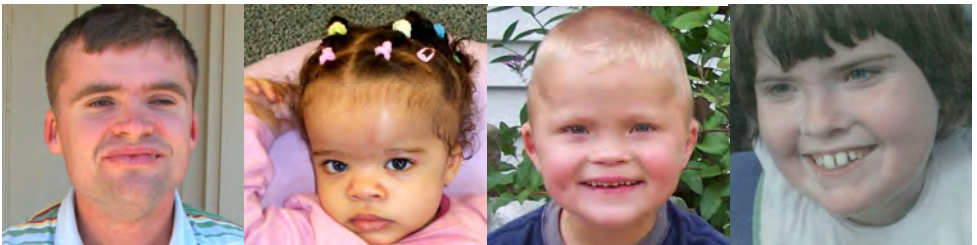




Kleefstra Syndrome



Sources and references

This leaflet tells you what is known about people described in the medical literature - around 75 by 2009 - and about *Unique's* members with Kleeftstra (9q34.3 deletion) syndrome.

Knowledge is still limited, but the oldest person was 52 years old when described.

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 (at www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain articles from *Unique*.

“ She has taught me more about life and about love, as well as about stretching the boundaries of human endurance, both mine and hers, than any other human being that I have ever encountered. ”

Kleeftstra syndrome is a rare genetic condition in which a tiny piece is missing from near the end of one of the body's 46 chromosomes. The condition can also be called 9q subtelomeric deletion syndrome. The missing piece includes a gene called *EHMT1*. Its absence is believed to cause the major symptoms of the syndrome.

What are chromosomes?

Chromosomes are the structures in each of the body's cells that carry the genetic information that tells the body how to develop and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. Each chromosome has a short (p) arm and a long (q) arm.

Looking at the long arm of chromosome 9

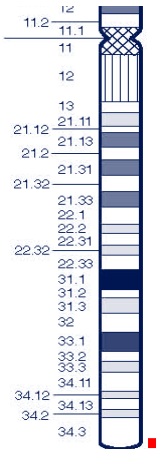
Chromosome analysis and molecular techniques

You can't see chromosomes with the naked eye, but if you stain them and magnify them many hundreds of times under a microscope, you can see that each one has a distinctive pattern of light and dark bands. In the diagram of the long arm of chromosome 9 on page 3 you can see the bands are numbered outwards starting from the point at the top of the diagram where the short and long arms meet (the centromere). A high number such as q34 is very close to the end of the chromosome, at the bottom in the diagram. The region close to the end of the chromosome is called the subtelomere.

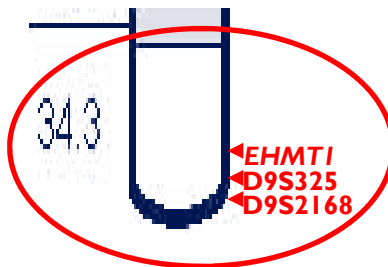
If you magnify chromosome 9 about 850 times, you may be able to see down a microscope that a small piece is missing. But in Kleeftstra (9q34.3 deletion) syndrome the missing piece is usually so tiny that the chromosome looks normal down a microscope. The missing section can then only be found using more sensitive molecular techniques such as FISH (fluorescence in situ hybridisation, a technique that reveals the chromosomes in fluorescent colour), MLPA (multiplex ligation-dependent probe amplification) and/or *EHMT1* sequencing, a method of searching specifically for the *EHMT1* gene. Commercial FISH probes can show a normal result in a child who has lost *EHMT1*, making correct diagnosis dependent on MLPA and/ or *EHMT1* sequencing. There are around 200 genes in the 9q34 region and *EHMT1* is the second gene from the end of 9q.

How important is the amount of deleted material?

Some children have much larger deletions than others. Geneticists in the past believed that people with larger deletions were more severely affected than people with smaller deletions, because they had lost more genes. This is only partly true. It's now believed that whenever the *EHMT1* gene is missing, broken or altered, the result is Kleeftstra syndrome (Kleeftstra 2006/1; Kleeftstra 2006/2).



The long arm of chromosome 9. The red line marks the approximate site of the 9q34.3 deletion. The diagram below shows an enlargement, with approximate site of the *EHMT1* gene and two markers commonly used in FISH diagnosis.



Results of the chromosome test

Your geneticist or genetic counsellor will almost certainly give you your child's karyotype, a way of describing what chromosomes look like. This usually shows the point/s where the chromosome has broken. It is likely to read something like this

46,XY.ish del(9)(q34.3)(D9S2168-)de novo

- 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, a combination of conventional chromosome analysis with molecular technology
- del A deletion, or material is missing
- (9) The deletion is from chromosome 9
- (q34.3) The chromosome has broken at band 9q34.3, indicating a small deletion of the end of the chromosome just short of the 'cap' that seals it at the 'telomere'
- (D9S2168-) A marker whose position on the human genome is known, in this case marker D9S2168, is missing
- de novo The parents' chromosomes have been checked and no rearrangement found involving 9q34. The disorder is then very unlikely to be inherited and has occurred for the first time in this family with this child

Comparing your child's karyotype with others, both in the medical literature and within *Unique*, will help to build up a general picture of what to expect. But there will still be differences between your child and others with apparently similar karyotypes. Your child is an individual!

Most likely features

- Developmental delay
- Learning difficulty or disability
- Recognisable facial appearance
- Low muscle tone, so babies and children feel floppy

Other common features

- Heart conditions
- Minor genital anomalies in males
- Sleep difficulties
- Seizures
- Behaviour difficulties
- Strabismus (squint) or other unusual eye features

Less common features

- Slightly unusual hands and/ or feet (single palm crease, incurving fingers, short or tapering fingers, unusually positioned feet)
- Hearing impairment
- Connective tissue disorders, including lax joints and hernias
- Patches of lighter skin colouring
- Anal atresia (the normal opening for the anus is not present)
- Possibly, overweight
- Kidney anomalies
- Dental anomalies

What are the first signs that a baby or child has the disorder?

