

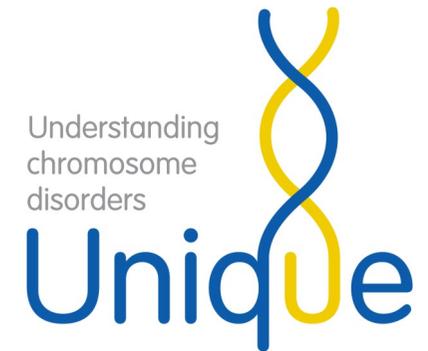
Support and Information



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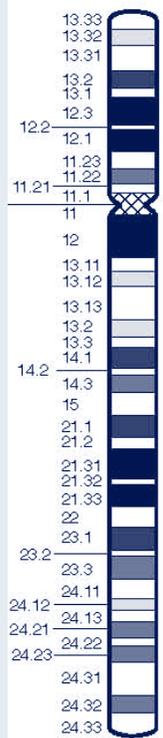
Duplications of 12p

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. It was compiled by Unique and reviewed by Professor Diana Bianchi, Tufts University School of Medicine, Boston, USA and by Unique's chief medical advisor, Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK. 2007 (PM). Minor revision 2017 (CA).

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Short 'p' arm



Long 'q' arm

Chromosome 12

Duplications of 12p

A chromosome 12p duplication means that part of one of the body's chromosomes has been repeated or duplicated. If the extra chromosome material contains important instructions for the body, learning difficulties, developmental delay and health problems may occur. How obvious these problems are will depend on how much of the chromosome has been duplicated and where the duplication is.

Genes and chromosomes

Our bodies are made up of billions of cells. Most of the cells contain a complete set of tens of thousands of genes. Genes act like a set of instructions, controlling our growth and development and how our bodies work. Genes are carried on microscopically small, thread-like structures called chromosomes. There are usually 46 chromosomes, 23 inherited from our mother and 23 inherited from our father, so we have two sets of 23 chromosomes in 'pairs'. The genes and chromosomes are made up of a chemical substance called DNA.

Apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy) the chromosomes are numbered 1 to 22, generally from largest to smallest. Each chromosome has a short arm (at the top in the picture on the left) called **p** from *petit*, the French word for small, and a long arm called **q** (at the bottom). In a 12p duplication, there is extra material from the short arm of one of the two chromosome 12s.

The duplicated piece can be small or large. When the duplication includes all or most of the short arm, it is sometimes called a **trisomy**. A smaller duplication will include just part of 12p. You may be told the 'breakpoints' where the chromosome has broken and rejoined; you can find these on the diagram (left).

In some people the duplication is so tiny that it can only be identified using new-generation molecular tests such as FISH, MLPA or microarrays. It is then called a **microduplication**. These tests are sometimes used to check if certain genes or parts of genes are repeated and to be more exact about where the chromosome has broken.

In some people, cells with a normal chromosome make-up are found as well as cells with extra material from chromosome 12p. This is called **mosaicism** and can lessen the effects of the extra chromosome material.

Behaviour

The evidence from the Segel 2006 study is mixed. Six/16 families said that their child had good social skills. Six families also reported challenging behaviour, specifically self-harming, self-stimulation, aggression and mood swings. Additional evidence from *Unique* confirms this picture, with even very young children as well as adults enjoying the company of others and showing genuine affection. Negative behaviours did not affect everyone and some families only reported a sociable, sunny outlook. In others, frustration and negative behaviours have developed when individuals were not allowed their own way, when routines were changed, during ill-health or care changeovers or even in response to loud noises and acute temper tantrums, rocking, hair pulling, pica (eating substances other than normal food), head banging and behaviour disturbances have been reported. These have been generally controlled with management techniques and medication.

“ Violent behaviours occurring more frequently, controlled by a rising dose of risperidone ” - 11 years

“ Very friendly and interested in people but not overly so. Affectionate and has a wonderful laugh ” - 9 years

Sleep

Seven/ 16 families said that sleep was significantly disrupted (Segel 2006) and evidence from *Unique* confirms this, with use of medication (melatonin) and special sleeping arrangements (padded cot with removable rail) considered helpful.

