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UNDERSTANDING GENES & CHROMOSOMES

TUBB3 syndrome

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with TUBB3 syndrome. 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 TUBB3 syndrome?

TUBB3 syndrome, which has several names but is typically referred to as TUBB3-related syndrome or TUBB3-related tubulinopathy, is a rare genetic condition associated with developmental delay, varying degrees of learning (intellectual) disability and impaired eye movements. The condition is part of a broader group of disorders known as tubulinopathies. TUBB3 syndrome is caused by certain changes (variants) in the TUBB3 gene. As is common with genetic conditions, each person can be affected differently - even among affected members within the same family. Not everyone with TUBB3 syndrome 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.

How common is TUBB3 syndrome?

TUBB3 syndrome is extremely rare, but it is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

What features and symptoms do people with TUBB3 syndrome have?

As is common with many genetic conditions, children and adults with TUBB3 syndrome can have a range of features and symptoms. These features and symptoms may be determined by the change (also known as a variant or mutation) in the TUBB3 gene, with certain changes resulting in a more severe condition.

Common features

Many people with TUBB3 syndrome have:

- Developmental delay
- Some degree of learning (intellectual) disability (LD/ID)
- An eye condition called congenital fibrosis of the extraocular muscles (CFEOM)
- Impaired eye movements
- Drooping of the upper eyelids (ptosis)
- Weakness of the facial muscles
- Underdevelopment (hypoplasia) or absence of the nerves that control the eyes and face (cranial nerves)
- Brain anomalies, such as malformations of cortical development (MCD)
- Short stature
- Low muscle tone (hypotonia)
- Progressive nerve damage in the limbs (peripheral neuropathy)

Other possible features include:

- A small head size (microcephaly)
- Characteristic facial features
- Inability to move the vocal cords (vocal cord paralysis)
- Severe breathing difficulty at birth
- Anomalies of the genitals in males
- Cyclic vomiting syndrome
- Curvature of the spine (scoliosis)
- Kallmann syndrome, which affects puberty and the sense of smell
- Progressive stiffening of the joints in the hands, feet and hamstrings (joint contractures)
- Issues with the autonomic nervous system (ANS), which regulates certain body processes, such as heart rate and body temperature

Pregnancy and birth

Concerns during pregnancy have been reported in some cases, sometimes following mid-pregnancy anomaly scans, including anomalies affecting the brain.

Some babies are born prematurely, often as a result of fetal distress. Some babies show signs of difficulty at birth, requiring immediate and intensive care. These difficulties can include breathing problems (respiratory distress). This is sometimes caused by vocal cord paralysis and may require immediate intervention to support the airway, including long-term tracheostomy. Sadly, for the more severe forms of the condition, there is a significant chance of stillbirth and babies passing away in the early new-born period.

Difficulties with feeding and swallowing in the new-born period are also common due to vocal cord paralysis and low muscle tone (hypotonia). Many new-born babies have been described as “unusually inactive and placid”, a feature that may alert doctors to an underlying condition. Other signs of TUBB3 syndrome in a new-born can include facial weakness, joint stiffness (contractures) and reduced eye movements, known as congenital fibrosis of the extraocular muscles (CFEOM).

“During pregnancy no issues were found. It wasn't until just before our daughter was 3 months old that we started the journey. At 4 months we knew she had a brain anomaly and then we started genetic testing at 6 months. A year later we found out our daughter had TUBB3. We had to wait a while to see a geneticist, and during that time we started to look into TUBB3. Our daughter is seen as being on the severe side when it comes to TUBB3.”

“I had a normal pregnancy, but labour was very hard and took almost 12 hours. Once born our son was a big baby (9lb 4ozs) and the size of a normal two-month-old baby. He fed nonstop for almost four hours and still cried. One of the nurses suggested giving him a bottle of formula milk and he drank the complete bottle in one go, but he did stop crying. The first night he was constantly being sick. The next day he settled down.”

Appearance

Certain facial features are found more often in children with TUBB3 syndrome than in other children, primarily due to underdevelopment (hypoplasia) or absence of the nerves that control the eyes and face, leading to weakness or paralysis of the facial muscles. This can lead to some children being diagnosed with Moebius syndrome, a rare neurological condition mainly affecting the muscles that control facial expression and eye movement. These features may mean that you see unexpected similarities between your child and others with TUBB3 syndrome.

Development

Gross and fine motor skills

Developmental delay is variable and is seen in some, but not all, children with TUBB3 syndrome. The degree of delay ranges from mild to profound. Developmental ‘milestones’, including walking, 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 typically-developing children and others showing more obvious delay. Some gene changes are known to be associated with a much more severe developmental delay and, for some, independent walking may not be achieved.

Low muscle tone (hypotonia) is common and may affect mobility, although the clinical picture is complex. Some children may also have muscle stiffness (spasticity). This is often caused by a progressive peripheral

nerve problem (axonal neuropathy). Muscle strength can also be affected, ranging from typical strength to significant weakness, particularly in the legs. Some children may have an unusual gait when walking because of stiffness, joint contractures, muscle weakness and poor joint alignment, meaning children may require walkers or other assistive devices. This is because motor difficulties are often progressive, with joint contractures worsening over time and overall motor function sometimes seen to decline by adolescence.

