

3p25 deletions



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) (Tazelaar 1991; Mowrey 1993; Knight 1995; Drumheller 1996; Green 2000; Cargile 2002; Fernandez 2004; Takagishi 2006; Malmgren 2007; McCullough 2007; van de Leemput 2007; Barber 2008; Fernandez 2008; Roohi 2009; Shuib 2009; Gunnarsson 2010; Pohjola 2010; Carayol 2011; Malhotra 2011; Synofzik 2011; Peltekova 2012; Riess 2012; Kellogg 2013; Grozeva 2014; Kuechler 2014).

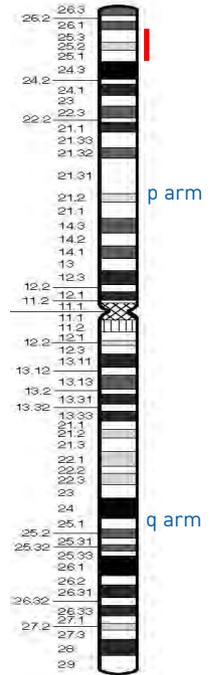
The guide also draws on Unique's database of members with a 3p deletion. When this updated guide was compiled, Unique had 47 members with a pure 3p25 deletion involving no other chromosome, from babies to adults.

Background on chromosomes

Our bodies are made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes carrying information that 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 3p25 deletion have lost DNA from the marked area at the top of the diagram.



Chromosome
3

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 3p25 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.

What is a 3p25 deletion?

A 3p25 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. A few people lose DNA from the end of chromosome 3 with very mild or apparently no effects; most are more significantly affected. The 3p25 deletion is usually found in all the cells of the body; occasionally, it is only found in some cells, while the others have 46 complete chromosomes. This is called mosaicism, and when it occurs the effects are expected to be milder.

3p25 deletion syndrome

When a particular set of features occurs as a result of a single cause in a recognisable and consistent pattern in enough people, the condition is called a syndrome. The main features of a 3p25 deletion can occur in this way, and when they do, the condition is known as 3p25 deletion syndrome. It can also be called 3p- (three p minus, or three p deletion) syndrome.

Researchers are seeking to identify a 'critical region' that, when deleted, causes features of 3p25 deletion syndrome. A region has been suggested in band 3p25.3, and loss of a single gene, *SETD5*, within the deleted region is thought to be responsible for many of the key features of 3p25 microdeletion syndrome (Grozeva 2014). Children with more than this gene deleted may have a range of additional features due to the loss of extra genes (Cargile 2002; Gunnarsson 2010; Peltekova 2012; Riess 2012; Kellogg 2013). See also [Genes](#), pages 22-23.

Looking at chromosome 3p25

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. 3p25 is near the top, divided into three bands – 25.1, 25.2 and 25.3.

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. One band 3p25 has around 7,860,000 base pairs. This sounds a lot, but is actually quite small: the DNA from 3p25 on one chromosome 3 is less than a half of one per cent of the total DNA in each cell. Even if you include the DNA from the 3p26 band, the total amount is only around half of one per cent of the total DNA in each cell.

How rare are 3p25 deletions?

This is not quite certain, but they are probably very rare. Since the first person was reported in the medical literature in 1978, around 50 people with a pure 3p25 deletion involving no other chromosome have been described in the medical literature. However, some people are apparently unaffected by their deletion, or only very mildly affected, and so would never be identified.

Are there people with a 3p25 deletion who have developed normally and have no health or learning difficulties?

Apparently, there are, but they are probably rare. While most babies born with a 3p25 deletion are obviously affected, a few people reported in the medical literature are unaffected or only very mildly affected. A mother, healthy and without developmental concerns, passed a 3p25.3 deletion on to her daughter, who was born healthy; when followed up 11 years later, neither had developed any problems likely to be related to the 3p25.3 deletion (Knight 1995; Takagishi 2006). While this family was identified using conventional chromosome testing, which is less precise than modern molecular tests (*see Genetic testing*, opposite), in another family with a 3p25.3 deletion identified using molecular tests the mother was healthy and without developmental concerns, the daughter was healthy and without developmental concerns, although she chose only to speak to family members and relatives; the son was more obviously affected by the 3p25.3 deletion (Pohjola 2010). A further mother: daughter pair also identified using molecular tests as having a 3p25.3 deletion showed no features typical of 3p deletion syndrome (Takagishi 2006; Barber 2008).

Families with a 3p25 deletion

A 3p25 deletion can be passed from parent to child. An inherited deletion usually stays the same size when it is passed from parent to child but can have different effects on different family members, sometimes mild, sometimes more severe. There is a small number of families in whom one apparently unaffected or only mildly affected parent has passed a 3p25 deletion on to their child or children (Tazelaar 1991; Knight 1995; Takagishi 2006; Barber 2008; Pohjola 2010).

Does everyone have the same size 3p25 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 3p25 or 3p26 bands so people have different sized pieces of chromosome missing (Malmgren 2007; Shuib 2009). The smallest deletion reported in the medical literature is a deletion of 643kb in band 3p25.3 (Peltekova 2012). Children with loss of *SETD5*, one of the genes in this small region have similar features to children with a larger deletion which suggests that having a deletion of *SETD5* alone is sufficient to cause the 3p25 microdeletion syndrome (Grozeva 2014). Your geneticist or genetic counsellor can advise you on the position of the breakpoint or breakpoints and if your child has had a molecular genetic test, any missing genes and their known or suspected functions.

How much do we know?

