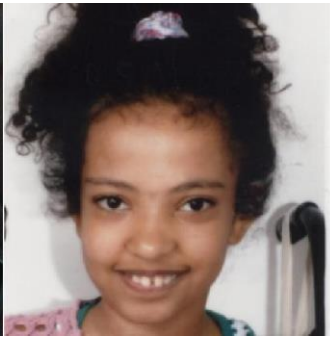
Understanding Chromosome & Gene Disorders

Phelan-McDermid syndrome: 22q13 deletions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Phelan-McDermid syndrome: 22q13 deletions

A 22q13 deletion is a rare genetic disorder caused by a missing piece of genetic information from chromosome 22. As with many other genetic disorders, the missing piece of chromosome increases the risk of having developmental delay, medical problems and difficulties with learning and behaviour. How each person is affected varies greatly.

Chromosomes are made from DNA, they are located in the cells in our body and contain our genetic information (genes). Normally each cell has 23 pairs of chromosomes, so 46 in total. Half of these chromosomes come from the mother and the other half from the father. Chromosomes are numbered from 1 to 22, mainly based on their length; in addition, there are the sex chromosomes that determine whether someone is genetically a boy or a girl (girls have two X chromosomes (XX) and boys have an X and a Y chromosome(XY)). Each chromosome has a short arm (p) and a long arm (q).

In a 22q13 deletion, one chromosome 22 is intact and the other chromosome 22 is missing a part of the long q arm. The size of the missing part varies between individuals. The deletion occurs equally often in boys and in girls.

The first description of a child with a 22q13 deletion was published in a medical journal in 1985. The name "Phelan-McDermid syndrome" refers to the people who first described the condition: Katy Phelan and Heather McDermid. Although there are differences between people with a 22q13 deletion, there are also similarities; this is called a syndrome, hence the term Phelan-McDermid syndrome or 22q13 deletion syndrome or, more accurately, 22q13.3 deletion syndrome (Watt 1985; Phelan 1992; *Unique*). In the Netherlands, it has been estimated that Phelan-McDermid syndrome occurs in approximately 1 in 30,000. This is probably an underestimate, because the diagnosis is often made later in life.

Looking at 22q

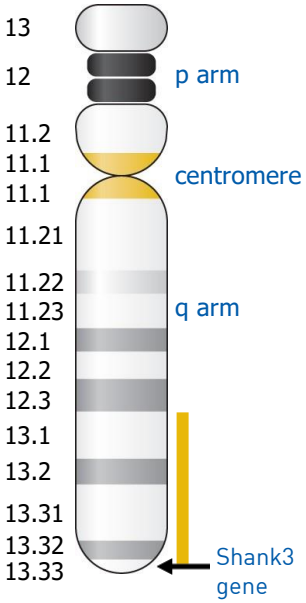
Chromosomes can't be seen with the naked eye, but when they are stained and magnified under a microscope it can be seen that each chromosome has a distinctive pattern of light and dark bands. By looking at chromosomes in this way it is possible to see the point (or points) where the chromosome is broken and roughly how much genetic material is missing. However, this type of classical chromosome analysis is not able to identify very small deletions and when it was in common use many years ago, people with very small deletions will have most likely remained undiagnosed. It has been reported that more than 30% of people with Phelan-McDermid syndrome needed two or more chromosome studies in order to identify their deletion. Partly for this reason there are certainly people, especially if they have had genetic testing done a long time ago, in whom the 22q13 deletion has not yet been diagnosed. Nowadays, more sensitive techniques are used (e.g. SNP array), which are able to detect much smaller deletions.

In Phelan-McDermid syndrome, part of the long (q) arm of chromosome 22 is missing. This may be a pure deletion and no other chromosome is involved (this has been found in about 80% of people), or it may be accompanied by a loss or gain of genetic material, following an exchange between chromosome 22 and another chromosome (this has been found in about 10% of people), or a ring chromosome may have formed (where part of the long arm and the short arm of chromosome 22 is lost and the two ends join together to form a ring; this has been found in about 10% of people).

It is important that everyone with a 22q13 deletion is investigated for an unbalanced chromosome exchange (this is called an unbalanced translocation and can be tested using a laboratory technique called FISH) or a ring chromosome (this can be identified using a classical chromosome staining technique). Research into an unbalanced translocation is necessary to determine whether it is likely that a family can have further children with a 22q13 deletion. Identifying whether a person has a ring chromosome 22 is important because extra checks are recommended due to an increased risk of tumours of the central nervous system (for more information, see page 15).

Most deletions of 22q13 lack the end of the chromosome (these are called *terminal deletions*). Sometimes the middle part of the q arm is missing (this is called an *interstitial* deletion) (Romain 1990; Fujita 2000; Wilson 2008).

The image opposite is a schematic representation of chromosome 22 showing how each band is numbered. Bands are numbered outwards starting from where the p and q arms meet at a place called the centromere. A lower number such as q11, lies near the centromere (bands nearer the centromere are known as proximal). A higher band number like q13, lies closer to the end of the chromosome (this is known as distal).



Sources

Some of the information in this leaflet comes from the published medical literature. The first author and publication date are mentioned so you can look up the abstracts or original articles in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). You can also receive most articles via Unique. Additional information comes from two studies of *Unique* members from 2004 and 2008, with reference *Unique*. When this information was written, *Unique* had 62 members with a pure 22q13 deletion with no loss or additional material from any of the other chromosomes, 72 members with a ring chromosome 22 and 16 members with involvement of another chromosome. These members range in age from very young children to an adult of 40 years.

In many more people, described in the medical literature and members of *Unique*, there is loss of or extra material from another chromosome in addition to the 22q13 deletion, usually as a result of a change called a translocation. These people may have additional features related to their other genetic changes and so are not considered in this guide. *Unique* has an overview of these people from the literature and the karyotypes *Unique* members is available on request.

In 2018, a Dutch guideline for the medical care and guidance of people with 22q13 deletion syndrome was published. A survey among parents was conducted for this guideline and parents were asked what the most important problems were for them. The guideline was written by a group of medical specialists and parents and can be found in the guideline database:
https://richtlijnendatabase.nl/richtlijn/22q13_deletiesyndroom_pms/startpagina_-_22q13ds_pms.html.