"From about a week old, I knew there was something not quite right but no one else noticed anything so I just put that thought to the back of my mind. As the months went by, he wasn't reaching any milestones. At 6 months, he was sent to see an asthma specialist as I was convinced he had asthma. The specialist told me he did have infantile asthma. At the appointment I told him my concerns and that he couldn't even hold his head up. He agreed something wasn't right. He finally learnt to walk at 5 years old."

"Yes, there are things she will never be able to do and that's fine. We celebrate all the little milestones because for her they are massive. Some will feel bigger than others. One of them being that she didn't laugh until she was three. But what people don't always see when meeting her is her immense love for music, the excitement at being caught in the wind that she once couldn't tolerate, how being by the sea and outdoors brings her so much joy, how she becomes a mermaid in the water and most importantly how she likes to be part of the conversation no matter how loud or quiet."

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Intellectual development and learning

Many children with TUBB3 syndrome have learning (intellectual) disability (LD/ID) or learning difficulties. The degree of LD/ID is highly variable ranging from average intelligence, which may allow for mainstream schooling, to profound disability. Even higher-functioning children may be diagnosed with specific learning difficulties, such as attention deficit hyperactivity disorder (ADHD), or have a weakness in certain subjects like mathematics. Many children will require significant additional support with their learning throughout their education.

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Speech and language

Children with TUBB3 syndrome may experience some degree of speech and language delay. A common observation is that a child's understanding of language (receptive language) is significantly better than their ability to speak (expressive language). In some cases, physical challenges can also affect speech. These include vocal cord paralysis, hearing difficulties and swallowing difficulties.

"By 7 years, he was beginning to speak. We were so proud of him!"

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Feeding

Feeding issues in the new-born period are common and often requires 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 difficulty swallowing (dysphagia), vocal cord paralysis, cyclic vomiting syndrome and aspiration (where fluid, food or saliva enters the airway or lungs). Aspiration may need to be treated with a procedure to help air and oxygen reach the lungs (tracheostomy) within the first few months of life. Cyclic vomiting syndrome has also been reported in children but may have a later onset (See page 8).

Unique publishes a separate guide to Feeding

Growth and stature

While some children have growth within the expected range, many are noted as having growth delay and a short stature. These growth differences may be present from birth, with some babies born small for their gestational age. Some children also have a smaller head size (microcephaly) than expected. Their bone age is also delayed compared to their chronological age, and some may have low bone density (osteopenia), which may require monitoring. Beyond infancy, height and weight are variable and some boys have been observed to not have a typical pubertal growth spurt. The causes for these growth differences are complex and may be partly due to poor nutritional intake resulting from swallowing difficulties.

Behaviour

"Wearing a special soft head guard as he would roll around the floor and bang his head on the floor and furniture for sensory feedback."

Children with TUBB3 syndrome typically tend to have behaviour in keeping with their overall degree of developmental delay. They are noted as having a happy disposition with 'pleasant and engaging personalities'. Speech comprehension and communication skills are areas of relative strength. Some children have an autism diagnosis or traits and other behaviours including anxiety have also been reported.

Understanding this complex profile is key to providing effective support. 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.

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Puberty

Certain changes in the TUBB3 gene are known to cause of a range of hormone-related (endocrine) conditions, including those that affect puberty. This means that while some boys and girls have gone through puberty as expected, for others puberty is delayed or did not start at all. The timing of puberty can vary considerably, even within the same family, including one report of identical twins with the same TUBB3 gene change, where one twin went through puberty at the expected time while the other had a delayed puberty.

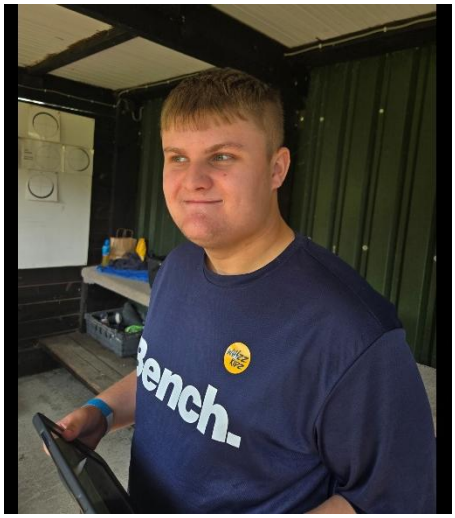
In boys, a small penis (micropenis) and/or undescended testes (cryptorchidism) can sometimes be seen at birth. Later, in adolescence, the testes may remain small. In girls, breast development may not progress as expected and periods may not begin (primary amenorrhoea). Skeletal development can also be affected, with bone age being younger than the child's actual age. A decrease in bone density (osteopenia) is also frequently reported and may require monitoring.

For some these hormone differences may lead to a diagnosis of Kallmann syndrome, which is characterised by delayed or absent puberty due to the body not producing enough of the hormones that trigger sexual development (hypogonadotropic hypogonadism). Sometimes, this can also be associated with a reduced or absent sense of smell.

An endocrinologist (a doctor who specialises in hormones) is often involved in the care of individuals with TUBB3-related conditions.

