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

A 22q13 deletion means that the cells of the body have a small but variable amount of genetic material missing from one of their 46 chromosomes – chromosome 22. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Like most other chromosome disorders, the incorrect amount of material increases the risk of birth defects, developmental delay and learning difficulties. However, the problems vary and depend very much on what genetic material is missing.

Chromosomes are made up mostly of DNA. They are the rod-like structures in the nucleus of the body’s cells. They carry genetic information (known as genes) that tell the body how to develop, grow and function. Chromosomes usually come in pairs, with one chromosome of each pair inherited from the father and the other from the mother. Of the 46 chromosomes, two are a pair of sex chromosomes, XX (a pair of X chromosomes) in females and XY (one X chromosome and one Y chromosome) in males. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short (p) arm (shown at the top in the diagram opposite) and a long (q) arm (the bottom part of the chromosome). People with a 22q13 deletion have one intact chromosome 22. The other 22 is missing a segment from the long arm and this can affect their learning and physical development. The size of the missing segment varies among individuals. Most of the clinical difficulties are probably caused by the presence of only one copy (instead of the usual two) of a number of genes. However, a child’s other genes and personality also help to determine future development, needs and achievements.

The first description of a person with a 22q13 deletion was in 1985. There have since been over 500 identified cases worldwide. The deletion occurs in equal frequency in males and females. It is now often referred to as Phelan-McDermid syndrome, named after the people who first described and characterised the disorder: Drs Katy Phelan and Heather McDermid. Although there is variability between people with a 22q13 deletion, there are enough similarities to define the loss of this region as a syndrome, hence the term Phelan-McDermid syndrome. It is also sometimes called 22q13 deletion syndrome or 22q13.3 deletion syndrome (Watt 1985; Phelan 1992; Unique).

Looking at 22q

Chromosomes can’t be seen with the naked eye but if they are stained and magnified under a microscope it is possible to see that each one has a distinctive pattern of light and dark bands. By looking at your child’s chromosomes in this way, it is possible to see the point (or points) where the chromosome has broken and to see what material is missing. However, because the amount of material missing is often quite small, in this type of routine analysis your child’s chromosomes may have looked normal and it has been reported that over 30 per cent of individuals with Phelan-McDermid syndrome have needed two or more chromosome studies before the deletion was found. Consequently there are certainly people with a 22q13 deletion who have not yet been diagnosed. New, more sensitive, molecular techniques such as fluorescent in situ hybridization (FISH) testing or array comparative genomic hybridisation (array-CGH) may be necessary to confirm or detect Phelan-McDermid syndrome.
In Phelan-McDermid syndrome part of the long (q) arm of chromosome 22 is missing. The deletion can be a simple, pure deletion (where no other chromosome is involved); be accompanied by loss or gain of material from another chromosome; or be due to the formation of a ring chromosome (where both the long arm and short arm of chromosome 22 have broken, leaving two ‘sticky’ ends that have rejoined to form a ring. In Ring 22 there will usually be material lost from both the long and short arm of chromosome 22). The majority of cases, around 75 per cent, are pure deletions (Phelan 2001a; Luciani 2003).

The vast majority of deletions of 22q13 are terminal. This means that the tip of the long arm is included in the deletion. However, some deletions of 22q13 are interstitial, in which a piece of the long arm of chromosome 22 is missing, but the tip is still present (Romain 1990; Fujita 2000; Wilson 2008).

In the diagram of chromosome 22 on the right the bands are numbered outwards starting from where the short and long arms meet (the centromere).

A low number, as in q11 in the long arm, is close to the centromere. Regions closer to the centromere are called proximal. A higher number, as in q13, is closer to the end of the chromosome. Regions closer to the end of the chromosome are called distal.

**Sources**

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed [http://www.ncbi.nlm.nih.gov/pubmed/]. If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from two surveys of members of Unique conducted in 2004 and 2008, referenced Unique. When this leaflet was written Unique had 62 members with a pure 22q13 deletion without loss or gain of material from any other chromosome, 72 members with a ring chromosome 22 and 16 members who have the involvement of another chromosome. These members range in age from babies to an adult aged 40 years.

Many more people, described in the medical literature and members of Unique, have a loss or gain of material from another chromosome arm as well as a 22q13 deletion, usually as a result of a chromosome change known as a translocation. As these people do not show the effects of a ‘pure’ deletion, they are not considered in this leaflet. Unique holds a list of these cases in the medical literature and the karyotypes of those in Unique; this is available on request.