In 2020, the information from this Dutch guideline was added to this *Unique* leaflet.

The missing piece of genetic material in region 22q13 contains an important gene called SHANK3. This gene codes for the SHANK3 protein, which is necessary for proper signalling between nerve cells and for normal brain development. In Phelan-McDermid syndrome, there is a deficiency of SHANK3 protein in nerve cells, which impairs signalling. As a result, the development and function of the brain is affected. The lack of a single SHANK3 gene is currently considered the main explanation for the overall developmental delays, speech and language difficulties and behavioural difficulties found in people with a 22q13 deletion (Luciani 2003; Wilson 2003). However, SHANK3 deficiency does not explain everything, as there are differences between people with Phelan-McDermid syndrome. These differences are probably due to the fact that other genetic factors are also important for development, such as the different genetic backgrounds of each person but also the size of the deletion and other genes that may be involved as well as environmental influences (for example, good support and guidance).

Diagnosis: the karyotype

Your clinical geneticist or genetic counsellor will be able to tell you exactly where your child's chromosome has broken and which piece of chromosome 22 is missing. You will most likely be given a detailed description of your child's results. This may include a karyotype, a picture of your child's chromosomes.

For a 22q13 deletion, identified by a classical staining technique, the description is likely to look something like the following:

46,XX,del(22)(q13.3)

46 The number of chromosomes in your child's cells.

XX The two sex chromosomes (XY for a boy, XX for a girl).

del A deletion, genetic material is missing.

(22) The deletion is in chromosome 22.

(13.3) The chromosome has a breakpoint in band 22q13.3, and material from this point to the end of the chromosome is missing.

The diagnosis may have been made with a different analysis, for example a SNP array. If so, the result will look something like the following example:

arr[hg19] 22q13.32q13.33(48624809-51169045)x1

arr The analysis was done using an array based technique.

hg19 Human Genome build 19. This is the reference DNA sequence against which the sample DNA was compared. This will change as more information about human DNA becomes available. When this happens, scientists agree on a new DNA sequence to compare a patient's DNA to.

22q13.32q13.33

Material is missing from band q13.32 to band q13.33 on chromosome 22.

48624809-51169045

Base pairs 48,624,809 through 51,169,045 are missing. If you subtract the smallest number from the largest number, you get 2,544,236 base pairs (2.54 million base pairs or 2.54 Mb for short). This is the size of the deletion.

x1 One copy of this piece of DNA is present in cells as opposed to the expected two (since we have two copies of chromosome 22).

Are there people with a 22q13 deletion who are healthy, have no major medical concerns or birth anomalies and have developed normally?

Yes, but this is very rare. In some people with a very small deletion, the deletion seems to have milder consequences. One mother described in the literature with a small deletion attended a standard primary school. She had speech difficulties which improved with speech therapy, although her speech continued to sound nasal. She had a long face and a large head, but otherwise there was no noticeable physical effect of the deletion. She was not diagnosed with the deletion until her son was diagnosed with hypotonia, speech problems and learning difficulties. Another child with a small deletion of 130 kilobases (kb: thousand base pairs of DNA) at the end of 22q13 had only a slight developmental delay and mild speech problems (Wong 1997; Wilson 2008).

Most common characteristics

Each child with Phelan-McDermid syndrome is unique, and has their own specific areas of medical and developmental concern. At birth, the characteristics of Phelan-McDermid syndrome are usually subtle or absent. Often a delayed development or muscle weakness (hypotonia) is the first or only indication that something is not as expected. The characteristics described here do not occur in all children. The severity of the individual characteristics can also vary greatly between children. Despite this, there are some common characteristics:

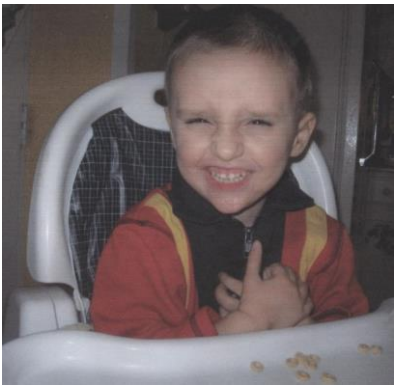
- Severe delay in, or failure to develop speech
- Learning disabilities or intellectual disabilities
- Subtle external body features
- Behavioural difficulties, usually fitting within an autism spectrum disorder
- Low muscle tone (hypotonia)

Pregnancy

Most mothers experienced no problems during pregnancy and had a normal delivery. Of the 25 families participating in the *Unique* study, two mothers reported that their baby moved less during pregnancy, two were small for gestational age, and four were born prematurely (between 33 and 34 weeks). Ultrasound revealed kidney anomalies in three babies: one had a larger kidney than the other, a second had reflux in one kidney, and a third had kidneys with multiple cysts. Ultrasound examination in the third baby also showed enlarged ventricles at 27 weeks of pregnancy (*Unique*).

There are a few descriptions in the medical literature of a prenatal diagnosis of Phelan-McDermid syndrome (following amniocentesis). In such cases, a DNA sample was taken from the fluid surrounding the baby (amniotic fluid) because unusual findings were observed during an ultrasound scan during pregnancy. Other reasons for the test were the mother's age (for older mothers), or because a blood test showed an increased risk that the mother was pregnant with a child with Down's syndrome. In one pregnancy, the parents opted not to carry the pregnancy to term. Three of the six children diagnosed during pregnancy had a mosaic form of a 22q13 deletion. This means that the deletion is

in some, rather than all, cells (Phelan 2001b; Maitz 2008). This diagnosis is not usually made during pregnancy since structural changes to internal organs are not common in people with Phelan-McDermid syndrome.



5 years

Feeding and growth

Chewing and swallowing difficulties occur in more than 50% of people with Phelan-McDermid syndrome. Common problems include low muscle tone, dental problems (including an open or high palate or widely spaced teeth) and typical chewing and mouthing behaviour. These include teeth grinding, chewing on inedible objects and eating inedible things.