Unique publishes a separate guide to Puberty

Adulthood



The long-term outlook for adults with TUBB3 syndrome is not yet clearly known. Experiences of adulthood are likely to vary considerably and will depend on many factors. These include the level of any learning (intellectual) disability, possible on-going medical and behavioural concerns and improvements in early intervention and therapies/treatments. A range of features present from birth (congenital) and those that develop over time (progressive), such as damage to the nerves outside of the brain and spinal cord (peripheral neuropathy) and later-onset cyclic vomiting, can persist into adulthood, requiring continuous health maintenance, and some features are progressive. Some people may require a long-term artificial airway, such as a tracheostomy. Endocrine and reproductive health are important considerations in adulthood and some features of the syndrome, including the underlying neurological differences, may contribute to reduced fertility.

Adults with TUBB3 syndrome have varying levels of independence. The capacity for independent living ranges from requiring support for all activities of daily living, to having a far higher level of functioning in daily life with fluent language skills. Some adults continue to live in supported settings such as a group/residential care home, with caregivers who can provide support. Assuming ongoing medical management is provided where necessary, there is currently no evidence to suggest that life expectancy is affected, though this is not certain for the more severe forms of the condition.

> ***Our son is now 18 years old and a big strapping man. For years we were told not to expect anything of him, yet our boy has proved them all wrong. We would never ever give up on him. He is so happy, in between his teenage strops and his terrible twos behaviour. He is just amazing and lives his life the best he can."***

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Medical concerns

The following medical concerns have been found in children with TUBB3 syndrome. They are not found in all children so not all children with TUBB3 syndrome will be affected.

Brain

Some children with TUBB3 syndrome 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:

- Malformations of the cortical development (MCD) - such as anomalies that affect the formation of the outer layer of the brain called the cortex (focal cortical dysplasia), which is a common cause of epilepsy
- Underdevelopment (hypoplasia) or partial/complete absence (agenesis) of the white matter connecting the two halves of the brain (corpus callosum)
- Anomalies of the basal ganglia, which are deep brain structures involved in movement control
- Underdevelopment (hypoplasia) or other structural anomalies of the area at the back of the brain that controls movement and balance (cerebellum), including the cerebellar vermis
- Anomalies of the brainstem, including underdevelopment (hypoplasia) or an asymmetrical appearance
- Underdevelopment (hypoplasia) of the cranial nerves, which connect the brain to other areas of the head, neck and torso. The nerves controlling eye movements (oculomotor nerves) are frequently affected
- Loss of white matter volume

It is important to note that the type and severity of brain malformations can vary significantly between individuals. In some cases, particularly those with specific genetic variants (such as p.Arg62Gln), the brain MRI scan may indicate that there is no brain anomaly.

Seizures

Rarely, children with TUBB3 syndrome 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. 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. 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.

Heart

A heart condition(s) has been found in some people reported so far with TUBB3 syndrome, which can be present at birth (congenital) or develop later in life. These problems mainly affect the heart's rhythm and electrical signalling (rhythm and conduction disturbances), rather than the structure of the heart. The types of heart conditions reported are variable but can include a fast heart rate (tachycardia), which may be present from birth, and problems with the heart's natural pacemaker (sinus node dysfunction). Fainting episodes (syncope) have also been reported. It is thought that these heart issues may be linked to the nerve problems (peripheral neuropathy or autonomic dysfunction) seen in this condition, as the TUBB3 gene is active in nerve cells (neurones) but not in heart muscle tissue. 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). Medical treatment may be necessary, and some may require surgery. Several people are known to have benefited from the fitting of a pacemaker.

Breathing

Respiratory issues can be a concerning feature for children with certain TUBB3 variants. For some, severe respiratory distress is seen immediately after birth, sometimes accompanied by high-pitched, noisy breathing (stridor). These challenges can be lifelong, although some upper airway complications may improve over time. The underlying causes are often related to the development of the brainstem and cranial nerves; vocal cord paralysis; low muscle tone in the trunk, neck and head (axial hypotonia); and swallowing difficulties. Other issues may include a floppy windpipe (tracheomalacia) and the later development of a curved spine (scoliosis and kyphosis). These can lead to a higher risk of secondary complications like recurrent respiratory and lung infections, such as aspiration pneumonia.

Movement Disorders

Delays in achieving motor skills are a characteristic feature of TUBB3 syndrome, affecting both larger movements (gross motor skills, such as walking) and smaller, more precise movements (fine motor skills, such as buttoning clothes or writing). Difficulties with posture and walking (gait) are common, especially in individuals with certain, specific genetic variants. The degree of delay is very variable, but for many there may be a progressive decline in motor skills, meaning the ability to carry out certain activities or tasks may worsen over time, particularly during adolescence.

Cyclic vomiting syndrome

Issues with the movement of the gut can cause slow or uncoordinated movement of food through the digestive tract (gastrointestinal dysmotility), which can lead to cyclic vomiting syndrome. These episodes may start later in life, can last for multiple days and may be triggered by specific foods, infections or strong emotions. They are often accompanied by severe nausea and abdominal discomfort.