Suggested clinical management of a child with a 12p duplication

- ◆ **Newborns:** Attentive follow-up for poor feeding in early days and weeks. Monitor for low blood sugar. Check for anomalies based on individual physical examination.
- ◆ **Children:** Regular hearing tests. Regular sight tests. Evaluate for behaviour and sleep problems.
- ◆ **Late childhood:** Examine for eczema. (Segel 2006)

Note: a 12p duplication as part of a more complex chromosome change

In many people with a 12p duplication, there is also a loss of material from another chromosome. Occasionally there is extra material from another chromosome arm or a more complex change still. These changes are very likely to affect the outcome in the child, so we have not considered them as part of this leaflet. But for parents or caregivers who wish to know of any cases with the same chromosome make-up as their child, *Unique* maintains a list of relevant papers from the medical literature and can consult its own database. When this leaflet was written, *Unique* had 25 members with a 12p duplication and an additional chromosome change. For more information, contact info@rarechromo.org.

Segel 2006 study showed that hypotonia affected 11/16 babies and this has been an almost constant finding in the *Unique* population. Babies with hypotonia tend to lie with their arms and legs loosely outstretched instead of bent at the knee or elbow. When held under the arms, their bodies easily slip through the hands. In the Segel group, the hypotonia resolved over time, but the pattern of resolution is not consistent: in some children it resolves with physiotherapy and maturity while in others it persists, making them highly dependent on standing and walking support to become mobile.

Using their hands: fine motor skills

Babies and children are expected to have immature grasping, holding and transferring skills. They benefit from early assessment and intervention by occupational therapy. Their immature hand use is one reason why they remain dependent on others for their personal care for an unusually long time. The evidence from *Unique* is, however, that hand use does improve with time and by adulthood individuals are able to play a limited part in daily living tasks such as feeding, personal care and dressing.

Learning

Children with a complete 12p duplication will benefit from considerable support with their learning. Delay is usually apparent by six months of age and early formal assessment and intervention at home, followed by placement in a nursery and later a school which can provide individualised support is usually the most appropriate course. In terms of formal academic skills, a small number of children may learn to read at a basic level and others may learn to use a simple computer switch but families usually find it more helpful to focus learning on personal independence and life skills. Overall, the expected level of learning disability is generally thought to be severe to profound but individual developmental quotients have ranged between 29 and 61 (Segel 2006; Stengel-Rutkowski 1981; Grace 1980; Uchida 1973; *Unique*).

Children with a partial duplication or a mosaic form may have a more moderate level of learning disability. Within *Unique*, one family has tried home-schooling (Back 1997; *Unique*).

“ He has a reasonable memory and is interested in what is happening round him. He doesn't read but can scribble ” - *full duplication, as adult*

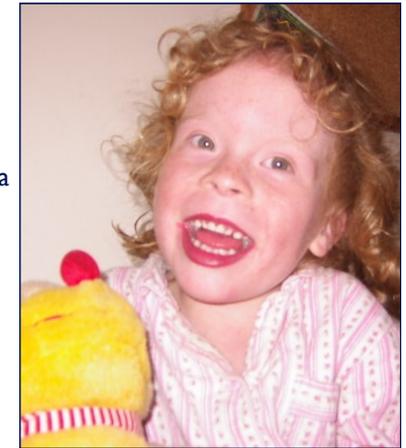
“ She adores books and reads at a learners' level. She won't hold cutlery or a pencil but clicks a computer mouse brilliantly and finger feeds with a full palm grasp ” - *duplication between p13.33 and p12.3, at 9 years*

Caring for your child with a 12p duplication

Children and adults with a 12p duplication are likely to have high-level care needs. In the Segel 2006 series, 10/16 were not toilet trained, and in five toilet training was achieved later than expected. The evidence from *Unique* confirms that toilet training occurs very late and may not be achieved even in adolescents and adults. Limited hand control and use means that despite being generally co-operative, children remain dependent for most if not all their daily care needs.