Comparing different people with a typical 3p25 deletion shows that some effects seem to be very broadly similar. This information guide tells you what is known about those effects. 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 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 unique.

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. 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.

A person's chromosomes make up is called his/ her karyotype. Someone with a 3p25 deletion might have a karyotype that looks like one of these three examples:

Rare chromosome disorders may be caused by subtle changes in the chromosomes that are too small to see using a microscope.

A technique that is commonly used is microarrays.

- 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.

46,XX,del(3)(p25.2) This result shows that the expected number of chromosomes [46] were found. It also shows that two X chromosomes were found, so this is a girl or a woman. del(3) means there is a deletion from chromosome 3. (p25.2) shows the band in the chromosome where the break was found; in this case, the DNA is missing from this point to the end of the chromosome.

46,XY,ish del(3)(p25.3pter)(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 p25.3 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.

arr cgh(hg 19) 3p25.3(9,329,274-10,035,209)x1 This result shows that a technology known as array comparative genomic hybridization (arr cgh) showed that only one copy (x1; the normal copy number is two) of part of the band known as 3p25.3 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 9,329,274 and the last is 10,035,209. By taking the first number from the second, you can work out that there are 705,935 missing base pairs, or about 0.71 Mb of missing DNA.

3p25 deletion syndrome: most common features

Each person with a 3p25 deletion is unique and will have different developmental and medical concerns. No one person will have all of the features listed in this guide – even if their chromosome deletion appears to be exactly the same. However, a number of common features have emerged:

- 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
- Unusual facial features, such as wide-spaced eyes, low set ears, and a long groove between the nose and upper lip
- Small head (microcephaly). The head is sometimes an unusual shape
- Autism and challenging behaviour

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
- Scoliosis or other mild skeletal problems
(Cargile 2002; Malmgren 2007; Fernandez 2008; Shuib 2009; Pohjola 2010; Unique).



Most common features

■ Growth

Most babies are small for dates. Most but not all children are short. Research reports show that growth delay starting in pregnancy is highly typical of babies with 3p25 deletions, and small children usually grow into short adults. Intrauterine growth retardation may be picked up before birth and may be the first sign of any problem. Typically, babies are proportionately small: they are short and light and have a small head circumference. At birth, their length and weight plot at or near the bottom of baby growth charts.

Low birth weight and short stature are not however inevitable. Some Unique members have large babies; among 30 Unique members the range of known birth weights at or around term is 1.8kg (4lb) to 3.4kg (7lb 8oz), and the average is 2.59kg (5lb 11oz).

Typically, babies continue to put on weight and grow slowly, and while a few

catch up in height, most do not and remain both short and slight for their age, wearing clothes for much younger children. As babies they may take longer than normal to regain their birth weight, and attract the diagnosis of 'failure to thrive', meaning that they are not putting on weight at the expected rate. This is not, however, true for all. A few Unique children and adults are of average height or tall (Cargile 2002; Unique).

These are some typical comments made by parents: 'He has always been underweight for his age and size'; 'Growth has been slow and erratic, periods of illness such as chest infections have resulted in considerable weight loss'; 'At 18 months he is wearing clothes for a 12 month old'.

"Now generally in correct size clothes, where she was previously always very small for her age. She is still shorter but wears normal size clothes. She always had a special diet, but from age 8 all special diets were removed and she eats everything now, just all puréed. She started to thrive from the moment she was given a 'normal' diet" - 3p25pter deletion, 15 years

■ Feeding

Feeding difficulties 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. A few mothers do succeed in breastfeeding, some with no problems at all, only giving up because their baby remains hungry after feeds. Other babies can take expressed milk by sipping from a spoon or cup or from an easy-suck nipple or bottle, but quite a few mothers are unable to maintain their milk supply in these difficult circumstances. Otherwise babies 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. Unique's experience is that many babies find it difficult to put on weight at the expected rate, 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.

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 Unique member, reflux was so severe that the skin around the mouth was



burned with acid secretions; in another, reflux returned in adolescence (Unique).

Moving on to solids is often late, as babies typically 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 and are usually very delayed in learning to feed themselves.

Babies' feeding problems may be enhanced by additional problems such as a tongue tie (the tongue is tethered to the bottom of the mouth by skin); or a high or cleft palate. Other feeding issues noted by Unique families include oral hypersensitivity and difficulties dealing with different textures of food.

Additionally, numerous children have had problems with constipation, needing extra fluids, fruit juice and fibre, and in most cases 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 (Unique).

"What helped with his thin and highly arched palate was a special needs teat (pumped breastmilk) and bigger, cherry-shaped pacifiers" - 3p25.3pter deletion

"She thinks she needs to eat all the time and will not stop until food is taken away. But even with her huge intake of food she is not large for her age, in an average height and weight range" - 3p25.3pter deletion, 2 years, 9 months

"After birth his weight rapidly declined, and he fell into failure to thrive. He would not latch on. I would pump for an hour and feed for another, then he would throw over half of it up. I couldn't move him too fast or lay him on his tummy or he would throw up. Only after he went onto solids at 4 months as instructed by a doctor did his weight pick up. As he gets older he does better with certain textures, but I never let him eat unsupervised in case he chokes" - 3p25.3 interstitial deletion, 3 years

■ **Development: sitting, moving, walking**

Delay is typical, but not inevitable

Babies and children are typically quite delayed in reaching their developmental milestones and benefit from early intervention with occupational therapy and physiotherapy. However, some children develop very much faster than others. 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. A few children become mobile enough to swim, dance, attend horse riding for the disabled and use outdoor playgrounds at school age.

