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UNDERSTANDING GENES
& CHROMOSOMES

Phelan-McDermid Syndrome-SHANK3 Related

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with Phelan-McDermid syndrome-SHANK3 related. 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 Phelan-McDermid syndrome?

Phelan-McDermid syndrome-SHANK3 related, also referred to as Phelan-McDermid syndrome or PMS-SHANK3 related, is a rare genetic condition associated with developmental delay, delayed speech, varying degrees of learning (intellectual) disability, low muscle tone (hypotonia) and behavioural differences. As is common with genetic conditions, each person can be affected differently - even among affected members within the same family. Not everyone with Phelan-McDermid 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.

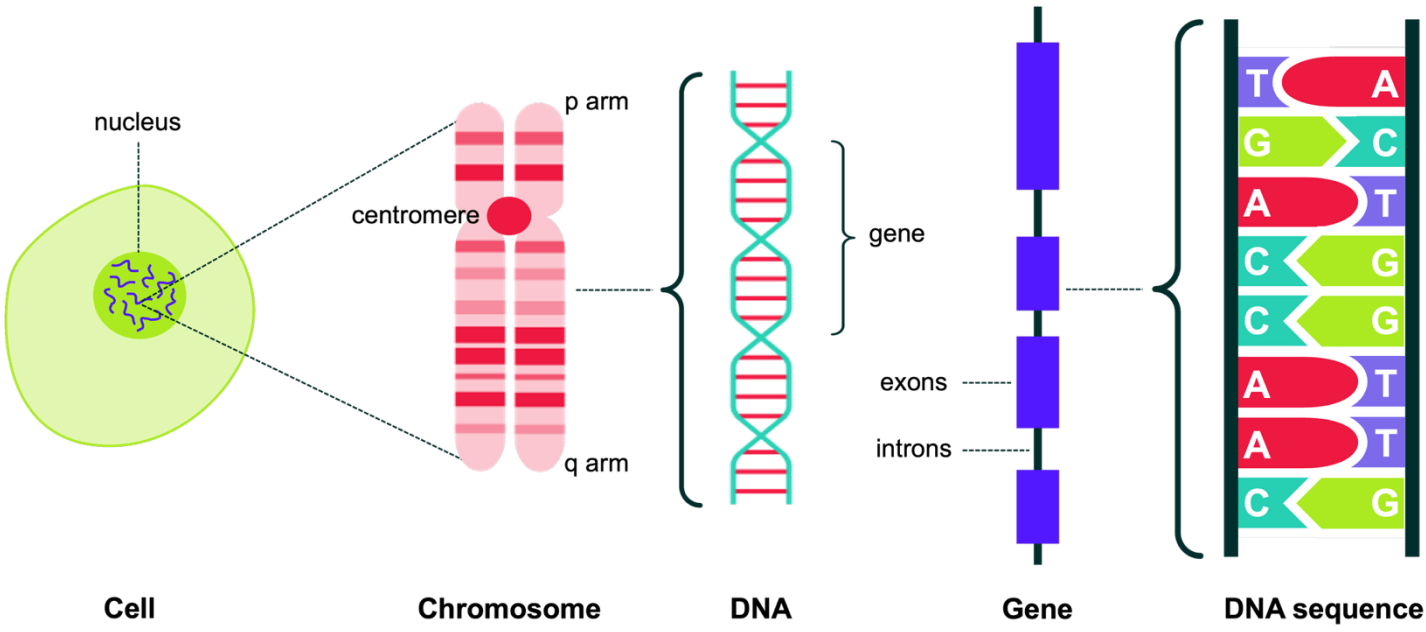
Phelan-McDermid syndrome-SHANK3 related is caused by a change (variant) in the SHANK3 gene or the loss (deletion) of one copy of the SHANK3 gene. The loss of the gene may occur as part of a larger deletion that affects the chromosome on which the gene is located.

Phelan-McDermid syndrome is most often caused by changes or deletions affecting the SHANK3 gene, but sometimes does not involve SHANK3. This guide contains information about Phelan-McDermid syndrome caused by changes to the SHANK3 gene.

What causes Phelan-McDermid syndrome?

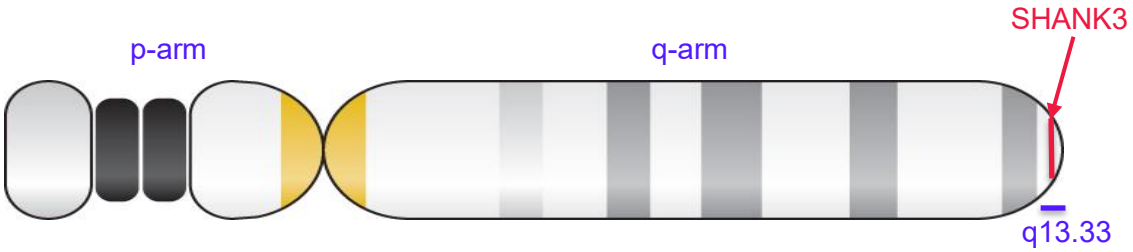
Genes are instructions that have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies. In people with genetic conditions, one or more of their genes don't instruct the body as we would expect, which can lead to changes in how their body works.