Key features

- Normal or high birth weight
- Relatively large head at birth (macrocephaly)
- Abnormal muscle tone. This may take the form of low muscle tone (hypotonia), making a baby feel floppy to hold, or high tone (hypertonia), making a baby feel stiff
- Somewhat unusual facial features
- Internal organs usually unaffected
- A degree of developmental delay
- Some learning difficulties or disability, ranging from mild to profound



How do we know about the effects of a 12p duplication?

The information in this leaflet is drawn partly from medical publications, including three significant reviews of duplication 12p: Stengel-Rutkowski in 1981; Rauch in 1996; Segel in 2006. In the Segel study, researchers from Boston, USA compared five people with a pure duplication of 12p, four people with a mosaic duplication of 12p, and seven people with a duplication of 12p as part of a more complex chromosome change. The first-named author and publication date of papers in the medical literature are given so that you can look for articles on the internet in PubMed. Many references in the medical literature include people who have a duplication of 12p as part of a more complex chromosome change that would be likely to affect the outcome, as in the third group of the Segel 2006 study. These cases are not included in this leaflet.

In this leaflet, we have included only people with a 'pure' 12p duplication with no other chromosome involved likely to affect the outcome. The leaflet also draws on *Unique's* database. When this leaflet was written, *Unique* had 37 members with a 12p duplication, of whom 11 had a 'pure' 12p duplication. The oldest member of *Unique* was 28 years old when this information was compiled and the oldest person reported in the medical literature was a man of 33 (Segel 2006).

Three groups

In all, we have gathered information on 40 people with a 12p duplication, from three groups. In **Group 1** are 22 people with a trisomy, a complete or almost complete duplication of the entire short arm of chromosome 12. In many cases, there is an additional chromosome change that involves the short arm of chromosome 13, 14, 15, 21 or 22 that is not expected to affect the outcome. In **Group 2** are nine people with a duplication of just part of 12p. The size of the duplication varies from very small to quite large. In **Group 3** are nine people with a mosaic form of 12p duplication.

How important is the amount of duplicated material?

The amount of duplicated material affects some aspects more than others. In terms of outcome, children with a smaller amount of duplicated material are believed to generally do better than those with a larger duplication. They appear to reach their developmental milestones earlier and their speech is more developed. They are also less likely to have seizures (Segel 2006; *Unique*).

The normal-to-high birth weight occurs regardless of the size of the duplication and most children have some of the typical facial features, whatever their duplication size. It's thought that the critical area for the facial features lies close to the tip of chromosome 12p in the bands between 12p13.2 and the end (Ausems 2004; Allen 1996; Rauch 1996).

Some people are found to have extra material from the long arm (12q) as well as the short arm. They seem to be much more likely to have particular birth defects, most obviously extra fingers or toes (polydactyly) (Allen 1996).

What is the difference between a child with a 12p duplication and one with Pallister-Killian syndrome?

Pallister-Killian syndrome is a disorder in which a proportion of the body's cells have additional chromosome material composed of two short arms of chromosome 12p. This means that the affected cells have four copies of 12p instead of three copies as in duplication 12p. As Pallister-Killian syndrome is a mosaic disorder, its effects can range from being scarcely noticeable to profoundly disabling. Generally speaking, children with a duplication of 12p are affected in similar ways to those with Pallister-Killian syndrome but somewhat less severely. All the same, the range of effects of a 12p duplication is also very broad. *Unique* publishes a separate leaflet on Pallister-Killian syndrome.

How many people have a 12p duplication?

12p duplications are rare. It's estimated that no more than one out of every 50,000 babies born will have a duplication of 12p (Allen 1996). Although only 40 people have been reported in the medical literature or registered on *Unique's* database, there are certainly many more people with a 12p duplication who haven't been diagnosed or who haven't been reported.

What is the outlook?