Hormones

Children with TUBB3 syndrome may have conditions that affect their hormones. One hormonal condition can present as Kallmann syndrome, which is characterised by delayed or completely absent puberty (see page 5). In some cases, individuals with TUBB3 syndrome have also been reported to have diabetes (diabetes mellitus).

Ears and Hearing

Some children have a hearing impairment, but hearing is unaffected in most. A hearing loss may be sensorineural, where there are problems with the inner ear. The underlying cause may be due to underdevelopment (hypoplasia) or absence of the cochlear nerve and other associated nerves. Functional testing has shown evidence of a disruption in the timing of nerve signals (neural dys-synchrony) and unusual or absent auditory brainstem responses (ABRs) in some individuals. Management with hearing aids or, in some cases, cochlear implants may be appropriate.

Unique publishes a separate guide to Hearing

Eyes and sight

Eye and vision anomalies are common in children with TUBB3. The most frequent finding is a condition called congenital fibrosis of the extraocular muscles (CFEOM), which is present from birth. For some TUBB3 gene variants, this is the only feature of the condition. This can severely limit eye movements, making it difficult for children to fix their eyes on an object and follow it. Other concerns include a squint (strabismus), where one or both eyes turn inward, outward, up, or down; uncontrolled repetitive eye movements (nystagmus); a drooping of the upper eyelid (ptosis); and a ‘lazy eye’ (amblyopia), which can result from untreated strabismus. Some

children may also have other unusual eye movements, such as Marcus Gunn jaw-winking syndrome (MGJWS), where the eyelid moves when the jaw moves. These issues can be caused by the nerves and muscles that control the eyes being underdeveloped. Other, less common, findings can include anomalies of the optic nerve, and a risk of damage to the surface of the eyes (corneal exposure) if the eyelids do not close completely. While these ophthalmological conditions are persistent throughout life, they are not thought to be progressive.

Hands and feet

Children with the more severe forms of TUBB3 syndrome may have anomalies of the hands and feet. These are often present from birth. Most common among these are:

- Stiffness (contractures) in the hands or feet
- Fingers or toes that curve inwards (clinodactyly), are unusually short (brachydactyly), or fused (syndactyly)
- Bent fingers that cannot be straightened (camptodactyly), persistently fisted hands, and inward deviation of the wrist leading to bending of a finger towards the little finger (ulnar deviation)
- Flat feet (pes planus)
- Club foot (talipes), where the foot turns inwards and the soles point towards each other
- 'Claw foot' (pes cavus)
- So-called 'banana foot', where the toes point inwards (pes adductus)
- Tightness in the heel cord (Achilles contracture)

Some children are only mildly affected and may not require treatment. Others may benefit from massage, orthotics (such as ankle foot orthoses, AFOs) and physiotherapy. Treatment is tailored to the individual child, and in some cases surgical correction will best enhance eventual mobility.

Spine

A few 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 twisted or tilted neck (torticollis) has also been reported.

Joints

Joint anomalies are a known feature of certain genetic changes in the TUBB3 gene. In some cases, joints are unusually tight (joint contracture) and may require surgery and tendon lengthening to extend their range of movement. These contractures are often present at birth, particularly in the hands and feet, and can worsen or develop over time. Examples include congenital bilateral Achilles contractures and progressive finger and hamstring contractures. The underlying cause of the contractures is thought to be neurological, rather than a problem with the muscles or joints themselves.

Teeth

Dental concerns are very common in children with genetic conditions. A number of issues have been described associated with TUBB3 syndrome including an unusual size of the jaw, leading to overcrowding or widely-spaced teeth. A high standard of dental care is important to minimise damage by decay and erosion (by grinding).

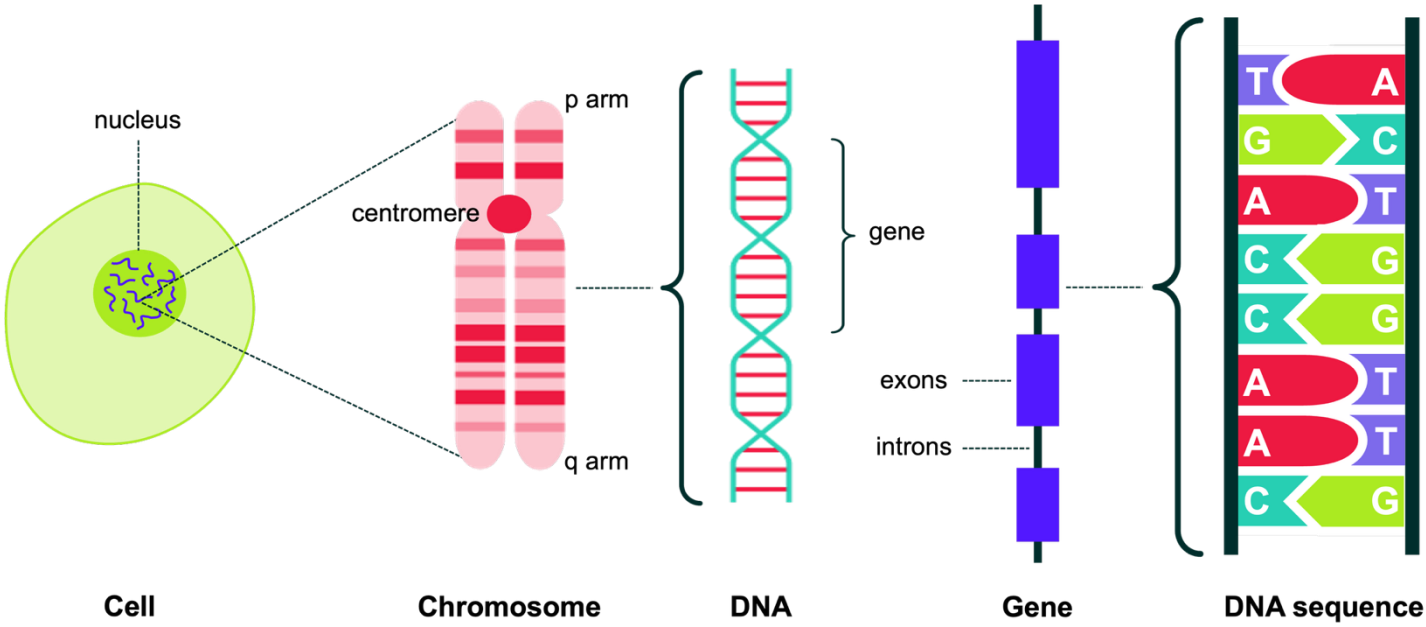
Unique publishes separate guides to Looking after your child's teeth and Teeth: common concerns

