



Understanding Chromosome & Gene Disorders

3p26 deletions



rarechromo.org

Genes and chromosomes

Our bodies are made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes; this genetic information tells the body how to develop, grow and function. Genes are carried on structures called chromosomes.

Chromosomes usually come in pairs, one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: (two Xs for a girl and an X and a Y for a boy). The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22, approximately from largest to smallest. These are called autosomes. Each chromosome has a short (p) arm (from petit, the French for small) and a long (q) arm (see diagram, right). People with a 3p26 deletion have lost DNA from the area of the diagram marked in red.

Chromosome Deletions

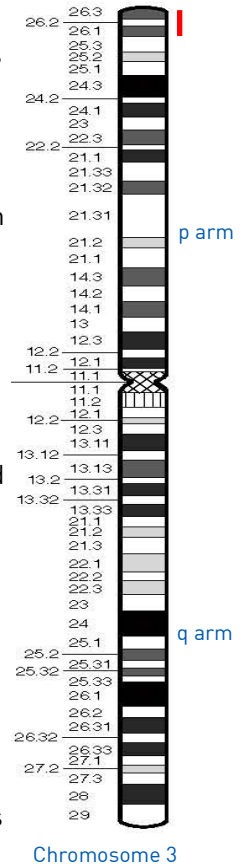
A sperm cell from the father and an egg cell from the mother each carries just one copy of each chromosome. When they join together they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human growth and 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 from usual.

People with a 3p26 deletion have one intact chromosome 3, but a piece from the short arm of the other copy is missing. We believe that most of the clinical difficulties are probably caused by having only one copy (instead of the usual two) of one or more genes from the missing piece. We are still learning the about the specific jobs or functions of the genes in this region. It is important to keep in mind that a child's other genes, environment and unique personality also help to determine future development, needs and achievements.

Sources

The information in this guide is drawn partly from the published medical literature. With the first-named author and publication date you can look for abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed) (Lozcano-Gil 1994; Cargile 2002; Frints 2003; Fernandez 2004; Rivera 2006; Malmgren 2007; Barber 2008; Fernandez 2008; Roohi 2008; Shuib 2009; Girirajan 2010; Gunnarsson 2010; Pohjola 2010; Cuoco 2011; Synofzik 2011; Peltekova 2012; Kellogg 2013).

The guide also draws on the Decipher database at <https://decipher.sanger.ac.uk> and on Unique's database of members with a 3p deletion. When this updated guide was compiled, Unique had 24 members with a pure 3p26 deletion involving no other chromosome, from babies to adults.



What is a 3p26 deletion?

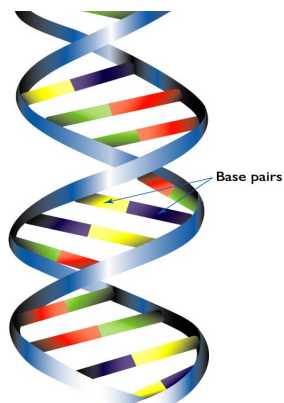
A 3p26 deletion means that some genetic material (DNA) has been lost from near the end of one of the two chromosome 3s. This can affect development, but how much, and in what way can vary a lot. Some people lose DNA from the end of chromosome 3 with very mild or apparently no effects; others are severely affected, and as adults need considerable levels of care.

Looking at chromosome 3p26

Chromosomes cannot be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. In the diagram of chromosome 3 on page 2, you can see the chromosome bands are numbered outwards from the point where the short arm meets the long arm. 3p26 is at the top, divided into three bands – 26.1, 26.2 and 26.3.

Each band contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. 3p26 has around 8,540,000 base pairs. This sounds a lot, but is actually quite small: the total DNA from 3p25 and 3p26 on one chromosome 3 is about a half of one per cent of the total DNA in each cell.

The human genome is constantly being revised. With each new revision, base pair numbers can change slightly. The base pair numbers in this guide follow the latest human genome build 19, known as hg19.



1 base pair = bp
1,000 base pairs = 1kb
1,000,000 base pairs = 1Mb

How rare are 3p26 deletions?

This is not quite certain, but they are probably quite rare. Since the first person was reported in the medical literature in 1994, only a handful of people with a pure 3p26 deletion involving no other chromosome have been described in the medical literature. However, many more people have been identified recently using a molecular genetic test such as microarrays and some of these are recorded on databases such as Decipher. Some people are apparently unaffected by their deletion or only very mildly affected, and so would never be identified.

Does everyone have the same size 3p26 deletion?

No, they don't. In some people the chromosome has one break and the end is missing (a **terminal** deletion). In others, there are two breaks and the DNA between them is missing (an **interstitial** deletion). The chromosome can break anywhere in the 3p26 bands so people have different sized pieces of chromosome missing. Your geneticist or genetic counsellor can advise you on the position of the breakpoint or breakpoints in your family.

Are there people with a 3p26 deletion who have no health or learning difficulties and have developed normally?

