heart

A heart condition(s) has been found in a few people reported so far with TRIO-NDD, which can be present at birth (congenital) or develop later in life. In children for whom heart problems are suspected, these can be diagnosed using tests like an electrocardiogram (ECG) (recording the electrical activity of the heart), echocardiogram (ultrasound scan of the heart), or chest X-ray. The type of heart condition(s) is variable but includes anomalies affecting the size and structure of the heart muscle and valves. These include:

- Changes in the heart valves such as the aortic valve having two flaps instead of three (bicuspid aortic valve); the aortic valve failing to close causing blood to flow in the reverse direction in the heart (aortic regurgitation); and an enlarged aortic root.
- Changes in the heart muscle such as a hole between the upper chambers (atria) and lower chambers (ventricles) of the heart (atrioventricular septal defect); a hole between the top two chambers only (atrial septal defect); failure of closure of the tube that carries blood between the aorta and the pulmonary artery during the foetal period (persistent ductus arteriosus); an incomplete aorta (type A interrupted aortic arch); and Tetralogy of Fallot.
- Some children have also been reported to have an irregular heart rhythm known as arrhythmia.

Some of these conditions are relatively minor and resolve naturally in time. Medical treatment may be necessary for others, and some may require surgery.

Kidney and urinary tract

A few babies are born with minor anomalies of the kidneys and/or urinary tract. Urinary tract infections (UTIs) are relatively common and may need to be treated with antibiotics. Repeated urinary infections may require preventive treatment with antibiotics.
Reported anomalies include loss of bladder control from brain, spinal cord or nerve dysfunction (neurogenic bladder), incontinence (enuresis) and recurrent UTIs.

Mouth

Anomalies of the roof of the mouth (palate) and lips, ranging from those that may be invisible to the casual onlooker such as a high/arched palate to more obvious conditions such as a cleft palate or lip, have been reported. Anomalies of the palate, particularly clefting, can cause difficulties in feeding, hearing, teething and speech production. As well as helping aesthetically, surgical repair eases these problems and may even eliminate them altogether.

Skin

It is rare for children with TRIO-NDD to have a skin condition(s). Some skin conditions have been reported in children such as cutis aplasia, where specific areas of the skin are underdeveloped; inverted and/or additional nipples (supernumerary nipples); and multiple darker moles that have a higher concentration of melanin (hyperpigmented nevi).

Breathing

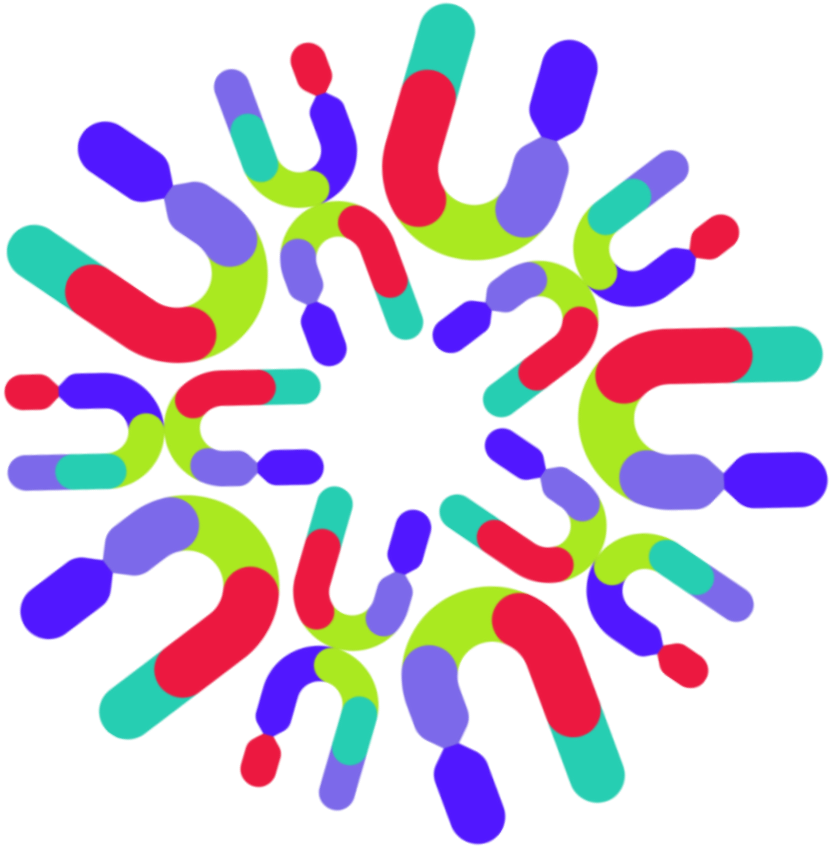
Babies and children with rare chromosome and gene disorders tend to have a higher rate of respiratory concerns, which may become less frequent with age and maturity, although they can persist throughout childhood. A few children with TRIO-NDD may be prone to frequent airway infections.

