Understanding Chromosome & Gene Disorders

TRAF7-related neurodevelopmental disorder

rarechromo.org

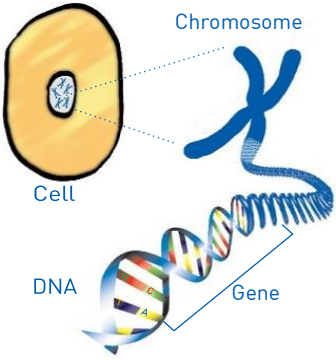
What is *TRAF7*-related neurodevelopmental disorder?

TRAF7-related disorder is a rare genetic condition that is caused by a change in function of a gene called *TRAF7*.

What are genes, DNA and chromosomes?

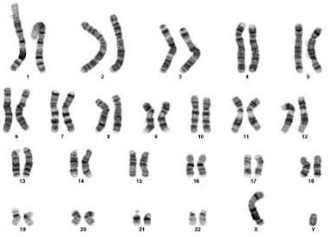
Genes are the 'instructions' that our bodies use for many functions including the control of growth and development. The majority of important genes, like *TRAF7*, code for proteins. Genes can be described as carrying instructions for our cells and proteins carry out specific tasks.

Genes are made from a complex structure called DNA. DNA, and therefore genes, can be described as a sequence of letters but unlike an alphabet, the sequence (or code) only uses 4 letters (G, A, T, C).



DNA sequences are incredibly long and include all the information for the thousands of genes included in our 'genome' (our complete set of DNA). However, they need to fit inside the microscopic cells that our bodies are made from. DNA is therefore tightly compacted into organized structures called chromosomes.

Most of our cells normally contain 46 chromosomes, organised as 23 pairs. We usually inherit one chromosome of each pair from our mother and the other from our father.



Chromosomes pairs 1-22, X and Y (male)

Chromosome pairs are numbered 1 to 22 and the 23rd pair comprises the sex chromosomes, which determine biological sex (whether we are male or female). Females usually have two X chromosomes (XX) and males usually have an X and a Y chromosome (XY).

Since chromosomes come in pairs, so do the genes contained within them. *TRAF7* is located on chromosome 16.

What does *TRAF7* do?

TRAF7 makes a protein called Tumor Necrosis Factor Receptor-Associated Factor 7, which is involved in a diverse range of biological processes that are important for the development of many different parts of our bodies.

Although this has a scary name, this gene is only associated with tumour development in other circumstances i.e. increased cancer risk is not currently known to be associated with this genetic condition.

All individuals with *TRAF7*-related disorder reported to date have just a single letter change in the genetic code of *TRAF7*. This is known as a 'missense' variant. This is one of the smallest types of genetic alteration possible and results in one amino acid (the building block of a protein) being changed. In some circumstances this has no effect on the protein but sometimes, as in the case of *TRAF7*-related disorder, the function of the protein is altered or lost. As a result, development of the brain, heart and other structures in the body can be impacted.

Why did this happen and can it happen again?

The majority of individuals with an alteration in one copy of the *TRAF7* gene reported so far have not inherited it; rather, it has occurred as a new event in them (this is called a *de novo* (dn) gene alteration). *De novo* gene alterations are random events so cannot be predicted. We all have a number of random *de novo* genetic changes, this is something that happens naturally in all of us, it's only when an important gene is affected that health and development can be affected.

So far (2022), there have only been two reports of *TRAF7*-related disorder being inherited, one where the affected mother only had the genetic change in a small proportion of her cells resulting in milder symptoms (this is called somatic mosaicism).

There is also a very small theoretical risk of a phenomenon called germline mosaicism (also known as gonadal mosaicism), where the egg or sperm of an individual carries a *TRAF7* gene alteration but the other cells of the body do not (so it would not be detected in a blood sample). It is currently not possible to test eggs or sperm for gene alterations, so there remains a small possibility that the *TRAF7*–related disorder can recur in another pregnancy, even when the parents are unaffected and have normal results for their genetic analysis.

It is for these reasons, parental testing and genetic counselling are recommended for families wanting to have further children. It is important to emphasize that when a child is born with a genetic condition, it is nobody's fault. There is nothing either parent did before, during or after pregnancy that could have caused this genetic change. If you have any concerns about having further children, or would like more information, please read our 'Planning your next child' guide and discuss with your genetics team.

How common is *TRAF7*-related disorder?

