



Support and Information

**Rare Chromosome Disorder
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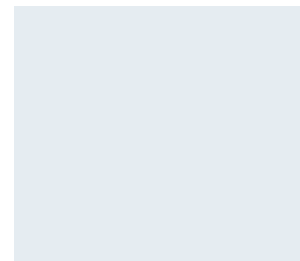
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This information sheet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication and the medical content has been verified by Professor Eamonn Maher, Professor of Medical Genetics, University of Birmingham, UK and by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, UK, 2005.

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3p25 deletions



Sources & References

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain abstracts and articles from Unique. The leaflet also draws on Unique's database. When this leaflet was written, Unique had 34 member families with this chromosome disorder. Eleven families completed a detailed questionnaire in 2004. Unique is very grateful to the families who completed the questionnaire. References to information from Unique are marked U.

3p25 deletions, also called 3p-

A 3p25 deletion is a very rare chromosome disorder. Out of a total of 46 chromosomes, your child has two chromosome 3s. One chromosome is complete, but the end is missing from the short arm of the other one and this missing (deleted) chromosome material is responsible for the effects on your child. This chromosome disorder is sometimes also called 3p- (three p minus, or three p deletion) syndrome.

Like most other chromosome disorders, a 3p25 deletion increases the risk of certain birth defects, developmental delay and learning difficulties. However, the likelihood of problems depends very much on what genetic material is missing. The features vary between individuals and a few people are apparently unaffected.

Frequent features

- Low birth weight. Most children grow slowly and remain short
- Small head (microcephaly)
- Delay in reaching developmental milestones
- Speech delay or absence of speech
- Hypotonia - floppiness
- Vision problems
- Ptosis – an inability to fully raise the upper eyelid
- Hearing impairment
- Extra fingers and/ or toes
- Heart conditions
- Triangular face with a small chin
- Almost all children have a degree of learning disability.

It is Unique's experience that up to four out of 10 children will experience seizures, although they may outgrow them (Witt 1985; Mowrey 1993; Benini 1999; Green 2000; U).

How rare are 3p25 deletions?

This is not quite certain, but they are probably very rare indeed. By 2005, only 35 people had been described in published research reports. However, some people are apparently unaffected by their deletion, and so would never be identified. At the time of publication, Unique had 34 affected family members and can put anyone who wishes in touch with others (Knight 1995; Green 2000; Rohrbach 2005; U).

Lifespan

The doctors looking after your child are in the best position to give you answers to this difficult question. Certainly, the majority of children with this rare disorder do survive. The oldest people described in the medical literature are in their twenties and the

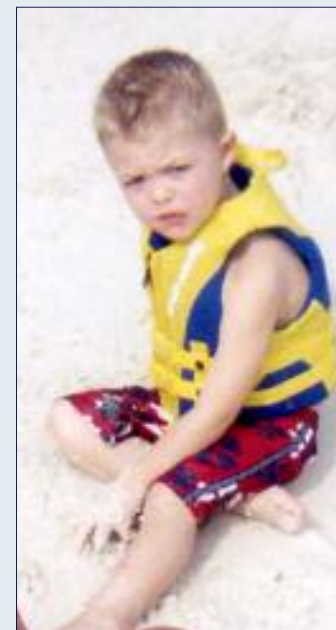
child's geneticist or paediatrician should be able to tell you whether in your child it is missing, in part or completely.

Researchers are hunting for genes near the end of the short arm of chromosome 3 that contribute to or cause typical features such as heart defects, hearing impairment and learning disabilities. By 2005, areas for certain genes had been narrowed down but no genes had definitely been found apart from the gene for von Hippel-Lindau disease (Phipps 1994; Green 2000; Cargile 2002; U).

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 between band 3p25.3 and the end of the short arm of the chromosome. Some people with a 3p25 deletion only have one copy of this gene (on their intact chromosome 3) and therefore have an increased risk of developing the disease. Although no-one with a 3p25 deletion has yet been found to have von Hippel-Lindau disease, it can be many years and sometimes decades before the first signs develop. In order to detect the disease as early as possible and maximise the benefit of treatment, your child should be screened regularly. A DNA test is available to determine which children with 3p25 deletions are likely to be at risk of von Hippel-Lindau disease (and so need screening) (Knight 1995; Drumheller 1996; Angeloni 1999; Rohrbach 2005). Screening involves a regular neurological assessment and examination of the eyes for angiomas (benign growths of blood vessels) on the retina. Once a child reaches puberty, they will usually also have periodic MRI scans of the brain. From age 16 years ultrasound scans of the abdomen are performed each year.