In 2018 a Dutch guideline on the management of people with 22q13 deletion syndrome was written by a group of medical specialists and parents. This Unique guide has been updated according to this new information. A questionnaire was sent to parents of children with 22q13 deletion syndrome prior to guideline production and included questions about the main problems experienced by parents. The guideline can be found at the following website: [https://richtlijnendatabase.nl/richtlijn/22q13_deletiesyndroom_pms/startpagina_-_22q13ds_pms.html](https://richtlijnendatabase.nl/richtlijn/22q13_deletiesyndroom_pms/startpagina_-_22q13ds_pms.html).
Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point where the chromosome has broken in your child. You will almost certainly be given a description of your child’s karyotype. The karyotype is the pictorial display of your child’s chromosomes. With a 22q13 deletion, the results are likely to read something like the following example:

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

46 The total number of chromosomes in your child’s cells
XX The two sex chromosomes, XY for males; XX for females
del A deletion, or material is missing
[22] The deletion is from chromosome 22
(q13.3) The chromosome has one breakpoint in band 22q13.3, and material from this position to the end of the chromosome is missing

In addition to, or instead of a karyotype you may be given the results of molecular analysis such as FISH or array-CGH for your child. In this case the results are likely to read something like the following example:

46,XY.ish del(2)(q13.3)(ARSA-)dn

46 The total number of chromosomes in your child’s cells
XY The two sex chromosomes, XY for males; XX for females
.ish The analysis was by FISH
del A deletion, or material is missing
[22] The deletion is from chromosome 22
(q13.3) The chromosome has one breakpoint in band 22q13.3
[ARSA-] The deleted part of chromosome 22 includes a gene called ARSA
dn The deletion occurred de novo (or as a “new event”). The parents’ chromosomes have been checked and no deletion or other chromosome change has been found at 22q13.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

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

arr The analysis was by array-CGH
hg19 Human Genome build 19. 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
22q13.32q13.33 The region that is deleted is between bands q13.32 and q13.33 on chromosome 22
48624809-51169045 The base pairs between 48624809 and 51169045 have been shown to be deleted. Take the first long number from the second and you get 2,544,236 (2.54Mb). 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
Are there people with a 22q13 deletion who are healthy, have no major medical problems or birth defects and have developed normally?

Yes. In a few people with very small deletions, the deletion appears to have a more mild effect. One mother described in the medical literature who had a small interstitial deletion of 22q13 attended mainstream school. She had speech problems which were improved by speech therapy, although her speech remained nasal. She had a long face and a large head but was otherwise physically unaffected by the deletion. Her deletion was only discovered when her son, with hypotonia, speech delay and learning difficulties, was diagnosed with Phelan-McDermid syndrome. A child with a small 130 kilobases (kb: a thousand base pairs of DNA) terminal deletion had only mild developmental delays and less severe speech delay [Wong 1997; Wilson 2008].

Most common features

Every person with Phelan-McDermid syndrome is unique with specific medical and developmental concerns. At birth the features of Phelan-McDermid syndrome can be subtle and often the first or only indicator is the presence of hypotonia (low muscle tone or floppiness). No one person will have all of the features listed in this leaflet. However, a number of common features have emerged:

- Hypotonia
- Significant delays in, or absent, speech
- Children will need support with learning. The amount of support needed by each child will vary
- Normal to accelerated growth
- Behavioural issues, often features of an autistic spectrum disorder
- Subtle physical features

Pregnancy

The majority of mothers carrying babies with Phelan-McDermid syndrome experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. Of the 25 families who participated in the Unique survey and have told us about their pregnancy experiences, two babies showed reduced fetal movement, two were small for dates and four were premature, arriving between 33 and 34 weeks. Ultrasound scans detected kidney problems in three babies: one had one kidney larger than the other, another had kidney reflux in one kidney and a third baby had multicystic kidneys. The ultrasound scan for this third baby also demonstrated enlarged cerebral ventricles (sections within the brain) at 27 weeks gestation (Unique).