The first signs can be incredibly diverse. Out of a group of 14 babies, five seemed fine at birth but concern grew later about their development: they failed to track visually, to watch their mother while feeding or their rate of development was slow. One baby seemed to progress as expected until developing a type of seizure at three months; another repeatedly failed hearing tests.

In nine babies there were signs immediately after birth of something wrong, varying from a weak cry, feeding difficulties and unusual facial features (twice thought to suggest Down's syndrome) to a small head, hernias in the groin and at the navel, a floppy larynx, heart problems, cataracts and seizures. Although a low muscle tone (floppiness) is usually characteristic of newborn babies with 9q34.3 deletion syndrome, this may not be obvious: in four babies, no floppiness was observed.

Pregnancy

For most of the 13 mothers who told *Unique* about their pregnancy, everything went normally. Three mothers noticed less fetal movement than they expected and one noticed more. One mother had an excess of amniotic fluid (polyhydramnios). Serum screening showed a very high risk of Down's syndrome in one mother and later ultrasounds (including 3D ultrasound) showed a small baby who often stuck her tongue out; ultrasound showed small arms and legs in another baby.

Most babies were born at or near their due date but five were born slightly early, at 34, 36 and 37 weeks. One baby was induced at 34 weeks when amniotic fluid levels fell.

Newborn

There isn't such a thing as a typical newborn baby with Kleeftstra syndrome. *Unique* babies vary greatly in birth weight – between 4.563 kg (10lb 1oz) and 2.6 kg (5lb 12oz) at term; a normal or high birth weight is most typical (Kleeftstra 2009). Some babies are well and thrive, while others are unusually quiet and passive and a few need to spend

time in special care. More babies are jaundiced than you would expect. Early feeding difficulties are common and so is silent reflux – where milk returns from the stomach up the food passage. Most babies with feeding difficulties only need help (tube feeding) for a short time.

Apart from these common difficulties of newborns, most babies with the syndrome have reasonable Apgar scores (a measure of well being at birth, scored from 0-10) and are quite well after birth and are able to go home after delivery at the normal time. A few babies have more obvious, specific health concerns. In the *Unique* sample, these included cataracts, hernias, a heart murmur, a rapid heartbeat or spells of turning blue or stopping breathing. One baby developed a serious chest infection at birth. One needed extra oxygen and had a floppy larynx, lung disease, kidney reflux and other difficulties. A baby’s cry may signal something unusual – sounding surprisingly weak or grunting. Two babies were found at birth to have a hearing impairment.

Will my child look different?

You may see a likeness between your child and one or more of these youngsters.



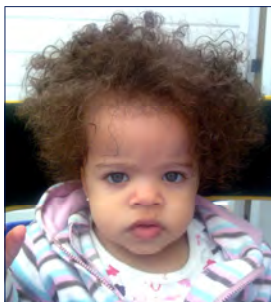
Your child may look more like the other babies and children with Kleeftstra syndrome in this leaflet than like your family or when he's very young, he may have a look of Down's syndrome. Young babies often have a broad head that is flat from front to back and may be unexpectedly small. Eyebrows may be low and sometimes meet in the middle and there may be a slant to the eyes which are typically set wide apart. Ears may be set low on the head and unusually formed. Typically, young babies hold their mouth open and have a large, thick tongue that sticks out. As children mature, they get better at keeping their mouth closed and the tongue is no longer obvious. Tongue tie can occur, where the tongue is tightly tethered to the bottom of the mouth by tissue and occasionally families comment on an unusual tongue shape – slightly forked at the tip or deeply creased. A few children have patches or spots of light skin and as the hair grows, there may occasionally be bald patches, although as you can see from the pictures, this is not obvious in *Unique* members.

Some of the other facial features that are said to be common in children and adults with Kleeftstra syndrome include a flat face with widely spaced eyes, arched or straight eyebrows, a short, upturned nose, a 'Cupid's bow' appearance to the upper lip and a pushed out lower lip. Other features commented on by *Unique* members include a high forehead; long eyelashes; almond-shaped eyes; blue eyes, unlike the family; and a narrow mouth (Iwakoshi 2004; Kleeftstra 2006/1; *Unique*).

Will my baby be healthy?

After early ill health for some babies, the great majority of parents told *Unique* that their children enjoy generally very good health, as good if not better than their brothers and sisters. These parental observations chart how often sickly babies generally mature into healthy children.

- “ She never seems to be a 'well' child. She is either fevering, seizing, constipated or has a cold – there's always something. On average we are at the doctor's two or three times a month. However, she's a very happy infant, often smiling or talking out loud. When she cries you know there is something wrong because she normally isn't a crier - 18 months
- “ When she's well, she's fantastic, sociable and happy; when she's unwell, she's floppy and doesn't interact much - 22 months
- “ After her early years with pneumonias, chest infections, kidney infections and being on antibiotics and poorly most of the time, her general health has been good - 14 years



Often sickly babies usually grow to be healthy children

Is there a typical growth pattern?

Most babies are born a normal weight and size, sometimes with a head measurement that is small but may be in proportion to the body. Postnatally there can be a drop-off in growth rate, made worse in some cases by feeding difficulties and a heart condition. As a result, the curve on a growth chart can be in the lower bands for a child with a 9q34.3 deletion. Occasionally, stature may be exceptionally low, right at the bottom of the growth chart and at least one family has tried growth hormone to boost growth. However, among *Unique* members it is just as common to have a perfectly normal growth rate and become an adult of average height. There is a small group of children (four/19 within *Unique*) who grow fast and are of above average height, at least until adolescence (Kleefstra 2006/1; Kleefstra 2009; *Unique*).