Yes, there are. When a child has a genetic test that shows a 3p26 deletion, the parents will usually also be tested. Parental testing has revealed some families where one parent has the same 3p26 deletion as the child, but is unaffected, or only very mildly affected (Shuib 2009; Pohjola 2010; Cuoco 2011; Decipher; Unique). What can then be uncertain is whether the 3p26 deletion is the cause of the difficulties for which the child was referred for genetic testing. Your geneticist or genetic counsellor can advise you on the situation for your family.

Families with a 3p26 deletion



Mother and son have the same 3p26.3 microdeletion

A 3p26 deletion can be passed from parent to child. The inherited deletion can be tiny and is most commonly from the 3p26.3 band. An inherited deletion can have different effects on different family members, sometimes mild, sometimes more severe. There is a growing number of families in whom one apparently unaffected parent has unknowingly passed a 3p26.3 deletion on to their child or children (Pohjola 2010; Cuoco 2011; Decipher; Unique).

No-one knows yet why different members of the same family are affected differently by the same chromosome deletion. But there are a number of theories. These include: the 'two-hit' hypothesis, where affected family members have a second chromosomal variation in addition to the 3p26 deletion, and gene modification, where factors which alter the timing or manner of the way the gene(s) in the deletion function(s) differ between individuals (Barber 2008; Girirajan 2010).

Genetic testing

Looking at chromosomes under a microscope, it may be possible to see the genetic material that is missing, if the piece is large enough. However, rare chromosome disorders can be caused by subtle changes that are too small to see using a microscope. Molecular DNA technology gives a more precise understanding of the size and position of the deletion. This is important as scientists identify genes and pinpoint their location on chromosomes.

Techniques that are commonly used include FISH and microarrays: fluorescence *in situ* hybridisation (FISH) uses fluorescent dyes to visualise under a microscope the number of copies of small sections of chromosomes. Unique publishes a separate guide to FISH. Microarray comparative genomic hybridisation (array CGH) is a sensitive technique which shows gains (and losses) of tiny amounts of DNA throughout the chromosomes. Array CGH identifies duplicated, disrupted or absent DNA. Unique publishes a separate guide to array CGH.

A person's chromosome make up is called his/ her karyotype. Someone with a 3p26 deletion might have a karyotype that looks like one of these three examples:

arr cgh(hg19) 3p26.2p26.1(3,057,863_7,963,180)x1 This result shows that array comparative genomic hybridization (**arr cgh**) showed that only one copy (**x1**; the normal copy number is two) of part of the bands known as 3p26.2 and 3p26.1 was found. **hg19** tells you which version of the human genome was used to make these measurements. At present, hg19 is the latest version. The first base pair missing is **3,057,863** and the last is **7,963,180**. By taking the first number from the second, you can work out that there are 4,905,317 missing base pairs, or about 4.9 Mb of missing DNA. This result shows that this is an **interstitial** deletion with two breaks.

46,XY.ish del(3)(p26.3pter)(tel 3p-)dn This result shows that the expected number of chromosomes [**46**] were found, and there was an X and a Y chromosome, so this is a boy or man. The test used the FISH technique [**ish**] and this showed that DNA was missing from chromosome 3 [**del(3)**]. The missing material started in the **p26.3** band and continued to the end of the chromosome [**pter**]. A marker at the end of chromosome 3 [**tel 3p-**] was missing. **dn** means that this chromosome change is a new occurrence [**de novo**] and has not been inherited from either the father or the mother.

46,XY.arr cgh 3p26.3(RP11-299N3)x1 This result shows that the expected number of chromosomes [**46**] were found. It also shows that one X and one Y chromosome were found, so this is a boy or a man. **arr cgh** shows that array comparative genomic hybridization showed that only one copy (**x1**) of a marker (**RP11-299N3**) was found whose position in the **3p26.3** band is known.

Comparing your child's genetic test results

Comparing your child's genetic test results with others, either in the medical literature or within Unique, will help to build up a general picture of what to expect. But there will still be differences, sometimes quite marked, between your child and others with apparently similar genetic test results. It is very important to see your child as an individual and not to make direct comparisons with others with the same results. After all, each of us is different.

Main effects of a 3p26 deletion

3p26 deletions can have different effects, depending chiefly on size and position.

Group 1 People in this group typically have a large terminal deletion starting in band 3p26.1 or 3p26.2.

Group 2 The breakpoint is in 3p26.3 and the deletion is either interstitial (two breakpoints) or terminal (one breakpoint). In some families, particularly those with an interstitial deletion, the deletion can be inherited from one parent. Typically, the parent is healthy, without developmental concerns; the child or children's development caused enough concern for genetic testing to be carried out.

Main effects of a 3p26 deletion

Group 1: 3p26.1 and 3p26.2 terminal deletions

Unique had 6 families when this guide was compiled. Two cases from the Decipher database are also included. There is one adult in the medical literature with a 3p26.1 deletion who is apparently unaffected, but has had recurrent miscarriages (Shuib 2009).