Unique babies started to roll over between 6 and 24 months (average age 11 months) and achieved sitting between 8 months and 5½ years (average age 18 months). They became mobile by crawling, creeping, rolling or bottom shuffling between 10 months and 5 years and with support started walking between 18 months and 8 years. Walking often remains unsteady at least at first and children often need support (holding on to furniture, splints, walking aids or a wheelchair) and protection out of doors, particularly as they may lack the ability to save themselves when they fall (Unique).

Information from the medical literature shows a similar mixed picture: some have normal or near-normal motor skills (Tazelaar 1991; Pohjola 2010), while others are delayed, walking at 2 years (Angeloni 1999; Riess 2012), 3 years (Gunnarsson 2010), at school age (Peltekova 2012) or are not yet moving (Malmgren 2007). A girl of 6½ years had the motor skills of a child of 3 or 4 years (Drumheller 1996). A 10-year-old boy with a terminal deletion from very close to the 3p25/3p26 boundary enjoyed different sports, but the coordination of simultaneous movements of hands and feet was difficult (Pohjola 2010). Difficulties with fine motor coordination were seen in others (Angeloni 1999).

Hypotonia – floppiness caused by low muscle tone – is typical of 3p- and underlies some of the mobility difficulties and although it improves and is usually very much helped by physiotherapy, it tends to persist. Some children also have very loose joints or, by contrast, tight, contracted joints, both of which impact on mobility.

One Unique member has been told that their son has lost the *ITPR1* gene (see [Genes](#), pages 22-23), which is associated with a disorder called spinocerebellar ataxia, a movement disorder causing difficulty with tremor and walking. They will watch for signs and symptoms and avoid medications that cause tremor (Unique).

“Until he could sit, he used to arch his back and bob his legs up and down the moment he was left alone”- 3p25.3pter deletion

“She is unable to walk, and still has very low tone in her legs but is unexplainably strong. Her grip is unreal” - 3p25.3pter deletion, 2 years 9 months

“He is floppy but every day is better for him. He is walking with much more self-confidence, but continues to need a wheelchair outdoors, as he doesn't feel secure away from home. He has little resistance to physical effort. He walks some metres, then suddenly feels insecure, stops walking and throws himself to the ground. His style of walking is irregular and insecure. His joints are very flexible, especially the knees. He cannot get up from the floor without the help of an object or furniture. But he loves going to the



swimming pool, where he can float with support and move more easily” – 3p25.3p25.2 deletion, 9 years



“Since our daughter started walking alone at 5 years, always accompanied by an adult, she has gone through periods of progress and setbacks, even stopping walking alone for months, with no clear explanation. Currently, she prefers to walk with the aid of an adult and complains when she has to walk without support” – 3p25 terminal deletion, 9 years

“Our son walked at the age of 5 and now he can walk for more than half an hour without any problem. He loves to swim with a lifejacket or to go to his balneotherapy session at school” - 3p25pter deletion, 12 years

“Her main problems are verbal dyspraxia (very severe) and motor dyspraxia (she knows what she has to do, but it is hard for her to initiate and execute all the steps). However she can walk, run, bike (still with training wheels...but I think she will learn soon to go without), climb, swim, eat well, pour water in the glass (lately she also finally learned to open the cap of the bottle which was very difficult for her), dance. People who don't know her, don't realize right away that she has some problems” - 3p25.3p25.1 interstitial deletion, 12 years



“He participates in Special Olympics at bowling, swimming and golf and is in his school's adaptive bowling league. He can't ride a bike due to balance; would love to get wheels for stability. He wears orthotic inserts in his shoes to correct a limp due to a bone fusion problem in his

heel” - 3p25pter deletion, 14 years

“Now essentially wheelchair bound, but still crawls at times in a bunny hop style, moving her arms forward and pulling herself along on her knees. Previously as a toddler she would walk holding our hands up to 50 steps” - 3p25pter, 15 years

“He can swim and is on the swimming team” - 3p25 mosaic deletion, 18 years

■ Need for support with learning

Children benefit from early intervention and learning support

Children are very likely to need early and ongoing support with their learning, although the extent varies. Some children and adults – probably very few in all - have no learning difficulties or scarcely noticeable problems. Typically, children with 3p deletion syndrome have moderate to severe learning difficulties and need a significant amount of learning support. Even those with tiny interstitial deletions can have severe learning disabilities.

Evidence from Unique shows a scattered pattern, with great variation in the skills that parents report. A small number of children are known to have learned to read and/ or write, generally around 7-9 years, but this is not possible or relevant for all. One child was considered advanced for their age; two children were considered to have a mild disability, in 3 it was moderate and 7 families categorised the level of intellectual disability as severe or profound.

The evidence from the medical literature shows a similar range, from a tiny number of individuals with no apparent learning difficulty or a borderline IQ to others with a profound level of developmental delay (Tazelaar 1991; Knight 1995; Angeloni 1999; Barber 2008; Pohjola 2010; Gunnarsson 2012; Peltekova 2012; Kellogg 2013; Unique).