DNA is made up of building blocks called 'bases' or 'nucleotides'. There are four DNA bases which can be abbreviated to the letters A, C, G, and T. These DNA bases are paired up in the DNA structure into 'base-pairs'. The full sequence of our DNA is over three billion base-pairs long.



Phelan-McDermid syndrome-SHANK3 related is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called SHANK3 (SHANK3 is an abbreviation of the gene's full name, SH3 and multiple ankyrin repeat domains 3). Phelan-McDermid syndrome can also be caused by the loss of SHANK3 due to a chromosome deletion. The SHANK3 gene is located in the long 'q' arm of chromosome 22 in a region called 13.33 as shown in the image below.

Chromosome 22



We have two copies of chromosome 22 in our cells, so we also have two copies of the SHANK3 gene. Phelan-McDermid syndrome occurs when only one copy of the SHANK3 gene is affected; the second copy is fully functional. This is known as autosomal dominant since all numbered chromosomes are called autosomes and genetic conditions that occur when only one copy of an autosomal gene is affected are known as dominant.

Unique publishes a separate guide to single gene disorders – autosomal dominant inheritance

Unique publishes a separate guide to deletions and microdeletions

The SHANK3 gene sequence is used to make the SHANK3 protein. This protein is important in the development and function of the brain by helping nerve cells (neurones) communicate with each other.

Genetic Tests

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

Unique publishes separate guides to DNA sequencing, arrayCGH and SNParrays

Genetic Test Results

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

An example result of a DNA sequencing test (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)), that can identify gene variants, is shown here for the SHANK3 gene:

p.Gln331His (Q331H) (CAG>CAT): c.993 G>T in exon 7 of the SHANK3 gene (NM_001372044.2)

p.Gln331His (Q331H)	signifies the change to the protein: the amino acid glutamine (Gln or Q) has been replaced by the amino acid histidine (His or H) at position 331 in the sequence of amino acids that make up the protein
CAG>CAT	signifies the gene sequence change; the G nucleotide has been replaced by a T nucleotide
c.993	signifies the base pair position of the change within the gene sequence (the position where the G nucleotide has been replaced by the T nucleotide)
exon 7	signifies which part of the gene has been altered, in this case exon 7
SHANK3	signifies the gene that is affected
NM	denotes the reference sequence used

The result of a chromosome microarray (CMA) test (e.g. arrayCGH or a SNParray), that can identify deletions, is shown here for a microdeletion within bands 22q13.2-13.3:

arr[hg38] 22q13.2-13.3 (42,826,246-50,739,836)x1 dn

arr	The analysis was by array (arr) comparative genomic hybridisation (cgh)
hg38	Human Genome build 38. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new 'builds' of the genome are made, and the base pair numbers may be adjusted. This means base pair positions change depending on the assembly used
22q13.2-13.3	the chromosome involved is chromosome 22 and the position of the deletion is in bands q13.2-13.3
42,826,246-50,739,836	the base pairs between 42,826,246 and 50,739,836 have been shown to be deleted. Take the first long number from the second and you get 7,913,590 (7.9Mb). This is the number of base pairs that are deleted
x1	means there is one copy of these base pairs, not two – one on each chromosome 22 – as you would normally expect, so this a deletion
dn	means *de novo*. The biological parents' chromosomes have been checked and no deletion or other chromosome change has been found at position 22q13.2-13.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child mat here would mean that the deletion has been inherited from the mother pat here would mean that it has been inherited from the father

Unique publishes a separate guide to Interpreting Genetic Test Results

What features and symptoms do people with Phelan-McDermid syndrome have?