The outlook for babies with a 12p duplication does vary a lot between individuals. In most babies, the major internal organs are not affected and survival into adulthood is perfectly possible.



Speech appears to be more likely to develop among children with a partial duplication and first words in this group have emerged between 15 months and 2.5 years, with word-joining following 1-2 years later. Among those with a mosaic form, the picture is extremely variable, ranging from a mild speech delay to no speech use (Segel 2006; Rauch 1996; Guerrini 1990; *Unique*).

“ She uses 1-3 word utterances and though she has difficulties with w and l sounds, her speech is getting clearer as she is more persistent. She can be very repetitive with her language and questions and will keep asking and asking. There is a huge difference between her understanding and expression. She has a memory like an elephant ” - duplication between p12.3 and p13.33, at 9 years

Sitting, moving: gross motor skills

Babies and children are expected to be late to achieve their 'milestones' of sitting and walking. There is a range of eventual ability, however, with some children showing more obvious delay and others with very small duplications generally experiencing less delay. In general, babies who are only slightly late in acquiring head control and learning to roll over show similar delay in sitting and becoming mobile,



while babies who are more delayed early on tend to walk much later. The age at which babies and children become mobile varies widely: from three months to 18 months for rolling from side to side; from five months to 4.5 years for sitting and from 18 months to 10 years for walking. Some children adopt alternatives to crawling such as bottom-shuffling or walking on their knees. Most children do walk, but the Segel 2006 study showed that the mean first walking age was 4.1 years. A small number of children have not progressed to independent walking without a stander or walking frame, and have remained mobile with a buggy or pushchair.

Mobility is affected by abnormal muscle tone. Newborn babies are typically hypotonic (they have low muscle tone and feel floppy to hold) and many children or adults either have low tone (hypotonia) or more unusually high tone (hypertonia, they feel stiff and resistant to hold) (Stengel-Rutkowski 1981; Uchida 1973). The

Is hearing affected?

Many children develop glue ear, a temporary, fluctuating type of hearing loss caused by a build-up of fluid behind the eardrum and this means that hearing should be regularly monitored and treatment started early to maximise potential.

A permanent hearing loss is much less common and most often affects one side only (Kim 2006; Tekin 2001; *Unique*).

What about teeth?

Dental problems are commonly reported among *Unique* members and in the medical literature. The most typical challenge for children with a 12p duplication is a mismatch between the teeth in the upper and lower jaws, with the bottom teeth jutting out, making biting and chewing difficult. Other unusual findings have included late teething, both for milk and adult teeth, as well as teeth coming through in an unexpected order or being slow to fall out. In some children teeth have been irregularly positioned, in others very widely spaced; in one child the incisors and canines at the front of the mouth were in a straight line instead of curved as normal. In one adult, the teeth had a high level of decay (Segel 2006; Allen 1996; Suerinck 1978; Armendaris 1975; *Unique*).

This high rate of dental problems means that children are likely to need ongoing specialist dentistry from an early age.

“ We use double fluoride daily toothpaste and mouthwash daily with a toothbrush to control mouth and gum infections ” - adult

Are there people with a 12p duplication who have been healthy, have developed normally and completed their education without any major difficulties?

With the exception of a 15-month-old girl with an inserted duplication of 12p11.2 to p12.2, who so far has shown normal development with no evident physical or learning disabilities, everyone reported or described has needed support with their development, including those with a mosaic form of the duplication. Recently individuals with a mosaic form of tetrasomy 12p (Pallister-Killian syndrome) who are only very mildly affected have been identified (Genevieve 2003; *Unique*), and it is fair to assume that normal or near-normal development should theoretically be possible for some people with a mosaic form of 12p duplication. However, this has not yet been formally described, so we cannot be certain that it happens.

How may communication be affected?

The ability to speak and converse generally reflects learning abilities, so children who need greater learning support tend to be those who start speaking later and develop less complex language. Speech appears to be a particular area of delay among children with a 12p duplication and in a significant number of cases, speech does not develop. Children then express themselves with expressive vocal noises, babbling, gestures, pointing and in some cases a repertory of signs and pictures.