Low muscle tone can cause a child to suck weakly and have difficulty swallowing. A baby with a high palate may also have difficulty drinking. Some mothers had difficulty breastfeeding and switched to bottle feeding. Seven of 14 mothers in the *Unique* study successfully breastfed for some time until the child switched to solid food. One of the 14 babies was temporarily tube-fed and one had a temporary gastrostomy tube placed (through which food is fed directly into the stomach).

Low muscle tone can also make a child vulnerable to gastroesophageal reflux (where food flows from the stomach back into the oesophagus). In the *Unique* survey 43% of babies with Phelan-McDermid syndrome suffered from reflux. Other studies have reported similar figures, with 30-50% of people with Phelan-McDermid syndrome having gastroesophageal reflux (Phelan and McDermid 2012; Sarasua 2014). Gastroesophageal reflux can generally be controlled by offering food in smaller portions, keeping the child upright when drinking, and slightly raising the head section of the bed when necessary. If this does not help sufficiently, food thickeners and antacids may be prescribed. If these measures are not enough, surgical intervention to improve the valve function of the stomach (fundoplication) may be considered (*Unique*).

Some older babies and toddlers have problems chewing and are quick to choke (or gag) on bits of food. They therefore continue to eat pureed foods longer than their peers. Parents indicate that changing the texture of the food by grating, chopping, using the slicer or adding sauce can help (*Unique*).

After the baby phase, appetite is almost always normal. Some children develop a large appetite and say they really like to eat (*Unique*).

“ She was breastfed exclusively for a year although it was very slow **”**– now 4½ years

“ As a baby she was re-admitted to hospital due to weight loss and she could not keep feeds down. She has a big appetite now **”** – 12 years

“ She has never had any feeding problems **”** – 13 years

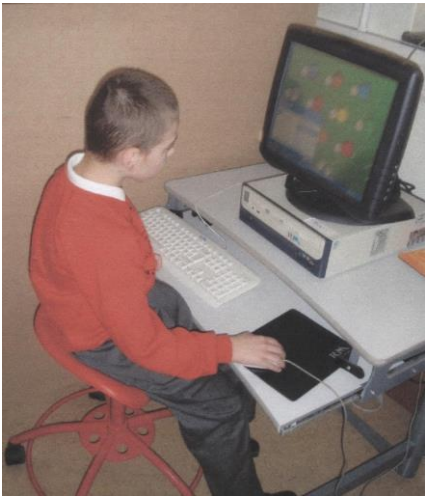
Despite some children having feeding problems at an early age, almost all children with Phelan-McDermid syndrome grow as expected (Phelan 2008, Rollins 2011).

“ She has accelerated growth. She is very tall with large fleshy hands and feet ” – 10 years

“ He was average height until he was about 6 years and then he started to have growth spurts. He is now tall for his age and of slim build ” – 10½ years

Appearance

Most people with Phelan- McDermid syndrome do not have a distinctive facial appearance. Some people have subtle features such as broad and straight eyebrows, full eyelids with long eyelashes, full cheeks, a broad nose with a bulbous nasal tip, a pointed chin or large ears. Large fleshy hands and feet, malformed nails, and widely protruding teeth of adult dentition have also been identified. Many children with Phelan-McDermid syndrome differ little in appearance from their brothers, sisters or parents (Cusmano-Ozog 2007; *Unique*). It is therefore difficult to suspect Phelan-McDermid syndrome on the basis of physical features.



9 years

Learning

Learning difficulties and intellectual disability are common to most children with Phelan-McDermid syndrome. There is always individual variation and a small proportion have little difficulty learning. Most children benefit greatly from early intervention programs and may be best placed in a special learning environment. Most of *Unique*'s children go to special education. A small number attend a regular school and receive one-to-one guidance in the classroom (Phelan 2008; *Unique*).

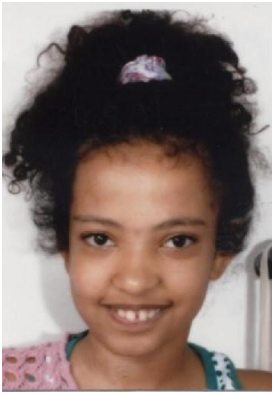
Some children lose previously acquired skills (most pronounced in the speech/language area). There is no conclusive explanation yet for this loss of skills. Some children with Phelan-McDermid syndrome are easily distracted. Learning can therefore be a great challenge. Many parents note that learning often goes better when it is done in the form of a game or with the help of music and songs (*Unique*).

“ Anything that is sung or associated with music works best to help him to learn ” – 5 years

“ She has made steady progress over the years and is improving all the time ” – 12 years

“ Music, which she loves, helps her to learn ” – 13 years

Speech and communication



8 years

The most problematic area of development in children with Phelan-McDermid syndrome is speech and language development. This is often severely delayed or can be absent. Some children with Phelan-McDermid syndrome never learn to talk. Language comprehension is usually better than language expression - many children understand much more than they can express. This becomes evident when they show that they understand words and follow instructions, respond when asked to perform tasks, demonstrate a sense of humour, and show emotion (Phelan 2001a; Cusmano-Ozog 2007; Phelan 2008; *Unique*).

Research has shown that children often start babbling at the expected age. Some children speak their first words around the age of 1, others much later. Sometimes children forget words they spoke earlier. This is often in early childhood, around the age of 4

Intensive speech therapy and training in communication skills do help somewhat. The 2018 national guideline recommends starting to support and guide speech/language development as early as possible, preferably around the first year. This requires a referral to an audiology centre, speech therapist or multidisciplinary team. Despite this, verbal communication often lags behind significantly. There is also individual variation in this area, but the experience of the *Unique* parents is that most children have a large speech delay. The most capable speaking children talk in sentences of several words and are quite understandable to strangers. There is only one *Unique* child who speaks in sentences. The medical literature confirms this picture: almost all children have severe speech difficulties, in half of the children spoken language is completely absent and only a small minority can formulate sentences (Phelan 2008; Philippe 2008; Sarasua et al. 2014; *Unique*).