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

Common features

Most children with Phelan-McDermid syndrome have:

- Some degree of developmental delay ranging from mild to severe
- Some degree of intellectual disability (ID) or learning difficulties (LD) ranging from moderate to profound
- Speech and language delay or are non-verbal
- Feeding difficulties which usually resolve after babyhood or early childhood
- Low muscle tone (hypotonia)
- Behavioural differences e.g. autistic spectrum disorder (ASD), ADHD, and anxiety
- Sleep issues
- Decreased perception of pain

Other possible features include:

- Characteristic facial features including full cheeks, droopy eyelids or a pointed chin
- Chewing and swallowing difficulties
- Anomalies of the hands and feet including large fleshy hands and underdeveloped (dysplastic) toenails
- Seizures
- Gastro-oesophageal reflux (GERD/GORD)
- Reduced sweating which can cause overheating
- Dental issues e.g. tooth-grinding, misaligned or widely-spaced teeth (malocclusion),
  and open or high palate
- Anomalies of the kidneys and genitals (urogenital anomalies)
- Heart condition
- Brain anomaly
- Eye/vision anomaly
- Hearing loss
- Swollen tissues (lymphedema)
- Constipation
- Glue ear/frequent ear infections
- Frequent respiratory infections
- Spinal curvature e.g. scoliosis, kyphosis
- Hormone (endocrine) anomalies

Pregnancy and birth

While most pregnancies are unremarkable and proceed without complication, some concerns during pregnancy have been reported, sometimes following mid-pregnancy anomaly scans. Where a cause for concern was noted, most often parents reported small size for gestational age or reduced foetal movements, though these are rare.

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

Appearance

Certain facial features are found more often in children with Phelan-McDermid syndrome than in other children. These features may mean that you see unexpected similarities between your child and others with Phelan-McDermid syndrome. The most common characteristic features include:

- Broad and straight eyebrows
- Full eyelids with long eyelashes
- A pointed chin
- Large ears
- A broad nose with a bulbous nasal tip
- Large fleshy hands and feet
- Malformed nails and widely protruding teeth in adults have also been identified

Development

Gross and fine motor skills

Developmental delay has been reported in most children with Phelan-McDermid syndrome so far (2025). The degree of delay ranges from moderate to profound. Developmental “milestones”, including rolling, sitting, walking, playing with toys, using cutlery, using zips and buttons, and toilet training, are often delayed, although there is a wide range of eventual ability, with some children acquiring mobility and other skills around the same age as “typical” children and others showing more obvious delay. Low muscle tone (hypotonia) is common and may affect mobility. Some children may have an unusual gait when walking because of stiffness, or balance issues (known as ataxia). For some, independent walking may not be achieved. Many children benefit from early intervention with treatments or therapies such as orthotics e.g. insoles, braces, splints and callipers; occupational therapy (OT); and physiotherapy (PT).

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Intellectual development and learning

Most children with Phelan-McDermid syndrome have intellectual disability (ID) or learning difficulties (LD). ID ranges from mild to profound but is usually in the moderate/severe range and most children have needed additional support with their learning. Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended.

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Speech and language

Children with Phelan-McDermid syndrome typically experience some degree of speech and language delay and many may find it difficult to coordinate movement of their lips, jaw and tongue to make the right sounds (apraxia of speech). The eventual range of achievement is broad, but many may remain non-verbal. Those who do develop speech may achieve single words, short phrases or basic sentences and some go on to develop conversational skills and a broad vocabulary. Many parents say that their child can understand a lot more than they can express.

An assessment by a speech therapist should be able to identify your child's specific difficulties, allowing regular therapy sessions tailored to your child's specific areas of need. Where individuals have no speech or very few words, Augmentative and Alternative Communication (AAC) methods, including pointing, pictograms, gestures, facial expression and simplified sign language and high-tech communication systems (aided communication) have enabled some to communicate their thoughts and needs well.

> ***Find ways to communicate early on. Don't wait for someone to recommend it, whether it's using signs, a device, or a picture board. Keep trying to find ways to communicate. Just because these kids can't speak doesn't mean they don't have anything to say, or that they don't understand. Even if they start to speak, introduce a device or picture board early."***

Unique publishes a separate guide to Communication

Feeding

Feeding issues in the new-born period are common. Low muscle tone may contribute to difficulties with swallowing and some babies will suck weakly and may need high energy milks to encourage weight gain. Many babies also suffer from gastro-oesophageal reflux (GERD/GORD) (in which feeds return readily up the food passage), which may require treatment, including careful positioning for feeds, medication, nutritional supplements or, in some cases, insertion of a nasogastric tube (NGT) or percutaneous endoscopic gastrostomy tube (PEG/G-tube).

Other common chewing and mouthing behaviours include teeth grinding, chewing on inedible objects and eating inedible things (pica). Other issues that have been reported include aspiration (where fluid, food or saliva enters the airway or lungs). Some older babies and toddlers have difficulties chewing and are quick to choke (or gag) on bits of food. They therefore continue to eat pureed foods longer than their peers.

Some children have benefited from attending a feeding clinic where an assessment can be made, and advice to help treat any eating and drinking difficulties provided.