Missense variants in the *TRAF7* gene (see page 3 for an explanation) causing a neurodevelopmental disorder was first described in seven children in 2018 and since then, about 50 children/people have been described in the medical literature worldwide.

Genetic testing was once a complicated, costly and time consuming process. Recently, there have been major advances in technology and cost efficiency, that have enabled a more prolific use of genetic testing, so it is likely that increasingly more people will be diagnosed with gene alterations in *TRAF7*.

What features and symptoms do people with *TRAF7*-related disorder have?

As with many genetic conditions, children with *TRAF7*-related disorder can have a range of symptoms. As more children are diagnosed, and information is shared, the range of difficulties and the likelihood of a child having these features will become more clear.

Common features:

- Heart anomalies
- Recognizable facial features
- Developmental delay and learning difficulties
- Hearing loss
- Protruding chest bone (pectus carinatum)
- Different appearances of hands and feet

Other possible features:

- Seizures
- Low muscle tone (hypotonia)
- Structural brain anomalies on a brain scan
- Spinal changes
- Neuroatypical behavior (autistic spectrum disorder)
- Feeding difficulties
- Vision abnormalities
- Cleft palate
- Short stature
- Structural kidney problems

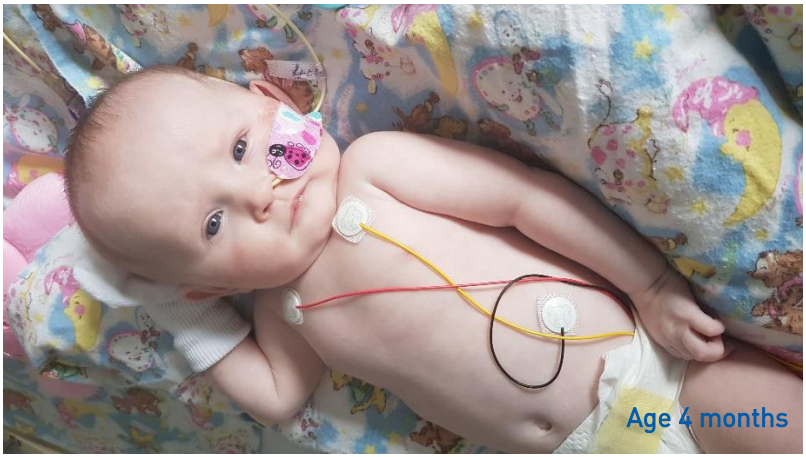
Pregnancy and Birth

Sometimes some unusual features are picked up during antenatal pregnancy scans of babies with *TRAF7*-related disorder. For example, increased thickness at the back of the neck (nuchal translucency) or heart abnormalities, but often nothing is suspected until after birth.


Age 3 weeks

Heart Anomalies

Heart anomalies are frequent in children with *TRAF7*-related disorder. Most have a condition where the opening between the two major blood vessels leading from the heart (a normal part of circulation for the fetus in the womb) fails to close after birth. This is called a patent ductus arteriosis or PDA for short. The opening can close with the help of medication, but sometimes surgical closure is required. Other children may have an opening between the left and right side of the heart or valve problems. Again, these may require surgery. Children may also have a combination of the above.


Age 4 months

“ She was born at 37 weeks, normal delivery although we were aware of her heart defect (Large VSD 11mm) which would need surgery within 6 months. When she was born she looked like any other normal child except after a few weeks she was constantly losing weight, not tolerating her feeds and just totally exhausted when trying to take a bottle. Little did we know she was in chronic heart failure. She was admitted to hospital at 4 weeks and was started tube fed along with heart medicines. ”

Development

Most children with *TRAF7*-related disorder have been described as having some degree of developmental delay. This means that they are delayed in reaching milestones like sitting and walking and may have a learning disability. All children with *TRAF7*-related disorder develop differently and the severity of developmental delay varies. Some children are able to sit and stand shortly after the standard milestone range but most take longer.

Often children with *TRAF7*-related disorder have hypotonia, which is low muscle tone causing a child to appear 'floppy' and this can have a significant effect on reaching certain milestones. Children may benefit from physiotherapy (also known as physical therapy) and occupational therapy to help them achieve their full potential. Once children have shown their individual pattern of development it will become easier to predict their longer term possibilities.