Some *Unique* children have learned sign language. Communication via a picture exchange communication system (PECs) can also support communication. Children are also able to communicate via eye contact, pushing and pulling and sounds. A speech computer with a touch screen can be used to improve communication and some children clearly benefit from this. Adapted sports, music therapy and sensory integration (link between perception and the activity that follows it) sometimes increase the child's alertness and perhaps enhance their ability to communicate (Phelan 2008; *Unique*).

There may be several reasons for the delay in speech development. One of them is low muscle tone, which is common. If the mouth muscles are weak, it is more difficult to learn to speak. Another reason is that the ability to learn also affects the extent to which the child learns to speak (learning to understand and use language is one of the most difficult processes in development). Hearing loss due to recurrent middle ear infections can also cause speech delays.

❝ PECs, Makaton, singing, clapping games and music therapy have all been great motivators ❞ – 4 years

❝ His comprehension is that of a 'normal' 5-year-old but his ability to express himself is at the level of a 2-year-old ❞ – 5 years

❝ He uses signs, gestures and some vocal noises. He takes my hand to show me that he needs help with something. He has had some loss/regression of words. He uses some words for a long time (3 months) and then they are gone. Some have come back again, but some haven't ❞ – 6½ years

❝ She understands more than she can express ❞ – 9½ years

❝ He makes lots of vocal noises. He has taken well to boardmaker symbols [picture communication symbols] ❞ – 10½ years

❝ He will take you to wherever he wants you to go and will now point. He is getting more and more vocal noises and is louder. He has excited body movements for 'yes' and pushes away for 'no' ❞ – 11 years

❝ She has very little speech, only a few words (Mum, Dad etc.). Her understanding is improving all the time. She helps to lay the table and will tidy up when asked. She uses some Makaton signs ❞ – 13 years

13 years

Sitting and walking (gross motor skills)

Some children reach their milestones in motor development within the expected age range, but delays in this are common. On average, children can sit up at around 18 months, crawl at 17 months (although some do not crawl) and walk at 33 months. The *Unique* experience is that babies start rolling over between 2 months and 2 years (average 8 months), sit up between 6 months and 4 years (average 15 months) and crawl between 8 months and 4 years (average 19 months). Incidentally, some children prefer to move about by hopping like bunnies or sliding on their buttocks. Walking was learned between the ages of 1 year and 9 years (mean 34 months) (Phelan 2001a; *Unique*).

Lagging motor development may be partly due to low muscle tone (hypotonia). Sometimes the hypotonia affects the whole body, sometimes only the upper part. The earliest signs of hypotonia may be visible immediately after birth, but this is not always the case. Babies with severe hypotonia are very limp and learn to hold their head up later than average.

If motor development is lagging behind, it helps to start physiotherapy and/or occupational therapy early on. Other activities, such as swimming and hydrotherapy, can also help in the development of muscle strength and motor skills. A physiotherapist or paediatric rehabilitation specialist can also advise parents on the use of aids such as a walking aid, standing aid, adjustments for proper sitting and suchlike (Koolen 2005; *Unique*). A poor sense of balance and some children's overly mobile joints can contribute to developmental delay (*Unique*).

Once a child with Phelan-McDermid syndrome starts walking, they usually continue to move rather precariously with an unusual gait. Children can stumble easily and may need protection or support, especially since there is often a lack of a sense of danger. Many children tire quickly and in early childhood require a wheelchair for when they go outside and sometimes when they are inside (*Unique*).

Most children eventually learn to run, jump, throw, catch and climb. Most *Unique* children have learned to swim and ride a bike. Some can ride scooters, ride horses, jump on trampolines, ski and roller skate, but this is not feasible for everyone (*Unique*).

“ He crawls and is walking with the support of an adult or Kay walker. He crawls up stairs and slides down on his bottom **”** – 4 years

“ With support he can walk. He can sit and swivel on the spot but cannot crawl due to poor arm strength **”** – 4½ years

“ She bunny hops and has started to walk with assistance – 4½ years

“ His hypotonia seems to be in his upper body: he is much stronger in his legs and hips than in his arms **”** – 6½ years

“ She cannot walk. She gets around on her knees by bunny hopping. She needs a wheelchair for daily living and she has a walking frame which she uses daily. She loves to swim wearing arm bands **”** – 10 years

“ He has flat feet and is pigeon-toed and has insoles in his shoes. He runs with an odd gait and has poor co-ordination. He loves football and kicks with his left foot. He can pedal a 3-wheeled bike and can use a scooter for a couple of paces. He cannot jump. He loves swimming **”** – 11 years

“ She had very severe mobility problems at a younger age. It has improved with age and she walks now **”** – 12 years

“ She had hypotonia when she was very young but she has grown out of it **”** – 13 years

Eye-hand coordination, fine motor skills and independence

Muscle weakness (hypotonia) can also affect the development of fine motor skills in children with Phelan-McDermid syndrome. Children need more time to reach for and pick up toys and to hold a bottle. Later, this can also cause difficulties with dressing (zips and buttons can be especially difficult) and holding a pen. Special cutlery with thicker handles, cups with handles and cutting food into pieces can help. For children who have difficulty holding and using writing tools, a keyboard can be helpful. Help from an occupational therapist in finding and learning to use aids is usually very valuable.

Despite this, many children have long-term difficulties with fine motor skills (*Unique*). As a result, children will continue to need help with dressing and undressing for a long time. They will also be dependent on help with things such as teeth cleaning and washing.

Going to the toilet is also something that usually requires a lot of practice. Some children have periods when potty training works, but only a few are fully potty trained by mid-childhood. This is also evident from the information provided by *Unique*. While some children manage to become potty trained at a young age, most did not achieve this until much later. Only two of eight children aged 4 to 8 years were able to control their bladder at night (Philippe 2008; *Unique*).