Unique publishes a separate guide to Feeding

Growth and stature

Most children with Phelan-McDermid syndrome described in the medical literature so far (2025) are noted as having growth within the expected range. Some of these children may have a larger (macrocephaly) or smaller (microcephaly) head size than expected.

Behaviour

Children with Phelan-McDermid syndrome typically tend to have behaviour in keeping with their overall degree of developmental delay, and most have a happy disposition and enjoy socialising. Many children have an autism spectrum disorder (ASD) diagnosis or traits. Other behaviours including attention deficit hyperactivity disorder (ADHD), anxiety, bipolar disorder, obsessive compulsive disorder (OCD) have also been reported.

Many children also have sleep problems. Children usually benefit from consistent routines, boundaries, rewards and other behaviour management techniques. Efforts to take into account and introduce strategies to tackle communication and other difficulties can also be beneficial.

> ***Our son is the sweetest soul. He is a calm and passive boy most of the time. Every time a behavior develops something is always wrong, trust your instincts, only you know your child. Also, if something's wrong or behaviors develop, it's almost always constipation related."***

"Catatonia is increasingly recognised in Phelan-McDermid syndrome, particularly in adolescents and adults, but it is often missed or mistaken for autism-related behaviours, depression, behavioural problems, or progression of developmental disability. Greater awareness may help families and professionals recognise symptoms earlier and seek appropriate assessment."

Unique publishes separate guides to Challenging Behaviour and Sleep

Puberty

There is limited information available about puberty in children with Phelan-McDermid syndrome. We do know that most boys and girls appear to go through puberty as expected but early (precocious) puberty has been reported in some children, more so for girls than boys (Phelan 2005 (updated 2024)). Some families of children with chromosome disorders and behavioural or learning difficulties can be particularly concerned at their daughter's ability to cope with menstruation, and for some discussing menstrual regulation options with a paediatrician may be beneficial.

Unique publishes a separate guide to Puberty

Adulthood

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

Adults with Phelan-McDermid syndrome have varying levels of independence. A few have gone on to have families of their own and manage to run their own households and work. Most continue to live with their parents or in supported settings such as a group/residential care home, with caregivers who can

provide support. A few adults with Phelan-McDermid syndrome only discovered that they had a SHANK3 variant or deletion when their child was diagnosed.

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Regression

Loss of already acquired skills (regression) occurs in some children with Phelan-McDermid syndrome. The age of onset is usually in mid-childhood, with an average age of six years. The loss of language, motor-skills and self-help skills are most commonly reported by parents. Many children recover skills that were lost and time for recovery varies between individuals. It is not yet known what causes regression in Phelan-McDermid syndrome.

Medical concerns

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

Seizures

Frequently, children with Phelan-McDermid 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. Age of onset can vary considerably, while seizures may be isolated to a single incident or occur more regularly. More than one type of seizure may be present in the same individual.

Seizure types include:

Febrile seizures: episodes only occur when the child has a high temperature, this is the most common type of seizure observed in individuals with Phelan-McDermid syndrome.

Absence seizures: change in behaviour as if the child 'switches off', sometimes with staring, eyelid flickering or lip smacking- absences are very brief often lasting less than half a minute).

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

Generalised tonic clonic: at the onset of a seizure, the abnormal electrical activity involves both sides of the brain- the seizure involves a phase of stiffening followed by jerking.

Myoclonic generalised seizures: involving jerky or shock-like contraction of different muscles anywhere in the body but usually the arms or legs- each myoclonic seizure lasts for a fraction of a second or a second at most.

Electroencephalograph (EEG) and video telemetry (video EEG) are medical tests that can be used to measure and record the electrical activity of the brain and are tools that, when used alongside other tests, can help diagnose the type of seizure experienced.

Seizures can cause a lot of worry for families and can be frightening to observe, but in most cases they self-resolve or resolve with medical treatment. There is no preference for a particular medication. 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.

Hearing

A few children with Phelan-McDermid syndrome have a hearing impairment, but hearing is unaffected in most children with this condition and hearing tests at birth often give a clear response. A hearing loss may be conductive, where sound is unable to travel effectively to the inner ear; sensorineural, where there are problems with the inner ear, sometimes with the cochlea or auditory nerve (the nerve that sends signals to the brain about sound); or a combination of both conductive and sensorineural hearing loss.

Many types of hearing loss can be managed by using hearing aids. As children are at risk of speech delay, parental concerns should be acted on early and home or school-based therapy provided.

Many children experience “glue ear”, where fluid builds up behind the eardrum, which may be made worse by unusually narrow external ear canals and excess wax in the ear canal. Glue ear is a type of conductive hearing loss and is typically treated by inserting aeration tubes (grommets) into the eardrum. This surgical operation may need to be repeated. Improved hearing may not be achieved with aeration of the space behind the eardrum (middle ear) and hearing aids may help as a temporary or longer-lasting measure, although this appears to be uncommon.

