Unique

Understanding Chromosome & Gene Disorders

CTNNB1 syndrome

This leaflet is based upon what is known about CTNNB1 syndrome (2021), from a small group of affected individuals. There are many gaps in knowledge and with time, and further research, further information will become available.

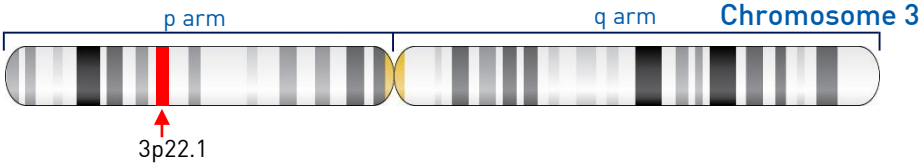
What is CTNNB1 syndrome and how is it caused?

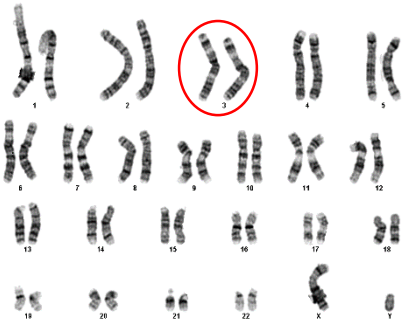
CTNNB1 syndrome is a genetic condition that can cause developmental delay and/or learning difficulties that can lead to a diagnosis of intellectual disability. Some people with this condition have also been found to have a small head circumferences (microcephaly), low muscle tone in their torso (hypotonia) and rigidity of the limbs (hypertonia) as well as some form of eye anomaly.

This syndrome was first discovered in 2012. In the decade that followed, many more individuals were diagnosed with CTNNB1 syndrome, and it is now recognized as one of the rare but relatively more common conditions. It is believed to be amongst the commonest genetic causes for misdiagnosed cerebral palsy.

CTNNB1 syndrome occurs when one of the two copies of the *CTNNB1* gene has lost its expected function. This can be caused by a change in the gene sequence (known as a pathogenic variant) or a loss of one copy of the gene (known as a deletion).

Genes are instructions, which have important roles in our growth and development. They are made of DNA and are incorporated along with many other genes into organized structures called chromosomes. The *CTNNB1* gene is on chromosome 3 in a band called 3p22.1 (see image below).





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

Most of our cells contain 46 chromosomes. We have 22 pairs of 'autosomal' chromosomes, numbered 1 to 22; and two 'sex' chromosomes, two Xs for a genetic female and an X and a Y for a genetic male. We have two copies of chromosome 3 (circled red) and therefore two copies of the *CTNNB1* gene.

CTNNB1 is important in the development and maturation of the brain and loss of its function causes challenges with learning and memory. This is why CTNNB1 syndrome is associated with developmental delay and/or intellectual disability. CTNNB1 syndrome has also been called 'Neurodevelopmental Disorder with Spastic Displegia and Visual Defects (NEDSDV)'.

How many people have CTNNB1 syndrome?

CTNNB1 syndrome is rare, but might not be as rare as we think. As of 2021, more than 60 individuals with CTNNB1 syndrome have been reported in the medical literature, but it is thought that about 200 people worldwide have been given this diagnosis. With the increasing use of the latest gene sequencing technology, it is expected that many more people will be diagnosed with this condition over the next few years.

Common features

- Developmental delay and/or intellectual disability
- Speech and language difficulties
- Low muscle tone (hypotonia) in the torso
- Altered muscle tone in legs making walking difficult
- Small head circumference (microcephaly)
- Vision may be affected
- Specific facial features, including a broad tip to the nose and a thin upper lip
- Behavioural difficulties

Less common features

- Involuntary muscle contractions (dystonia) and movement disorders
- Intrauterine growth restriction (IUGR)
- Short stature and poor growth after birth
- Feeding difficulties
- Curvature of the spine (scoliosis)

Medical concerns

- Low muscle tone in the torso and altered muscle tone of limbs

Most babies with CTNNB1 syndrome have low muscle tone (hypotonia) at birth. This can lead to a delay in reaching their motor milestones and sometimes feeding difficulties. In addition, most children develop an increased muscle tone in their legs, and sometimes the arms, in early childhood. Many are diagnosed with cerebral palsy (where weakness or difficulties using muscles is thought to be due to an affected part of the brain) or pyramidal tract disorder (where part of the spinal cord is thought to not function correctly). The increased muscle tone and spasticity (where a muscle remains contracted) can be progressive, leading to spinal curvature (scoliosis), foot deformities and tightness of the heel cord (Achilles tendon). Children can walk with support of a walker frame or independently. They often walk on tiptoes and can have a broad-based or unsteady (ataxic) way of walking. Children with low muscle tone may benefit from physiotherapy, and tightness of the limbs may show improvement upon treatment with botulinum neurotoxin injections or surgery.