It's common to have a normal growth rate

What about food and eating?

Feeding and eating problems occur in some (not all) babies and children. Some babies breastfeed successfully, although the underlying hypotonia can make it hard for them to meet their own nutritional needs, making a high calorie feed supplement advisable at least as a temporary measure. Others do not succeed in sucking and/or swallowing effectively and benefit from a period of feeding via a nasogastric tube threaded up the nose and down the throat. Hypotonia also affects chewing so while some children move on to solids at the expected age, most are late in weaning and need their food cutting up small for a long time. Even then, they may continue to gag or choke on solid foods. Children with a high palate may store food in the top of the mouth as they eat. But by school age some children are sitting at the table and feeding themselves and other children are gradually learning to drink from a cup and to feed themselves with a spoon and fork.

Gastro-oesophageal reflux and vomiting are very common and can be severe, with a risk of aspiration pneumonia. Reflux may resolve once milk feeding is over or may persist. Careful feeding, using feed thickeners and medications prescribed to inhibit gastric acid have controlled reflux in most *Unique* children. If not, an operation called a fundoplication can improve the function of the valve from the stomach to the food passage. Babies may need to be fed by tube when they are ill and it is occasionally necessary to insert a gastrostomy tube for direct feeding to the stomach, but this is

unusual. The length of time that thickeners are needed varies widely from a few months to well into childhood.

There are reports in the medical literature of food-seeking behaviour and obesity (not coinciding with a high birth weight), but *Unique* has no evidence of real obesity and only one instance of unusual food choices (pica). On the contrary, out of fourteen children, twelve were not overweight and controlling food input and weight gain was a challenge for only one family (Cormier-Daire 2003; Kleefstra 2009; *Unique*).

Constipation is common in children with chromosome disorders and is very significant in this group. Most babies and children are taking prescribed stool softening medications, sometimes together with mildly stimulant glycerin suppositories and some also eat dried fruits and take linseed oil. One family found reflexology helpful.

A feeding or speech therapist will help in finding ways to feed babies with marked facial hypotonia, those whose tongue still thrusts forward or those with an uncut tongue tie. One advantage is that the oral stimulation phase lasts longer than in other children.

“ For the first 4 weeks I breastfed exclusively and that was extremely difficult. She was on the breast for about 90 minutes but would then rest and be hungry 90 minutes later. From what we know she wasn't getting very much and breastfeeding was extremely taxing on her. I started to pump my milk about the fourth week and noticed she did much better on a bottle. There was discussion of having a G-tube placed but as a parent I wasn't eager for this. We changed eating positions so she was more upright and early in her second year she had four months of Vital Stimulation Therapy (they put electrodes on the neck and face which send electrical impulses to muscles to help strengthen them) and also put elastic adhesive (Kenesio) tape on her face to help strengthen the muscles. We saw improvements: she started eating thickened foods and showed signs of beginning to chew

“ He has had gastrointestinal discomfort with burping and wind with pain and after trying the prescribed treatments, he is doing well with a homeopathic remedy and an organic diet, occasionally using symethicone drops - 9 years

“ He has a tendency to eat anything he can get into his mouth – bits of twigs, trees, bites out of swimming floats. His bowel movements have also been the biggest area of concern for us. Without medication his bowels don't move. We'd love to be able to get control of them but have failed so far - 14 years



By school age some children are sitting at the table and feeding themselves

Development: Learning

Children will need support with their learning, although the level is variable. They benefit from early intervention programmes and from attending special pre-schools and schools where their individual needs can be met properly. Depending on local schools, children thrive both in a mix of inclusion and special provision and in a special needs environment.

In common with others with a similar level of learning ability, children may well be late to show interest or curiosity in their surroundings, have a short attention span and require longer than normal to process information and project a response. Some children have strong retentive memory skills. Families say that their children learn best by repetition and reinforcement, with 1:1 teaching, where routines are familiar and praise and encouragement are generous. Some children respond well to visual aids but music and singing are also important aids to learning.

From the information available at present, there is a range of learning disability, with some children not reading or writing and communicating most of their needs non-verbally, while others progress faster and further and achieve some drawing, writing and reading skills. Although published developmental quotients have been below 50, a number of children seem to be more mildly affected (Cormier-Daire 2003; Iwakoshi 2004; Kleefstra 2006/2; Stewart 2007; Kleefstra 2009; *Unique*).

- “ She learns best by being shown and by repetition. In learning how to hold her bottle, we had to bring her hands to the bottle many times for a while to keep showing her how to do it. As far as sitting up, it is continuous work with her to put her hands down and then show her when she is about to fall to put her hand to the side - *18 months*
- “ She learns best by playing with things she enjoys. Enjoys water play/ being in the bath or swimming baths; wind from hairdryer and blankets; being tickled; being outside seeing trees - *22 months*
- “ He is functioning as a 4-5 month old. In terms of schooling, he loves the sensory room and loves music and being sung to. He also loves running around and wrestling with his daddy - that is sure to get a belly laugh - *2 years 6 months*
- “ She focuses well on Baby Einstein - *2 years 10 months*
- “ He is compared to a 19-month-old. He learns by repetition and loves music and dance. Moderate level - *35 months*
- “ She has made the most progress in Applied Behavioral Analysis (www.bacb.com). She completes puzzles, matches items and pictures, and she is learning her shapes and colors. She is also learning to copy block patterns and sort items into categories - *4 years*
- “ He loves to watch and then have a go when he’s comfortable - *5 years*
- “ He has just received a 100% on a reading comprehension quiz about Thanksgiving. He was able to answer five questions about the story that they had just read by using PECS pictures. He can read functionally - *7 years*
- “ Reads at school with help of Makaton symbols and some words without. Tries to write name but finds it very difficult - *9 years*