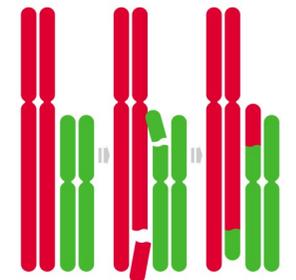
Where speech does develop, first words may not emerge until very late – the latest seen so far is 9 years – and families generally consider that understanding is well in advance of expression. In one adult who uses gestures, vocal noises and nodding for communication, understanding has been estimated at the level of a seven-year-old child.

How did the 12p duplication happen?

A blood test to check the parents' chromosomes is needed to find out why the 12p duplication occurred. Most 12p duplications are the result of a rearrangement in one parent's chromosomes. This is usually a change known as a **balanced translocation** in which material has changed places between chromosomes. As no material has been lost or gained, the parent usually has no difficulties with health or development, although they may have fertility or childbearing problems. Balanced translocations are not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers. The eggs or sperm of someone with a balanced translocation risk containing too much or too little chromosome material. With a 12p duplication, the eggs or sperm would contain too much chromosome material.

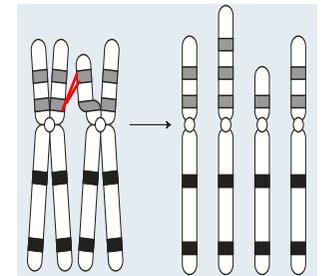
Some 12p duplications occur when both parents have normal chromosomes. The term that geneticists use for this is **de novo (dn)**. De novo 12p duplications are caused by a change that occurred when the parents' sperm or egg cells were formed or around the time of conception. We know that chromosomes must break and rejoin when egg and sperm cells are formed but this only occasionally leads to problems.

It's recently come to light that some de novo duplications of 12p may be caused by a mismatch between the chromosomes. This works as follows: at one point in the formation of the sperm or egg cells, all the chromosomes including the two chromosome 12s pair up and swap segments. To pair up precisely, each chromosome 'recognises' matching or near-matching DNA sequences on its partner chromosome. However, throughout the chromosomes there are many DNA sequences that are so similar that it's thought that mispairing can occur. The short arm of chromosome 12 contains three clusters of similar DNA sequences and it is quite likely that they can cause a mismatch (de Gregori 2005). Although no-one has ever seen this happen, it is believed that when the next step, the normal exchange of genetic material known as 'crossing over' occurs, after mismatching it is unequal, cutting out or doubling up a length of the chromosome. What is certain is that as a parent there is nothing you could have done to prevent the 12p duplication. No environmental, dietary or lifestyle factors are known to cause them. There is nothing that either parent did before or during pregnancy that caused the duplication to occur.



A balanced translocation

The eggs or sperm of someone with a balanced translocation risk containing too much or too little chromosome material. With a 12p duplication, the eggs or sperm would contain too much chromosome material.



One way that a deletion and a duplication could theoretically arise. On the left are two matching chromosomes, each split to the centromere and ready to pair and exchange segments. The shaded bars show similar sequences of DNA that enable correct pairing. But just above the centromere mispairing has occurred. When the chromosomes separate (right), the mispairing has given rise to two normal and two abnormal chromosomes, one with a deletion and one with a duplication.

Can it happen again?



If parents have normal chromosomes, the duplication is unlikely to happen again

The possibility of having another pregnancy with a 12p duplication depends on the parents' chromosomes. If both parents have normal chromosomes, the duplication is very unlikely to happen again.

If either parent has a balanced translocation involving 12p, the possibility is greatly increased of having other affected pregnancies. Parents should 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 very accurate, although not all of these tests are available in all parts of the world.

Babies at birth

Most babies born at term have a normal to high birth weight and only a few babies are small for dates. The range is 4lb 14oz/ 2.21 kg to 10lb 4oz/ 4.66kg.