The aim of these tests is to identify as early as possible the abnormal growths of blood vessels and tumours that characterize von Hippel-Lindau disease. Small non-cancerous knots of capillaries called haemangioblastomas or angiomas may grow in the retina at the back of the eye or in the brain or the spinal cord. Other tumours may also develop in the kidney, pancreas, liver or the adrenal glands. Cysts (fluid-filled sacs) and non-cancerous or cancerous tumours may develop around the knots of blood vessels and people with the disease have a raised risk of developing certain types of cancer, especially kidney cancer. The point of the regular screening is to identify any tumours as early as possible and treat them or remove them surgically.



How does a *de novo* deletion occur?

Changes to the structure of chromosomes such as 3p25 deletions occur most often during the cell divisions that lead to the creation of eggs or sperm. In this process, each of the 46 chromosomes first doubles lengthwise into two strands that are held together at the point where the short and long arms meet, known as the centromere. The chromosomes then arrange themselves in 23 pairs, with pairs lying alongside each other. The two members of each chromosome pair 'recognise' each other because the DNA sequence ladder that comprises them is in a similar order. However, when a small region of DNA on a chromosome has a twin region of DNA located further down the same chromosome, the pair of chromosomes may not align correctly. Usually, after chromosomes pair, the members of a pair exchange segments of DNA with their pair-mates, in a process known as crossing-over (recombination). After this point, the chromosome strands repel each other but are held together at the cross-over points known as chiasmata. Deletions can arise during this process when the chromosomes have lined up incorrectly. An unequal cross-over means that the exchanges are not equal between the members of a chromosome pair. In this case, a piece of one chromosome can loop out and be lost from the middle of the chromosome (interstitial deletion) or from the end of the chromosome that then 'heals' (terminal deletion).

Rearrangements in chromosomes occur as part of evolution. They affect children from all parts of the world and from all types of background. They also happen naturally in plants and animals. So there is no reason to suggest that your lifestyle or anything that you did caused the loss of chromosome material from chromosome 3.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 3p25 deletion. Where a parent has a chromosome rearrangement, there is a risk of having another affected child. Where a parent has the same 3p25 deletion as the child, the risk of passing it on can be as high as 50 per cent.

Does it help to know a child's exact chromosome pattern?

Families who wish can be given a technical description of their child's chromosomes known as a karyotype, showing how much chromosome material has been lost. The end of the short arm of chromosome 3 can break at many different points and there do not appear to be any sites near the end of the chromosome where it is especially likely to break. In most children with a deletion involving 3p25, the end of the chromosome is missing (a terminal deletion). A few children have recently been found to have only a segment missing from near the end of the chromosome (an interstitial deletion).

Since 3p25 deletions were first described in 1978, commonsense and many researchers have suggested that a larger deletion means that a child will be more severely affected. From *Unique's* experience that does not always appear to be true. The child who is least affected has a deletion as large as any other child's, while a child with a small interstitial deletion is more severely affected. However, it does appear that losing a specific segment of chromosome 3 is likely to cause the typical features of 3p-syndrome. This so-called 'critical' segment lies in the 3p25.3-p26.2 region and your

reason that older people are not described is probably because their chromosomes were never studied. At the time of writing, *Unique's* oldest member was 15 years old.

A small number of children have died. Of three babies described in the medical literature, one had persistent respiratory difficulties and was on oxygen when he died in his sleep at home at the age of six months; one died without treatment as a newborn baby and another at four weeks with a severe heart defect. Two *Unique* children have died, one with a respiratory syncytial virus (RSV) infection at 22 months, and the other when she was three years old of a cause not known to us (Reifen 1986; Nienhaus 1992; Mowrey 1993; U).