9 years

❝ He still doesn't have pincer grip or the ability to point ❞ – 4 years

❝ He is in nappies all of the time. He cannot wash or brush his teeth, although he likes to grab the toothbrush. He cannot dress/undress himself but if a T-shirt is put over his head he will pull it down ❞ – 4½ years

❝ He does not feed himself but can hold a cup to his mouth and drink a little ❞ – 9 years

❝ He can feed himself with a spoon but cannot use a fork. He drinks using a sports cup. He can take his shoes and socks off himself ❞ – 11years

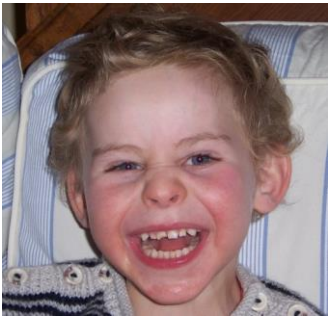
❝ She has poor co-ordination. She is in nappies full-time. She cannot brush her teeth or dress herself but will help and knows what to do, she just cannot do it fully on her own ❞ – 12 years

❝ She is clean and dry during the day and uses the toilet herself ❞ – 13 years

Growing up with Phelan-McDermid syndrome

14 months

2 years



4½ years

Medical concerns

Epilepsy

Epilepsy is more common in children with Phelan-McDermid syndrome than in healthy children in the general population, estimated to occur in approximately 25% (Kolevzon 2014) to 33% (*Unique*). Another study found that the incidence of epilepsy in this syndrome increases with age (Sarasua 2014). Thus, it is possible that epilepsy develops after childhood. In general, the epilepsy is well controlled with medication. There is no preference for a particular medication (Phelan 2008; Holder and Quach 2016; *Unique*).

Kidneys and urinary tract

People with Phelan-McDermid syndrome have an increased risk of being born with a kidney anomaly or other renal feature. This was the case in approximately 30% of *Unique* children, a particularly enlarged renal pelvis (hydronephrosis) and/or frequent urinary tract infections were reported. Hydronephrosis can occur when the urine cannot be drained from the kidney to the bladder. Often, this is caused by a blockage in the ureters (the tubes that carry urine from the kidneys to the bladder). Two children had a non-working kidney and reflux (when urine from the bladder goes back into the kidney) in the other kidney. Another child, who also suffered from such reflux, underwent ureter reimplantation. This surgery is done when the ureter is not positioned correctly in the bladder causing reflux. In this operation, the ureter is detached from the bladder and reinserted correctly (*Unique*).

Eyes and vision

In some children, there is a delay in visual development. The child is then less able to focus and follow things than would be expected. Approximately 20% of children with Phelan-McDermid syndrome have a squint or a lazy eye (*Unique*). A minority of children cannot see in 3 dimensions (3D) or cannot see depth. Farsightedness and nearsightedness have also been described in several children (Phelan 2008; *Unique*).

Ears

Hearing problems can occur in children with Phelan-McDermid syndrome. A number of children suffer from regularly recurring ear infections. Forty percent of families questioned by *Unique* reported that their child had experienced fluid accumulation in their middle ear (called glue ear) or experienced middle ear infections. A glue ear usually disappears as children get older and their ear tubes widen, making them less likely to become blocked. Most hearing loss caused by glue ear or ear infections is therefore temporary. But persistent fluid in the middle ear can reduce a child's hearing at a time when it is very important for speech and language development. For this reason, many children with persistent problems have tubes fitted (called grommets) (Cusmano-Ozog 2007; *Unique*).

Two *Unique* children were found to have difficulties localising the direction of sound. Two other children were found to have a central processing disorder of the auditory stimuli: this is when sound reaches the inner ear as expected, but the processing of signals in the brain does not proceed as expected. This causes a delay in the child's reaction. The child hears what is said, but does not react within the expected time. Children may also have difficulty filtering out background noise, which may cause them to not respond when they are in a noisy environment (*Unique*).

Feet

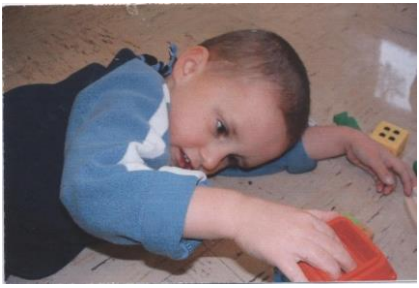
Thin and poorly formed toenails are relatively common in children with Phelan-McDermid syndrome. This was the case in more than 70% of *Unique* children. There is also an increased risk of ingrown toenails. However, as children grow older, their nails become stronger (Phelan 2008; *Unique*).

Quite a few children have flat feet. Sometimes children therefore have to wear insoles or special shoes. One *Unique* child needed foot support to prevent him from walking on the outside of his feet. Two children walk with their feet turned inwards.

In some children, some toes are partially fused with each other (syndactyly) (Cusmano-Ozog 2007; *Unique*).

Heart problems

Heart problems are not clearly associated with Phelan-McDermid syndrome. Cardiac problems were described in less than 20% of *Unique* infants for whom data was available. In the medical literature, congenital heart defects are not commonly reported (in 5% of children, if at all) and were usually relatively mild problems. One *Unique* child had a mild narrowing (stenosis) of the aorta (the large artery from the heart to the rest of the body), another child had a slightly leaking heart valve, which he is expected to grow out of. Another child had a small opening in the heart at birth which closed by itself and no treatment was necessary (*Unique*). Heart problems therefore do not seem to occur more frequently than in the general population.



9 years

Cyclical vomiting

Approximately 25% of children have attacks of cyclic vomiting (Phelan and McDermid 2012; Sarasua 2014). In the worst cases, this can lead to dehydration and drowsiness. It is not known why cyclic vomiting is more common in Phelan-McDermid syndrome. If a child with Phelan-McDermid syndrome experiences cyclic vomiting, it is important to exclude other medical causes, like for example an infection or bowel obstruction. Sometimes dehydration is so severe that hospitalization is necessary, so a child can get extra fluids through a nasal tube or an infusion (Phelan 2008).

Constipation

Constipation occurs in approximately 40% of people with the Phelan-McDermid syndrome (Kolevzon 2014). Adequate fluid intake, adequate dietary fibre intake, encouragement of exercise and attention to medication (constipation can occur as a side effect of medication) are important. Sometimes drug treatment is also necessary. This usually has a good effect.