Most babies have a high Apgar score (measure of well being) within five minutes of being born but breathing difficulties may occur and a low blood sugar (hypoglycaemia) may be found in the newborn period. In one study of 16 babies, 12 reported difficulties in the newborn period, including feeding difficulties in seven, a low blood sugar (hypoglycaemia) in five and transient diabetes mellitus in one, erratic breathing and turning blue (cyanosis) in two, a low body temperature (hypothermia) in two, a raised level of bilirubin and pulmonary hypertension (raised blood pressure in the arteries that supply the lungs) in one; duodenal atresia (the first part of the small bowel has not developed properly and stomach contents cannot pass through); and a broken collar bone in one (Segel 2006; Zumkeller 2004; Karki 1990; Stengel-Rutkowski 1981; *Unique*).

Umbilical hernia

This has been seen in 5/40 babies. It shows as a soft, skin-covered bulge at the umbilicus (navel, belly button) that can look bigger when a baby strains or cries. The bulge contains a small piece of abdominal lining and sometimes part of the abdominal organs. It is caused by incomplete closure of the ring of muscle that the umbilical cord passed through during fetal life. The hernia may be quite small and can be left to resolve naturally. Some babies have a very large hernia (2"/5cm across) or one that does not improve, in which case it can be surgically stitched in a small operation.

Minor genital anomalies

Boys with a 12p duplication appear to be at risk of having undescended testicles (cryptorchidism), with 6/15 affected. Treatment for undescended testicles depends on the suspected cause but whatever the cause, treatment is usually needed if the testicles

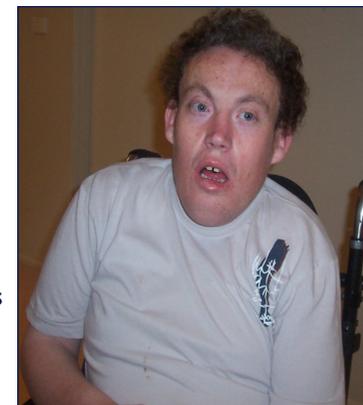
should and the heart has to work too hard. It can be closed using minimally invasive surgery. In this instance, the baby was treated with medication. A second baby was born with a weakness in the tricuspid valve that regulates blood flow between the upper and lower chambers of the right side of the heart and a patent foramen ovale (an opening between the two upper chambers of the heart that does not close soon after birth, as expected. When it remains open, extra blood passes from the left to the right side of the heart) (Rauch 1996; Biederman 1977; *Unique*).

Puberty

Puberty in boys occurred somewhat later than usual (14-21 years) (Segel 2006).

Outlook

Of the 40 people we know about with a pure 12p duplication, only five are adults, aged up to 33 years (Segel 2006; Karki 1990; Suerinck 1978; *Unique*). The total is small largely because the technology for identifying chromosome disorders is relatively new and adults would not necessarily have been tested. The tiny number makes it difficult to predict the outlook for babies born with the disorder. In general, most babies born without major abnormalities of the internal organs do have a better outlook. Just one early death in childhood has been described, of a girl with an ovarian tumour (Parslow 1979). Life expectancy has been suggested to be similar to Down's syndrome (Allen 1996). In the Segel 2006 study, it was noticed that 2/3 adults reported early greying of the hair.



Are there any effects on eyesight?

Vision and the functioning of the eyes appear to be commonly affected, with a problem needing attention in 16/30 children. The most common problems are nystagmus (uncontrolled movement of the eyes, often from side to side. Most people with nystagmus have reduced vision. While nystagmus cannot be cured, there are several treatments that can help) and strabismus (a squint, for which treatment depends on the cause but can include patching the stronger eye, exercises, glasses to correct a focusing error such as long sight and surgery to realign the muscles that hold the eye in place). A number of children appear to have immature vision and have needed expert vision teaching; at least one is known to have visual processing problems, where the eye sees but does not interpret correctly. Focusing errors such as long or short sight and astigmatism, where the front of the eye curves in a way that makes objects appear blurred, have also been found. As well as these problems with vision, eyelid problems including microblepharon (see: *Babies at birth*) and ptosis (a droop of the upper eyelid) have been observed (Segel 2006; Rauch 1996; Stengel-Rutkowski 1981; *Unique*). This high rate of vision problems means that parents should be alert to their child's possible difficulties and children should be regularly screened.