"Excellent fine motor skills though generally developmental delays in some areas. Right now only about six months behind regular development: he can build towers, open/ close bottles, thread wooden pearls on a string, sort coloured/ big/ small objects" - 3p25.3pter deletion, 2½ years

"He has just finished his kindergarten, he is behind and receiving therapy for speech and motor skills. He can write words if instructed. His attention span and ability to 'tune out' when he is not interested in what is going on is our biggest struggle when it comes to learning" - 3p25.3p25.2 deletion, 6 years

"She attends a regular school but is far behind other children in her class" - 3p25pter deletion, 9 years

"He will never be able to talk (he uses pictograms and a little bit of sign language), to read, write or count. But he loves books" - 3p25pter deletion, 12 years

"Cognition is good, but she has a lot of performance anxiety. Sometimes it is hard to demonstrate that she is so advanced" - 3p25.3p25.1 interstitial deletion, 12 years

"He is in 8th grade although more at 4th grade level, and now falling further behind. He can write but is very messy when has to write a lot, so uses a computer. He is mainstreamed for social, science and extra classes but goes to the resource room for reading and maths" - 3p25pter deletion, 14 years

"Our biggest area of concern. He is going into 9th grade but is at 2-3rd grade level. His biggest challenge is reading, writing, and math. We work to a programme given us by a neurodevelopmentalist and are having success with it as part of a homeschool plan of therapy, exercises and curriculum" - 3p25 mosaic deletion, 18 years



Communication and speech

Speech can be the most obviously affected area of development

Information at Unique on 32 children and adults shows that speech is typically the most affected area of development and this has been noted in the medical literature (Fernandez 2004). Over half the children, regardless of age, use only isolated words or communicate non-verbally with gestures, babbling, vocal noises, laughter and crying and facial expression. Children are typically good communicators (Peltekova 2012), and their understanding can be ahead of their speech. Most typically, they babble and make vocal noises, and some children learn to sign effectively. Some children have a specific difficulty making the sounds of speech, and two children have a diagnosis of speech apraxia or dyspraxia (a speech disorder in which the person has trouble saying what s/he wants to say correctly and consistently). In one child, speech quality was affected by the soft palate at the back of the roof of the mouth not moving properly (Angeloni 1999).

Unique's experience is that some children do experience speech delay but go on to develop enough speech to communicate their wants and needs. Others are able to express themselves better using a picture or signing system, a communication board or device, or are able to express their needs by taking people to what they want. Speech and language therapists will work with the family to identify the best ways to promote and support communication. One family has found their daughter was helped by facilitated communication, a system in which a facilitator supports the hand or arm of the affected individual to use a keyboard or other device to communicate. (Facilitated communication is controversial and mentioning it does not imply that Unique endorses it.)

In the Unique cohort, verbal children most typically started to use words from the age of 4 or 5, but children reported in the medical literature have talked earlier (Tazelaar 1991; Angeloni 1999; Riess 2012). In one case, a verbal child became a non-verbal adult; regression has also been seen in the Unique cohort (Peltekova 2012; Unique).

"Very clear non-verbal communication, though limited vocabulary: about 10-15 words. This might be also connected to his glue ear, which we hope to get sorted out soon. He likes to communicate and calls out 'MAMA!' about 100 times a day, thus looking forward to more words" - 3p25.3pter deletion, 2½ years

"She is still unable to speak but does use some sign language. It seems that she is very aware of what is going on around her and understands quite a bit, but can't seem to get her body to follow" - 3p25.3pter deletion, 2 years 9 months

"He has a very limited vocabulary" - 3p25.3p25.2 deletion, 6 years

"Our daughter has started typing with Facilitated Communication and we have found out that she is very smart and that she understands everything we say. She would like to interact more with her peers, but since she doesn't talk it is hard for her" - 3p25.3p25.1 interstitial deletion, 12 years

“She doesn’t talk or walk now, despite previously as a toddler walking holding our hands up to 50 steps and speaking a few words too. She now seems to understand most things and makes noises and a few gestures/signs, so you can understand what she likes/dislikes etc” – 3p25pter deletion, 15 years

“A little slow to speech” - 3p25 mosaic deletion, 18 years

■ Ptosis, and other issues with vision

Ptosis, or drooping of the upper eyelid so the eye is not fully open, is very common.

This can affect one eye or both and was found in more than three in four individuals with a 3p deletion (Fernandez 2008). 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. Ptosis has been found in babies and children with large deletions from 3p25 as well as much smaller deletions from close to the tip of the chromosome at 3p26.3, and in a girl with the smallest reported deletion of just 643kb from the 3p25.3 band (Malmgren 2007; Shuib 2009; Peltekova 2012; Unique).

A smaller number of children have eyes with a narrow opening, a condition known as blepharophimosis. The evidence so far is that this occurs in children with a deletion from the 3p25 band, rather than 3p26, but as with ptosis, it has been found in the girl with the tiniest reported deletion from 3p25.3 (Peltekova 2012; Unique).

Strabismus, or a squint, where one eye or both turns in, out, up or down, has also been seen in around 25 per cent of Unique members with a reported eyesight problem. If steps like patching, exercises or glasses do not work or are impractical, strabismus can be corrected in a surgical operation. Other problems with vision include long or short sight (correctable with glasses); cataracts affecting central vision; and Duane syndrome – a problem with turning the eye. Four Unique members are blind or have a substantial visual impairment.

“Apparently he can see well, but he needs to situate objects spatially and then he picks them up pretending not to see them, looking elsewhere” - 3p25.3p25.2 deletion, 9 years

■ Appearance

Short stature is the feature that might make most, although not all, children stand out. Children are typically small and many have a slim build. The head is typically small and may be flat from front to back (brachycephaly), or seen from on top it may look pointed or triangular (trigonocephaly). The back of the head may be noticeably flat.