The effects can be very similar to those of a 3p25 deletion, and vary from very mild to severe

Unique publishes a separate guide to 3p25 deletions. The chief effects are:

- Low birth weight. Most children also grow slowly and remain short
- Feeding problems
- Delay in reaching baby 'milestones' and later developmental delay
- Hypotonia - floppiness
- Need for support with learning
- Ptosis – an inability to fully raise the upper eyelid

Other features

- Cleft palate or other palate anomalies
- Extra fingers and/ or toes
- Dimple near the base of the spine
- Bowel or intestinal problems
- Seizures
- Hearing impairment, temporary in some children
- Kidney problems
- Heart conditions
- Pits/ tiny holes in the cheek just in front of the ears
(Cargile 2002; Malmgren 2007; Fernandez 2008; Shuib 2009; Pohjola 2010; Unique).

Most common features

■ Growth

Babies are typically small for dates. Most but not all children are short Unique's records show that many babies were quite tiny at birth. Additionally, out of 4 babies, 3 were born early, between 32 and 36 weeks. Typically, babies continue to grow slowly, and while one became a tall child, most did not and remained both short and slight for their age. As a baby one attracted the diagnosis of 'failure to thrive', meaning that he did not put on weight at the expected rate.

■ Feeding

Feeding difficulties and reflux are common

Most families have considerable feeding difficulties while their babies are young. The typical low muscle tone can affect babies' ability to latch on, suck from the breast or bottle, seal the lips round the nipple or teat and to coordinate sucking with swallowing and breathing. Additionally, a tiny or erratic appetite and lack of

interest in feeding mean that early support is usually vital. Babies who cannot breastfeed can be fed by bottle, by spoon or syringe or, if this is not possible, initially by a naso-gastric tube passed up the nose and down the food pipe to the stomach.

Gastro-oesophageal reflux is common. In babies with reflux (where milk flushes back from the stomach up the food pipe) there is a possibility that babies will inhale milk, putting them at risk of aspiration pneumonia. Careful feeding and positioning can help reflux as can feed thickeners and medication to inhibit gastric acid. Babies often grow out of reflux, especially when they start solids, although even on solids some children continue to bring back small amounts of food after meals. Reflux can be persistent, although most families can control it using prescription medication. If simple measures are not enough, it is possible to treat reflux with a surgical operation known as a fundoplication, in which the action of the valve between the food pipe and the stomach is improved. In one baby, reflux vomiting was so frequent that his lips and the area surrounding his mouth were burned by stomach acid.

Moving on to solids is often late, as babies have difficulty with handling lumps and new textures, sipping from a spoon and particularly with chewing. As a result many babies stay on baby or puréed food well into the toddler years or later. They may also have difficulties drinking thin liquids and tend to gag easily. Additionally, children have had problems with constipation, needing extra fluids, fruit juice and fiber, and frequently prescribed stool softeners and laxatives. Feeding problems tend to improve with time but in the meantime there are many ways to help a baby who is having difficulty feeding and, if necessary, it is possible to feed temporarily by nasogastric tube or through a gastrostomy tube direct into the stomach to ensure that a baby or child gets enough nutrients. One Unique adult continues to be fed by gastrostomy tube.

“He was completely texture adverse as an infant / toddler. He had an over prominent gag reflex and could not tolerate any food with texture. Any bit of solid texture in food caused gagging and vomiting with aspiration. In his early years he was unable to manage thin liquids such as water or juice without aspirating, choking and vomiting. Gradually this dissipated and occupational therapy at school to reduce sensitivity has worked. Now he still can't chew food, but he can handle a bit more texture/ lumps although he generally he eats food such as yoghurt with mashed fruit added. He can handle soft, small pasta as long as he doesn't have to chew and can now drink his PediaSure from a cup and water without choking” - 3p26.2 deletion, 13 years



Boy, 4, with a 3p26.2 terminal deletion

■ **Developmental delay: sitting, moving, walking**

Delay is typical

Babies and children are typically quite delayed in reaching their motor developmental milestones and benefit from early intervention with physiotherapy. While some children are simply late in walking, this is not possible for all. Even mobile children may need to use a wheelchair outdoors or for distances when they tire.

Unique babies were able to sit between 8 and 17 months, became mobile between 15 months and 2 years, and those who walked started walking between 18 months and 3 years. Walking often remains unsteady at first and children need support (splints, walking aids or a wheelchair) or protection out of doors, particularly as they may lack the ability to save themselves when they fall.

Hypotonia – floppiness caused by low muscle tone – is very common and underlies some of the mobility difficulties and although it improves and is usually very much helped by physiotherapy, it tends to persist.

“Hypotonia meant that our son could not get to a sitting position by himself at age one. This also resulted in delays for critical motor skills such as his first steps which he didn't take until after two. He now toe walks, just like a ballerina. The problem is that this can cause shortening of the Achilles tendons and foot structure issues. He has been fitted with ankle foot orthotics which improve his gait and keep him off of his toes” - 3p26.2 deletion, 13 years

■ **Need for support with learning**

Most children benefit from early intervention and learning support

Children may need some support with their learning, although the extent varies widely. One adult with a 3p26.1 deletion has no known learning difficulties; Unique has members with similar deletions who are severely affected.