Circulation

In very few cases of TRIO-NDD, newborns have been reported to have very low red blood cell counts (profound neonatal anaemia) which can occur from blood loss, decreased red blood cell production or increased destruction of red blood cells. Intervention may be required such as blood transfusions.

Fatigue

A few families have reported fatigue in their children, which may require management through several strategies.



How common is TRIO-NDD?

TRIO-NDD is extremely rare. Currently [2025] about 450 individuals with a TRIO gene variant have been reported in the medical literature, but more are known to have been diagnosed. 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 TRIO gene then a child will have TRIO-NDD. In almost all people identified so far [2025] with TRIO-NDD, the genetic change was a random (or "*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 TRIO-NDD 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).

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 currently reported with TRIO-NDD (2025) the genetic alteration has been found to be *de novo* (dn), which means neither parent was found to have the same TRIO gene change as their child, and neither parent was found to have a chromosomal rearrangement that might have resulted in a TRIO deletion in their child. Therefore, the chance of having another child with TRIO-NDD 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. Recurrence due to germline mosaicism has not been reported in TRIO-NDD to date.

Unique publishes a short general guide to Mosaicism

In families where the TRIO variant has been inherited from a parent, the possibility of having another child - either a girl or a boy - with TRIO-NDD rises to 50% (I in 2) in each pregnancy. However, the effect on the child's development, health and behaviour cannot be reliably predicted. Your local genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a TRIO variant goes on to have children of their own, the chances of passing on the variant to their child are 50% in each pregnancy. Your child's ability to look after their own child is very likely to be closely related to their own learning ability and behaviour.

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

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 TRIO-NDD be cured?

There is no cure for TRIO-NDD 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

No clinical practice guidelines for TRIO-NDD have been published [2025]. The following suggestions have been provided by clinicians, who have personal experience of managing/treating individuals with TRIO-NDD, to improve quality of life and reduce complications.

Children and adults with TRIO-NDD should be under the care of a multidisciplinary team. The team should include a geneticist and paediatrician (for children) 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, behavioural therapy. Individuals may have evaluations with paediatricians, neurologists, cardiologists, ophthalmologists, gastroenterologists, urologists, orthopaedic surgeons , dentists, orthodontist, immunologists and nephroloists

Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of TRIO-NDD that are present in the child or adult who has been diagnosed with this genetic condition should be carried out. This can determine which of the features of TRIO-NDD are present and how severe they are.

Supportive care

Children with TRIO-NDD are likely to be under the care of a multidisciplinary team. The team should include a community or hospital paediatrician who can oversee care; monitor growth, development and behaviour; and link in with affiliated services.

How a person with TRIO-NDD is supported is likely to require co-ordinated care by a team of specialists, which may include:

Neurologist – a doctor who specialises in conditions of the brain, spinal cord and nervous system.

Cardiologist – a doctor who specialises in heart conditions.

Urologist – a doctor who specialises in diagnosing and treating conditions affecting the urinary system.

Nephrologist – a doctor who specialises in conditions affecting the kidneys.

Surgeon – doctor who is specially trained to perform medical operations.

Occupational therapist (OT) – a health care professional who uses activities to aid self-management of a condition and can provide equipment.

Physiotherapist (PT) – a health care professional who uses exercise, movement, manual therapy, education and advice to help with the body's strength and mobility.

Speech and language therapist (SALT) – a health care professional who helps with speech, language communication and sometimes feeding/swallowing difficulties.

Psychiatrist – a doctor who specialises in mental health.

Specialist nurses and/or other healthcare professionals may need to systematically and comprehensively plan a child or adult's treatment.

Treatments and therapies

Early intervention can be beneficial and formal testing to assess specific, individual needs is recommended. An education, health and care plan (EHCP) in the UK, individualized education plan (IEP) in the US, or equivalent document in other countries, may be issued after a child has undergone an assessment, to help ensure that the educational, health and social provisions deemed necessary to support the child's needs are delivered.