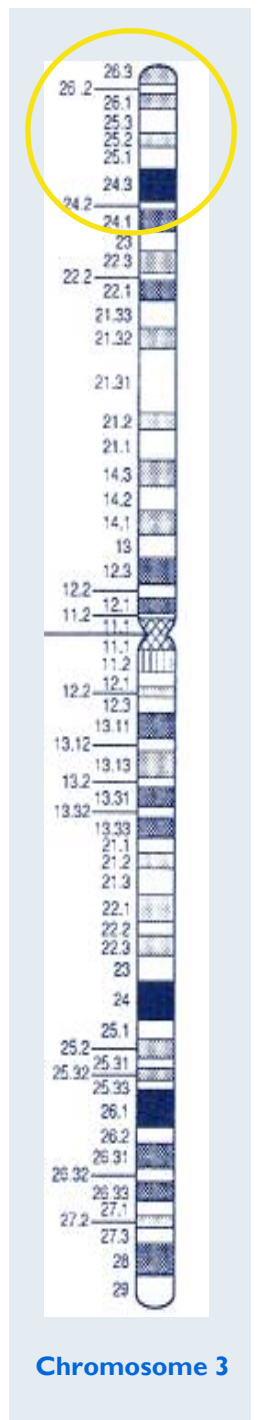
First signs

The first signs of a 3p25 disorder are usually developmental delay in a baby, often together with failure to thrive and unusual facial features. Out of 12 people whose first signs were described in the medical literature, only two were identified as newborn babies. Five were diagnosed as older babies or toddlers when they showed a delay in development. Two older children were diagnosed with developmental delay, at six and at 12 years old. One baby was identified by chance on amniocentesis when a chromosome study was performed for maternal age reasons. Two mothers were identified by studies of the parents' chromosomes after their child had been diagnosed with a 3p25 deletion, and of these two, one mother was entirely healthy and without any learning disability, as was her daughter.

Among *Unique* members, we have information on seven children. One baby was diagnosed from an amniocentesis. Two babies were diagnosed at birth because of defects (extra toes, unusual eyes) and other signs, including breathing difficulties and a two-vessel cord. All other *Unique* members were diagnosed after showing some degree of developmental delay (Witt 1985; Reifen 1986; Narahara 1990; Tazelaar 1991; Mowrey 1993; Phipps 1994; Knight 1995; Drumheller 1996; Angeloni 1999; Cargile 2002; U).

Diagnosis

At present, the most widespread technique for examining chromosomes is looking at them directly under a microscope, and then using molecular tests such as a FISH (fluorescent in-situ hybridisation) study that show whether certain sequences of DNA are present or not. Direct examination of chromosomes has revealed the great majority of the chromosome disorders we know today. FISH studies and other molecular techniques can help to give a clearer picture – by pinpointing with greater precision where the chromosome has broken, by helping to



Chromosome 3

positively identify 'mystery' pieces of unidentified chromosome material or by revealing the nature of extremely subtle chromosome rearrangements.

The approximate position of some of the genes that cause or contribute to particular features of 3p25 syndrome is already known, so it is helpful to know whether your child has lost or retained these segments. Sometimes only a molecular study will reveal this. Yet many people with a 3p25 deletion have not had a molecular study. Of the 25 people described in the medical literature with a 3p25 deletion, only 13 have had an additional molecular analysis of their chromosomes. At the time of writing, only three *Unique* members had a molecular diagnosis.

This lack of precision means that descriptions of 3p25 deletions can only be general. Your child's other genes as well as environment, expectations and opportunities will also affect their development and achievements.

Appearance

Short stature is the feature that might make many children stand out. Children are typically small and many have a slim build. 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. Doctors sometimes look for what are known as dysmorphic features – unusual facial features that may suggest a chromosome disorder. However, these can sometimes be subtle. Among the features found especially often in children with a 3p25 deletion are upper eyelids that do not open fully, widely spaced eyes, a small chin, unusually low and sometimes oddly formed ears, a thin upper lip that may turn down at the corners, a short nose with a broad tip and a particularly long groove (philtrum) between the nose and the mouth. Some children have a small head, while others have bushy eyebrows that may join in the middle, a tiny fold of skin across the inner corner of the eye or tiny holes on the cheek in front of the ears (Narahara 1990; Tazelaar 1991; Drumheller 1996; Green 2000; Cargile 2002).