“He does have profound intellectual developmental delays. His situation is complex. He is quite adept at playing his Nintendo Gameboy and also with tablets and computers” - 3p26.2 deletion, 13 years

“He is able to hold and play with a toy” - 3p26.1 deletion, 27 years

■ **Communication and speech**

Information at Unique shows that speech is typically the most affected area of development. Unique's experience is backed up by reports in the medical literature, which show a wide range from being non verbal but a keen and interactive communicator to verbal fluency.

“In his earlier years he had quite a vocabulary and could label common items, as well as letters, numbers, shapes, colours, animals etc. He could never use speech though to ask for things or to enquire etc... only labelling. His speech was also not clear, words were approximations that could be understood. Eventually around age 7 to 8, his speech started to decrease. He is now for all intents and purposes non-verbal” - 3p26.2 deletion, 13 years

“No recognisable communication, but he laughs spontaneously and grunts when in pain, also grinds his teeth” - 3p26.1 deletion, 27 years

■ Appearance

Short stature is one feature that might make most children stand out, although not all. Children are typically small and many have a slim build.

Doctors sometimes look for what are known as ‘dysmorphic features’ – facial features that are unusual and may suggest a chromosome disorder. These can sometimes be subtle and only apparent once they are pointed out. Among the features that have been seen are tiny pit marks on the outer ear, a large mouth, and prominent eyebrows. Facial features can also affect function.



Boy, 6 years, with 3p26.2 terminal deletion

“Our son has a small mandible that is not quite symmetric, so we qualify for extra support for out of the ordinary dental costs. His jaw is small and because of the irregular shape causes crowding of his teeth so he has required some extractions. Also, because he could not eat solid foods, his baby teeth did not fall out and he required dental surgery under anaesthetic to remove them as they were causing pain and problems. One of the symptoms was excessive drooling. Another trait is dysmorphic teeth. His front teeth are quite large and not normally shaped. There was a ridge on the back of the tooth near the gum that appeared so large that at first we thought it was an adult tooth coming through behind his front teeth. The groove had to be filled in to prevent decay” - 3p26.2 deletion, 13 years

■ Ptosis

Ptosis (drooping of the upper eyelid so the eye is not fully open) is common. This can affect one eye or both. The approach to ptosis depends in part on how severe it is, but if there are possible complications with eyesight, a surgical operation can be carried out to ensure the eyelid does not obscure vision.

“The ptosis required surgery done by a plastic surgeon specializing in the eyes and face. The “sling” surgery shortened the muscle band that holds the eyelid open. The issue is more than just cosmetic. Because our son’s eyelids drooped so low they limited his field of vision. This impacted on his ability to learn to walk etc. as he couldn’t raise his head high enough to be able to get a clear view of what was ahead” - 3p26.2 deletion, 13 years

Other features

■ Heart conditions

One Unique member with a 3p26.2 deletion was born with a heart condition, involving holes between both upper and lower chambers of the heart and the heart valves.

■ Seizures

Three Unique members have been reported with seizures, and one has been diagnosed with epilepsy. One child had absence seizures, in which he would flop to the ground 'as if the brain were unable to send any corrective commands to his muscles'. At 13, he no longer has seizures. A Unique adult, 27 years, has epilepsy, treated with multiple anti-epilepsy medications.

"The epilepsy medications appear to knock him out, so he sleeps a lot. But he is usually awake between 3-9pm and 3-9am" - 3p26.1 deletion, 27 years

■ Breathing

A small number of children have continuing breathing difficulties, and these can be severe. Underlying these may be structural difficulties and there may also be underlying neurological problems, as in central sleep apnoea, where breathing stops and starts repeatedly during sleep. Babies and children who have gastro oesophageal reflux (*see* page 7) may be at risk of developing aspiration pneumonia, an inflammation of the lungs and airways caused by inhaling part of a feed, and in other children respiratory infections can be severe and develop quickly into pneumonia (Unique).

"Our son has allergies and sinus infection issues and these typically aggravate a breathing issue where he pants heavily and then stops breathing altogether. He doesn't do this when sleeping. He seems to have difficulties clearing phlegm from his throat, resulting in quite a loud grunting/throat clearing noise" - 3p26.2 deletion, 13 years

"At the age of 24, my son spent six weeks in hospital, two of those weeks in intensive care, one on a ventilator, as he had one collapsed lung and a mucus plug in the other" - 3p26.1 deletion, 27 years

■ Hearing

One Unique member with a 3p26.2 deletion has a permanent hearing impairment in both ears.

■ Other features

One Unique member with a 3p26.1 deletion has been diagnosed as an adult with kidney stones, but will not be treated, as the risks outweigh the benefits. Other issues include: dimples near the base of the spine; hypospadias (the hole normally at the end of the penis lies on the underside), corrected surgically; hernias in the groin, also corrected surgically; undescended testes; intestinal closure (duodenal atresia); gall stones; a tethered spinal cord, where the end of the cord is fixed instead of free-floating; hip dislocation; abnormal kneecaps; and unusually lax joints (Decipher; Unique).

■ Behaviour

We do not have enough reports of behaviour among Unique members to draw any conclusions. However, some families have noticed traits reminiscent of autism spectrum disorders. One family has written a detailed account of their

search for recognition and treatment of their son's autism and other behaviour disorders. This is available to Unique members on request. It has been suggested that one cause of autism in someone with a 3p25 or 3p26 deletion is disruption or loss of the *CNTN4* (Contactin 4) gene (*see Genes*, page 19), but autism has also been seen in children in whom this gene is intact (Roohi 2008; Kellogg 2013).