There are several examples in the medical literature of prenatal diagnosis of Phelan-McDermid syndrome by amniocentesis performed either after a fetal anomaly, such as a heart defect, was detected on prenatal scans; because of an increased risk for Down’s syndrome determined by maternal serum or for increased maternal age. Three out of six diagnoses were mosaic: only a proportion of the baby’s cells had the 22q13 deletion, the remaining cells had two complete copies of chromosome 22, as is usual. In one of the non-mosaic cases (where all of the baby’s cells had the 22q13 deletion) the parents chose not to continue with the pregnancy. It is important to note
that internal organ defects are uncommon in Phelan-McDermid syndrome, hence prenatal diagnosis of Phelan-McDermid syndrome due to anomalies found during prenatal scans is relatively unlikely (Phelan 2001b; Maitz 2008).

Feeding and growth

Feeding difficulties in babies can be a problem. The hypotonia that is common in babies with Phelan-McDermid syndrome can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a high palate can also find the action of sucking and swallowing difficult. Seven of the 14 mothers surveyed by Unique attempted to breastfeed their babies. A few had difficulties and moved on to bottle feeding after a few weeks but many were successful and breastfed their babies up until weaning onto solid foods. One of the 14 babies surveyed by Unique benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat) and one had a temporary gastrostomy tube placed (a G-tube, feeding direct into the stomach). The floppiness can also affect their food passage and contribute to gastro-oesophageal reflux (in which feeds return readily up the food passage). In the Unique survey, around 43 per cent of babies had reflux. This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Unique).

Some older babies and toddlers have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers and the start of finger feeding may be delayed. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems (Unique).

Once past babyhood, appetite does not seem to be a problem. On the contrary, a few children develop a big appetite and are said to love food (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

In spite of any early feeding troubles, the majority of children with Phelan-McDermid syndrome have normal growth. In fact, accelerated growth has been reported in around a third of all children. The Unique experience is that children are often tall and thin, but their build would not make them stand out from the crowd (Fujita 2000; Luciani 2003; Phelan 2008; Unique).

“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

5 years
**Appearance**
Children with Phelan-McDermid syndrome sometimes have facial features in common. They may have a pointed chin and prominent, unusually-formed ears. The nasal bridge can be flat and broad. They commonly have long eyelashes and puffiness around the eyes. There may be drooping eyelids (ptosis; 53% of people (Sarasua 2014)) or an extra fold of skin covering the inner corner of the eye (epicanthic folds). They often have a long and narrow head (dolichocephaly) and full cheeks. However, many children look little different to other children and closely resemble their siblings or parents (Cusmano-Ozog 2007; Unique). Eleven percent of people have a small head (microcephaly) and 18 per cent have a large head (macrocephaly) (Sarasua 2014).

**Learning**
Learning difficulties and intellectual disabilities are common in children with Phelan-McDermid syndrome with most children severely affected and a small minority profoundly affected. As always, there is individual variation, and a few children have moderate or even mild learning difficulties. However, most children benefit from early intervention programmes and may thrive best in a special learning environment. Indeed the vast majority of Unique children attend a special education school, although a small number attend mainstream school, often receiving 1:1 help in the classroom (Phelan 2008; Unique).

Certain common features have been noticed. Children need skills constantly reinforced or they will be forgotten. One area which is currently being studied in more detail is the skill loss or regression that is seen in children with Phelan-McDermid syndrome. The loss is usually specific to one area, with the loss of a particular skill while development is occurring in another area. At present the reasons for these losses are not known. The skill loss is most often in the area of speech (see section Speech and communication) (Unique).

Children with Phelan-McDermid syndrome are often easily distractible which can make learning more of a challenge. Many parents note that the most successful methods for learning involve learning through play and making learning fun. Children with Phelan-McDermid syndrome seem to share a passion for music (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**
Speech appears to be the most problematic developmental area in children with Phelan-McDermid syndrome and language skills are likely to be significantly delayed or absent. Receptive language is markedly better than expressive language skills - many
children understand far more than they are able to express. This is shown by their ability to understand words and follow instructions, respond when told to do tasks, demonstrate a sense of humour and express emotions (Phelan 2001a; Cusmano-Ozog 2007; Phelan 2008; Unique).

Studies have shown that children often babble at the appropriate baby age and may even start to speak but many lose this skill by the age of 4. This loss, or regression, of speech appears to be common in Phelan-McDermid syndrome. Although active speech therapy and communication skill training may help to retrieve some of the vocabulary, verbal communication will remain severely impaired.