Sweat

More than 70% of children with Phelan-McDermid syndrome in the *Unique* study, sweat insufficiently. As a result, these children can overheat. It is not yet known exactly what causes the reduced sweat production in Phelan-McDermid syndrome (Phelan 2001a; *Unique*).

Pain

4 years

Most children with Phelan-McDermid syndrome (more than 90% in the *Unique* study) 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). (Phelan 2001a; *Unique*).

Many children with Phelan-McDermid syndrome have a different perception of stimuli (including a different perception of pain). In general terms, this is called sensory dysfunction. Specific research on sensory information processing (SI) is necessary. 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.

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 infection of the ears, respiratory or urinary tract), so that a targeted treatment can be considered.

“ Sometimes it is hard to understand when he is in pain. When he was younger he didn't cry if he fell down although now he does **”** – 6½ years

Fluid accumulation (lymphoedema)

Lymphedema is an accumulation of fluid in the legs, for example, because the lymphatic system is not working properly. There will cause swelling because the supply and removal of fluid is not balanced. This can also accelerate inflammation caused by cellulitis (a bacterial infection of the deeper connective tissue). Lymphedema is more common in people with Phelan-McDermid syndrome but the exact figures are very variable in the literature. The underlying mechanism why lymphedema occurs in Phelan-McDermid syndrome is not known, most likely it is because the lymphatic system is not well constructed. The treatment is the same as for other causes of lymphedema. 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

Children with Phelan-McDermid syndrome often have dental problems. A mismatch between the upper and lower jaw (malocclusion) and widely spaced teeth are common. Weak muscle tone, incessant chewing and teeth grinding may contribute to this (Phelan 2001a; *Unique*). Most children with Phelan-McDermid syndrome develop all deciduous ‘baby’ teeth and all adult teeth.

Ring chromosome 22

Ring chromosome 22

Some people have a loss of genetic material on the short and long arms of chromosome 22, and the ends join together to form a ring chromosome. People with a ring chromosome 22 have an increased risk of tumours of the central nervous system. These are "benign" tumours. This means that it is not cancer and the tumours do not spread. But they can cause problems if the tumour affects certain tissues.
For example, if the auditory nerve is affected, this can cause hearing loss, balance problems, epilepsy, nerve failure and/or difficulties walking. The exact risk of tumours in people with a ring chromosome 22 is not yet known, although the risk seems to be relatively low.

The increased risk of tumours with a ring chromosome 22 is due to a gene called NF2 (Neurofibromatosis type 2) that is found on chromosome 22. This gene protects against the development of nerve tumours. Since we all usually have two copies of chromosome 22, we usually have two copies of the NF2 gene. This gene is also usually found in a ring chromosome 22 but because the ring chromosome is unstable, it can be lost when new cells are formed. If the NF2 gene on the remaining chromosome 22 does not function (due to, for example, a different genetic change), which results in cells having no functional copy of NF2, then this can lead to tumour formation.

Since people with a ring chromosome 22 have an increased risk of tumours, extra check-ups are recommended, including periodic examination by a paediatric neurologist, hearing checks and MRI examination of the brain and spinal column. These check-ups apply from the age of 10 to 12 years. They are preferably carried out at an Expertise Centre for neurofibromatosis.

Other features

Children with Phelan-McDermid syndrome have arachnoid cysts more often than children without the associated genetic change. An arachnoid cyst is a fluid filled sac in one of the meninges (membranes that enclose the brain and spinal cord). Small cysts usually do not cause problems, but larger ones can put pressure on the brain (Phelan 2008).

Other brain anomalies have been reported in people with Phelan-McDermid syndrome in the medial literature. Brain MRIs have identified an underdevelopment of the brainstem in 36% of people. White matter anomalies such as delayed myelination (delayed coating of nerve fibres with an insulating layer of myelin), global disappearance of white matter and MRI bright spots (nonspecific hyperintensities) of white matter have been reported in 39% of people. A dilatation of the cerebral ventricles has been reported in 32% of people and brain cysts (vesicles containing fluid) in 14% (Kolevzon 2014).

If the diagnosis of Phelan-McDermid syndrome has been made, there is no reason for a (periodic) MRI examination of the brain. An exception to this is if there is a ring chromosome 22, because this carries an increased risk of tumours.

The thyroid gland can be slowed down; this has been reported to happen in approximately 5-6% of people with Phelan-McDermid syndrome (Sarasua 2014). A slow thyroid gland can cause non-specific symptoms such as behavioural changes, fatigue, difficulty defecating, dry skin and an increase in body weight. It is often difficult to recognise, especially in people with intellectual disabilities. It is therefore important to have regular blood tests, at least once a year. Treatment with medication usually works well.

Behaviour in childhood

Most children with Phelan-McDermid syndrome are cheerful and social. They are also, like other children with communication difficulties, vulnerable to frustration. Emotional outbursts can be challenging for caregivers. Many parents report that their children respond well to basic disciplinary techniques, such as ignoring unwanted behaviour and rewarding positive behaviour (e.g., giving hugs and attention when they listen/stop). Some children with Phelan-McDermid syndrome have difficulty with change and their parents find that a rigid daily routine helps to make them feel safe and secure (Phelan 2008; *Unique*).

In addition, some children have difficulties processing stimuli from the outside world. They react to a lesser degree to pain or verbal stimuli, but they can also be hypersensitive (for example, they do not like being touched) and panic at sudden noises or movements (Phelan 2008; *Unique*).

Many children with Phelan-McDermid syndrome have behavioural characteristics that are also seen in people with autism spectrum disorders. In the medical literature, such characteristics are described in approximately 50% to 75% of children. The *Unique* experience is that about 25% of the children with a 22q13 deletion have the diagnosis of autism spectrum disorder. Typically, children fail to make good eye contact, often play alone, find it difficult to interact with other children and have difficulty recognising emotions in others. These characteristics can be present from early childhood, but a diagnosis can sometimes be a long time coming. Nevertheless, a diagnosis can be very helpful in accessing help and support for a family (Goizet 2000; Phelan 2008; *Unique*).