This section includes some more complicated scientific terms and concepts - don't worry if it's a lot to take in, you can always come back to this section later if you want to.

Genes and chromosomes

Genes are instructions which 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 expected, which can lead to changes in how their body works.

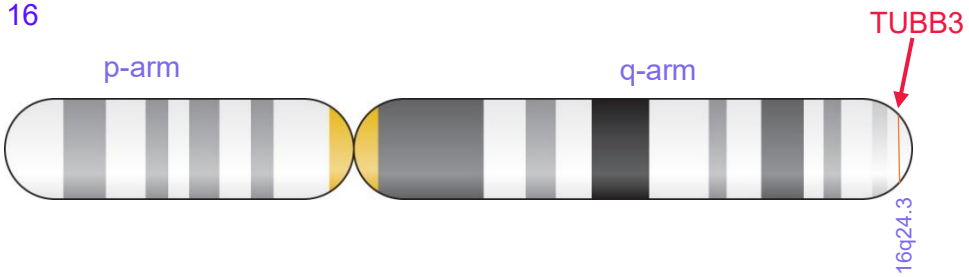
DNA is made up of building blocks called 'bases' or 'nucleotides'. There are four DNA bases which can be abbreviated to the letters A, C, G, and T. These DNA bases are paired up in the DNA structure into 'base-pairs'. The full sequence of our DNA is over three billion base-pairs long. There are changes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



What causes TUBB3 syndrome?

TUBB3 syndrome is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called TUBB3 (TUBB3 is an abbreviation of the gene's full name, tubulin beta 3 class III). Very rarely, the features and symptoms related to TUBB3 syndrome can also be caused by the loss of TUBB3 due to a chromosome deletion. The TUBB3 gene is located in the long 'q' arm of chromosome 16 in a region called 16q24.3 as shown in the image below.