Within this picture there is individual variation although the experience among Unique children is that most are significantly delayed: the most articulate are able to say single words spontaneously and reasonably clearly with only one Unique child speaking in sentences. Reports in the medical literature seem to confirm this picture: all reported children have some speech problems, with the majority having severely delayed or absent speech and only a minority mastering sentences (Phelan 2008; Philippe 2008; Unique).

Some Unique children master modified sign language but a picture exchange communication system (PECs) is often more successful because the child’s poor muscle control can make signing more difficult. Children are often able to communicate their needs by eye contact, pushing and pulling, gestures and vocal noises. Computer touch screens and voice based systems can also be used to increase communication skills. Adaptive sports, music therapy and sensory integration increase a child’s awareness and may improve their desire to communicate (Phelan 2008; Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which as well as insufficient sucking, can also affect the development of speech. Those with a cleft or high palate may also have specific difficulty with certain sounds (Unique).

“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

Development: sitting, moving, walking (gross motor skills)

For some children, early developmental milestones are reached at an appropriate age although delays are not uncommon. Studies in the USA show a picture of sitting on average at 18 months, crawling on average at 17 months (although some children do not crawl) and walking at 33 months (with a range of 7 months to 36 months). The Unique experience is that babies start to roll between 2 months and 2 years (average 8 months); sit between 6 months and 4 years (average 15 months) and crawl between 8 months and 4 years (average 19 months). Some children, however, do not crawl but instead move around by bunny hopping, knee-walking or bottom shuffling. Walking was mastered between 1 year and 9 years (average 34 months), (Phelan 2001a; Unique).

The delays in mobility are attributed to the muscle weakness (hypotonia) in many children with Phelan-McDermid syndrome. Almost 100 per cent are thought to have hypotonia which is sometimes global but most often affects only the upper body. The earliest signs are an unusual floppiness as babies and delayed head control. The hypotonia often improves as children mature; however, early physiotherapy and occupational therapy benefit most children. Other activities such as swimming and hydrotherapy have helped some children. A walking frame, standing frame, leg braces and/or adapted, supportive seating can help overcome the problems of hypotonia for some children (Koolen 2005; Unique).

Poor balance and in some children loose joints can also contribute to these delays (Unique).

When children master walking they typically remain unsteady and have an unusual gait. They may trip easily and need protection or support as they often lack a sense of danger. Many tire quickly and in early childhood at least still need a wheelchair on outings and in some cases indoors (Unique).

Many children progress to running, jumping, throwing and catching and climbing. Physical activities enjoyed by Unique children include swimming, riding a bike or scooter, horse-riding, trampolining, skiing and skating. However, this is not possible for all (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

**Development: hand-eye co-ordination and dexterity (fine motor skills) and self care**

Hypotonia can also affect fine motor skills in children with Phelan-McDermid syndrome and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles and cutting up food have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard can often be easier. Many children have occupational therapy in order to help improve these skills but difficulties with fine motor skills often persist (*Unique*).

As a result of these difficulties, children are likely to continue to need help with dressing and undressing. They will also require assistance in tasks such as brushing teeth and washing. Toilet training is also likely to be affected. Although many children have periods of successful toilet training, only a few are completely toilet trained by mid-childhood. The information at *Unique* shows that consistent toilet training has been achieved by only three children and was mastered between 3 years and 2 months and 5 years. In one published medical report five out of eight children achieved daytime bladder control between the ages of 4 and 6 years, but night bladder control was achieved by only two of the eight children at the age of 4 and 8 years (Philippe 2008; *Unique*).

“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” – 11 years

“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
Medical concerns

- **Seizures**
  Epilepsy appears to be slightly more common in children with Phelan-McDermid syndrome than the general population. In the *Unique* survey around a third of children were affected. Anti-epileptic drugs may be prescribed in an attempt to protect the child from further seizures [Phelan 2008; *Unique*].

- **Kidney and urinary tract**
  Kidney problems may occur, although they are usually minor. Among *Unique* children around 30 per cent of children are affected, and problems include enlarged kidneys and frequent urinary tract infections.