Motor skills and self-care

The number children known to have this condition is small so the current information may not be representative of everyone with *TRAF7*-related disorder. In the limited information we have, most children with *TRAF7*-related disorder have mild to moderately delayed motor milestones. So far, most children with this condition have walked independently by 2 years.


Age 3.5 years

Intellectual abilities and schooling

Many children with *TRAF7*-related disorder will have some degree of learning difficulty. This ranges from mild to more severe. Individuals are likely to need additional help at school or may require special needs schooling.

Speech, language and communication

Speech and language skills can be very variable between children with *TRAF7*-related disorder, however most have only mild to moderate delay.

Speech and language therapists can help by assessing communication skills. They can help with speech development and introduce communication devices if needed. They can also help to ensure that whatever a child's ability, they are supported in achieving their full communication potential.

Behaviour

Although behavioural difficulties have not been fully described for all children reported in the medical literature, behavioural, social and communication difficulties are occasionally seen in children with *TRAF7*-related disorder. Vulnerability in these areas means that children should be monitored and families offered early support. Autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) has been diagnosed in some children with *TRAF7*-related disorder.

"She has global development delay and is awaiting assessment for ASD."
Age 3.5 years

From birth to at least 3 years of age, most children are routinely screened for developmental milestones. If there are any concerns about a child's development or behaviour they should be referred for developmental evaluation, which may include an autism assessment.

Depending on a child's abilities, joining a social skills group may help with social difficulties, to learn and practice important skills. A parenting course for autism may also help parents to learn behaviour management tools and help to encourage communication and cooperative behaviour in their child to strengthen their emotional wellbeing. Some parents have tried medication to help control their child's behaviour.

Appearance

There is quite a strikingly similar facial appearance in children with *TRAF7*-related disorder. Almost all children present with small eye openings (blepharophimosis) along with a skin fold of the upper eyelid covering the inner corner of the eye (epicanthic folds) and up or down slanting eyes. Most children have low set ears, that are prominent and rotated backwards slightly. Some children may also have an unusual skull shape. Making a note of these facial features may help establish common features observed in children with the same genetic change and therefore aid diagnosis.


Age 4 months

Feeding and Growth

Many children with *TRAF7*-related disorder have feeding difficulties. These vary from mild to more significant. Babies with this condition often require tube feeding for a short period during infancy though many will improve. Several children with this diagnosis have been reported to have problems with palate

development which may exacerbate feeding issues further. If poor feeding persists, it may be appropriate to ask your clinician for a referral to a cleft team for assessment of a possible subtle cleft which may not have been overtly apparent during newborn screening.

“ Our child has what is called velopharyngeal insufficiency (VPI) which is linked to his poor feeding as a baby and delayed speech as a child. This has required surgical intervention of his soft palate. ” Age 6 years

About half of children reported with *TRAF7*-related disorder so far (2022) were noted to have short stature. Many children also have either a small or large head size.

“ She spent 7 months in hospital, her weight gain was the main struggle and the surgeons had to take her to theatre before she got any worse and could have ended up being extremely unwell. Being in hospital for that length of time especially with your first born child can cause a lot of stress and anxiety. ” Age 3.5 years

“ She had her heart repaired, she was still being constantly sick, tube fed and had a drainage bag in as she was NJ* fed. Her list of conditions continued to grow to include gastro-intestinal dysmotility. She is now fully peg fed** and takes nothing by mouth, she also has had a fundoplication*** to stop her from the extreme vomiting that she was going through although she still would retch and try to be sick. ” Age 3.5 years

* NJ = nasal jejunum. This is a type of feeding tube, that like other feeding tubes, enters the nose and runs down the esophagus. While some tubes enter the stomach (NG) and others enter the first part of the small intestine (ND = nasal duodenum) an NJ tube enters further down the intestine into another section known as the jejunum.
** PEG (percutaneous endoscopic gastrostomy) feeding is where a narrow tube is passed through the skin directly into the stomach to enable liquid, food and medicine to be provided without the need for the child to chew or swallow.
*** A fundoplication or nissen fundoplication is when a section of the stomach is surgically folded around the stomach entrance to help prevent stomach content from entering the esophagus.


Age 4 months

Seizures and the brain

A small proportion of children with TRAF-7 related disorder have experienced some form of seizure (sudden and unexpected electrical activity in the brain). These can be of different types, from absence seizures (when the child appears

vacant and unresponsive for a short period of time) to 'generalised tonic clonic seizures' which means that the whole body is involved and, when seizing, alternate stiffening and shaking of the body is seen (dropping to the ground and jerking). More than one type of seizure may be present in the same individual.