The *Unique* study shows that about 75% of children with Phelan-McDermid syndrome make stereotypical, repetitive movements or wave their hands (characteristics that can occur with autism spectrum disorders). Another behavioural characteristic is chewing on non-edible things. They continue chewing longer than other children and may also chew and suck on clothes, toys and furniture. Some children have a chew rubber (a rubber tube that is safe to chew on) or teething ring. Other behavioural characteristics include teeth grinding (in three quarters of children) and in a small minority aggressive behaviour (Phelan 2001a; Phelan 2008; *Unique*). Characteristics of ADHD with hyperactive behaviour can also occur.

“ She is happy. Her behaviour is not a problem **”** – 3½ years

“ He has a great laugh and loves to share a joke. When he is excited he flaps his arms **”** – 4 years

“ He has a fabulous sense of humour and an infectious giggle. Life is enormous fun to him and he brings great joy to others. He has a tendency to rock which can be frustrating when trying to feed him **”**– 4½ years

❝ She grinds her teeth. She has had one tooth extracted due to grinding: it split in half. She is even tempered and happy. Her biggest problem currently is pica [eating non-food items]. She eats her clothing when bored and unattended ❞– 4½ years

❝ If he has a meltdown, holding him close and singing to him works best to calm him down ❞ – 5 years

❝ She is acutely sensitive to sounds. She can be inappropriately friendly and does not always respond to social cues ❞ – 6 years

❝ A good day is when the routines are working and he understands what is going to happen ❞ – 6½ years

❝ He is constantly on the go ❞ – 9 years

❝ She is a very happy, content little girl but does get frustrated sometimes and smacks, pulls hair and punches ❞ – 9½ years

❝ He is a quiet, shy boy but can get loud vocally when he gets excited. He likes routine and can get anxious when things are changed. Different circumstances and busy places can upset him ❞ – 11 years

❝ She has behaviour problems which are mostly controlled. She tends to erupt when bored or out of routine ❞ – 12 years

❝ She does not have any serious behavioural problems ❞ – 13 years

Adult behaviour

Mood disorders are common in adults with Phelan-McDermid syndrome. This is similar to what is seen in manic-depressive disorder: a very cheerful and active mood can alternate with a sombre and passive mood. These mood disorders can sometimes be severe. Medication (mood stabilisers) can help with this (Egger 2016).

Drug treatment for development and behaviour

Limited research has been done on drug treatment for development and behaviour in people with Phelan-McDermid syndrome.

The Phelan-McDermid syndrome Expertise Centre at the University Medical Centre Groningen, in the Netherlands, has investigated the effect of insulin nasal spray treatment on the development and behaviour in children with Phelan-McDermid syndrome. Although in some children no effects were seen, others clearly benefited from this treatment. Across the whole group, there were cautious positive effects on development, especially for communication and social behaviour. Based on these findings, the Expertise Centre offers a trial treatment with insulin nasal spray if the parents/legal representatives want it and under certain conditions. These conditions are listed in the Dutch guideline for the care of people with Phelan-McDermid syndrome (available online via the website https://richtlijnendatabase.nl/richtlijn/22q13_deletiesyndroom_pms/ startpage_-_22q13ds_pms.html).

Another treatment mentioned in the literature is a treatment with IGF-1, which stands for Insulin-like Growth Factor-1. This treatment is injected under the skin. Too little research has been done into this drug to be able to say anything about the effect on development and behaviour.

Psychiatric difficulties in adulthood, including mood disorders, often require drug treatment. Valproic acid (Depakine) and atypical antipsychotics are the drugs most frequently used. There is currently no preference for one particular drug or combination of drugs, but knowledge about this is still limited. When a severe mood disorder does not respond sufficiently to treatment with the medicines mentioned above, treatment with lithium may be considered. In some people, this treatment normalises the mood.

Sleep

Sleep problems or sleep disturbance are common and have been reported in more than 50% of *Unique* children. The figures for the occurrence of sleep problems vary widely in the medical literature, from 15% to 88%. Sleep problems reported include both excessive daytime sleepiness or prolongation of the night-time sleep period (hypersomnia) and problems falling asleep or staying asleep (insomnia). In *Unique*'s experience, insomnia is more common. Parents report that children have difficulty falling asleep at night or regularly wake up during the night. Some children seem to need less sleep than average. Sleep medication was necessary in a small minority of children (Philippe 2008; *Unique*).

Sleep problems may be related to being overexcited or frustrated. This is more common in children with Phelan-McDermid syndrome who also have an autism spectrum diagnosis. In addition, sleep problems can be due to a physical cause such as pain, sleep apnoea, gastroesophageal reflux, constipation, dental problems or an infection of the ears, respiratory tract or urinary tract. If a child experiences restlessness during the night, that is not well understood, it may be useful to investigate (nocturnal) epilepsy. This requires additional assessments in a specialised epilepsy centre. A specialist paediatrician or doctor can carry out further research into the causes of sleep problems and provide advice and treatment. If problems persist, referral to a specialised sleep centre may be considered.

❝ He will wake 2-3 times a night ❞ – 5 years

❝ He does tend to get out of bed quite a lot before he goes to sleep. He then will get up in the night and wander. We've had to shut his bedroom door ❞ – 9 years

❝ He goes to bed OK, but needs little sleep ❞ – 10½ years

Puberty and fertility

For children with Phelan-McDermid syndrome, puberty usually begins at the regular age and usually proceeds as expected. Occasionally a child might start puberty early, but this also happens in children with no known genetic condition.

Fertility is not known to be affected in people with Phelan-McDermid syndrome but most people with this syndrome do not have children.

Life expectancy

At present it seems that most people with Phelan-McDermid syndrome have a normal life expectancy. Not many adults with Phelan-McDermid syndrome are known to be over 50 years old today, due to the fact that the diagnosis was often not made in the past.