  Hydronephrosis, or swelling of the kidney, can occur if urine is unable to drain from the kidney to the bladder, usually caused by blockage in the ureters (the tubes that carry urine from the kidney to the bladder). Two children had one non-functional kidney and kidney reflux (where urine flows upwards from the bladder back to the kidney) in the second kidney. Kidney reflux also affected another child who underwent ureteral re-implantation. This surgical procedure is performed when the ureters do not join the bladder in the correct place which can cause kidney reflux. The procedure disconnects the ureters from the bladder and reconnects them in the correct place (*Unique*).

- **Eyelids and vision**
  Delayed visual maturity is a feature of Phelan-McDermid syndrome in a small number of children who fail to focus and track as expected as babies. A number of children, around 20 per cent in the *Unique* survey, have a lazy eye or a squint (strabismus).

  An inability to see things in three dimensions (3D) or a lack of depth perception seems to affect a small minority of children. Short sight has also been reported [Phelan 2008; *Unique*].

- **Ears**
  Hearing problems can affect children with Phelan-McDermid syndrome. A number of children have recurrent ear infections. Forty per cent of those surveyed by *Unique* had a build up of fluid in the middle ear called glue ear, or otitis media. Glue ear usually resolves as children get older and the ear tubes widen and become more vertical resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear and glue ear can reduce a child’s hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum (Cusmano-Ozog 2007; *Unique*).

  Two *Unique* children have no directional hearing – they struggle to localise sounds. Auditory neuropathy or central auditory processing disorder affects two of the *Unique* children. These terms are used when sound enters the inner ear normally but the transmission of signals from the inner ear to the brain is impaired. This impairment may lead to a delayed response time, meaning that the child hears the spoken word but does not react within the expected time frame. Children may also have difficulty separating spoken words from background noise so they may not respond to vocal prompts when they are in a noisy environment (*Unique*).
**Feet**
Thin, flaky, poorly formed toenails appear to be a relatively common finding in individuals with Phelan-McDermid syndrome, affecting more than 70 per cent of children. A number of *Unique* children also suffer from an increased risk of ingrown toenails. As children mature, their nails strengthen (Phelan 2008; *Unique*).

Evidence at *Unique* suggests that a number of children are flat-footed; the arch of the foot has collapsed resulting in the entire sole of the foot coming into contact with the ground. In some cases this has necessitated wearing insoles in the shoes or supportive footwear. Another child needs foot supports to prevent him walking on the outsides of his feet and two are described as pigeon-toed – they walk with their feet turned inwards. A very small number of children have webbed, or slightly webbed toes (syndactyly) (Cusmano-Ozog 2007; *Unique*).

**Heart problems**
Heart conditions are relatively uncommon, having been observed in less than 20 per cent of *Unique* babies with Phelan-McDermid syndrome and in most cases are relatively minor. One child has mild stenosis (narrowing) of the aorta (the blood vessel through which blood flows from the heart to the rest of the body) and another has a slightly leaky heart valve which he is expected to outgrow. Another was born with a small hole in the heart which closed by itself and needed no treatment (*Unique*).

**Cyclical vomiting**
Some children have experienced bouts of vomiting every few months leading to dehydration, lethargy and headaches. The children may have to be re-hydrated by intra-venous fluids and, in extreme cases, may require hospitalisation (Phelan 2008).

**Sweating**
Many children, over 70 per cent in the *Unique* survey, do not sweat enough and have a tendency to overheat. The sweat glands have not been studied yet to see if they are abnormal (Phelan 2001a; *Unique*).

**Pain**
The great majority of children (over 90 per cent in the *Unique* survey) have a very low perception of pain. They can be in considerable discomfort before it becomes clear that something is wrong (Phelan 2001a; *Unique*).

“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

**Teeth**
Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers. Misalignment of the teeth (malocclusion) has been reported to be common in those with Phelan-McDermid syndrome. Poor muscle tone, incessant chewing and tooth grinding (see Behaviour) may contribute to the malocclusion) (Phelan 2001a; *Unique*).

**Other**
Arachnoid cysts (fluid filled sacs on the surface of the brain) occur more frequently in children with a deletion of 22q13 than in the general population. While small cysts may pose no problems, larger cysts may result on increased pressure on the brain (Phelan 2008.).) MRI scans revealed also other brain abnormalities in 73 per cent of people.
These include thinning of the corpus callosum (36 per cent); changes in the white matter such as delayed myelination, general atrophy of white matter and nonspecific white matter hyperintensities (39 per cent); enlargement of the ventricles (32 per cent) and cysts in the brain (14 per cent). Therefore an MRI scan is recommended (Kolevzon 2014). Sometimes the thyroid does not produce enough thyroid hormone. It is important to test thyroid function (Sarasua 2014). Twelve per cent of people had an immunodeficiency (Sarasua 2014).