Age 3 years

If a child does have seizures, so far (2022) they have been reported to generally start during infancy, although one child has been reported to have started to experience seizures at age 10.

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. If your child has a seizure for the first time it's important to remove nearby hazards so they can't hurt themselves. Absence seizures can be difficult to identify, if you think your child might be experiencing absence seizure, but are unsure, it might help to record an episode of unusual behaviour to show to your child's doctor.

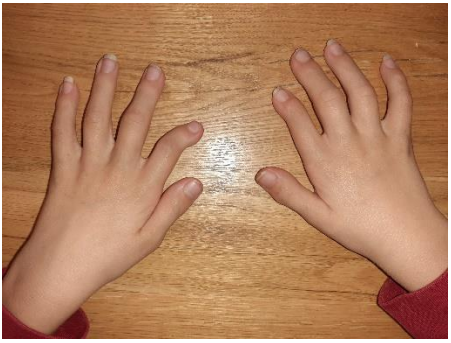
"Her staring episodes are being investigated as possible absence seizures." Age 3.5 years

Children who experience seizures may have investigations to check the activity of their brain and to rule out any revisable causes. This may include an 'EEG' (electroencephalogram). This is done by attaching stickers to the scalp, that are connected by wires, to the machine used for analysis.

Some children have been offered an MRI (magnetic resonance imaging) scan of their brain, to look for structural changes. Different types of structural anomalies have been found including a wide range of non-specific changes (the most common of which is enlarged ventricles or fluid filled spaces).

Skeletal features

Most children with *TRAF7*-related disorder described so far (2022) have different appearances of their hands or feet. Sometimes fingers are deviated, curved, short or fused. Feet can be flat with overlapping toes or have a sandal gap (large gap between toes). Some children have been found to have joint hypermobility and dislocation. Many children have a short neck and some have an unusual chest shape.



Spinal changes have also been noted so a clinician should assess for this too. These includes: exaggerated curvature of the spine (lordosis/kypohosis), the bones of the spine (vertebrae) slipping slightly out of alignment (spondylolisthesis) and structural anomalies (e.g. hemivertebrae, small vertebrae).

Eyes and vision

Some children with *TRAF7*-related disorders have a squint (strabismus - when eyes do not look in the same direction) which can be managed by an eye doctor (ophthalmologist). It is important to identify a squint since it is correctable and can cause damaged vision if not corrected. Some children have also been found to have short or long sightedness. If you are concerned about your child's vision, please inform your clinician.


Age 3 years

Ears and Hearing

About half of children with *TRAF7*-related disorder described so far (2022) have been found to have some form of hearing loss. Both conductive (when sound waves through the outer and middle ear are blocked or reduced) and sensorineural (when the inner ear or the nerves that relay information from the ear to the brain are affected) hearing loss have been reported. All children should therefore be referred for an audiology assessment.

Adults

We do not currently have much information regarding adults with *TRAF7*-related disorder. The oldest people reported in the medical literature are in their 30's.

Other observations

Other occasional observations have been described in people with *TRAF7*-related disorder, currently (2022) these include kidney anomalies, undescended testes, hernias and inverted nipples.

CAFDADD

TRAF7-related neurodevelopmental disorder has sometimes been referred to as "CAFDADD". This stands for Cardiac, Facial and Digital Anomalies with Developmental Delay. CAFDADD is a description of the set of features that can be associated with pathogenic changes to the TRAF7 gene.

"The shock of being told your child has anything wrong with them is totally stressful but to hear your child has an extremely rare genetic condition that effects roughly 50 children worldwide is just completely mind blowing."

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 cardiology/neurology/neurodevelopment teams may also be required.
- Seizure activity may need monitoring.
- Health visitors and community nurses play an important role in caring for individuals with *TRAF7*-related disorder.
- Monitoring weight gain in infancy is important. Feeding difficulties and reflux may need medical support.
- Progress with development and learning should be monitored to ensure that appropriate strategies and support can be put in place early where needed.


Age 1 year

Age 3 years

Inform Network Support

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

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

TRAF7 Tribe https://www.facebook.com/groups/688600681517431

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.

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Version 1 (AP) 2022

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Registered in England and Wales

Charity Number 1110661
Company Number 5460413