“The first time he opened his eyes”



Occasionally children may be born with extra fingers or toes, but once these are removed, there is nothing to show on the hands or feet. See [Extra fingers and/or toes](#), page 15.

Doctors sometimes look for what are known as 'dysmorphic features' – facial features that are unusual and may suggest a chromosome disorder. These can be obvious, or subtle and only apparent once they are pointed out. Among the features that have been seen repeatedly in children with a 3p25 deletion are widely spaced eyes which may slant upwards or downwards and may themselves have small openings; bushy eyebrows that join in the middle; a small and receding lower jaw (micrognathia); a small chin; a narrow forehead; unusually low and sometimes oddly formed ears; a thin upper lip that may turn down at the corners; a flat or deep bridge to the nose which can be broad and upturned; and a particularly long, flat or prominent groove (philtrum) between the nose and the mouth. Some children have rather puffy eyes (periorbital fullness). In others, the eyelids do not open fully. See [Ptosis](#), page 13. Some children have a skinfold across the inner corner of the eye; or tiny holes in the cheek in front of one or both ears (Malmgren 2007; Fernandez 2008; Unique).

["She doesn't have any dysmorphic features, she is actually very good looking](#)

[and she is becoming a beautiful young woman"](#) - 3p25.3p25.1 interstitial deletion, 12 years

["He looks and acts 'normal' and is 5'11" tall \(180cm\)"](#) - 3p25 mosaic deletion, 18 years



■ Head and Brain

A small head is typical. The head is sometimes an unusual shape. Babies and children with 3p- syndrome typically have a small head (microcephaly), which may also be flattened at the back (brachycephaly) or pointed or triangular when seen from on top (trigonocephaly). Typically, a baby's head is proportionately small, but a small head is not a consistent feature (Fernandez 2008). Magnetic resonance imaging (MRI) may be performed to identify any anomalies of brain structure. So far as we know, there are no specific structural anomalies typical of 3p- syndrome. If your child has an MRI scan of the brain, the results will be interpreted for you by your paediatrician or neurologist (Unique).

Other features

■ Cleft palate

A cleft palate has been found in a few babies with a 3p25 deletion, including one with the smallest reported deletion of 643kb within the 3p25.3 band (Shuib 2009; Peltekova 2012). A cleft palate is a split in the roof of the mouth. The hard palate at the front of the mouth may be split or the split may be found further back in the soft, fleshy tissue at the back of the top of the mouth. A cleft palate causes difficulties both in feeding and in speech production. Surgical repair of the palate eases these difficulties and may eliminate them altogether. Two children in Unique have a cleft palate, both with large deletions from 3p25 (Unique). Some babies also have an unusually high palate; four out of 10 babies are reported to have some palate anomaly (Fernandez 2008).

■ Extra fingers and/ or toes

Most babies with 3p- syndrome are born with 10 fingers and 10 toes. A minority, upto 40 per cent, are born with an extra finger or toe, either on both sides or one. The extra fingers or toes may be completely formed, a stub, or a flesh tag that can be quite tiny. If necessary, they can be simply removed by tying off or surgery and do not usually cause any long-term problems. This feature is called polydactyly, and is sometimes described as postaxial, meaning that the extra finger or toe is on the outer side of the hand or foot. Extra fingers and/ or toes have been seen in babies with large deletions from 3p25 as well as tiny deletions from the 3p26.3 band (Malmgren 2007; Unique).

In a few children, the hands and feet can be affected in other ways as well, but these features are not specifically typical of the 3p- syndrome. Features seen within Unique include: fingers or toes may be fused together (syndactyly); they may curve inwards (clinodactyly); they may be shorter or longer than is typical; hands may be clenched; there may be a single continuous crease across the palm; the sole of the foot may be curved (rocker-bottom feet); there may be a double big toe (hallux duplex); one foot or both may be positioned at an unusual angle (talipes); toes may override each other. Some of these features have also been reported in the medical literature (Fernandez 2008; Peltekova 2012).

■ Dimple near the base of the spine

A small pit or hole near the base of the spine has been seen in some babies with a 3p25 deletion, including nine Unique babies with deletions varying from a large deletion from 3p25 to a small deletion from 3p26.3. This feature has been reported in 38 per cent of babies (Fernandez 2008). The dimple may be shallow so you can see the base, but stools can collect there before your child is toilet trained, so keeping it clean and protected is important. The pit can also be deep and 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. In two Unique babies the spine was found to be tethered, meaning that the bottom end of the spinal cord which is usually free within the spinal column is attached to

the lower bones of the spinal column. If necessary the cord can be surgically released so that it can hang freely (Unique).

Pits and dimples on other parts of the body have also been seen (Unique).