Hands are often large and fleshy (Phelan 2001a; Unique).

**Behaviour**

Many children with Phelan-McDermid syndrome are happy, sociable, and can be friendly and affectionate. However, they are as vulnerable to frustration as other children with a communication difficulty and temper tantrums and aggression can present carers with challenges. Many parents report that children with challenging behaviour have responded well to standard discipline techniques such as ignoring unwanted behaviour and rewarding them with cuddles and attention when they stop. Some children with Phelan-McDermid syndrome are resistant to change and parents find that a daily routine where the child understands what happens and when helps children to feel safe and secure (Phelan 2008; Unique).

Sensory processing problems affect some children. They may display lack of response to pain or verbal stimuli but conversely they may be tactile hypersensitive (dislike being touched or dislike the feel of certain textures) and panic at sudden noises or sudden movements (Philippe 2008; Unique).

Additionally, behaviour within the autistic spectrum is a recognised feature of Phelan-McDermid syndrome and the Unique experience is that around a quarter of children with a 22q13 deletion also have a diagnosis of an autistic spectrum disorder (ASD). Typically children fail to make consistent eye contact, they often play alone and struggle to interact or play with other children. The features may be apparent from early childhood but diagnosis may be slow. However, a diagnosis can be extremely helpful in increasing access to resources for the family (Goizet 2000; Phelan 2008; Unique).

However, recent research into the behaviour and social skills of eight children demonstrated that although seven of the children had behaviour suggestive of ASD, clinical evaluation did not confirm autism, and showed that their language development and the nature of their behaviour was distinct from autism (Philippe 2008).

The Unique survey suggests that as many as three quarters of children with Phelan-McDermid syndrome also have stereotypical, repetitive movements or flap their hands. Another behavioural characteristic, reported in over 80 per cent of children, is chewing/mouthing non-food items. They continue to ‘mouth’ for longer than other children and may chew and suck on clothes, toys and furniture at the age of 11 or 12. Some children have a chewing tube (a rubber tube which is safe to chew). Other behavioural characteristics include teeth grinding (in three-quarters of children) and in a small minority, aggressive behaviour (Phelan 2001a; Phelan 2008; Unique).
“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

Sleep
Sleep problems or disturbances are common, affecting over 50 per cent of Unique children. Sleep problems reported include both hypersomnia (excessive daytime sleepiness or prolonged night-time sleep) and insomnia (difficulty falling asleep or staying asleep). The experience at Unique suggests that insomnia is a more frequent problem. Parents report that children can be difficult to settle to sleep in the evening or may wake up regularly throughout the night. Some children just do not seem to need as much sleep as the average person. Sleep medication has been necessary for a small minority of children (Philippe 2008; Unique).

“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
Growing up with Phelan-McDermid syndrome

Puberty and Fertility
From the limited information that is available, puberty in girls generally appears to occur at the normal time and to proceed as expected, although puberty began early, at 6 years, for one Unique girl. There is little available information on males (Phelan 2008; Unique). Another report described puberty beginning early in 12 per cent of people (Sarasua 2014).

To date, there is only one individual who has been known to pass on a 22q13 deletion. A mildly affected woman, with a small interstitial deletion of 22q13, passed the deletion on to her son, who was more severely affected with hypotonia, speech problems and learning difficulties (Wilson 2008).

Adults with a Phelan-McDermid syndrome
Since there are no life-threatening problems associated with Phelan-McDermid syndrome life expectancy is thought to be normal. There are limited reports of adults in the literature; however lymphoedema (accumulation of fluid in the arms and legs causing puffiness) and cellulitis (bacterial infection of deeper skin tissues) may develop during teenage and adult years (Phelan 2008).