Growth

Research reports show that growth delay starting in pregnancy is highly typical. *Unique's* experience is that while all families have reported growth delay in pregnancy and have had a baby of low birth weight, the pattern of postnatal growth is more variable. The range of known birth weights among 16 members is from 1959g (4lb 5oz) to 2953g (6lb 8oz), and two babies were born especially tiny at 595g (1lb 5oz) and 1361g (3lb). However, eight families volunteered the information that their baby was born early (between 34 and 38 weeks) and this may be true of others (Green 2000; Cargile 2002; U).

Out of 14 *Unique* families who have given information on their child's growth pattern, nine families report that growth has been remarkably slow. 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'. Within this group, the predicted adult height of one child was 5' (1.5m).

By contrast, four children are of average or above average height – in each case despite a low birth weight.

with increasing maturity. Some school age children may be hyperactive and have difficulty in focusing their attention but in *Unique's* experience these difficulties have been successfully managed with medication where needed.

“ She leads a sweet, loving, fun-filled, happy life. Her worst behavioural problem was flushing things she had taken a dislike to down the loo.

“ When she gets bored she will cry and bang her head but it doesn't last long.

Will a child be able to live independently?

The wide range in severity makes it difficult to answer this and it will be easier to reach a judgement once a child's abilities become clearer. A few children become clean and dry by mid childhood, although this may not be reliable, and most need considerable help with personal care including washing and dressing. Although the evidence from *Unique* and from the medical literature suggests that almost all children will need full support in adult life, there are healthy adults leading normal lives who have been found by chance to have this chromosome disorder.

What do children enjoy?

There is no clear pattern to children's interests. The snapshots that follow give an idea of the child's stage of development and may act as pointers to the future for other families.

At 18 months: Enjoys clearing objects off his feeding tray, throwing them off the side and looking for them, batting dangling toys under his gym, pulling people's hair and grabbing the cat's fur

At 5 years: Enjoys musical light-up toys. Interacts better with adults than children, but enjoys having others around even if she doesn't play with them

At 10 years: TV, videos, computer, music, drawing, playing with her dolls

At 10 years: Loves helping with the housework or cooking. Loves taking the dogs for a walk. Watching the video of *Matilda*. Music, dancing and 'singing' to her favourite songs.

At 14 years: Music, TV, watching fish in a fish tank, bubble tubes, noisy toys, teething rings

Why did the chromosome deletion happen?

A chromosome 3p25 deletion can occur as a result of a rearrangement in one of the parent's chromosomes or it can happen out of the blue, so the child with the chromosome disorder is the only person in the family with rearranged chromosomes. Technically, when the parents' chromosomes are normal, the child's deletion is called a *de novo* rearrangement.

If a blood test on the parents shows a chromosome rearrangement in one of them, this is usually balanced so that all the chromosome material is present, and the parent is then almost always healthy. Very occasionally chromosome studies on the parents reveal that one parent has exactly the same 3p25 deletion as their affected child. This has not occurred in any families known to *Unique* but two cases have been described in the medical literature. In one case, the mother was unaffected and the child apparently too; in the other case, the child was more severely affected than the mother (Tazelaar 1991; Knight 1995).

inside the brain caused damage to the optic nerves. Surgical release at the age of seven months was successful. Magnetic resonance imaging has identified modest ventricular enlargement in two children and asymmetry in another (Rohrbach 2005; U).

■ Genital features, kidneys and urinary system

Among boys, the penis or scrotum may be small and hypospadias (the hole normally situated at the end of the penis lies on the underside) has been found. A very mild hypospadias where the hole is still on the glans and the penis is straight does not usually need treatment, but if it is further down it can be corrected with surgery. Two further boys had undescended testes. In a minority of children, one kidney or both were unusually formed or small (Witt 1985; Reifen 1986; U).

■ Hernias

Hernias may be found. In *Unique's* experience, umbilical and inguinal hernias occurred in four out of 18 children.

■ Breathing problems

A small number of children have respiratory difficulties and recurrent respiratory infections that can be severe (Mowrey 1993; U).

■ Extra fingers and/ or toes

Extra fingers and toes have been found in 5/18 *Unique* children. They are simply removed and do not usually cause any long-term problems.