Unique publishes a separate guide to Hearing

Hands and feet

Children with Phelan-McDermid syndrome often have anomalies of the hands and feet. Most common among these is underdeveloped (dysplastic) or thin toenails but these usually become stronger as children grow. A wide variety of specific anomalies of toe and foot position are also an occasional feature. Most notable are flat feet (pes planus) and toes that are fused (syndactyly). Most children do not require any specific treatment for mild anomalies. Others may benefit from massage, orthotics and physiotherapy. Treatment is tailored to the individual child, and in some cases surgical correction will best enhance eventual mobility, though this is rare.

Constipation

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

> ***Our biggest struggles are constipation and communication. Not many doctors know about Phelan-McDermid syndrome so the parents are the advocate and the expert. I recommend seeing a neuro gastroenterologist if the child is having GI issues.”***

“Our child passes bowel motions every day and takes constipation medication daily, but can still become significantly impacted. For years, constipation was only identified on X-ray. We noticed a repeating pattern of increased agitation, hyperactivity, poor sleep which we now recognise as a sign that he is becoming impacted. Once the constipation is treated and cleared, his behaviour settles again.”

Pain

Most children with Phelan-McDermid syndrome have an increased pain threshold. As a result, they do not experience stimuli as pain, or do so much later than expected. It can be difficult to recognise that a child with Phelan-McDermid syndrome is in pain. Many children are not able to indicate or communicate associated

sensations or may show their reaction as an unusual behaviour (for example, difficult behaviour). The most important thing is that when there is a change in behaviour, pain is considered and an underlying cause is sought (for example dental problems, gastro-oesophageal reflux, constipation or an ear infection of the ears, respiratory or urinary tract), so that a targeted treatment can be considered.

A specialist therapist, for example, a physiotherapist or occupational therapist with this area of expertise, may be able to help provide an assessment and recommend appropriate support and/or therapy. This may also help with behavioural difficulties.

Sweat

Many children with Phelan-McDermid syndrome sweat insufficiently, as a result, they can overheat. It is not yet known what causes the reduced sweat production in Phelan-McDermid syndrome. This is an important health concern, children should be monitored for signs of overheating and carers should react accordingly.

Excess fluid (lymphedema)

A few children with Phelan-McDermid syndrome experience an accumulation of fluid (lymphedema), for example, in their legs. This will cause swelling because the supply and removal of fluid is not balanced. The treatment is the same as for other causes of lymphedema. This may include use of massage (to encourage drainage), compression therapy (such as pressure stockings/tight socks), elevation or exercise. At an older age the swelling can be worse. A centre of expertise for lymphedema can then help with further assessments and advice for treatment.

Teeth

Dental concerns are very common in children with chromosome disorders. A number of issues have been described by parents of children with Phelan-McDermid syndrome including:

- A mismatch between the upper and lower jaw (malocclusion)
- An unusual size of the jaw, leading to overcrowding or widely-spaced teeth
- Feeding difficulties and delayed eating and chewing activity
- Tooth grinding (bruxism), which can prematurely wear down the enamel

Most children with Phelan-McDermid syndrome developed all baby (deciduous) teeth and adult teeth. A high standard of dental care is important to minimise damage by decay and erosion (by grinding). Children and adults may also benefit from specialist hospital dental services and may require treatment under general anaesthetic.

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

Brain

Some children 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:

- Partial/complete absence (agenesis) of the white matter connecting the two halves of the brain (corpus callosum)
- Fluid filled sacs on the surface of the brain (arachnoid cysts)
- Slow insulation of nerve fibres (delayed myelination)
- Thinning of white matter in the brain
- Larger than normal ventricles of the brain (ventriculomegaly)
- An enlarged space around the brain

Kidney and urinary tract

Some babies with Phelan-McDermid syndrome are born with anomalies of the kidneys or urinary tract. Urinary tract infections (UTIs) are relatively common and may need to be treated with antibiotics. Repeated urinary infections may require preventive treatment with antibiotics.

Reported anomalies include an enlarged kidney(s) (hydronephrosis) due to a build-up of urine inside, which may sometimes be diagnosed during mid-pregnancy anomaly scans. In mild cases this requires monitoring but no treatment. More serious cases can cause UTIs, which can be treated with antibiotics or, very occasionally, a catheter may need to be inserted to remove the build-up of urine and prevent damage to the kidney. Kidney (urethral) reflux, where urine flows upwards from the bladder back up to the kidney, potentially damaging the kidneys and leading to frequent UTIs, has also been reported. Other conditions that have been described include cases of babies born with only one kidney; a horse-shoe kidney, where the bottom points of the two usually separate kidneys are joined, creating a U (horseshoe) shape; and cystic kidneys, where fluid-filled sacs form in the kidneys, usually during foetal life. A solitary cyst may not interfere with function unless it is large, but multiple cysts may stop the affected kidney from working. A multicystic kidney may be removed if it is causing discomfort. The important thing is to ensure optimal functioning of the other kidney.