■ Intestine problems

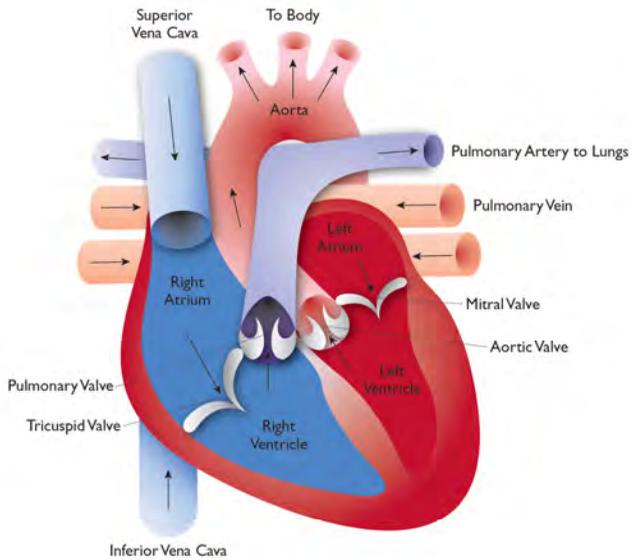
Problems with the development of the bowel or intestine have been occasionally seen; according to one estimate almost one in three children has a gastrointestinal anomaly (Fernandez 2008). One reported problem is intestinal malrotation, where the intestine has not developed and fixed properly within the abdomen. Some babies and children with malrotation have no symptoms or problems but if the intestine twists (volvulus), surgical repair is performed as soon as possible. Duodenal atresia has also been reported, where the first part of the small intestine just beyond the stomach (the duodenum) has not developed properly so food and fluids cannot pass through; surgical repair is needed. One Unique member has a slight anal stenosis, making it harder to push out bowel motions (Peltekova 2012; Unique).

■ Heart conditions

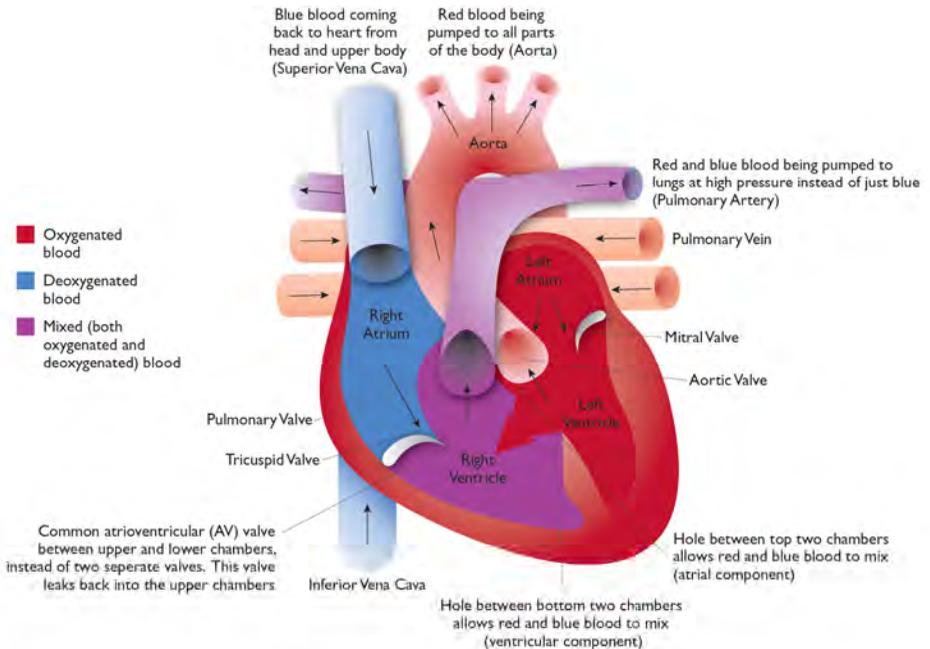
Around one third of babies are born with a heart condition, most typically an atrioventricular septal defect (AVSD). Due to abnormal development before birth, there is a problem with the heart's structure and function. A complete AVSD creates a large hole between the upper filling chambers (atria) and the lower pumping chambers (ventricles) of the heart. A partial AVSD is very similar but there is no hole between the ventricles. In an intermediate AVSD there is a small hole between the ventricles. In all types, the heart's inlet valves - tricuspid on the right and mitral on the left - are also abnormal. In complete AVSD, the middle part of the two valves is shared between the left and right sides of the heart. Normally the valves open to allow the ventricles to fill with blood and then close to allow blood to be pumped out of the heart. Abnormal valves may leak, allowing some blood to flow back from the ventricles into the upper heart chambers. Most babies with an AVSD don't need immediate treatment but if they become breathless they may have medicines to improve their symptoms until surgery is carried out. Babies with a complete AVSD usually need surgery when they are 3-6 months old. In babies with partial AVSD the operation is not usually necessary until they are a few years old.

A smaller number of babies do not have AVSD but instead have holes between the lower two heart chambers (ventricular septal defect; VSD), sometimes with holes between the upper two chambers as well (atrial septal defect; ASD). In Unique's experience these can be large enough to need surgical correction, or may resolve spontaneously (Green 2000; Shuib 2009; Unique).

*The text on AVSD is reproduced with the kind permission of the British Heart Foundation
www.bhf.org.uk*



A normal heart



AVSD

■ Seizures

Around one in three children have been reported to have problems with epilepsy or have abnormal electrical function in the brain, as traced by an electroencephalograph recording (EEG) (Fernandez 2008), including children with very small interstitial deletions (Gunnarsson 2010; Peltekova 2012; Unique). Seizure types vary and they may be transient or persistent; the evidence from Unique is that they generally respond well to anti-epileptic medication. A few children have seizures when their temperature rises in response to infection; one family has reported a rise in temperature after seizures. Both focal (partial) and generalized seizures affecting both sides of the brain have been observed, including absence seizures (a brief loss of awareness); atonic (loss of muscle tone) seizures, also known as drop attacks; as well as tonic-clonic (grand mal) seizures. Status epilepticus has occurred (a convulsive seizure that lasts for longer than 5 minutes; or convulsive seizures that occur one after the other with no recovery between). One baby had seizures that resembled infantile spasms at 2 months and had generalized epilepsy at 15 years (Drumheller 1996; Malmgren 2007; Gunnarsson 2010; Peltekova 2012; Unique).