Other features

These additional features have been noted by medical researchers in descriptions of children with a 3p25 deletion but as numbers are small, it is uncertain whether they are typical. They include: cleft palate, scoliosis, a dimple near the base of the spine, joint tenderness, imperforate anus (covered with tissue), fusion of part of the ribs, wedge-shaped, incomplete vertebrae and premature growth of body hair (Witt 1985; Reifen 1986; Narahara 1990; Tazelaar 1991; Mowrey 1993; Angeloni 1999; Green 2000; Cargile 2002).

■ Hearing

Unique's experience and that of some medical researchers is that most children have a temporary or permanent hearing loss. Five *Unique* children have a permanent hearing loss and one is registered deaf. In addition, six children have had glue ear that was sufficiently severe and persistent to need treatment (Narahara 1990; Drumheller 1996; U).

■ Vision

Abnormalities of the vitreous body, the transparent inner part of the eyeball and optic atrophy (a dysfunction of the optic nerve) have been noted by medical researchers in two children. *Unique's* experience is that eyesight problems are both common and varied in type. Ten out of 18 children have a vision problem, ranging from a surgically corrected squint (strabismus) in two children, to three children with short sight corrected with glasses and one who is blind. One child had optic atrophy as a result of craniosynostosis, the premature fusion of the skull bones (Schinzel 2001; U).

Behaviour

In general, families have reported that their children have a pleasant temperament. A few families perceived autistic traits, but it is uncertain whether children outgrow these

Feeding

Five out of 12 *Unique* families reported considerable feeding difficulties while their babies were young. Weak sucking, a tiny appetite and in some babies gastro oesophageal reflux - where feeds flush back up the food pipe from the stomach - led to slow weight gain and many babies needed high calorie or thickened milks. In nine babies, reflux was severe and three babies needed feeding direct into the stomach through a gastrostomy tube.

By contrast, five babies were successfully breastfed and two mothers only stopped breastfeeding because their baby remained hungry after feeds. Persuading babies to latch on in the early days was not always easy. One mother said it was a huge struggle and another used a bottle with an enlarged hole in the teat to encourage her sleepy, reluctant feeder.

These are two families' experiences.

“ I breastfed K for a week, but stopped because she always wanted more. She has trouble eating lumps but she's getting better due to massive help from her school teachers. She has no speech so doesn't move her tongue around, and doesn't chew anything - K, age 5

“ C was fed by nasogastric tube for one week then breastfed. He struggled to gain weight so he had formula top ups. Due to his poor weight gain he was eventually put on a high-energy feed. He started solids at about six months, but struggled to keep food down due to reflux. Ranitidine (an antacid medication) seemed to help. Recently C has made vast improvements with eating due to treatment from a homeopath - C, age 20 months

The move to solids appears to come late. Many toddlers stayed on baby or pureed foods until at least the age of two and seven out of nine families with a child of school age said that they were reluctant to chew. Of the four families who reported average or above average height in their child, none had a significant feeding difficulty.

Learning

There are some people with a 3p25 deletion with no learning difficulty, but children typically need very considerable help with learning. Out of 11 families who gave information about schools, one *Unique* member attends a mainstream (regular) primary school, but other children's needs are met better in a special school. The comments and experiences that follow reflect individual achievements. Not all children will be able to learn at this level.

“ K has come on in leaps & bounds since starting nursery - K, age 5

“ M draws faces, probably reads about 75 words and can read most numbers. She writes all the letters and small numbers and can use a keyboard. Her memory is very good in areas to do with household routines and she is often the member of the family who remembers useful information. However, she has to understand



something in order to remember it. She tends to improve in one area and plateau in others. Recently, M has been successful in picking up basic addition which she found very difficult for years. Her determination, interest and concentration have kept her going – M, age 8

“ C is reading early books and has been writing her name since she was 8 – C, age 9

“ E tries to draw lots of things and pretends to write names and to read books. She has been reading basic books at school since she was 7 but needs prompting. She can copy her name and she uses a keyboard at school. Her short term memory seems good, but long term is probably sketchy. She is more able at practical things that she enjoys – E, age 10

Communication and speech

Research reports have suggested that most children with a 3p25 deletion do not talk, but that is not *Unique*'s experience. Out of eleven children over the age of three, six use some spoken words and one child, who may be exceptional, has a vocabulary of many hundreds of words. Speech was however delayed in all children. Among pre-school children, there was little evidence from the *Unique* sample that social communication was impaired and babies and toddlers expressed themselves with gestures, babbling, vocal noises, laughter and crying. Some children learned to sign from around 18 months and one child progressed from being an able sign communicator at three years to using around 30 words and short phrases by four years. From the information that *Unique* holds, there does not appear to be an obvious relationship between the extent of the deletion and the ability to communicate with speech.