“ When she’s well, she’s best at singing, provided she has a microphone and an audience, and at remembering everyone’s news at circle time. She could read familiar word shapes if the topic interested her, for example she could read out to you what was on the TV listings. She can write her name and copy letters when she is well. If you ask her to draw a person, there is no relation of body parts to where they are drawn: very Picasso-esque! If she is very relaxed, she will ‘play’ by walking up and down the room relaying conversations from years gone by, very often putting herself in the position of authority such as the teacher or school bus driver
- 14 years 10 months

Development: Communicating

Eye contact and smiles are typically delayed, so breastfeeding babies do not always look into their mother’s eyes and first smiles arrive late, typically between three and six months. Babies communicate their needs by crying, facial expression and, as they mature, by gestures, intonation, vocal noises and approximations. Recognisable words may emerge in a few children in the second year, usually after a phase of copying, but they typically come later and in some children may not emerge at all. By 2 or 3, children may be babbling and communicating with a variety of vocal noises, intonations and signs as well as by gestures and words. Communication is supported by children’s generally sociable temperament but some children scarcely seem to make eye contact or communicate their needs.

Children usually understand more than they can express, especially when they are given maximum help using focused attention, short phrases and words are supplemented by body language and physical manipulation.

Many children learn a useful single word signing vocabulary and may learn to link words.



Enjoying water



Learning the sign for water

Others use assisted communication devices, including objects of reference and pictures, to signal their needs and thoughts.

Many children sing recognisably in tune and remember the words in lyrics.

Since hearing impairment can occur, babies and children should be regularly screened (Ayyash 1997; Neas 2005; Kleefstra 2006/1; Stewart 2007; *Unique*).

“ She pushes away a bottle if she no longer wants it, screams and laughs when happy and pulls toys towards her when she wants them. She slaps you or the ground in excitement but is unable to sign and has no words - *18 months*

“ She has a vocabulary of around 50 words, including phrases like Don't touch and Heart boom boom, sings and mimics activities - *age 4*

“ He can tell you what he wants, what he sees, or if he's sick. He is using 3-5 word sentences consistently and is learning new words at school all the time. But his speech can be unclear at times - *age 6*

“ He is using more spoken words and signs than two years ago and is putting two or three signs together - *age 7*

“ No words. He pushes or pulls for us to do something. If he wants a drink, he brings a glass, gets in the bath when he wants one or sits on a chair in the porch if he wants to go out. He babbles and laughs all the time - *age 11*

“ Very, very rarely does she initiate communication. She waits for us to provide her with the appropriate question and a choice of answers – although she had a 50-word vocabulary at the age of four. If she has been given an appropriate question, she can use 2-3 word phrases and will fill in the missing word in a sentence. 'Next we'll go to.....?' 'School.' When well, she has a lovely singing voice - *14 years 10 months*

“ Anyone who spent a day with him would understand what he wants – mainly drink, a food and to go out! - *15 years 6 months*

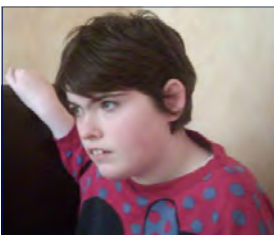
To get your message across, you can point ...

... or sign (here 'bear')



... look thoughtful

... or laugh



Development: sitting, moving: gross motor skills



All children achieve some degree of mobility. While some need persistence, practice, physiotherapy and special exercise programmes, others are walking well by their third year.

Babies are typically unusually floppy (hypotonic) and acquire head control late. The low muscle tone generally affects the whole body, including the arms and legs. In addition to regular physiotherapy and sometimes special clothing to support the upper body, some families have experimented with taping the trunk to promote stability.

Babies reach their early milestones, although later than other typically developing babies. They learn to roll from five months and become able to sit alone - at first in a slumped position - as early as seven months but often much later. Supportive clothing helps to counteract upper body floppiness. Once sitting independently, babies may lack a 'save' reflex, so need

seating in safe surroundings. Children may become mobile, some by conventional crawling but others using ingenious alternatives including commando crawling (creeping), bottom shuffling (scooting) or continuous rolling as early as 12 months, but this is not possible for all. First supported or unsupported steps may be possible in a few children as early as 18 months but usually emerge later, most typically between 3 and 7 years, and may follow years of persistent practice. Some children need supports or insoles and especially supportive footwear to steady their loose joints and benefit from practice with a walker. Some children have flat feet and many have a slightly unusual style of walking and remain liable to trip and fall for many years. Those who have had a club foot corrected may also have an awkward walking style (Kleefstra 2009).



1 year 11 months



3 years



5 years

Children become mobile and learn to walk at very different ages

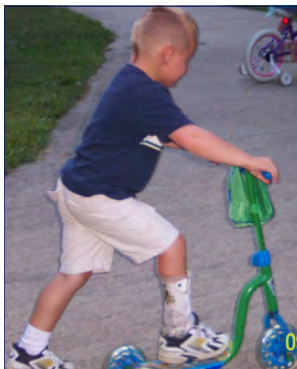
Problems with balance can persist and while climbing stairs may be possible by 4 years with an adult hand to steady, running can be more difficult and fast-walking is an alternative strategy. In general, problems with hypotonia ease considerably once children are mobile although they remain prominent when tired or ill. Outdoors, some children will use a wheelchair and may need one indoors as well. Other children can walk well indoors and out by school age, learn to ride a two or three-wheeler and go on to enjoy jumping, dancing, swimming and using playground equipment.