The adults reported in the published medical literature include a 22-year-old woman with the facial features of Phelan-McDermid syndrome and absent language. A 33-year-old woman with a very small 22q13.3 deletion had epilepsy, mild learning difficulties, speech delay and autistic symptoms. She lived in a sheltered home and attended a daycare centre for adults. A 46-year-old woman had hypotonia as a child which improved with age. She was epileptic, had decreased mobility and some of the facial features of Phelan-McDermid syndrome (Flint 1995; Anderlid 2002; Manning 2004; Phelan 2008).
22q13 deletion syndrome (Phelan-McDermid syndrome) Guideline
Themes addressed in the Dutch Guideline (see the ‘sources’ section for further details) for families of children with 22q13 deletions are summarised as follows:

- **Genetic testing and counselling**
  What genetic test needs to be done? Why is it important? For example: people with a ring chromosome 22 need a specific medical follow-up. Genetic testing is also important to determine the recurrence risk.

- **Language and speech problems**
  Children with a 22q13 deletion often have serious speech problems. Therefore early identification and management of these problems is important.

- **Problems with chewing and swallowing and gastro-intestinal problems**
  Often children have reflux, vomit or have constipation.

- **Sensory dysfunction**
  According to many parents, their children often have a low perception of pain (a high pain threshold). In the guideline a summary is given of the medical literature on sensory dysfunction and the impact on a person.

- **Epilepsy**
  About 25% of people with 22q13 deletion syndrome have epilepsy. The treatment of epilepsy in people with 22q13 deletion syndrome does not differ from the treatment of epilepsy in people without this syndrome.

- **Sleeping problems**
  Sleeping problems occur very frequently. It is always important to rule out an underlying (physical) cause. An EEG can be necessary if a child routinely wakes up during the night.

- **Lymphoedema**
  About 25% of people with 22q13 deletion syndrome have lymphoedema (a malfunction of the lymphatic system that causes swelling in the bodies tissues, commonly the arms and legs). No specific treatment is known, but the person can be referred to an expert centre on lymphoedema.

- **Psychiatric disorders**
  In the Guideline much attention is paid to behavioural aspects of 22q13 deletion syndrome. Autistic symptoms, especially regarding social communication are often present in childhood. Young adolescents often have mood disorders (periods of passivity alternating with periods of hyperactivity).

- **Treatment of developmental and behavioural problems with medicine**
  Studies that have focussed on these subjects are limited. Also the results are often not very convincing. At the moment studies are done on the effect of oxytocin on behaviour and attention. The Guideline elaborates on studies regarding insulin nasal spray and subcutaneously injected IGF-1. There is some minor evidence that that insulin has a positive effect on development. The evidence for IGF-1 is very limited.

- **Organisation of care**
  The guideline describes a list of expert centres and the way care is organised.

- **Guidelines for follow-up**
  The Guideline includes an overview of the recommended follow-up at different ages.
Ongoing research involving 22q13

Chromosome 22 represents about one and half to two per cent of the total DNA in cells and has been estimated to contain between 500 and 800 genes. Phelan-McDermid syndrome is due to the loss of a small portion of the long arm of chromosome 22: a variably sized piece of the region 22q13. The features of Phelan-McDermid syndrome are likely to be a result of the loss of a number of different genes found in this region.

The size of the deleted region in Phelan-McDermid syndrome varies widely ranging from a very small deletion of 100 kb to a very large one of 9 megabases (Mb: one million base pairs of DNA). Although there are two examples of individuals with small deletions who seem to be more mildly affected, there are also individuals who also have small deletions but who are more severely affected. Therefore, it seems that there is no strong link between deletion size and the features of Phelan-McDermid syndrome: individuals who are missing smaller pieces of chromosome 22 often have similar features to those who are missing larger pieces. Likewise, the majority of individuals, regardless of the deletion size, had learning difficulties and delay or absence of expressive speech (Luciani 2003; Wilson 2003).

Although many people have different breakpoints within 22q13, there does appear to be a recurrent breakpoint or breakpoint ‘hotspot’ in Phelan-McDermid syndrome towards the end of the chromosome within the SHANK3 gene (see diagram opposite) (Wong 1997; Bonaglia 2006).

The SHANK3 gene [also called PROSAP2] is found at 22q13.3 and is currently thought to be the cause of the major neurological features (developmental delay and absent/delayed speech) associated with Phelan-McDermid syndrome. SHANK3 codes for a structural protein involved in the signalling pathways in the brain: the SHANK3 protein is important in the formation of synapses or connections between the nerve cells. These synapses allow impulses to travel from one nerve cell to another (Bonaglia 2001; Luciani 2003; Wilson 2003).