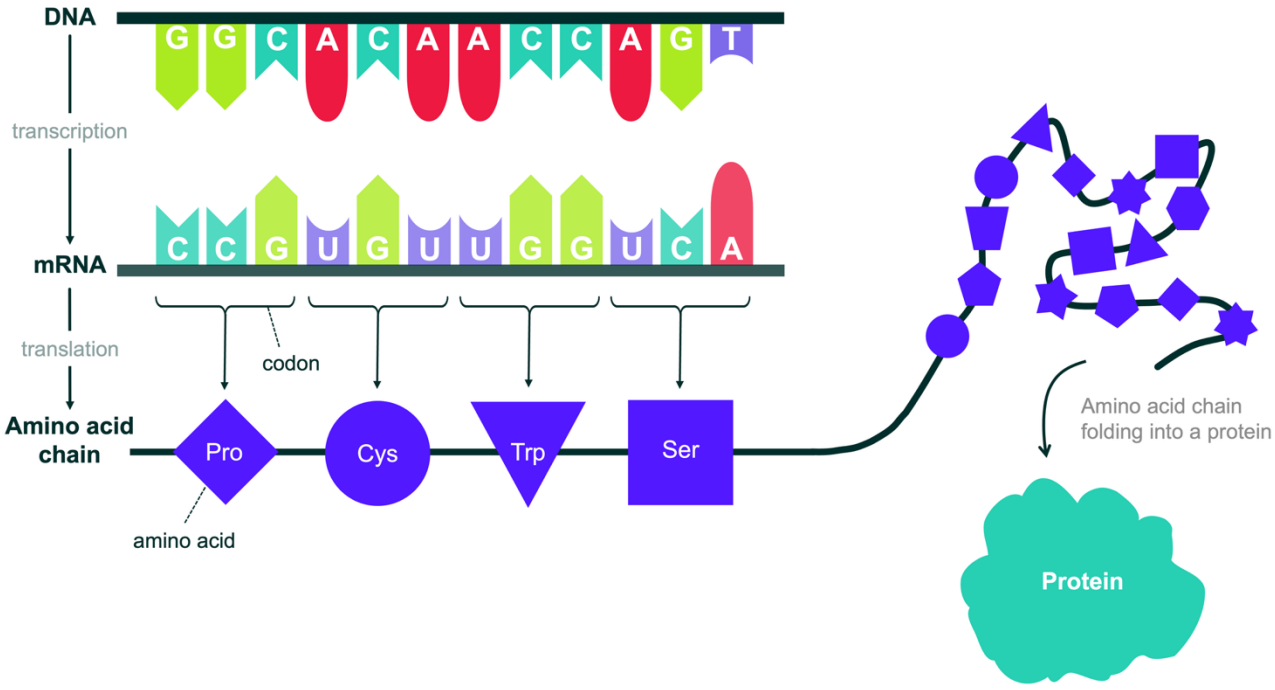
Chromosome 16



We have two copies of chromosome 16 in our cells, so we also have two copies of the TUBB3 gene. TUBB3 syndrome occurs when only one copy of the TUBB3 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

Most genetic conditions are caused by changes to genes that provide instructions for making proteins; these are called protein-coding genes. TUBB3 is one of thousands of these protein coding genes. Proteins are molecules that are made up of long chains of chemicals called amino acids and play critical roles in the body. This is because proteins are essential for lots of processes such as breaking down food, moving our muscles and growing the body's organs and making sure they function properly. To make these amino acids a copy of the DNA sequence is created, called messenger RNA (mRNA). mRNA uses the same A, C and G bases as DNA, but the 'T' bases are swapped to 'U' bases. Within a gene, each three-letter sequence (codon) of mRNA bases provides the instructions for one amino acid. Changes to the amino acid sequence can affect the function of the protein.



The role of the TUBB3 protein

The TUBB3 gene provides the instructions for making a protein called tubulin beta-3. This protein is mainly found in nerve cells (neurones) and is a key building block of microtubules. Microtubules are tiny, rigid, hollow rods that form each cell's internal 'skeleton'. In the developing brain, they are essential for the healthy development and function of the nervous system, since they play a crucial role in key processes such as guiding new neurones to their correct positions and directing the growth of nerve cell extensions (axons) to make the right connections.

Different types of genetic changes

The specific type of genetic change in the TUBB3 gene that a person has is an important factor that can influence that individual's symptoms and features. Research suggests that different types of variants can affect the tubulin beta-3 protein in different ways, accounting for some of the variability in symptoms and features, or their severity, in different people with TUBB3 syndrome.

Gene Sequence Variants

People with TUBB3-related syndrome are most commonly found to have a gene sequence variant, as opposed to a deletion of the entire gene. Such variants include missense variants, which result in a single building block (amino acid) being changed in the tubulin beta-3 protein, thereby producing an altered protein.

The smaller or altered protein that is produced is thought to interfere with the normal function of the full-sized protein produced from the unaffected TUBB3 gene on the other chromosome 16. This is known as a dominant-negative effect, where the altered tubulin protein is incorporated into neuronal microtubules and disrupts their function. This can interfere with important cellular processes, including axon guidance and transport. There is a strong correlation between the specific amino acid change caused by the particular variant a person has and the resulting clinical features.

Genetic Tests

TUBB3 syndrome is almost always caused by gene sequence variants (rather than deletion of the gene), which can be identified by a type of genetic test called sequencing, such as whole exome sequencing (WES) or whole genome sequencing (WGS).

Unique publishes separate guide to DNA sequencing

Genetic Test Results

The results of genetic (genomic) testing are likely to be provided by a geneticist, a genetic counsellor or the clinician who ordered the test. Depending on the test that was carried out, someone with a TUBB3 syndrome might have results that look like the following example:

NM_006086.4(TUBB3):c.1138C>T (p.Arg380Cys)

NM_006086.4	this is the specific ‘reference sequence’ or blueprint of the gene that scientists use to identify the location of the variant
TUBB3	signifies the gene that is affected
C>T	signifies the gene sequence change: the C nucleotide has been replaced by a T nucleotide
c.1138	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)
p.Arg380Cys	signifies the change to the protein: the amino acid arginine (Arg) has been replaced by the amino acid cysteine (Cys) at position 380 in the sequence of amino acids that make up the protein

Unique publishes a separate guide to Interpreting Genetic Test Results

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 TUBB3 gene then a child will have TUBB3 syndrome.

In most people identified so far (2026) with TUBB3 syndrome, 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. These de novo variants are often linked to a more severe range of neurological symptoms. Occasionally, TUBB3 variants are inherited from an affected parent (typically the parent has mild features). It is important to recognise 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 the severe forms of TUBB3 syndrome, the genetic alteration has been found to be de novo (dn), which means neither parent was found to have the same TUBB3 gene change as their child. One reason why there is some residual chance of recurrence is due to the rare phenomenon called germline mosaicism. 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. Germline mosaicism has been reported for some TUBB3 variants.

Unique publishes a short general guide to Mosaicism

For the milder forms of TUBB3 syndrome, the condition is often inherited from a parent, who may or may not have signs of the condition.