Treatment will depend on the specific features and symptoms experienced by the person with TRIO-NDD but may include:

Physiotherapy for gross motor dysfunction, which usually includes the use of movement and exercise, manual therapies, education and advice to improve stability and postural control as well as provide advice for pain management.

Occupational therapy for fine motor dysfunction, which can include feeding therapy as well as using equipment for co-ordination and sensory exercises to improve fine motor skills, co-ordination and difficulties with feeding.

Speech therapy for communication and speech issues, which can include augmentative and alternative communication (AAC) methods ranging from low tech, such as picture exchange communication, to high tech, such as the use of an iPad or speech generating devices, to support optimal speech and language development.

Behavioural therapy for social and behavioural concerns, which can include applied behavioural analysis (ABA) and consultations with developmental paediatricians and paediatric psychiatrists, to address a child's strengths and weaknesses, as well as provide advice on management strategies and medication.

Medications may be prescribed, such as anti-seizure medicines (anticonvulsants) to treat and prevent seizures, and medication for ADHD, when necessary.

Diet, such as a high-fibre diet or stool softeners and/or laxatives may be recommended to help relieve constipation. Some benefit from enemas when symptoms are particularly severe.

Surgery, such as Ladd's procedure to treat intestinal malrotation or scoliosis surgery to correct spine curvature (scoliosis).

Surveillance

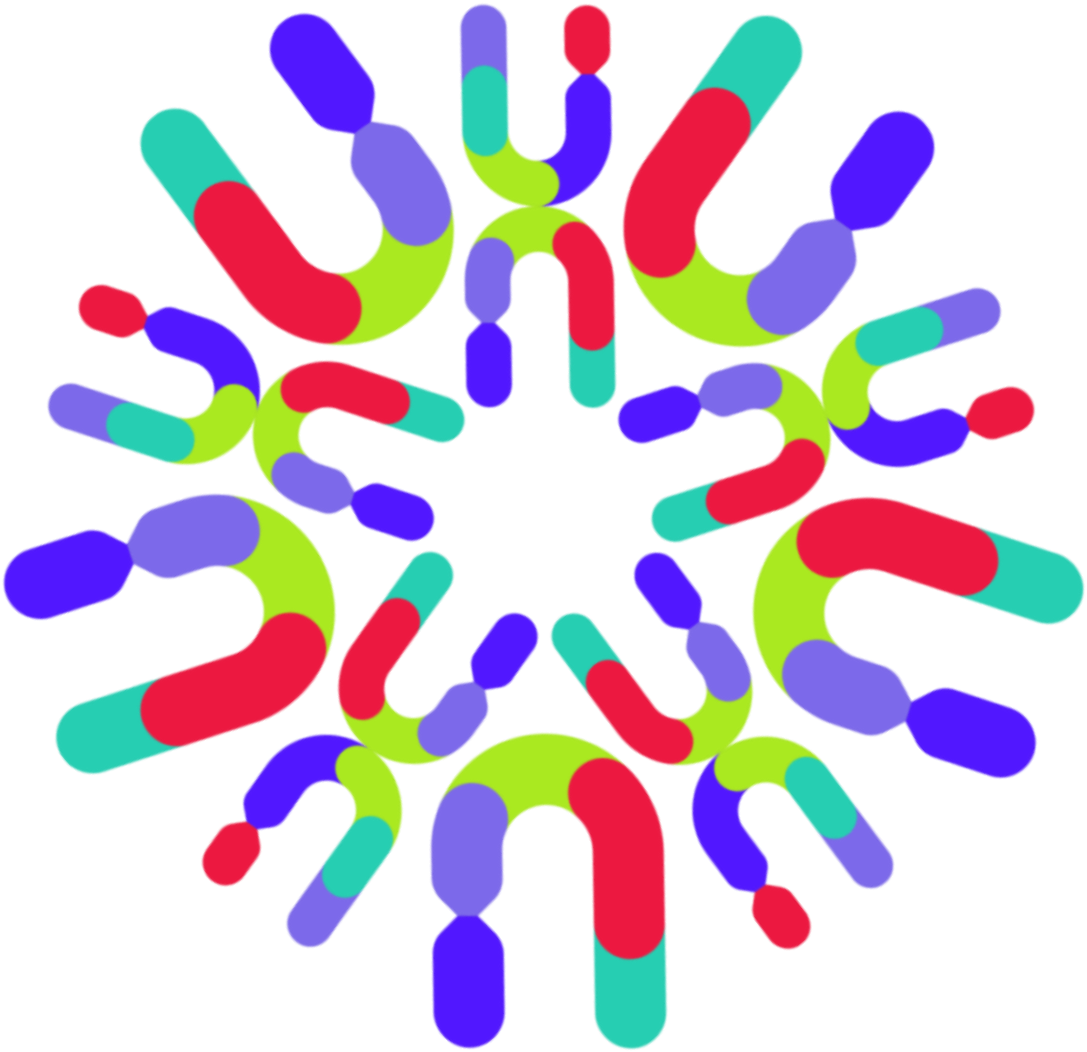
It is recommended that the following evaluations are carried out/considered to monitor an individual's existing symptoms, how they respond to care and treatment and whether any new symptoms emerge over time:

- Regular dental check-ups
- Monitor developmental progress and educational needs
- Behavioural assessment for attention, aggression and/or social communication difficulties
- Consider a palate review (particularly if there are feeding difficulties or speech concerns)
- Assess for GERD and constipation
- Assess for frequent infections
- Consider an annual cardiac review
- Consider a neurologic review (including MRI and EEG, if indicated by seizures)
- Consider a skeletal review
- Consider an abdominal ultrasound and review
- Consider family need for social work support, care co-ordination and genetic counselling for further questions

Research into new treatments for TRIO-NDDs

Research into improved treatments and management for various features of TRIO-NDD, like ASD and seizures, is ongoing. In addition, although TRIO-NDD is a relatively rare condition, the TRIO gene is the subject of a lot of research. One avenue of research is using mouse models to analyse how a protein called Rac1 is affected from alterations in the TRIO gene. Research has shown that these changes in TRIO affect the brain through this Rac1 protein and are now exploring whether normalising this activity will have an effect and lead to future treatments.

Details of clinical trials related to a particular condition or gene can be found at **ClinicalTrials.gov** and **EU Clinical Trials Register**.



Families say …

"My daughter is 30 years old, chatty, joyful, kind and friendly, loves to sing, jigsaw puzzles, colouring books and all things Disney. She still learns and makes progress and enjoys a fulfilled life.

It's not about what your child can't do, it's what they can do. Learn to recognise and appreciate the small achievements that are made."

"My daughter is nearly 18 and has achieved things I didn't think was possible. She is improving her communication skills each day and able to confidently express her diagnosis and how it impacts her. She has epilepsy, microcephaly, autism, learning disability, scoliosis (needing surgery), and ADHD. She has required ENT surgery, had dental issues and has mental health struggles.

She has a passion for music and spins in a circle without getting dizzy. Nothing is impossible. She loves socialising, music, animals and trampolining."

"During the first six years of her life, our daughter was tested for many different things, and she was misdiagnosed with having cystic fibrosis and Angelman syndrome. But we still didn't have any answers for her behaviour and development. It wasn't till we were invited to take part in the 100,000 Genomes Project in the UK and after two years we got the diagnosis of TRIO.

Our genetic doctor at the time knew nothing of TRIO so couldn't give us any information, only a link to a research paper that was full of medical words and phrases that we didn't understand. Then that was it we were on our own! I'm so glad there is now a guide for newly diagnosed TRIO- NDD families to help and guide them in their journey.

Our daughter is truly amazing with everything she has been through. She's now 13 and thriving at a special school. In the future she wants to work at a hospital to help people when she's older."

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2025, Unique had 16 members with TRIO-NDD. 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 (**pubmed.ncbi.nlm.nih.gov/**).

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*Pengelly R.J (2016). Mutations specific to the Rac-GEF domain of TRIO cause intellectual disability and microcephaly. Journal of Medical Genetics 53(11): 735-742. **Link to article**

Note: an asterisk indicates articles which are “open access” and available to everyone at **pubmed.ncbi.nlm.nih.gov**

Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey, RH8, 9EE, UK
Tel: +44(0)1883 723356
help@rarechromo.org I rarechromo.org

Join Unique for family links, information and support:

Become a member

Please help us to help you!

Unique is a charity without government funding, existing entirely on donations and grants.
If you can, please make a donation:

Donate via our website

Facebook groups and other links:

- Simons Searchlight
- Simons Searchlight Facebook group
- Team TRIO
- Team TRIO Facebook page
- Team TRIO 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.

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