Dystonia and movement disorders

Various movement disorders have been described in the medical literature in people with CTNNB1 syndrome, but dystonia is by far the most common. Individuals with dystonia have involuntary muscle contractions. This can lead to abnormal postures, twisting or repetitive movements. Some individuals reported improvement in symptoms after being given Levodopa, a prescription medicine.

Eyes and eyesight

Most people with CTNNB1 syndrome have eye and eyesight problems, which are quite varied and can include long-sightedness, nearsightedness and a squint (strabismus). Some individuals have a rare eye condition called familial exudative vitreoretinopathy (FEVR) which affects the blood vessels at the back of the eye (retina) and may cause vision loss. This condition may require treatment by laser therapy or surgery.

Neuroimaging abnormalities

Most people with CTNNB1 syndrome have unaffected brain magnetic resonance imaging (MRI) scans. A minority have unusual findings on neuroimaging, which are diverse and include dilated ventricles (the fluid-filled parts of the brain), underdevelopment of the corpus callosum (the band of nerve fibres that links the two sides of the brain) and brainstem, abnormal wrinkles and folds on the surface of the brain, and/or delayed myelination (a delay in the formation of the white matter in the brain and spinal cord). In addition, in a few people, spinal cord abnormalities have been found.

Feeding and gastrointestinal problems

Feeding problems occur in some babies and children with CTNNB1 syndrome. Some babies with hypotonia may experience difficulties breastfeeding. Occasionally a child may require a period of feeding via a nasogastric tube (an NG tube), where food is delivered directly to the child's stomach via a tube inserted through their nose. Some children have difficulties coordinating the muscles for chewing and swallowing. Chronic constipation has also been reported in a minority of children in the medical literature. A feeding or speech therapist will help to find ways to feed children with feeding difficulties.

General health

A structural heart problem has been reported in six children in the medical literature but kidney problems are much more rare. Although frequent infections have been reported in a minority of individuals with CTNNB1 syndrome, there is no evidence to suggest extra precautions need to be taken to avoid infections.

Growth

While the majority of babies with CTNNB1 syndrome are born at term, after an otherwise uneventful pregnancy, some may have a small head circumference and low body weight at birth. Head growth often remains behind expected

measurements and eventually most children have a small head circumference. Most children have a height and weight within the expected range for their age but some children have difficulties gaining weight and some have a short stature.

Development and behaviour

Sitting, moving and walking

Most children show significant delays in reaching motor milestones due to low muscle tone in their torso and increased muscle tone in their legs and sometimes arms. Children do learn to walk, albeit mostly very late (over 6 years) and with an unusual style. In later years, ambulation may become more difficult with progressive spasticity of the limbs. Older children and adults may need a walker frame and some may rely on the use of a wheelchair.

Speech

Speech and language is affected in most people with CTNNB1 syndrome. Some children eventually acquire the ability to speak in simple sentences but more than half of those reported so far have severe difficulties and use no or only single meaningful words. Speech is usually affected more than language, which can be in the (low) normal range. Understanding can be much better than speaking and some children and adults benefit from assisted communication devices and sign languages to signal their needs and thoughts.

Learning

The majority of children with CTNNB1 syndrome reported in the medical literature so far, have learning difficulties and many have been given the diagnosis of intellectual disability (ID). This can range from mild to severe. Children usually benefit from the support of a special education environment.

Adults

Some adults are known to be able to take care of themselves and raise their own children with support. Although the medical literature reports low measures of motor, language, behaviour and personal skills (developmental quotients), some people have no reported developmental concerns, and only their vision is affected. A few people have experienced some form of loss of acquired skills (regression).

Behaviour

Most children with CTNNB1 syndrome generally have a friendly disposition. About half have behaviour difficulties, which can include sleep problems, autistic behaviour, ADHD (attention deficit hyperactivity disorder), and aggression to others or themselves. Repetitive behaviours, tics and anxiety have also been reported.

Facial features

Facial features said to be common in children and adults with CTNNB1 syndrome include a full nose tip with small nasal wings, a long and flat philtrum (the groove between the nose and the upper lip) and a thin upper lip. Some children have sparse and thin hair and eyebrows, with a lighter color of skin and hair compared to other family members. Less commonly reported facial features include low set ears, closely spaced eyes and a high palate.