diuretic hormone (vasopressin) is produced or the body is unresponsive to it (Rauch 1996); mitochondrial dysfunction, successfully treated with Coenzyme Q10 supplements (Segel 2006); and moyamoya disease, in which the walls of the internal carotid arteries that supply blood to areas of the brain become thickened. This slows blood flow to the brain, increasing the likelihood of blood clot formation which can lead to strokes and transient ischaemic attacks (Kim 2006); one child developed an ovarian tumour from which she died (Parslow 1979).

■ Seizures

While it seems that most children with a 12p duplication are not affected by seizures, a minority (9/38) are. Seizures can take a fairly benign form and are usually well controlled with anti-epileptic medication. Children with a mosaic form may possibly be less vulnerable and those with a partial duplication are less likely to develop seizures at all (Segel 2006; *Unique*). Children who did not have breathing problems as newborn babies and who have a structurally normal brain are also likely to be relatively protected against a seizure disorder (Kim 2006; Elia 1998; Guerrini 1990).

Various different types of seizure have been described, including generalised seizures (involving both sides of the brain) of various types, including clonic spasms (repeated, rhythmic muscle contractions causing the limbs or whole body to twitch or jerk); myoclonic seizures (sudden, jerky contractions, usually in the arms or legs, lasting at most a second); as well as febrile seizures (triggered by a sudden rise in body temperature, often during an infection) (Kim 2006; Guerrini 1990; Stengel-Rutkowski 1981; Kondo 1979; Parslow 1979; Serville 1978; Biederman 1977; *Unique*).

Children who have experienced seizures will have an EEG (electroencephalogram, a test to record and measure the tiny electrical signals in the brain). Certain electrical patterns ('generalised spike and wave discharges') may possibly be typical of epilepsy in children with a 12p duplication, but this is not yet certain. The discharges occur against relatively normal or slightly slow background activity (Elia 1998; Guerrini 1990).

■ Brain

Various different anomalies have been found including enlargement of the ventricles, the fluid-filled spaces within the brain; a build-up of fluid within the brain; reduction in brain size relative to head size and in the white matter in the brain; absence of the corpus callosum (the band of nerve fibres that connects the two hemispheres of the brain) (Elia 1998; Allen 1996; Rauch 1996; *Unique*). While it is true that more children who have a structural brain anomaly develop seizures, not all do. Some children who develop seizures have structurally normal brains.

■ Heart

The great majority of babies and children were born with a structurally normal, healthy heart. In a small minority (2/40) a significant problem was found, including a newborn baby who was born with a persistent ductus arteriosus. This is a channel between the aorta and the pulmonary artery that takes blood to the lungs which usually closes shortly after birth. When it stays open, the lungs receive more blood than they

do not descend naturally in time. If a hormone problem is suspected to be the cause, a short course of hormone treatment may be suggested. Otherwise, or if hormone treatment does not work, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy.

Eyelids

Two babies have been described who couldn't close their eyes while asleep because the eyelids were too short (microblepharon), needing treatment with eye drops and ointment with the possibility of reconstructive surgery later. The eyelids start to form as folds in the fetus at around seven weeks gestation. Disruption of the development of the eyelid folds leads to anything from absent eyelids to mild microblepharon. Overexpression or disruption of a gene in the duplicated region could have caused this problem (Tekin 2001; *Unique*).