These snapshots illustrate the range shown in the *Unique* sample:

“ K makes vocal noises but may understand more than she can tell - K, age 5

“ M has a wide spoken vocabulary. Her first words came around 2 and she slowly built up to a good vocabulary. She is 8 but uses sentences probably typical of a 3-4 year old. Her understanding has always exceeded her powers of expression although the gap has narrowed considerably. When she is tired her speech is quite indistinct and 'vowelly' and generally she has more problems with hard consonants, so she says *cholate* rather than *chocolate* - M, age 8

“ E has poor speech but she understands 99% of what is said to her. At 3 she could manage basic baby words. At 10 her speech is becoming more understandable and she has more words and occasionally 2-3 word sentences. She cannot make certain sounds (*sh, t, f, j, l, qu, z*). She has speech therapy in school and we encourage sounds at home which seems to be more beneficial to her - E, age 10

“ A uses vocal noises, no words or gestures and can only express that he is unhappy by crying. It is very hard to know what he understands - A, age 14

Sitting, moving, walking

Children are typically delayed in reaching their developmental milestones and some will need very considerable help. While some children eventually become quite mobile and a few children swim, dance and use outdoor playgrounds at school age, this is not possible for all.

Information from *Unique* shows that babies started to roll over between nine months

and 24 months and achieved sitting between nine and 36 months. First steps were taken from two years but walking usually remained unsteady and children needed support (splints, walking aids or a wheelchair) or protection out of doors, particularly as they had a diminished sense of danger. Hypotonia (floppiness) underlies some of the mobility difficulties; it generally improves but may persist.

This passage describes a 10-year-old girl.

“ She has been delayed, but she gets there in the end. She was unstable on her feet at first but was able to run by the age of 8. Apart from being unaware of danger, she needs no other help. She swims at school, loves dancing and comes downstairs on her bottom.

Medical concerns

The risk of your baby having a particular medical condition depends at least in part on which genes are missing from chromosome 3p. Your geneticist can advise you on the position of the breakpoint or breakpoints.

■ Heart conditions

Around one third of babies are born with a heart condition, most typically an atrioventricular septal defect (AVSD). This is a group of defects (also known as endocardial cushion defects) affecting the development of the walls that separate the two upper and lower chambers of the heart (the atria and ventricles) and the valves that control the blood flow between them.

Among *Unique* members, one baby also had a persistent ductus arteriosus (PDA, where a channel between the aorta and the pulmonary artery that usually closes shortly after birth stays open, sending too much blood to the lungs and making the heart work too hard) and two had pulmonary stenosis, where the entrance to the artery that takes blood to the lungs is unusually narrow, but in one child this was resolving without surgery. Three children had successful open heart surgery before the age of one and one child was being monitored (Green 2000; U).

■ Seizures

Seizures affect a minority of children with 3p25 syndrome. The *Unique* experience is that seven children out of 18 (39 per cent) have experienced seizures, although they may be rare or occasional and in one child were febrile convulsions (Reifen 1986; Narahara 1990; Tazelaar 1991; Phipps 1994; Drumheller 1996; Schinzel 2001; U).

■ Ptosis

Ptosis (drooping of the upper eyelid so the eye cannot be fully opened) is common and was found in seven out of 18 *Unique* children. Very mild ptosis does not need treatment. If it affects vision, it can be corrected with a surgical operation in which an artificial material or some of the tendon from the outer side of the thigh is used as a sling to hold the eyelid up (Drumheller 1996; Green 2000; Cargile 2002; U).

■ Brain

Five *Unique* children have been found to have an unusual size, structure or function of the brain. Two have an unusually small head, reported by some to be characteristic of a 3p25 deletion; one has a notably large head. Two children have craniosynostosis (premature fusion of the plates of the skull) and in one child the resulting pressure