“Her seizures are forever changing, but most are at night and a total mixture of absences through to status. She has never been seizure free since they started at about 20 months, despite different medications” 3p25pter deletion, 15 years

■ Hearing

Some children with a 3p25 deletion have a temporary hearing loss caused by glue ear; others, less commonly, have a permanent hearing loss. Hearing impairment has been reported in 16 Unique children. In a few it is the temporary, fluctuating hearing loss caused by glue ear and can be relieved by the insertion of tubes (grommets) to relieve pressure in the middle ear. In others the hearing loss is permanent, affecting both ears and may be first detected when a baby fails their newborn hearing test. Some children wear hearing aids; one child is registered as deaf; another child had surgery to correct a hearing impairment in one ear. Unique records show that hearing loss can affect children with deletions in either band 3p25 or 3p26, although it appears to be more common in those with a large deletion from the 3p25 band (McCullough 2007; Unique). *See Genes*

“He plays drums very well by ear and listens to music all the time. He knows the names of groups and has memorised songs from all decades. Amazing knowledge in all genres” - 3p25 mosaic deletion, 18 years

■ Kidney problems

Kidney problems have been reported in people with a 3p25 deletion, according to one estimate affecting one individual in four. Horseshoe kidney has been reported, in which the two usually separate kidneys are joined at the bottom in a U-shape. Under-sized kidneys have also been reported (Fernandez 2008; Unique).

Further features and concerns

■ Genital anomalies

Some minor anomalies of the genitals have been found in a few Unique members, although these are not reported in the medical literature as part of the 3p- syndrome. These include undescended testes; a twisted penis; and hypospadias (the hole normally at the end of the penis lies on the underside). If necessary, hypospadias can be corrected with surgery (Unique).

■ Breathing

A small number of children have continuing breathing difficulties, and these can be severe. Underlying these may be structural difficulties. Narrow airways have been seen, and also laryngomalacia, where the structural framework of the larynx (voicebox) is soft and limp. 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* pages 7-8) 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 (Mowrey 1993; Pohjola 2010; Unique).

■ Hypothyroidism

A number of cases of hypothyroidism have been seen, both in the medical literature and in Unique. Congenital hypothyroidism, where not enough thyroid hormones are present from birth, and primary hypothyroidism, which develops later, have been seen, as has Hashimoto's disease, an autoimmune reaction that causes an underactive thyroid. Hypothyroidism is treated by giving thyroid hormone replacement (Phipps 1994; Pohjola 2010; Malhotra 2011; Unique).



■ Von Hippel-Lindau disease

Von Hippel-Lindau disease causes abnormal growth of blood vessels and tumours. The gene that holds von Hippel-Lindau disease in check is situated in band 3p25.3. Although no-one with a 3p25 deletion has been reported in the medical literature with von Hippel-Lindau disease, it can be many years and sometimes decades before the first signs develop. Your geneticist or genetic counsellor can tell you if your child has lost the *VHL* gene, and if so he or she will be screened regularly (Malmgren 2007; Shuib 2009; Unique).

Behaviour

Marked contrasts between children. Autism or autistic features may occur. Among 21 Unique families who have described their child's behaviour, a general picture emerges of happy children, some content to play alone or with others. In general children are markedly immature for their age. However, there are very marked contrasts between different children, even with similar deletion sizes. A number of families have mentioned an autism spectrum disorder; other families have noticed repetitive behaviour, speech, or both, as well as poor concentration and gaze avoidance, and sensory issues. A delay in eye contact has been noticed; first smiles may arrive late and one child was reported not to smile until he was 18 months old. Some children do not seek to communicate with others – but other children are reported to be sociable.

Other behavioural issues reported by Unique families include obsessive-compulsive disorder (OCD); pervasive developmental disorder (delay in the development of socialization and communication skills); an extremely high pain threshold and a delayed perception of pain; sensory integration disorder, in which the brain cannot correctly process information brought in by the senses; frustration due to limited communication or when out of routine; complete unawareness of safety issues. (Kellogg 2013; Unique).

“She has recently been diagnosed as autistic and shares many characteristics with the classic diagnosis. She tends to favour adults and not children. She doesn't like to be overwhelmed and has a lot of issues with sensory processing. A therapy using brushing helped immensely with her overall sensory problems. She does not necessarily like to make eye contact or be held and cuddled. She has gotten better as she gets older, but it has to be on her time, and when she is done, that is it” - 3p25.3pter deletion, 2 years 9 months

“He has no natural fears of most children, he will wander off in a crowded store and not be afraid if parents are not around, and his speech is not good enough to tell a stranger his name so they understand what he is saying. He doesn't understand the concept of consequences and does not understand punishment when he is being punished” - 3p25.3p25.2 deletion, 6 years

“His problem is considered to be an autism spectrum disorder: poor eye contact, lack of social skills, not asking for help, not seeking to communicate with others” 3p25.2p25.2 deletion, 9 years

“He is much more sociable than before. He loves to go to his specialized school, makes friends there. He is less into rituals and is very happy most of the time. He’s had horse therapy sessions for more than three years and I think it really helps. He sleeps very well. He never wakes us up” - 3p25pter deletion, 12 years

“She has a diagnosis of autism spectrum so she has sensory issues. For example she doesn’t like to go to crowded indoor places (shops, malls etc.); when she is in these places she starts sitting on the floor, grabbing mom’s hair etc. She doesn’t like to change plans either” - 3p25.3p25.1 interstitial deletion, 12 years

“Happy, non-verbal, very social, loves people; with age getting more determined to have her own way” – 3p25 terminal deletion, 13 years

“I’ve thought for a long while that she has certain autistic traits, particularly poor concentration and a lot of eye avoidance” - 3p25pter deletion, 15 years



How did this happen?