Main effects of a 3p26 deletion:

Group 2 : Deletions from 3p26.3

Deletions from the 3p26.3 band can be harmless. First seek the advice of your geneticist or genetic counsellor as to whether a 3p26.3 deletion found in yourself or your child is the likely cause of any developmental, behaviour or health concerns.

Unique had 12 affected families when this guide was compiled. Six cases from the Decipher database are also included. There are four cases in the medical literature with a 3p26.3 deletion. One child in the medical literature (Lozcano-Gil 1994; Rivera 2006) is reported with a 3p26 deletion; this child is included here, because two genes significant for 3p26.3 deletions – *CHL1* and *CNTN4* – are known to be missing. In at least 7 families, the 3p26.3 deletion was passed from an apparently unaffected parent to their child (Lozcano-Gil 1994; Rivera 2006; Pohjola 2010; Cuoco 2011; Decipher; Unique).



Boy, 8 months, with 3p26.3 interstitial microdeletion

■ Growth

Babies are usually born a good size and weight. Typically, growth does not appear to be affected.

Babies are usually a normal size and weight at birth. Four out of eight pregnancies resulted in preterm labour. Birth weights at term of five babies ranged from 3kg (6lb 10oz) to 3.9kg (8lb 10oz). There is no consistent effect of the 3p26.3 deletion on growth: out of 14 children for whom we have information on growth, six are short for their age, five are neither short nor tall, and three are tall. Two babies attracted the diagnosis of 'failure to thrive', meaning that they did not put on weight at the expected rate; typically, they were proportionately small (Lozcano-Gill 1994; Pohjola 2011; Cuoco 2011; Decipher; Unique).

"He continues to be below the 3% growth chart for his age in both weight and height; however he continues to grow consistently on 'his own' growing curve. I have the same microdeletion and I am also very petite. Our heads are very small and we even wear the same helmet size for horse back riding" - Familial 3p26.3 deletion, 10½ years

■ Feeding

Feeding difficulties are common in the early days, and occasionally persist. Families can face considerable feeding difficulties while their babies are young. Low muscle tone can affect babies' ability to latch on, suck from the breast or bottle, seal the lips round the nipple or teat and to coordinate sucking with swallowing and breathing. Additionally, a tiny or erratic appetite and lack of interest in feeding mean that early support is needed. Breastfeeding can pose a challenge and some babies take expressed milk from a spoon, cup or easy-suck nipple or bottle. Babies can take formula by bottle, spoon or syringe or, if this is not possible, initially by a naso-gastric tube passed up the nose and down the food pipe to the stomach. Unique's experience is that some babies find it difficult to put on weight, known medically as 'failure to thrive'. They may need enriched or fortified milk, high-energy supplements and a high calorie diet once they move on to solid foods. It is sometimes necessary to give feeds direct into the stomach through a gastrostomy (PEG) tube.

Gastro-oesophageal reflux can occur. In babies with reflux (where milk flushes back from the stomach up the food pipe) there is a possibility that babies will inhale milk, putting them at risk of aspiration pneumonia. Careful feeding and positioning can help reflux as can feed thickeners and medication to inhibit gastric acid. Babies often grow out of reflux, especially when they start solids, although even on solids some children continue to bring back small amounts of food after meals. Reflux can be persistent, although most families can control it using prescription medication. If simple measures are not enough, it is possible to treat reflux with a surgical operation known as a fundoplication, in which the action of the valve between the food pipe and the stomach is improved.

Moving on to solids can be late, as some babies have difficulty with handling lumps and new textures, and particularly with chewing. As a result many babies stay on baby or puréed food for longer than normal. Additionally, children have had problems with constipation, needing extra fluids, fruit juice and fiber, and in most cases prescribed stool softeners and laxatives. The good news is that feeding problems and often constipation tend to improve with time and children eventually adapt to a normal family diet (Unique).

"My son still chokes when he drinks water, but can drink any other liquid. He continues to have poor coordination for chewing and avoids 'gummy/sticky' textures. He is more apt to try new foods, but will only try them rather than have a meal with them even if he likes the taste/texture. Getting new foods into his food rotation continues to be difficult. He craves salt and prefers to drink water as his source of hydration" - Familial 3p26.3 microdeletion, 10½ years

■ Developmental delay: sitting, moving, walking

Delay can occur, but is not inevitable

Babies and children can be delayed in reaching their developmental milestones and benefit from early intervention with physiotherapy. The size of the deletion from 3p does not seem to affect children's difficulties with mobility: children with tiny microdeletions can need as much support as children with large terminal deletions. Some children with sizable 3p26.3 deletions have normal motor skills: a 12 year old boy with a 1 Mb terminal 3p26.3 deletion most enjoyed snowboarding and skateboarding (Pohjola 2010; Cuoco 2011; Unique).

Babies achieved sitting between 5 months and 2 years. They became mobile by crawling, creeping, rolling or bottom shuffling between 7 and 18 months and with support started walking between 9 months and 2 years, 9 months.