Eyes and sight

Problems with eyes and vision are uncommon in children with Phelan-McDermid syndrome. A wide range of conditions have been reported and an individual may have more than one vision or eye-related concern. Known concerns include short or long-sightedness (myopia and hypermetropia), which can usually be corrected by glasses; a squint (strabismus), where one eye or both turns inward, outward, up or down, which may be treated with patching, glasses, exercises or surgical correction; a “lazy eye” (amblyopia), and droopy upper eyelids (ptosis). Some individuals may find it harder to process cluttered images and have trouble judging how far away things are (depth perception).

“As a parent of a child with Phelan-McDermid syndrome and a diagnosis of CVI, I feel this is an area that may be under-recognised. My son’s CVI was only identified by an Occupational Therapist relatively recently, despite longstanding difficulties. I am aware that CVI is recognised within the PMS community and may be more prevalent than is currently reflected in the literature. Increased awareness could help families access assessment and support sooner.”

Heart

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

ASD (atrial septal defect): a hole between the top two chambers of the heart.

TAPVR (total anomalous pulmonary venous return): the pulmonary veins connect to the right side of the heart rather than the left.

PDA (patent ductus arteriosus): failure of closure of the tube that carries blood between the aorta and the pulmonary artery during the foetal period.

Aortic regurgitation: the aortic valve does not close properly.

Tricuspid valve regurgitation: the tricuspid valve does not close properly so blood leaks back into the heart

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

Hormones

Children with Phelan-McDermid syndrome may have conditions that affect their hormones. These conditions include early (precocious) puberty which is more common in females than in males, and an underactive thyroid (hypothyroidism).

Breathing

Babies and children with rare chromosome and gene disorders tend to have a higher rate of respiratory concerns, which may become less frequent with age and maturity, although they can persist throughout childhood. Children may be prone to upper respiratory infections and other issues may include sleep apnoea (when there is an abnormal breathing pattern during sleep).

Palate

Anomalies of the palate (roof of the mouth), most commonly a high/arched palate which is usually invisible to the casual onlooker, have been reported. Anomalies of the palate can occasionally cause difficulties in feeding, hearing, teething and speech production and surgical repair may ease these problems.

Chromosome 22q13.33 deletions

The information in this guide concerns children and adults with a variant in one copy of their SHANK3 gene. The information is also of use to individuals who have a deletion (loss of genetic material) at the end of the q arm of chromosome 22 (a 22q13.33 deletion or microdeletion) that includes the SHANK3 gene. 22q13.33 deletions can vary considerably in size and involve one, a few or multiple additional genes that may have different additional effects on health and development.

Unique publishes a separate guide to 22q13 Deletions Phelan McDermid Syndrome

Ring chromosome 22

Some people with Phelan-McDermid syndrome have a deletion of genetic material from one or both ends of chromosome 22, and the ends join together to form a ring chromosome. The deletion of genes from the end of the q arm of chromosome 22 and formation of a ring chromosome can cause additional health concerns.

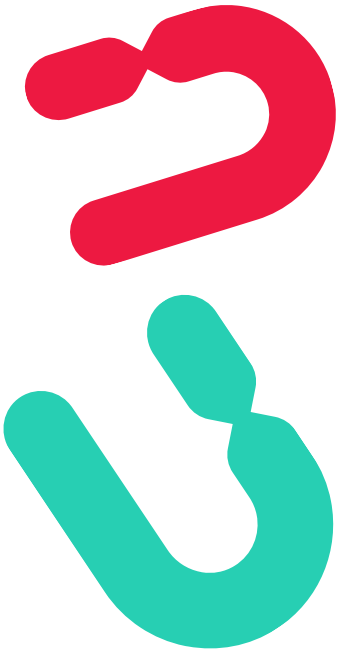
Unique publishes a separate guide to Ring 22

How common is Phelan-McDermid syndrome?

Phelan-McDermid syndrome is extremely rare. Currently (2025) over 600 individuals with a SHANK3 gene variant have been reported in the medical literature, but more are known to have been diagnosed. It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

Why did this happen?