- “ Due to therapy several times a week his skills have improved immensely. He can walk, fast-walk (not run), climb things slowly (his balance is not great) and sit unassisted - 2 years 10 months
- “ After casting and surgery to correct talipes, she has learned to walk and climb stairs with the help of physiotherapy.
- “ She can't swim yet but she likes to get into the swimming pool. We are trying to cycle and think it will come - 4 years
- “ He's running, riding a bike with training wheels and a 3-wheel scooter, swinging himself in a swing, climbing ladders and on play equipment and swinging on a rope - 6 years
- “ Very mobile, but cautious. Will climb stairs using his hands and sits to come down. Wobbly walk and very unaware of surroundings. Loves running after balls and out in big wide spaces. Goes horse riding with school – fantastic balance and posture. Loves swimming but cannot ride a bike. Will take the easy option when walking and get in his buggy – but we don't let him! - 11 years
- “ He's walking more and nearly running, so less reliant on his buggy. We only use it for safety around the shops - 15 years



Below: at five years

Above, right: at eight years



Development: hand use and coordination (fine motor skills) and personal care

Weak hands, low muscle tone and poor coordination mean that children are very likely to experience some delay in learning to use their hands for everyday jobs such as holding a bottle, using cutlery, playing with toys and dressing and undressing. The extent of the delay varies widely between individuals and does not always reflect the delay in mobility (gross motor skills). Early developers seem to keep their advantage and grow into youngsters with the most complex hand use, while late developers need more training, exercise and play to promote their development. Some children can handle a bottle and drink from it before their second birthday, while others never consistently acquire this skill. Similarly, a few children feed themselves with table cutlery but many use a spoon. Undressing comes before dressing and even the most deft operators still need help with fiddly items like zips and buttons for a long time.

Personal care skills generally go hand in hand with the ability to grasp, hold onto and manipulate objects and toys and again there is very wide variation, with a few children washing, brushing teeth, dressing and taking showers semi-independently by the age of 6, others depending entirely on family and carers into their teenage years and most operating between these two extremes. Toilet training is delayed and may be significantly late. A small group of children acquire bladder and bowel control by the early school years (4-6), but most do not. They may well comply with toilet timing and day-time dryness usually emerges with consistent training.

“ He can draw lines and cut with scissors, but not with accuracy though he uses scissors to cut open snacks for himself. He loves to operate remote control cars, trucks or boats and does so with purposeful control. He loves to go fishing and though he can't cast a fishing pole, he sure can catch them and reel them in. He uses the bathroom by himself: pulls his pants down, uses the potty, flushes, washes and dries his hands. He needs assistance most of the time with getting his pants pulled up completely. He is taking showers now and is able to wash himself when given verbal and visual reminders and brushes his teeth with help. He can undress, but has problems dressing himself - 6 years



Emerging skills

Therapies

Families can expect their children to be assessed for the standard trio of therapies – physical (physio), occupational and speech, as well as early intervention play and learning therapies. The great majority of children qualify for the full range of therapies and generally make consistent progress. Early physiotherapy is especially helpful in addressing low muscle tone. Children with hearing and eyesight difficulties will generally also qualify for specialist sensory teaching.

Families have additionally tried a wide range of therapies including music, hippotherapy (riding for the disabled), massage, relaxation, craniosacral, aromatherapy and water therapies – all with a measure of success. One family reported improvements after 12 weeks of Vital Stimulation therapy, a system that involves putting electrodes on the face and neck with the aim of stimulating and strengthening muscles. Another family reported great success with Applied Behavioral Analysis. One family reported marked improvements after ozone and urine therapy.



Children qualify for therapies

Behaviour

It is not yet known whether there is a typical behaviour pattern for children and adults with Kleefstra syndrome but children are generally described by their families as sociable, calm, fun-loving, loving and outgoing. Generally, children relate better to adults than other children and have little or no stranger anxiety and can be overfriendly. Problem behaviours including invading others' space, aggression (biting, hitting, hair pulling) and unpredictable mood swings can occur as well as difficulties such as a high pain tolerance, being easily frightened, feeling insecure and disliking changes in routine.

A change in behaviour can be due to ill health but sometimes no cause can be found.

There are many reports in the medical literature of children with behaviour that families could find challenging. These range from chewing objects to self stimulatory behaviours (biting, hand in mouth and chomping), obsessive-compulsive disorders, stereotypic movements, outbursts of anger, self injury and aggression towards others. Many children with special needs, including those with Kleefstra syndrome, show

behaviours that fall within the autistic spectrum. These range from repetitive behaviours and social incomprehension to a cyclical state of profound passivity diagnosed as autistic catatonia.

Puberty may bring a sudden increase in these hard-to-handle behaviours and moods. There is some recovery in adulthood but psychiatric care may be needed meanwhile. Two children are reported to have seasonal affective disorder, with low mood and responsiveness throughout the winter and a recommendation of light therapy.

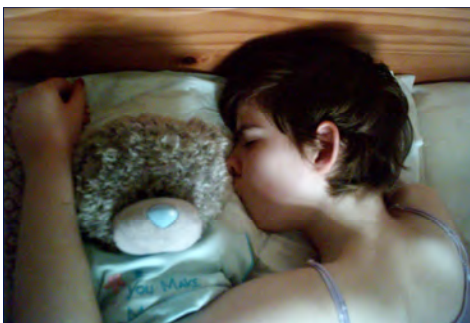
Parents should be offered full behavioural support. Some parents are reluctant to use medication for their child's behaviour but the right medication in the right dose can be transformative (Anderlid 2002; Cormier-Daire 2003; Kannu 2005; Sanger 2005; Kleefstra 2006/1; Stewart 2007; Kleefstra 2009; *Unique*).

