How common is CNOT3-related disorder?

CNOT3-related disorder is very rare. Currently (2023) around 25 children and adults with a CNOT3-related disorder diagnosis 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, the genetic material is copied in the egg and sperm that make a new child. The biological copying method is not perfect, and random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. This happens naturally and is not due to any lifestyle, dietary or environmental factors. No one is to blame and nobody is at fault. Such changes happen to everyone but it's only when a change affects an important gene that health and/or development are affected.

In most children diagnosed with CNOT3-related disorder so far, the change in the *CNOT3* gene occurred by chance in that child (this is known as *de novo*) and was not found in their parents. In a few others, the gene variant has been inherited from an affected parent.

Can it happen again?

The chance of having another child affected by a rare gene disorder depends on the genetic code of the parents. If the change in the *CNOT3* gene has been shown to be *de novo*, that means neither parent was found to carry it, the chance of having another child with CNOT3-related disorder is low (less than 1%). There is still a very small chance if the variant is present in egg or sperm cells (this is called germline mosaicism). If a parent is found to carry the genetic variant, the chance of passing on the variant is usually 50% for each pregnancy. A clinical geneticist can give specific advice for each family.

Can it be cured?

CNOT3-related disorder cannot be cured at the present time. However, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

Families say ...

" When our daughter was born we knew straight away there was something not quite right, she wasn't alert like our first child, she failed her newborn hearing screening and was significantly delayed in all her milestones. We were referred for genetic testing as part of the Deciphering Development Disorders study and after a short time we found out she had CNOT3 gene disorder. At the time it was a relief to discover the cause of her difficulties but we needed to know more about the condition and found there was nothing available. It would have been great if we had a guide like this to help us understand and now, thanks to Unique, families can get information from the very beginning about their child's diagnosis. "

" It was a relief to find a diagnosis that explained all of our daughter's complex issues. She is a friendly chatterbox who is excited to start a special school after going to mainstream primary. Her reading has come on massively in the past year and she's gone from struggling to sound out a single word to reading whole picture books by herself! She loves our pets and wants to run a dog rescue when she's grown up. "

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

Websites, Facebook groups and other links:

https://www.facebook.com/groups/379879422717213

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 www.rarechromo.org/donate Please help us to help you!

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Understanding Chromosome & Gene Disorders

CNOT3-related disorder

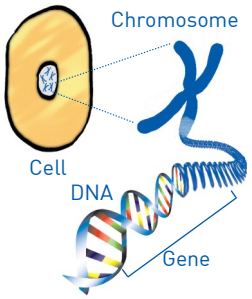
rarechromo.org

What is CNOT3-related disorder?

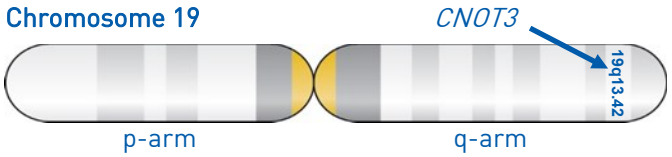
CNOT3-related disorder is a rare genetic condition that causes developmental delay and affects a child's learning abilities and behaviour. As is common with many genetic conditions, each person is affected differently.

What causes CNOT3-related disorder?

CNOT3-related disorder is caused by specific changes (known as pathogenic variants) to a gene called *CNOT3* (*CNOT3* is an abbreviation of the gene's full name, *CCR4-NOT transcription complex Subunit 3*).



The *CNOT3* gene is located on the long 'q' arm of chromosome 19 in a region called 19q13.42 (as shown in the image below).



We have two copies of chromosome 19 in our cells, so we also have two copies of the *CNOT3* gene. The *CNOT3* gene codes for the CNOT3 protein. It is thought that the pathogenic variants that cause CNOT3-related disorder stop the protein from being made or cause the loss of it's function.

CNOT3-related disorder occurs when only one copy of the *CNOT3* gene is affected, this is known as autosomal dominant since the change occurred on an autosome (any of the chromosomes numbered 1-22) and features are apparent when only one copy of the gene is altered (this is known as dominant).

The CNOT3 protein is part of an important group of proteins that control the activity of other genes. CNOT3 is found in many different cell types at different stages of our development. Changes in the amount or function of this protein are thought to cause neurodevelopmental difficulties such as those associated with learning and behaviour.

CNOT3-related disorder features

Most children with CNOT3-related disorder have:

- Developmental delay including motor skills delay
- Learning difficulties/disorders or intellectual disability (ID)
- Speech and language difficulties
- Low muscle tone (hypotonia)
- Relatively short stature

Other possible features include:

- Neurobehavioral features e.g. features of autism / ASD
- Seizures and epilepsy
- Brain anomaly identified by MRI

Development

Intellectual Development and Learning

All children diagnosed with CNOT3-related disorder to date (2023) have some level of learning difficulty or intellectual disability ranging from mild to severe. Additional learning support is expected in a mainstream school and some children may benefit from attending a special needs school.

Speech and language

Some form of speech and language delay is expected. The range of abilities in children and adults with CNOT3-related disorder varies greatly from speaking in full sentences to being non-verbal.

Physical Development

Developmental delay of gross motor function, for example balance and walking, has been reported in most children with CNOT3-related disorder. Independent walking is expected albeit delayed. Some children with CNOT3-related disorder have difficulties with fine motor skills e.g. holding a pencil.

Behaviour

Some children with CNOT3-related disorder have been diagnosed with a neurobehavioral disorder or difficulty. Features of ASD (autism spectrum disorder) have been diagnosed in quite a number of children.

Medical concerns

Brain anomaly

Not all children diagnosed with CNOT3-related disorder have had a brain MRI, but of those who have, sometimes unusual changes have been found but these are not the same for each child.

Eyes and Sight

Eye anomalies have been reported in some children with CNOT3-related disorder but conditions vary. A squint (strabismus) is the most common finding.

Heart anomaly

A few children reported to date (2023) had a structural heart anomaly, but each was different and generally considered to be mild.

Unusual facial features

Some children with CNOT3-related disorder have slightly unusual and mild facial features. No firmly recognisable pattern of features has been established and children may look much like their other family members and peers.

Seizures

A few people with CNOT3-related disorder have experienced at least one seizure (irregular electrical activity of the brain) or have epilepsy. Seizure types vary. Most people reported so far in the medical literature don't have seizures.

Growth

There appears to be a tendency towards a shorter height than might be expected; although most people remain within the normal range for height. Head circumference is generally within the expected range.

Management recommendations:

Children with CNOT3-related disorder should be under the care of a multidisciplinary team including a geneticist, paediatrician, neurodevelopmental paediatrician/ neurologist and an epilepsy specialist if needed. Children may benefit from speech and language therapy, physio and/or occupational therapy as well as periodic evaluations by a developmental specialist.