Hypotonia – floppiness caused by low muscle tone – is common and underlies some of the mobility difficulties and although it improves and is usually very much helped by physiotherapy, it tends to persist (Cuoco 2011; Unique).

“He moves with ease and enjoys running around and playing in the garden” - 3p26.3 microdeletion, 4½ years

“She moves around like any other 8 year old, and most enjoys dance” - 3p26.3 microdeletion, 8 years

“He walked at 18 months, but with poor quality, due to poor balance and strength. His global hypotonia/dyspraxia continues to impede his motor skills as well as poor motor planning/coordination. But his gross motor skills have now greatly improved and he is very good at baseball and basketball” - Familial 3p26.3 microdeletion, 10½ years

■ Need for support with learning

Children with learning difficulties benefit from early intervention and learning support

Children may well need some support with their learning, although the extent varies widely and cannot usually be accurately predicted from the size or position of the deletion. There is a gene in the 3p26.3 band that has been associated with learning difficulties, *CHL1*, near the end of the chromosome between base pairs 238,279 and 451,090, but some people have lost this gene and have no learning difficulties. In one family in the medical literature, a terminal deletion only including the *CHL1* gene was found in a father who is a dentist, and two sons, who both have mild learning difficulties (Cuoco 2011). Another boy with a larger terminal deletion of around 1Mb, still including only the *CHL1* gene, had marked problems in language and mathematics but was talented at drawing; his mother had the same deletion with no learning difficulties (Pohjola 2010). A 14 year old boy with an unquantified 3p26 deletion was of normal intelligence, with an overall IQ of 95, but processed information slowly (Rivera 2006). Recurrent concerns for Unique families are fine motor skill problems, which make handwriting difficult, and issues with concentrating and focusing.



Girl, 8 years, with 3p26.3 interstitial deletion

“Drawing: 60months; early number concept: 93% percentile; matching letter-like forms: 92%; recognition of pictures: 96%. He is very focused on what he is doing , and he has a good memory. He can write his name and certain letters, and will draw whatever you ask him. When he starts mainstream primary school he will have a teaching assistant for 20 hours a week” - 3p26.3 microdeletion, 4½ years
“She is mostly at the same stage as her peers and has no learning disabilities or support. She learns best when she is interested in the topic and because she wishes to please. She uses a slant board and grooved paper for handwriting” - 3p26.3 microdeletion, 8 years

“My son needs to type as he cannot physically hand write letters independently, even though he knows the letter formation. If I support his wrist/elbow, he can write his name broadly in script. Printing his name is far more difficult because he has to pick up the pencil after each letter. His body still has difficulty differentiating its separate parts - arms moving separately from legs etc. His core muscles continue to be very weak. He continues to struggle with academics in school and is in a self-contained special education class. At fifth grade, he is at second grade level in reading, but comprehends at a much higher grade. It seems his speech affects his oral decoding when reading. Math continues to be significantly impaired and his math skills continue to be at the first grade level. Although he understands numeracy, he continues to struggle with memorizing rote facts. His visual memory is amazing and he can usually remember words, places, pictures, directions by just seeing them once. His most significant and on-going weakness is attention/distractibility. We recently had his IQ tested and he scored in the low average range. However, the professor who tested him felt that this was an underestimate of his true abilities due to both significant inattention to task as well as his expressive language disorder” - Familial 3p26.3 microdeletion, 10½ years

■ **Communication and speech**

Speech and language can be the most affected area of development, more than expected from the child’s cognitive profile, and the first sign of the chromosome deletion. Some babies never babble and within Unique, children started to speak between 12 months and 3 years, although understanding outstripped expression in most children. Some children had problems speaking clearly; in others, speech was one means of communication alongside gestures, babbling, vocal noises, laughter, crying and facial expression. Some children learn to sign. One child has speech apraxia (a speech disorder in which the person has trouble saying what s/he wants to say correctly and consistently).

With support, some children go on to develop a wide vocabulary and to talk fluently. From the information that Unique holds, the relationship between the extent of a child's chromosome loss and their ability to communicate with speech is unclear. Unique's experience is backed up by reports in the medical literature, which show a wide range of abilities. In one child with a 3p26.3 deletion inherited from a father who worked as a dentist, speech was specifically affected (Cuoco 2011).



Boy, 10 years, with 3p26.3 microdeletion

"As a baby, he didn't really babble: he was very quiet. At around 2½ or 3, a couple of words were said but were unrecognisable. He didn't start to talk until a week before his 3rd birthday. A recent assessment showed that his spoken language was at a 12 month level; understanding was at a 3½ year level; non-verbal communication at a 3 year level. He scored at the 21st percentile on naming vocabulary and at the 98th for verbal comprehension. He now uses speech with signalong. He can speak in fluent conversation but it is very hard to understand what he is saying. He understands but can find it frustrating when people don't understand what he says. He can pronounce his sounds individually, but when talking the sounds at the beginning and ends of words are missed eg. Banana is said as nana. He sees speech therapy every 3 weeks and has an app on the iPad called Articulation Station" - 3p26.3 microdeletion, 4½ years