- “ Playful, observant, extremely easy to care for. Lots of therapy keeps her busy.
- “ Very social – smiles, plays with faces, laughs, gives kisses - 15 months
- “ Her behaviour is one of contentment most of the day and in the afternoon can become vocal with some high pitched ‘talking’ or laughing - 18 months
- “ Very happy and pleasant to be around. Blows bubbles most of the day, only stopping to eat, potty and sleep - 6 years
- “ He is a loving boy who gives hugs in the morning and when he sees you after being gone. He does become angry when not given his way and on occasion will bite himself or whoever is close - 7 years
- “ He was biting his hand and screaming but after two months of ozone therapy there is no more biting and very little yelling - 9 years
- “ She finds it difficult to sit and stay quiet, and walks up and down, moving her hands and fingers. She is developing more and more autistic traits - 9 years
- “ Every day can be heaven or hell. He can be aggressive or compliant. He can be interested or he can be vacant. He can be on fast forward or on go slow. When he was younger we used to have 6-week behaviour cycles but now it is more volatile with moods changing almost daily - 14 years 4 months



Young children are generally sociable

“ The UK experts in autistic catatonia say that they have no firm evidence for a definitive regime but US psychiatrists have been keen to make use of either lorazepam or more often, long courses of electroconvulsive therapy (ECT). She had a very negative reaction to lorazepam and have not been keen to try ECT yet. Think of the most passive person you know and then imagine her more passive than that, withdrawing into herself physically and emotionally in any sort of noisy, crowded or unfamiliar atmosphere and that’s what she is like most of the time. She is described as passive/social, ie passive but much more sociable with familiar adults than would be the case in classical autism - *14 years 10 months*



Sleep

Sleep disorders do occur, but with no consistent pattern. Some children sleep without problems especially when they are well, but others experience major disruptions, particularly persistent night-waking. While awake they may be destructive, for example, by shredding their nappy. Children with reflux may sleep better with the head end of the mattress raised. A small group of children have been diagnosed with sleep apnoea - periods during sleep when the flow of air to the lungs is obstructed - and in some of these children removing enlarged tonsils and/or adenoids may prove helpful. In children whose day-time behaviour cycles between overactivity and passivity, sleep disturbance can be a problem during periods of hyperactivity. Some families only achieve a regular sleep routine by using medication. Melatonin is popular and most families believe it is at least partly effective but quite a few children need other prescribed medication to ensure they stay asleep. Families whose children persistently wake at night need regular, consistent respite care (Neas 2005; Kleefstra 2006/1; Stewart 2007; *Unique*).

“ He has had numerous sleep studies, had sleep apnoea, has had adenoids and tonsils removed and is taking medication to keep his small tubes within his face uncongested. He still gets up at night demanding attention. When you go in he is on the floor half asleep. You either pick him up or make him get up and get back into bed and he goes straight back to sleep. This is driving us crazy - *5 years*

“ To stop her shredding her nappy, we tried an all-in-one sleepsuit and it seems to work. Now I’m looking for washable cotton nappies - *9 years*

“ He can be so hyper that he refuses to go to sleep and remain up all night or sleep for only a few hours - for weeks on end. If we give him melatonin before he starts his hyper mood it can help to send him off to sleep - *14 years*

Medical matters

■ Will my baby have a heart condition?

One third to one half of the babies with Kleeftstra syndrome are born with a structural problem with their heart and for this reason any baby diagnosed with the disorder should have echocardiography. It's *Unique's* experience that in the great majority of babies the heart problem is not severe and usually resolves naturally in time. Out of 20 *Unique* babies, eight were born with a completely healthy heart, nine had a heart condition that cleared up naturally and three needed surgery to correct the defect. In general, babies with a heart condition will have significantly more ill health until their problem has been corrected than those born with a healthy heart.

The most common defect is a hole between the upper (filling) chambers of the heart (atrial septal defect, ASD). This may occur alone or together with a narrowing of the entrance to the artery that takes blood to the lungs (pulmonary stenosis). Holes between the lower pumping chambers of the heart (ventricular septal defect, VSD) are slightly less common, but again may occur together with pulmonary stenosis or persistent ductus arteriosus (PDA), a persisting feature of the fetal circulation where a channel between the aorta and the pulmonary artery that usually closes shortly after birth fails to do so, supplying the lungs with more blood than they should have and making the heart work too hard. Narrowing of the valve in the pulmonary artery that takes blood to the lungs or in the valve at the outlet to the aorta can also occur.

In some babies, the heart condition has no obvious effect, while other babies may tend to get blue or breathless while feeding. Mild cases may well need no treatment, especially if the defect improves over time. When surgical intervention is needed, it may be possible to use a minimally invasive technique, such as catheterisation.

Occasionally, a baby with Kleeftstra syndrome is born with a more complex heart condition, such as tetralogy of Fallot, a complex heart condition involving both a hole between the lower pumping chambers of the heart and an obstruction just below the valve in the artery that leads to the lungs. Blue (deoxygenated) blood cannot easily get to the lungs to pick up oxygen and some of it flows through the hole into the other pumping chamber from where it is pumped around the body. Babies with tetralogy of Fallot need a surgical operation. If there are no other risk factors, more than 95 per cent of babies with tetralogy of Fallot successfully undergo surgery in the first year of life and as surgical techniques are refined, the outlook for babies with a heart condition is constantly improving (Schimmenti 1994; Ayyash 1997; Stewart 2004; Neas 2005; Stewart 2007; Kleeftstra 2009; *Unique*).