Some individuals with Phelan-McDermid Syndrome may acquire a certain skill, such as speaking a few words, and later lose that skill. The skill may be regained at a later time. This skill loss may also be related to a deficiency of SHANK3. It is possible that synapses that have a reduced amount of SHANK3 may be less efficient than those with the correct amount of SHANK3. As new skills develop and more extensive synapses form, the risk of failure of the neural network increases. Eventually, as the neural network fails, the individual may experience a loss of a particular skill (Wilson 2003).

Loss or mutation of the SHANK3 gene is also thought to be responsible for the autistic features that often accompany a 22q13 deletion (Durand 2007).

This evidence would seem to indicate that the SHANK3 gene was the gene that is responsible for the majority of the features of Phelan-McDermid syndrome.
However, the story is not so straightforward. There are two individuals in the medical literature with interstitial deletions of 22q13, who retain two complete copies of SHANK3, but still have features similar to those with terminal 22q13 deletions, who are missing one copy of SHANK3. Indeed, these two individuals have a portion of 22q13 missing that does not overlap at all with the piece of 22q13 that is missing in a small number of individuals who have a small terminal deletion of 22q13 [which includes SHANK3]. This means that although these two groups of people have a similar set of features and all have Phelan-McDermid syndrome, they are missing completely different portions of 22q13 containing a completely different set of genes. The similarity in features of this two sets of people emphasises the non-specific nature of Phelan-McDermid syndrome and indicates that there must be genes, other than SHANK3, located within 22q13 that have major effects on development (Wilson 2008).

It is also important to remember that while identifying the responsible gene(s) is interesting, it does not lead directly to improved treatment. Additionally, even if the supposedly responsible gene is missing it does not mean that the feature will necessarily be present. Other genetic and environmental factors may have a role in determining the presence or absence of a particular feature.

**Why did this happen?**

A blood test to check both parents’ chromosomes is needed to find out why the 22q13 deletion occurred. In around 80 per cent of published cases the 22q13 deletions occur when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn). *De novo* 22q13 deletions are caused by a change that occurred when the parents’ sperm or egg cells were formed. Some 22q13 deletions are accompanied by a gain of material from another chromosome and are often the result of a rearrangement in one parent’s chromosomes. This is usually a rearrangement known as a balanced translocation in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. Balanced translocations involving one or more chromosomes are not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers. Whether the deletion is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 22q13 deletion and nothing you could have done would have prevented it occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. It is no-one’s fault.

*De novo* 22q13 deletions are caused by a sporadic mistake that is thought to occur when the parents’ sperm or egg cells are formed. The diagram on page 20 shows one way that a deletion and a duplication could theoretically arise during the formation of egg or sperm cells. On the left are two matching chromosomes, each split to the centromere and ready to pair and exchange segments. The shaded bars show similar sequences of DNA in the chromosome that enable correct pairing. But just above the centromere mispairing has occurred. When the chromosomes separate (right), the mispairing has given rise to two normal and two abnormal chromosomes, one with a deletion and one with a duplication.
Possible parental chromosome crossover errors leading to a deletion and duplication in chromosomes of an egg or sperm

Can it happen again?

The possibility of having another pregnancy with a 22q13 deletion depends on the parents’ chromosomes. If both parents have normal chromosomes, the deletion is very unlikely to happen again. If either parent has a chromosome rearrangement involving 22q13, the possibility is greatly increased of having other affected pregnancies. If they wish, parents should have the opportunity to meet a genetic counsellor to discuss the specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother’s uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby’s chromosomes. Testing is generally very accurate, although not all of these tests are available in all parts of the world.
Inform Network Support

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can please make a donation via our website at www.rarechromo.org/donate

Please help us to help you!

Phelan-McDermid Syndrome Foundation
Attn: Sue Lomas, 200 Capri Isles Blvd. Suite 7F, Venice, Florida 34292, USA
www.22q13.org
https://www.pmsf.org/
http://www.22q13.org.es/en (Spanish)
Family support Group on FaceBook
www.facebook.com/groups/22Q13PMS/

Unique mentions other organisations’ message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by Unique and reviewed by Dr Katy Phelan, Greenwood Genetic Center, USA and by Professor Maj Hulten BSc, PhD, MD, FRCPath, Professor of Medical Genetics, University of Warwick, UK 2008. This guide was updated in 2015 and 2016, additional information from Prof. Conny van Ravenswaaij-Arts was added in 2019.


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