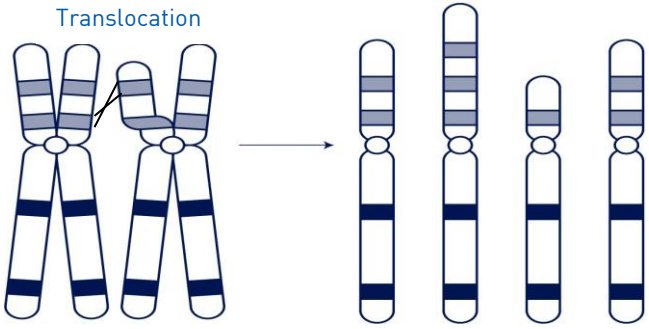
Why did this happen?

Sometimes Phelan-McDermid syndrome can have a hereditary cause. Chromosome testing of parents can provide an answer to this question. A special technique is used (called FISH – *Unique* publishes a separate guide to FISH) which specifically colours the 22q13 region. This is important because the missing piece of chromosome 22 can be very small.

In approximately 80% of families it appears that both parents have unaffected chromosomes. In such a situation, clinical geneticists would describe a genetic change found in a child with Phelan-McDermid syndrome as *de novo* (dn). The genetic change is expected to have occurred by chance in that child. The chance of a recurrence in any subsequent pregnancy is expected to be very small. There is still a very small chance of having another child with the same genetic change due to a phenomenon called germline mosaicism. This is when a small number of egg or sperm cells carry a specific genetic change, but the cells of the body do not, so a person would be unaffected and unaware that a few of their cells carry the genetic change.

Sometimes (in about 10% of families) the genetic change is the result of a rearrangement, called a translocation, of the chromosomes of one of the parents. An important piece of chromosome 22 is accidentally relocated on another chromosome. This is called a balanced translocation, because pieces of chromosomes have swapped places but no genetic material is missing from the parent or duplicated. The parent will therefore usually not be aware of their translocation. However, the parent may experience difficulties with fertility or having children. In general, a balanced translocation is not rare: it is thought to occur in 1 in 500 people. *Unique* publishes a separate guide to balanced translocations.

Parents with a balanced translocation between chromosome 22 (containing the 22q13 region) and another chromosome have an increased chance of having more than one child with Phelan-McDermid syndrome. There may also be an increased chance that other family members carry the translocation. Specific genetic testing can be carried out to detect or rule out a translocation (the FISH test mentioned above).



In about 10% of families, a 22q13 deletion is the result of a ring chromosome 22. A ring chromosome 22 usually occurs as a new (de novo) event in a child, but exceptions have been described in which a healthy parent also has a ring chromosome 22 in a small proportion of their body's cells (including the egg or sperm cells). This is called a mosaic form of ring chromosome 22. This means that this parent has an increased chance of having another child with Phelan-McDermid syndrome. A referral to a Clinical Genetics Outpatient Clinic may help identify suspected ring chromosome 22 mosaicism.

As a parent, there is nothing anyone can do or not do to prevent a genetic change from happening. There are no environmental or dietary factors that cause chromosomal changes. It's not anyone's fault. We all have different genetic changes, it's only when important genes or pieces of DNA are changed that health and development are affected.

Can it happen again?

The chance of having another child with Phelan-McDermid syndrome is determined by the results of complete genetic testing of the child and parents (as described above). Parents can ask a clinical geneticist or genetic counsellor for information about the chances in their individual situation. All parents of a child with Phelan-McDermid syndrome can opt for prenatal diagnostics (via chorionic villus testing or amniocentesis) in any subsequent pregnancy. This does not depend on the exact recurrence rate.

It is also technically possible to carry out embryo selection (preimplantation genetic diagnosis, PGD) in the event of a clearly increased recurrence rate. In PGD an attempt is made to fertilise an egg cell via test tube fertilisation. An embryo with an unaffected chromosome pattern is then selected and introduced into the uterus.

If parents prefer to conceive naturally, there is the option of prenatal diagnostics early in pregnancy. *Unique* publishes a separate guide to 'Planning Your Next Child' that includes more information about prenatal diagnostics.

Organisation of care

Most children with Phelan-McDermid syndrome have multiple medical caregivers involved from an early age. In addition to, for example, a physiotherapist, speech therapist and a GP, there are several hospital specialists, such as a paediatrician, clinical geneticist, neurologist and rehabilitation specialist that may be involved. It is recommended that people with Phelan-McDermid syndrome have a coordinating doctor that takes responsibility for the coordination of care and should bear the final responsibility (the primary medical practitioner). Until the age of 18 years, this is often a paediatrician. From the age of 18 onwards, this coordinating role is often transferred to a doctor for adults with special needs. For specific questions, for example about behavioural problems or sleep problems, a specialist doctor for adults can also be asked for advice before the age of 18.

It is also strongly recommended that anyone with Phelan-McDermid syndrome be referred to a recognised expertise centre for rare chromosome anomalies, at least once. In the Netherlands, there is a Phelan-McDermid syndrome expert centre located in the University Medical Center, Groningen (UMCG).

Inform Network Support

Rare Chromosome Disorder Support Group
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Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Become a member of *Unique* for contact with other families, information and support. *Unique* is totally dependent on donations and gifts. If you can, please make a donation via our website www.rarechromo.org/donate Please help us to help you!

Websites

Phelan-McDermid Syndrome Foundation https://pmsf.org

VGnetworks
www.vgnetwerken.nl
m.vanleeuwen@vgnetwerken.nl

Erfocentrum
www.erfelijkheid.nl
info@erfocentrum.nl

VKGN
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Unique lists the websites of other organizations to assist families searching for information. This does not mean that we endorse or are in any way responsible for the content of that website.

This information is not a substitute for personal medical advice. Consultation and advice from a clinical geneticist and paediatrician is essential for anything related to the diagnosis, treatment and health of their child. Every family has a right to this. The information gathered here is the best available at the time of publication. It was compiled by *Unique* and checked for accuracy by Dr Katy Phelan, Greenwood Genetic Center, USA and Professor Maj Hulten BSc, PhD, MD, FRCPath, Professor of Medical Genetics, University of Warwick, UK 2008. 2005 Version 1 (PM). 2008 Version 2 (SW).

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