When children are conceived, their parents' genetic material (DNA) is copied in the egg and sperm that makes a new child. The biological copying method is not perfect, and random changes occur in the genetic code of all children that are not seen in the DNA of their parents. This happens naturally and is not due to the parents' diet, environment or lifestyle. Most of these DNA changes have no obvious effect. But in rare instances these random DNA changes can lead to health issues or affect development. When such a random change disrupts the function of the SHANK3 gene then a child will have Phelan-McDermid syndrome. In most people identified so far (2025) with Phelan-McDermid 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. Rarely, one parent may have a chromosomal rearrangement that led to Phelan-McDermid syndrome in their child, or one parent may have the same change (or variant) in some of their egg or sperm cells and pass it on to their child (this is known as germline mosaicism). In some families with Phelan-McDermid syndrome, a parent was found to be a carrier of a balanced chromosomal rearrangement. This is when a piece of chromosome is relocated, usually onto a different chromosome, but no DNA is lost. When a child is conceived, the change in the parent's chromosome(s) can lead to a deletion in one or more of the child's chromosomes. This parent therefore has a higher probability of having further children with Phelan-McDermid syndrome.



Unique publishes a short general guide to balanced translocations

However, it is important to recognize 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 most people reported with Phelan-McDermid syndrome so far [2025] the genetic alteration has been found to be de novo (dn), which means neither parent was found to have the same SHANK3 gene change as their child, and neither parent was found to have a chromosomal rearrangement that might have resulted in a SHANK3 deletion in their child. Therefore, the chance of having another child with Phelan-McDermid syndrome is usually less than 1%.

One reason why there is some residual chance of recurrence is due to the rare phenomenon called germline mosaicism that was mentioned above. This is when a parent carries a genetic change, but it is limited to some of their egg or sperm cells. The genetic change would not, therefore, be detected in the parents' blood tests.

Unique publishes a short general guide to Mosaicism

In families where the SHANK3 variant has been inherited from a parent, the possibility of having another child - either a girl or a boy - with Phelan-McDermid syndrome rises to 50% (1 in 2) in each pregnancy. However, the effect on the child's development, health and behaviour cannot be reliably predicted. Your genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a SHANK3 variant goes on to have children of their own, the chances of passing on the variant to their child are 50% in each pregnancy. Your child's ability to look after their own child is very likely to be closely related to their own learning ability and behaviour and most individuals with Phelan-McDermid syndrome do not go on to have children.

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

Unique publishes separate guides to Planning your next child, Prenatal genetic testing and diagnosis, A clinical genetics appointment and Supporting siblings of children with a rare genetic condition

Can Phelan-McDermid syndrome be cured?

There is no cure for Phelan-McDermid syndrome since the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and interventions can be put in place.

Management

The first guidelines for assessing and monitoring individuals with Phelan-McDermid syndrome were published in the medical literature in 2014. Since then, numerous professionals in multiple different specialities have worked together and with families to update clinical practice guidelines (Srivastava 2023).

Children and adults with Phelan-McDermid syndrome should be under the care of a multidisciplinary team. The team should include a geneticist and paediatrician (doctor for children) who can oversee care so that development and behaviour can be monitored, and the best help given in the form of physiotherapy, occupational therapy, speech therapy and, if needed, behavioural therapy. Individuals may have evaluations with neurology, ophthalmology, audiology, gastroenterology, cardiology, endocrinology, urology and nephrology.

The Phelan-McDermid syndrome Medical Advisory Committee offers information regarding **important treatment considerations** and has noted that many individuals with Phelan-McDermid syndrome have significant difficulty tolerating some psychiatric medications that are commonly prescribed for behavioral, mood and anxiety disorders as well as sleep disturbance. The committee has also noted that some individuals experience a significant adverse reaction to anesthesia.

Immediately following diagnosis

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

Supportive care

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

How a person with Phelan-McDermid syndrome is supported may require coordinated care by a team of specialists, which may include a/an:

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

Gastroenterologists – a doctor who specialises in the digestive system.

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

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

Cardiologist – a doctor who specialises in heart conditions.

Endocrinologist – a doctor who specialises in hormones and their effect on the body.

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

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

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

Ophthalmologist – a doctor who specialises in conditions affecting the eyes.

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

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

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

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

Psychiatrist – a doctor who specialises in mental health.

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

Treatments and therapies

Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended. An education, health and care plan (EHCP) in the UK, an individualized education plan (IEP) in the US or equivalent document in other countries, may be issued after a child has undergone an assessment,

to help ensure that the educational, health and social provisions deemed necessary to support the child's needs are delivered.

Treatment will depend on the specific features and symptoms experienced by the person with Phelan-McDermid syndrome but may include:

Physiotherapy for mobility and muscle strength, which usually includes gait training to improve standing and walking.

Occupational therapy for fine motor skills, sensory processing and self-care skills, which can include sensory integration therapy to help sensory sensitivities related to intellectual disabilities and regulate responses to sensory input.