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 particular genes or specific parts of a chromosome are affected that there is an impact on health and/or development.

In most children diagnosed with CTNNB1 syndrome reported so far, the change in their *CTNNB1* gene occurred by chance in that child (this is known as *de novo)* and was not found in their parents. However, one family has been reported as having two affected siblings. Neither parent was found to carry the genetic change by analysis of their DNA from a blood sample. This suggests that either some of the mother's egg cells or father's sperm cells carry the genetic variant. This is known as germline mosaicism and is very rare.

Can it happen again?

The chance of having another child affected by a rare gene disorder depends on the genetic code of the parents. It is thought that CTNNB1 syndrome occurs almost always *de novo*, which means that the parents are not thought to carry the genetic change. The chance of having another child with CTNNB1 syndrome is in this case very low. The risk for healthy brothers and sisters of having a child with CTNNB1 syndrome is not increased and is the same as for anyone else in the population. In rare cases, parents can have more than one child with CTNNB1 syndrome even though their genetic test, from a blood sample, does not show the genetic change. If one of the parents is found to carry a pathogenic CTNNB1 gene variant or deletion, the chance of them having another child with CTNNB1 syndrome is much higher, in most cases, 50%. Each family situation is different and a clinical geneticist or genetic counsellor will be able to give you specific advice for your family.

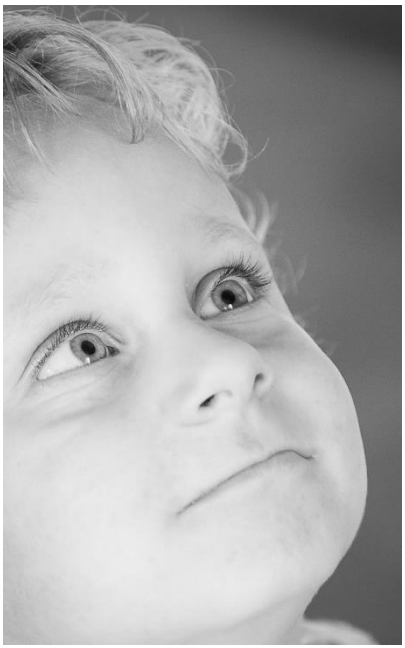
Can CTNNB1 syndrome be cured?

There is no cure for CTNNB1 syndrome since most effects of the genetic change take place early during a baby's formation and development. However, knowing

this diagnosis means that appropriate monitoring and treatment can be put in place for each child.

Management recommendations

Children with CTNNB1 syndrome should be followed up by a general pediatrician who can oversee care so that development, behaviour, and complications of muscle spasticity can be monitored and the best help can be provided. Physiotherapy, orthopaedic shoes, bracing, occupational, behaviour and speech therapies are recommended. Dystonia and other movement disorders may benefit from prescription medications such as levodopa. Eyesight should be checked at diagnosis and follow-up, and certain eye conditions may require laser therapy or surgery.



"Our son is a very happy, enthusiastic and sociable boy. He can also get very scared when seeing people or children he is unfamiliar with or when he is confronted with unexpected situations. He can also get completely beside himself if he is not understood properly. From birth, his legs have had high muscle tone, but his motor development still keeps progressing. He is able to crawl, he can climb the stairs to a certain level, and can stand independently at the table. Moreover, he is very handy with his walker that we take everywhere. What the future will bring for him we do not know exactly, but due to his very positive attitude we have every trust that it will bring all the best for him!" Age - 3½ 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!

Websites and Facebook pages

Website for CTNNB1 Syndrome Awareness Worldwide: www.ctnnb1.org
Website for CTNNB1 Foundation: https://ctnnb1-foundation.org/
Website for Advancing CTNNB1 Cures & Treatments: https://www.curectnnb1.org/
Facebook CTNNB1 syndroom [in Dutch, with English speaking members]:
www.facebook.com/groups/787268954682708

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.

This guide was compiled by Dr Tjitske Kleefstra, Clinical Geneticist, Nijmegen Medical Center, Netherlands, with contributions from Marjolein Willemsen (2015).

This guide was updated by Dr Stephanie Ho, Clinical Genetic Service, Department of Health, Hong Kong; Dr Brian Chung, Clinical Geneticist, Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong and Chief Scientific Officer, Hong Kong Genome Institute; Mandy Tsang and Mianne Lee, Postgraduate students, Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong; and Unique (AP).

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