"She had speech delay but speaks normally now, in fluent conversation. Intensive speech therapy was very helpful" - 3p26.3 microdeletion, 8 years

"We saw significant improvements with oral motor therapy, Augmentative Communication and PROMPT therapy (www.promptinstitute.com). He no longer needs an AAC device to communicate. However, his speech intelligibility continues to be only about 65% when the context is known with a familiar person. He struggles with multisyllabic words and longer sentences. Although his vocabulary is age-appropriate, he struggles with morphology and syntax and tends to leave out small words such as articles (the, an) and prepositions (in, at) in his conversational speech" - Familial 3p26.3 microdeletion, 10½ years

■ Appearance

Doctors sometimes look for what are known as 'dysmorphic features' – facial features that are unusual and may suggest a chromosome disorder. These can sometimes be subtle and only apparent once they are pointed out. Features that recur include a prominent nose or nasal bridge; wide set eyes; and thick eyebrows that may join in the middle. Among Unique members, there are no reports of 'typical' facial features (Rivera 2006; Decipher).

■ Head and brain

Babies' and children's heads can be small, normal-sized or large: no consistent picture has been reported. Two children have been reported with a head shape that is unusually flat from front to back (brachycephaly); and two more children have a head shape that points forwards when seen from on top (trigonocephaly). In one child with a terminal 3p26.3 deletion, the head was re-shaped to allow the brain better room for growth; this child also has an unusually thin band of nerve fibres connecting the right and left hemispheres of the brain and is missing part of the frontal lobes (Rivera 2006; Pohjola 2010; Cuoco 2011; Decipher; Unique).

■ Ptosis and other eyesight issues

Ptosis, or drooping of the upper eyelid so the eye is not fully open, can occur. Ptosis can affect one eye or both. The approach to ptosis depends in part on how severe it is, but if there are possible complications with eyesight, a surgical operation can be carried out to ensure the eyelid does not obscure vision (Decipher; Unique). Three children have been diagnosed with strabismus, the medical term for squint or crossed eyes. The crossed eye can look inwards, outwards, up or down. The main effects of strabismus are that usually the person will have one eye which is stronger than the other because the brain has to give priority to one eye over the other with the result that the weaker one does not learn to see as well as the stronger eye. Treatment depends on the cause but can include patching the stronger eye, exercises, glasses to correct a refractive error such as long sight and surgery to realign the muscles that hold the eye in place (Cuoco 2011; Decipher; Unique). One child was diagnosed with very short sight; another has a depth perception disorder and has prisms in his spectacle lenses to help see things in 3D (Rivera 2006; Unique).

"He has a depth perception/ visual disorder in which he needs glasses for close vision and has prisms in his lenses to help with seeing things in 3-D. Walking down stairs and urinating in the toilet were instantly learned with his glasses!" - Familial 3p26.3 microdeletion, 10½ years

■ Heart conditions

Most babies with a 3p26 deletion are born with a normal, healthy heart. One child with a terminal deletion from 3p26.3 was born with holes between both upper and lower chambers (atria, ventricles) of the heart, and one child with a small interstitial deletion within 3p26.3, reported on the Decipher database, had a hole between the lower heart chambers.

■ Seizures

Most babies and children with a 3p26 deletion do not have seizures, but some do. Two children have been reported with a type of seizure called tonic clonic (grand mal), but in one of these children, seizures ceased without treatment by the age of 8. Two other children have been reported with seizures, but we have no information on the type of seizure (Cuoco 2011; Decipher; Unique).

■ Spine

Two babies were born with a dimple at the base of the spine. This can be shallow, but stools can collect there before your child is toilet trained, so keeping it clean and protected is important. A sacral pit can be deep and even connect to the spinal canal or the colon. If there is any concern about this, your baby's spine will be imaged, usually with ultrasound or an MRI scan.

■ Toilet training

Information suggests that training is delayed. Two children were trained in the day by 3 and one by four. One child was dry at night by 3, one by 5, and two other children were not yet fully trained by adolescence (Pohjola 2010; Unique).

■ Features observed in only one child

One child with a large 5Mb deletion inherited from a parent has unspecified kidney problems; a baby was born with an omphalocele, a sac containing part of the bowel that protrudes at birth through a hole in the abdomen near the base of the umbilical cord; this was surgically corrected; one child was born extra fingers and toes. One child has weak dental enamel and has needed repeated treatment and fillings; this child also has asthma; at 11, she cannot lick her top lip and has only recently learnt to blow through her mouth. She can sniff but cannot blow her nose (Decipher; Unique).

■ Behaviour

We do not have enough information to make general statements about behaviour. The following are cameos of individual children.