■ Do children with Kleeftstra syndrome have epilepsy?

Some babies and children do not have seizures but quite a lot do. The type of seizure seen most often is infantile spasms, usually starting in the first twelve months and generally well controlled with medication, with most babies outgrowing this type of seizure. Other types of seizure can occur, with a known age of onset ranging from six months to 27 years, including absence seizures ('staring spells'), febrile convulsions and complex partial seizures. The evidence is that medication keeps seizures under good control, they diminish in severity and children may well outgrow them. Meanwhile, families recommend a referral to a specialist epilepsy centre (rather than a general

paediatric neurologist) for any child with hard-to-control seizures (Iwakoshi 2004; Stewart 2004; Sanger 2005; Kleefstra 2006/1; Stewart 2007; *Unique*).

“ She started to have startle episodes, which turned out to be infantile spasms - 2 months

“ Before the epileptic seizures we noticed a pattern of her breathing increasing and getting rapid, she has blue lips and her oxygen levels are low. She has a low fever and then about 20 minutes later she will have a seizure after her fever escalates to around 105 degrees - 18 months

“ He does have staring spells, so we are watching - 3 years

■ Respiratory infections

Generally speaking, babies with Kleefstra syndrome are particularly vulnerable to respiratory infections in their early months and years. In early infancy, some babies seem vulnerable to RSV (respiratory syncytial virus) infection, frequently developing bronchiolitis. Other babies develop pneumonia. They usually outgrow the tendency between their second year and school age and most grow into healthy children. Some older children have experienced a marked health improvement once their tonsils and adenoids were removed. A small number of babies (3/19) were entirely free from respiratory infections.

There are many reasons for the frequent infections and some interplay between the causes. At birth, babies may have noisy or ‘coarse’ breathing. Some babies have an unusually soft, flexible structure to the windpipe and voicebox (laryngomalacia, tracheomalacia) that makes them liable to collapse. Uncoordinated sucking and swallowing may lead young babies to inhale part of their feeds. Babies with reflux, where part of a feed returns up the food passage, are at particular risk of aspiration. If milk is aspirated into the lungs, it can set up an infection. In some babies the respiratory centre in the brain may not function perfectly and this may lead to episodes where the baby turns blue. Additionally, babies with a heart condition may become breathless and their lungs may need to work abnormally hard. When a baby or child catches an infection, these factors may make it harder for him to get over it.

Doctors should treat respiratory infections in a child with Kleefstra syndrome aggressively. Some children are prescribed a preventive dose of antibiotics. The great majority of children recover fully from their respiratory infections and outgrow them. All the same, those most severely affected may be left with lingering asthma symptoms or long-term lung damage (Kannu 2005; Neas 2005; Yatsenko 2005; Stewart 2007; Kleefstra 2009; *Unique*).

“ She was 7 months in the hospital during her first year of life caused by RSV - 4 years

“ Craniosacral therapy seemed to help boost her immune system - 14 years

“ He’s been coughing for months but with no obvious other ill health. It sounds like the same phlegm that’s always been there. He’s unable to cough it out or blow his nose so it just sits there - 14 years



He outgrew his frequent respiratory infections

■ Small or immature genitals

Around half of the boys with a 9q34 deletion have been born with small or immature genital features and one girl is also affected. A small penis or having the hole on the underside of the penis rather than at the end (hypospadias) is harmless and some boys do not even need corrective surgery. An operation may be needed if the hole is a long way from the end of the penis and it may also be offered to boys born with undescended testicles (cryptorchidism) or boys in whom the testes readily retract into the abdomen (Kannu 2005; *Unique*).

■ Hernias

A few babies are born with a hernia or one is found later. Typically it is in the groin (inguinal hernia) or at the navel (umbilical hernia). An umbilical hernia shows as a bulge and develops when an opening in the abdominal muscles for the umbilical cord does not close after birth. Part of the lining of the abdomen and intestine and sometimes fluid can pass through the opening. Many umbilical hernias close naturally by the age of three or four but a large hernia or one that stays open can be closed surgically.

In an inguinal hernia, part of the bowel loops through an opening in the inguinal canal in the groin. In fetal development, the testes descend into the scrotum through this opening which usually then closes. If it fails to close or re-opens, the hernia usually appears as a swelling in the groin or enlarged scrotum. An inguinal hernia should be assessed and usually needs surgical repair.

■ Urinary tract and kidneys

Most children have a healthy urinary tract and kidneys that work well. In a minority of children a concern has arisen, usually following investigation of a urinary tract infection and for this reason, children should have their renal and urinary tracts imaged. Conditions reported include hydronephrosis (enlarged kidneys) for which there are many causes, including a blockage in urine drainage, reflux of urine from the bladder, a double ureter leading from the kidney to the bladder and a non-functioning, cystic kidney. Treatment depends on the cause.

Three *Unique* children have either had frequent urinary tract infections or had kidney reflux, a condition in which urine, in addition to passing out of the bladder, also flushes back towards the kidneys. One child had a double ureter. The kidneys were not harmed although in one child they got infected. These children took preventive antibiotics until they outgrew the tendency to reflux. One child had small cysts on the kidneys but these caused no problems (Kannu 2005; Stewart 2007; *Unique*).

■ Other conditions

Other conditions have been found either in the *Unique* series or in children described in the medical literature but are not necessarily typical of children with a 9q34 deletion: a tethered spinal cord (the normally mobile and free spinal cord is held in one place, causing pulling on it and decreased blood supply); multiple strawberry marks at birth; a life-threatening cerebral abscess; congenital pectus excavatum, where the chest is hollowed and the breastbone depressed. This can be mild or very obvious and is usually considered cosmetic but can affect cardiac and respiratory function and cause pain in the chest and back (Iwakoshi 2004; Stewart 2004; *Unique*).