Speech therapy for speech and language delay, which can include apraxia therapy to help coordinate movement of lips, jaw and tongue to make correct sounds.

Behavioural therapy for intellectual disabilities and autism, ADHD, anxiety or other behaviours, which can include applied behaviour analysis (ABA) to teach new skills and reduce challenging behaviours.

Medications may be prescribed such as antiepileptics drugs; sleep aids including antihistamines; and stimulants and anti-anxiety drugs for seizures, sleep issues, and behavioural difficulties.

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

Surgery, such as grommet insertion to improve hearing following 'glue ear' or middle ear infections.

Surveillance

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

- Regular dental check-ups
- Consider a palate review (particularly if there are feeding difficulties or speech concerns)
- Consider a cardiac review
- Consider a neurologic review (including MRI and EEG, if indicated by seizures)
- Consider an annual audiology review
- Consider an annual ophthalmology review
- Consider an abdominal ultrasound and review

Research into new treatments for Phelan-McDermid syndrome

The genetic change causing Phelan-McDermid syndrome affects 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 Phelan-McDermid syndrome, like autism spectrum disorder, is ongoing. In addition, although Phelan-McDermid syndrome is a relatively rare condition, the SHANK3 gene is the subject of a lot of research. One avenue of research is to identify the link between SHANK3 variants and common Phelan-McDermid syndrome symptoms including epilepsy and developmental delay to provide more effective treatments.

Details of clinical trials related to a particular condition or gene can be found at **ClinicalTrials.gov** and **EU Clinical Trials Register**. There are currently (2026) a few clinical trials in progress for SHANK3-related Phelan-McDermid syndrome.

Families say ...

Hearing the news that our son would never catch-up to his peers was hard. Reading all the possible complications was scary. We grieved the loss of the life we expected for our son and for our family. But with a diagnosis we found strength in preparing for his future and giving him the tools to be successful in his life. We are accessing regular speech therapy, occupational therapy and physical therapy and while progress is slow it is visible. Everyday he brings an abundance of joy to our lives and everyone he meets. He is very sociable and loves being around other children. Having a diagnosis has enabled us to connect with a community of families through the Phelan-McDermid Syndrome Family Support Group on Facebook. It is wonderful to see the achievements of every child and to have a place to ask questions from those with lived experience."

"Rely on the other Phelan-McDermid Syndrome families, the Phelan-McDermid Syndrome Foundation and CureSHANK. These 3 resources are a wealth of knowledge that will help you constantly and they are invaluable. You are not alone."

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2025, Unique had 19 members with a SHANK3 variant and Phelan-McDermid syndrome, and over 200 members with a 22q13.33 deletion and Phelan-McDermid 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 (**https://pubmed.ncbi.nlm.nih.gov/**).

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

Inform Network Support

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

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Phelan-McDermid syndrome specific websites and Facebook pages:

- Phelan McDermid syndrome foundation
- CureSHANK
- CureSHANK Facebook page

This guide was written by Dr Adam Hodgson, Duncan Baker, Molly Durbidge, Haien Chen, Dr Sarah Patterson | Julia Garnham Centre, The University of Sheffield and Sheffield Children's NHS Foundation Trust in Partnership, and Unique (AP) and verified by Dr Emily Woods, Clinical Genetics Registrar | Sheffield Children's NHS Foundation Trust, UK.

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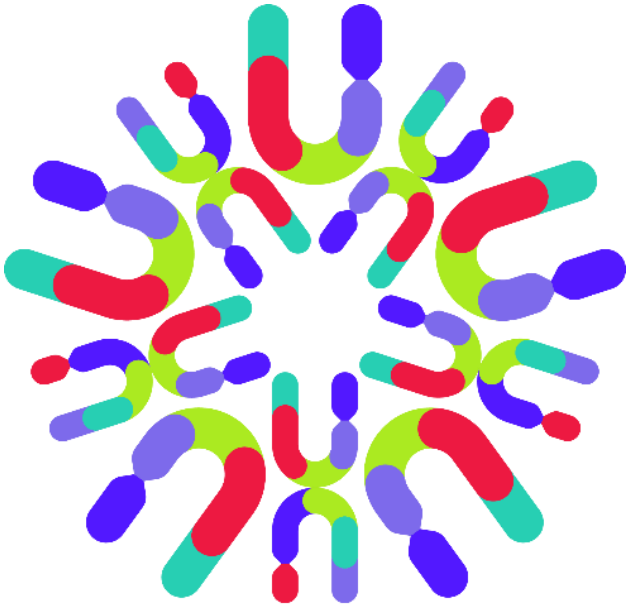

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