"His play skills are almost age-appropriate. We are still in the process of deciding whether to get him tested for autism. He is attentive, and eager to follow out instructions, but does not like being disturbed from the activity he is doing. He finds it very hard to interact with other children and steps back from social play. His key worker at his playschool has worked very hard to encourage him to make a couple of friends, which has taken nearly a year. He will interact with these children but when spoken to he shies away. He loves playing with the iPad, and likes playing in the garden and the local park. He loves bandages and will spend hours bandaging himself or toys up. He also likes cars and Lego and crafty things like cutting, sticking and colouring" - 3p26.3 microdeletion, 4½ years

"She has difficulty focusing, is very scatterbrained, anxious, and hyperactive. ADHD. Socially she shows reduced eye contact, but is not autistic. She enjoys iPad, TV, computer, pets, and pretend play" - 3p26.3 microdeletion, 8 years

"Happy all the time unless tired or hungry, when he whines a lot. Speech has improved significantly but he still struggles socially for fear that he will not be understood. Depending on his anxiety level, he shortens his sentences to one or two words or uses gestures. But with familiar peers in a familiar setting his social interaction is age appropriate. It is one of his strengths and he yearns to be with other children" - Familial 3p26.3 microdeletion, 10½ years

How did this happen?

In some people, the 3p26 deletion has occurred out of the blue for no obvious reason. The genetic term for this is *de novo* (dn) and a blood test shows that neither parent has a relevant chromosome change. A new 3p26 deletion is caused by a mistake thought to occur when the parents' sperm or egg cells were formed or in the very earliest days after fertilisation.

In other families, a blood test will show that the deletion, most often a tiny interstitial microdeletion within the 3p26.3 band, has been inherited directly from the mother or the father. In the quite common situation where the parent has no developmental problems themselves, it can be unclear whether the 3p26.3 microdeletion is responsible for developmental concerns in the child. Your geneticist or genetic counselor will talk this over with you and give their view (*see Families with a 3p26 deletion*, page 4).

What is certain is that as a parent there is nothing you could have done to prevent this from happening. No environmental, dietary or lifestyle factors are known to cause 3p26 deletions. There is nothing that either parent did before or during pregnancy that caused the deletion.

Can it happen again?

Where one parent has the same deletion as the child, the possibility of having another child with the deletion can be as high as 50 per cent in each pregnancy. Where both parents have normal chromosomes, it is unlikely that another child will be born with a 3p deletion or any other chromosome disorder. Very rarely, a blood test shows that both parents have normal chromosomes, but a few of their egg or sperm cells carry the 3p deletion. Geneticists call this germline mosaicism and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the deletion. However, this has not yet been reported with 3p26 deletions. 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 tests are available in all parts of the world.

Genes

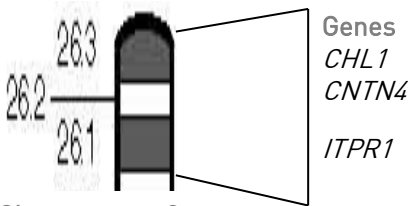
If your child has had a genetic test using molecular DNA technology, such as array CGH, your geneticist or genetic counsellor may be able to tell you which genes have been deleted, and give you information on what is known about them. The p26 bands of chromosome 3 are rich in genes, and there has been much research to work out which genes cause which features of the syndrome, but much uncertainty remains. While identifying the gene(s) responsible for certain features of 3p deletion syndrome is valuable and may help guide future

studies, it does not lead directly to immediate improved treatment. Also, even if the supposedly responsible gene is missing, it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

One gene linked with mental function is *CHL1*, near the end of the chromosome in band 3p26.3 between base pairs 238,279 and 451,090 (Frints 2003; Cuoco 2011). Losing this gene can cause a relatively mild learning disability, but does not always do so.

A further gene that plays a role in the developing nervous system and neural networks is Contactin 4 (*CNTN4*), situated in 3p26.3 at 2,140,497-3,099,645. Disrupting the gene is known to cause developmental delay and learning disabilities and may play an important role (Fernandez 2004; Malmgren 2007; Roohi 2008; Gunnarsson 2010). Overall, it is very likely that more than one gene underlies learning disabilities (Peltekova 2012; Kellogg 2013).

The *ITPR1* gene in the 3p26.1 band at 4,535,032-4,889,524 is associated with a type of movement disorder known as spinocerebellar ataxia 15, or SCA 15. People with the condition have a very slowly progressive difficulty in walking and coordination, as well as tremor (van de Leemput 2007; Synofzik 2011).



Chromosome 3:
the three bands
of 3p26

Support and Information



Understanding Chromosome & Gene Disorders

Rare Chromosome Disorder Support Group,

The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel/Fax: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

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!

There is a Facebook group for families affected by a 3p Deletion at:

www.facebook.com/pages/Deletion-3p-Syndrome/121385104582497

The Chromosome 3 Disorder Registry and Support Group exists to support and inform families affected by any anomaly of chromosome 3 www.chromosome3disorder.com

www.facebook.com/groups/801819427421051 - a private support group for 3p25-26 deletion families

This guide is dedicated to the memory of David Willgress, 27, one of the first people diagnosed with a 3p26 deletion.

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.

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.

The guide was compiled by Unique and reviewed by Professor Eamonn Maher, Professor of Medical Genetics and Genomic Medicine, University of Cambridge, UK 2013 (PM) v1.1 2023 (CA) v1.2 2023 (CA)

Copyright © Unique 2023

Rare Chromosome Disorder Support Group Charity Number 1110661
Registered in England and Wales Company Number 5460413