In families where the TUBB3 variant has been inherited from a parent, the possibility of having another child - either a girl or a boy - with TUBB3 syndrome rises to 50% (I in 2) in each pregnancy. Some inherited variants may be associated with milder symptoms like congenital fibrosis of the extraocular muscles (CFEOM3). However, the effect on the child's development, health and behaviour cannot be reliably predicted. This is known as variable expressivity, and some individuals with a pathogenic TUBB3 variant may be asymptomatic or have very mild, unrecognised symptoms.

If your child with a TUBB3 variant goes on to have children of their own, the chances of passing on the variant to their child are 50% (1 in 2) in each pregnancy.

A clinical geneticist or genetic counsellor can provide specific advice for each family about the chance of having further children with TUBB3 syndrome.

Can TUBB3 syndrome be cured?

There is no complete cure for TUBB3 syndrome since most of 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 TUBB3 syndrome have been published (2026). The following suggestions have been provided by clinicians, who have personal experience of managing/treating individuals with TUBB3 syndrome, to improve quality of life and reduce complications.

Children and adults with TUBB3 syndrome 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 different therapies. Individuals may also have evaluations with various specialist doctors.

Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of TUBB3 syndrome that are present in the child or adult who has been diagnosed with this genetic condition is recommended. This can determine which of the features of TUBB3 syndrome are present and how severe they are.

The following assessments are recommended:

- A physical examination to look for features such as joint contractures
- An ophthalmology assessment to evaluate and manage complex eye movement disorders such as CFEOM, strabismus and ptosis
- A cardiac assessment to check heart rhythm and function
- An audiological (hearing) assessment to determine the severity of any hearing loss and ensure early intervention; this may include pure-tone thresholds, tympanometry and auditory brainstem responses (ABR)
- A neurologic assessment, which should include long-term management of epilepsy and screening for behavioural and emotional concerns, as well as autism spectrum disorder. Brain magnetic resonance imaging (MRI), a technique that can be used to visualise the brain, should be carried out as changes to the white matter of the brain are a known feature of TUBB3 syndrome, alongside other structural brain anomalies such as MCD, cerebellar dysplasia and anomalies of the corpus callosum. For individuals with severe brain malformations, it is recommended that discussions are held about the level of care to be provided during severe illnesses
- An endocrinology assessment to monitor bone density and to induce puberty if required
- Developmental assessments with a focus on early intervention therapies such as physical therapy, occupational therapy, speech therapy and vision therapy
- An assessment of feeding, nutrition and respiratory function, which is especially important for infants and those with severe features of the condition

Genetic counselling for affected individuals and their families should also be offered together with the provision of signposting to family support and resources.

Supportive care

How a person with TUBB3 syndrome is cared for is likely to require co-ordinated care by a multidisciplinary team of specialists, which may include:

Audiologist – a health care professional who assesses, treats and helps manage a condition that involves hearing or balance.

Cardiologist – a doctor who specialises in heart conditions, particularly to monitor for cardiac conduction problems.

Developmental Paediatrician – a doctor who specialises in the physical, mental and social health of children from birth to young adulthood.

Endocrinologist – a doctor who specialises in hormones and their effect on the body, who may be needed to induce puberty and monitor bone density.

Gastroenterologist – a doctor who specialises in the digestive system and may help to manage feeding and swallowing difficulties, gastro-oesophageal reflux disease (GERD) and constipation.

Clinical geneticist – a doctor who specialises in the diagnosis and management of genetic disorders.

Neurologist – a doctor who specialises in conditions of the brain, spinal cord and nervous system. They oversee long-term care and manage seizures.

Occupational therapist (OT) – a health care professional who helps individuals develop skills for daily living, fine motor control and sensory integration.

Ophthalmologist – a doctor who specialises in conditions affecting the eyes, such as CFEOM and strabismus.

Orthopaedic specialist/Physiatrist – a doctor who specialises in conditions affecting the bones, joints and muscles.

Paediatrician – a doctor who specialises in the physical, mental and social health of children from birth to young adulthood

Physiotherapist/physical therapist (PT) – a health care professional who helps support gross motor development, manage increased muscle stiffness (spasticity), maintain range of motion and address joint contractures.

Pulmonologist - a doctor specialising in diagnosing and treating diseases of the respiratory system.

Otolaryngologist (ENT) – a doctor who specialises in conditions of the ear, nose and throat and may evaluate for upper airway obstruction.

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

Surgeon – a doctor who is specially trained to perform medical operations, such as surgical treatments for eye conditions or creating a definitive airway (tracheostomy).

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.

There are no treatments that target the underlying genetic cause of TUBB3 syndrome; management is supportive, individualised and focuses on specific symptoms. A multidisciplinary team approach, often coordinated by a paediatric neurologist, is essential. Treatment will depend on the specific features and symptoms experienced by the person with TUBB3 syndrome but may include:

Physiotherapy to manage low muscle tone (hypotonia), muscle stiffness (spasticity) and gross motor delays. It is also crucial for managing progressive joint contractures to maintain range of motion. Therapy usually

includes exercises to build core strength, improve balance and enhance coordination to help children achieve motor milestones like sitting, crawling and walking, and to improve overall mobility. Some individuals may require orthoses or other assistive devices for walking.