■ Eyesight



Some children have a degree of visual impairment despite having structurally normal eyes. This is known as cortical visual impairment, a condition in which the visual systems in the brain do not consistently understand or interpret what the eyes see. As a parent you may notice that your baby is not visually responsive either to you or to lights or moving objects. At least one child has slow visual maturation, so he reacts to visual stimuli as a younger child would do. One child also has a delay in processing visual information.

One child and possibly one other have needed the removal of cataracts from the lens of the eyes. Other children are longsighted and will

need to wear glasses for correction. Strabismus (a squint) is also fairly common and may be caused by the underlying muscular hypotonia. Although this can be corrected surgically, it may recur (Schimmenti 1994; Stewart 2004; Stewart 2007; *Unique*).

“ He appears to have optic albinism and central vision impairment. His eyes can move independently, especially when he’s tired. He wears different glasses for different occasions - 9 years

“ Her eyes didn’t seem to focus properly when she was little. The consultant never found anything wrong, although lack of communication made it difficult to be sure. After diagnosis she was referred to a consultant who thought her eyes seemed fine, except for an extremely slow blink reflex - 14 years

■ Hearing

Most children have normal hearing but the risk of a permanent or temporary hearing impairment is increased. Where a baby fails a newborn hearing screening test, a permanent loss is more likely. Some babies pass their newborn screening tests but do not appear to respond to sound. Failure in this case may indicate delayed maturation of the hearing pathways. Babies and children with Kleeftstra syndrome are also vulnerable to upper respiratory tract and ear infections, and may additionally have a conductive hearing loss that can be relieved by placing grommets (tiny plastic tubes) in the eardrum. If this measure does not improve hearing to useful levels, hearing aids will be considered (*Unique*). Some children have spells of acute hypersensitivity to sound (*Unique*).



■ Teeth

Generally speaking, children with chromosome disorders have a high rate of dental anomalies and may need specialist treatment. Among children with Kleeftstra syndrome the most common feature is late eruption of milk teeth; the teeth may also not come through in the expected order and may be preceded by teeth already present in the mouth at birth. Milk teeth may fail to fall out. Some teeth may be small, others large, and there may well be gaps between them. Teeth may be notched or poorly calcified (Kannu 2005; Kleeftstra 2006/1; Kleeftstra 2009; *Unique*).

■ Overheating

Families have reported that some children overheat easily due to a malfunction of the sweat glands. If you notice that your child overheats easily or never appears to sweat, consult your doctor. Cooling garments and blankets can be helpful.

A 20-year-old with a 9q34.3 deletion



“ Our son was born at full term by Caesarean and at birth had an innocent heart murmur and pneumonia. He was a floppy baby, was about one before he sat unaided and 2 to 2½ before he walked.

“ I did the physiotherapy, occupational and the speech therapies with him, as well as going to the hearing centre. He has mild to moderate hearing loss and wore hearing aids until a few years ago when we stopped putting them in due to ear infections.

“ Despite extensive therapy, our son is non verbal, only using one or two words together and mainly getting his message across with natural gestures, pictures and some signs. But he understands what you say to him.

“ He needs help with all aspects of his daily life but loves music and dance, has pretty good ball skills and used to ride a bicycle until he was 16. At that age, he started to

have behavioural problems and spells of vagueness, something like absence seizures. With help and medication he's nearly back to his old self but he did lose some of his personal and social skills. In the past you could take him anywhere but he likes a routine and now gets a bit agitated in unfamiliar surroundings.

“ He went to a mainstream school until he was eight and then to a special school until 19. He is now in a fully supported group home with three other men. He goes to a day programme during the week and comes home every second weekend. ”

Why has this happened?

To answer this question both parents of a child with Kleeftstra syndrome should have their chromosomes tested. In most cases, both parents will have normal chromosomes. The chromosome break is then said to have occurred out of the blue (*de novo*, meaning a new event). *De novo* changes are caused by a change that usually occurred when the parents' sperm or egg cells were formed or just after conception. When a sperm cell from the father and egg cell from the mother first join together, each carries just one chromosome from each pair. Together they form a single cell that now carries two chromosomes from each pair. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes can break off or become arranged differently than usual.

Occasionally, 9q34.3 deletions are 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 health or development problems, although they may have experienced difficulties with fertility.

Whether the deletion is inherited or *de novo*, what is certain is that there is nothing you could have done to cause it 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. They are no-one's fault.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with Kleeftstra syndrome or any other chromosome disorder. Where a parent has a rearrangement of their chromosomes with a break at 9q34, the risk of having another affected child is much higher.

If they wish, parents should have the opportunity to meet a clinical geneticist or genetic counsellor to discuss their specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD will not be needed for families where the deletion is a *de novo* occurrence but can be an option for families with a family translocation. The technique 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 very accurate, although not all of these tests are available in all parts of the world.

“ Everything he does is special.

Even though he can't communicate with us, when he smiles, it lights up a room and his laugh is contagious.

He is amazing and we are lucky to have him in our lives. ”

Support and Information



Rare Chromosome Disorder Support Group,

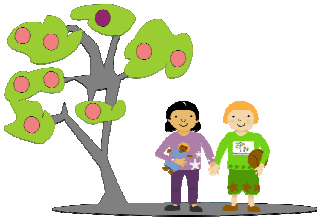
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Kleefstrasynndrome.org

A website and forum for anyone affected by Kleefstra syndrome

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. It was compiled by Unique and reviewed by Dr Tjitske Kleefstra, Department of Human Genetics, Nijmegen, Netherlands and by Unique's chief medical advisor, Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK. 2007 Revised 2009. (PM)

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