In most people described so far, the 3p25 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 3p25 deletion is caused by a mistake that is thought to occur when the parents’ sperm or egg cells were formed or in the very earliest days after fertilisation.

Less often, a blood test will show that the deletion has been inherited directly from the mother or the father (*see Families with a 3p25 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 3p25 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, both parents have normal chromosomes by a blood test, 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. This has never been reported with 3p25 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 of these tests are available in all parts of the world.

Genes

3p25 deletion syndrome is believed to be caused by the loss or mutation of the *SETD5* gene as well as other genes in those with larger deletions.

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 p25 and 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 (Shuib 2009).

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 play a role in determining the presence or absence of a particular feature.

The numbers showing the position of genes follow the most recent human genome, called hg19. When the genome is updated, the numbers usually change a little. Always check the hg number. If in doubt, ask your geneticist or Unique.

One gene that is sometimes missing in the 3p25 deletion is the *VHL* gene that causes von Hippel-Lindau disease. Von Hippel-Lindau disease causes abnormal growth of blood vessels and tumours. The *VHL* gene that holds von Hippel-Lindau disease in check is situated in band 3p25.3 at 10,182,692-10,193,904. People who have lost one copy of this gene have an increased risk of developing the disease. Your geneticist or genetic counsellor can tell you if your child has lost the *VHL* gene, and if so he or she will be screened regularly.

Researchers have suggested other genes that may be responsible for other features of the syndrome.

An attempt to identify a gene or genes whose loss causes permanent hearing impairment in children with 3p- syndrome pinpointed the *ATP2B2* gene in the 3p25.3 band at 10,365,707-10,749,716 as the most likely candidate (McCullough 2007); however this was disputed by other researchers (Malmgren 2007).

Over the years, a number of different genes have been suggested as contributing to the developmental delay and learning difficulties in 3p25 deletions. These genes include the *SRGAP3* gene in 3p25.3 (Shuib 2009; Gunnarsson 2010); and

for those with 3p25 deletions that include the end of 3p, *CHL1* (*CALL*), near the end of the chromosome in band 3p26.3 (Pohjola 2010); and Contactin 4 (*CNTN4*), a gene that plays a role in the developing nervous system and neural networks, also situated in 3p26.3 (Fernandez 2004; Roohi 2009).

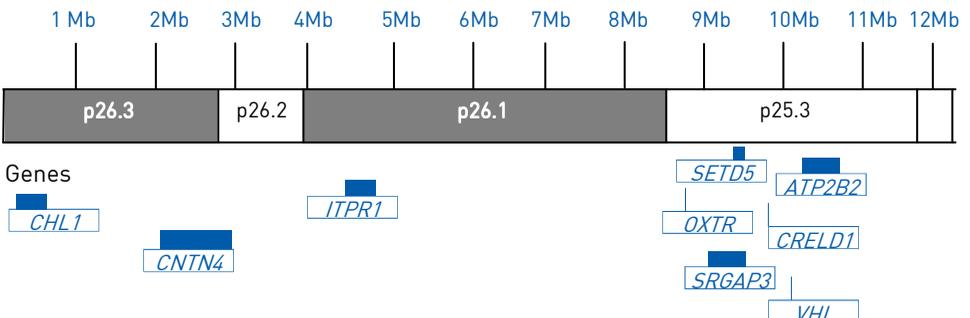
However, there is now strong evidence that the *SETD5* gene in 3p25.3 is the main player, both in 3p25.3 microdeletions, and in 3p25 deletions. People with small changes (mutations) within the gene have very similar features to people who have lost the entire gene: learning difficulties, low muscle tone, a low bridge to the nose and a long groove between the nose and the upper lip, and in some cases heart problems or a cleft palate. Other features sometimes found when the *SETD5* gene is not working properly include eyebrows that meet, a small head, drooping eyelids, unusual eye openings, extra fingers or toes, spinal curvature, anomalies of the gastrointestinal system and epilepsy (Grozeva 2014; Kuechler 2014).

Uncertainty over the causes of the heart problems seen in 3p25 deletions has led to suggestions that a gene named *CRELD1* is responsible (Robinson 2003; Zatyka 2005) or multiple genes, or that different genes are responsible in different people (Shuib 2009; Peltekova 2012). However, it now looks likely that *SETD5* is the gene underlying the heart problems seen in some people as well (Grozeva 2014).

It has also been suggested that loss or changes in *SETD5* are responsible for the autistic features seen in some people with 3p25 deletions (Grozeva 2014). The function of the *SETD5* gene is not yet fully understood, but it provides the DNA code for a protein that is found throughout the body, especially in the brain. When the gene is missing or changed, not enough *SETD5* protein is produced, leading to the effects seen in 3p25 deletions.

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).

Position of genes on 3p26 and 3p25



Support and Information



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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

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

There is also a closed 3p Deletion Syndrome family support group:
www.facebook.com/groups/309999732398027

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

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. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Professor Eamonn Maher, Professor of Medical Genetics and Genomic Medicine, University of Cambridge, UK and by Dr Lucy Raymond, Reader in Neurogenetics and Honorary Consultant in Medical Genetics, University of Cambridge, UK 2014 Version 2.1 (PM)

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