Occupational therapy for fine motor skill delays and sensory sensitivities, which can include activities to improve hand strength and coordination for daily tasks (e.g. feeding and dressing) and sensory integration therapy to help individuals better process and respond to sensory information from their environment.

Speech therapy for a range of speech and language delays or difficulties (including articulation) and feeding/swallowing difficulties. For children with moderate to severe difficulties, this can include regular sessions focusing on augmentative and alternative communication (AAC) methods (e.g. sign language, picture exchange systems and high-tech communication devices) and provides a functional means of communication for individuals who are non-verbal or have very limited speech.

Vision therapy may be beneficial for impaired eye movements and misaligned eyes (strabismus).

Medications may be prescribed such as anti-seizure medications (ASMs) to help control or prevent seizures (prompt seizure control is important as it can worsen feeding difficulties and increase aspiration risk) and prophylactic medications for other conditions such as cyclic vomiting syndrome.

Hormone treatment for absent or delayed puberty (hypogonadotropic hypogonadism) to replace hormones. Monitoring of bone density is also important.

Surgery, such as the placement of a gastrostomy tube (G-tube) for severe, long-term feeding difficulties; procedures to correct a squint (strabismus) to improve vision; orthopaedic interventions for progressive joint contractures; or a long-term tracheostomy for significant respiratory distress.

Since individuals with TUBB3 syndrome may be at risk for other conditions, regular monitoring may be recommended. For example, individuals experiencing symptoms like fainting (syncope) may require cardiac evaluation for potential heart rhythm issues (cardiac conduction anomalies).

Families are also offered genetic counselling to provide information on the nature of the disorder, its inheritance pattern and the implications for the family to support informed medical and personal decisions.

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. A multidisciplinary clinical approach is recommended, tailored to the specific symptoms present:

- Monitor for growth and adequate nutritional intake, including an evaluation for swallowing difficulties
- Neuropsychiatric and learning assessments
- Consider a palate review (particularly if there are feeding difficulties or speech concerns)
- Check position of testes in boys, as part of monitoring for hypogonadotropic hypogonadism using hormonal assessments
- Consider a cardiac review, including physical examinations, monitoring of vital signs for asymptomatic elevated resting heart rates and further assessment with electrocardiograms (ECGs) and echocardiograms, especially if syncope occurs
- Consider audiologic assessments, including comprehensive audiometric evaluations
- Consider a neurologic review, which may include regular physical and neurological assessments of motor function, muscle tone, strength and reflexes to monitor for spasticity and neuropathy; tracking of gross motor milestones; and electrodiagnostic testing (nerve conduction studies and electromyography) to assess for peripheral neuropathy (including MRI and EEG, if indicated by seizures)
- Consider a skeletal review, including ongoing monitoring for the development or worsening of features such as joint contractures, as well as bone density studies and monitoring of bone age

- On-going examinations by an ophthalmologist
- Kidney function should be monitored
- Consider regular meetings with an endocrinologist to monitor hormonal levels (for conditions like hypogonadotropic hypogonadism) and bone health (including bone age and vitamin D levels)
- Monitoring for cyclic vomiting syndrome and its triggers

Research into new treatments for TUBB3 syndrome

The genetic changes that cause TUBB3 syndrome affect 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 TUBB3 syndrome is ongoing. In addition, although TUBB3 syndrome is a relatively rare condition, the TUBB3 gene is the subject of a lot of research. Research is currently focused on understanding the underlying molecular basis of the condition. The way that the altered TUBB3 protein disrupts the function of microtubules (important components of the cell's internal skeleton) suggests several potential future therapeutic strategies. These could include correcting the faulty gene, reducing the amount of the altered protein or developing drugs that stabilise microtubule function. However, it is important to note that such approaches are not yet in the clinical phase.

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

Families say ...

"We were told that our son was one of only a handful of people with TUBB3 syndrome and that we were the only family in the UK with it. We were told to go home and try to research it ourselves as we might find out more. We were totally lost and didn't know what to expect, but one thing was for sure: we were never going to stop trying to help our son progress.

I found a few bits of information, but I didn't understand any of it, until I went on Facebook and typed in TUBB3. To my surprise a private page showed up, so I joined it. At the time, I think there were maybe another 8 families, but all over in America.

Over time our wee group has slowly grown. The parents on it are all so nice, the kids are all so different to each other. One day I would love to meet up with them."

"After meeting with our geneticist and expressing our wishes to be put in contact with other families we met another family and have been in contact with them for a few years. Last year on a trip to London we were able to meet up. Finding a community has been so helpful for us pre- and post-diagnosis. It's enabled us to gain so much knowledge to support our daughter.

Our daughter is medically complex and there will be incredibly hard days, but for us as a family we choose not to focus on those days. She has taught us so much, and we've all grown and developed with her. From learning to see things in a different way to advocating fiercely for her needs to be met. Remember, your child's diagnosis and needs do not define who they are.

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2026, Unique had 11 members with TUBB3 syndrome. 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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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

Websites, Facebook groups and other links:

- TUBB3 Foundation

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