Babies' appearance



Babies and children with 12p duplications may have unusual facial features or their face may have unusual proportions, making your child stand out from the rest of your family. You may also find that your child looks surprisingly like other children with a 12p duplication or those with Pallister-Killian syndrome. Particular features common among other children with duplications of 12p are a relatively large box-shaped head, a long face with a high, prominent forehead with a high (receding) hair line, wide irregular eyebrows, small openings for the eyes, widely spaced eyes sometimes with a skinfold across the inner corner, a short nose with a broad, flat bridge and upturned nostrils, a long groove between the nose and

the upper lip, a thin upper lip and a pushed-out lower lip, a wide mouth and a prominent chin that becomes more obvious with age. The prominent chin and large lower face have been described as like an hour-glass and contribute to a characteristic wide-mouthed smile. A few babies and children have an unusually large tongue (macroglossia), but this is more typical of Pallister-Killian syndrome (Segel 2006; Rauch 1996; Stengel-Rutkowski 1981; Grace 1980; Alfi 1977).

Some babies have a protruding abdomen and extra nipples have occasionally been seen, although not in babies with a partial duplication (Back 1997; Allen 1996; Rauch 1996; Stengel-Rutkowski 1981). Another unusual feature seen is a hollowed chest (pectus excavatum) (Tayel 1989).

Hands

Your baby or child's hands may look slightly unusual. Both the palms and the fingers are sometimes relatively short and broad, but even stubby or stocky fingers may taper towards the tips. You may find unusual hand creases or a single crease instead of two across the palm and if you look at the back of the hands, you may notice dimples or furrows over the knuckles. The little fingers typically curve inwards. More obvious anomalies, such as extra fingers (or toes) are seen occasionally but more commonly when part of the long arm is also duplicated (Kim 2006; Back 1997; Allen 1996; Rauch 1996; Alfi 1977; *Unique*). Other occasional unusual aspects include tiny nails on the little fingers (de Gregori 2005) and overlapping fingers (Kondo 1979; Suerinck 1978).

Feet

Quite a few babies and children have unusually formed or angled feet. Most typically the big toe and other toes point towards the outside edge of the foot (valgus). When your child starts to put their feet flat on the ground and to walk, you may notice a clearly flat-footed gait (pes planus) (Ausems 2004; Allen 1996; Rauch 2006; *Unique*). If your child does show these features, s/he will be regularly assessed and splints, supports, insoles or support boots provided to improve their gait. Other unusual aspects seen in individual children include a double big toe with a double nail (Rauch 1996); a wide 'sandal gap' between the big toe and the second toe (Dallapiccola 1980); and upturned big toes (Tenconi 1977; Armendaras 1975).

Feeding



Babies are typically big at birth but then have feeding difficulties and may 'fail to thrive', leading to relative weight loss (Rauch 1996). In some babies, breastfeeding is possible but where sucking is inefficient, using a variable-flow teat or a feeder suitable for babies with a cleft palate (split in the roof of the mouth) usually helps. Some babies need to be fed by nasogastric tube for a while until they have matured enough to control their own

sucking and swallowing and occasionally babies need to be fed through a tube direct into the stomach (a gastrostomy or G-tube) for a while. Some babies experience gastro-oesophageal reflux (the contents of the stomach return up the food passage) and may need treatment with prescribed medication or milk to help keep stomach contents down.

Moving on to textured and solid foods and weaning usually occur somewhat later than in other babies and some families retain their baby's bottle well into childhood to ensure a high enough fluid intake.

Constipation is probably more common among children with rare chromosome disorders than in other children and has been seen in children with a 12p duplication. Some reasons are obvious: fluid intake may be low, children with a small appetite may find it hard to take enough high-fibre food; and activity levels may be lower than in other children. In at least one child, constipation improved when treatment for an underactive thyroid was started (see below: *Health in childhood*). Malabsorption has also been seen but it is not certain whether this was due to the 12p duplication or not.

Growth

The conventional view is that growth is normal in babyhood and childhood although the head is disproportionately large (Allen 1996). In reality, the picture is more

individualised: out of 21 children and adults for whom growth data are available beyond the age of two years, 14 showed a normal growth rate, with final heights similar to others with no chromosome disorder. By adulthood, 3/3 adults were of normal height or taller (Segel 2006). However, around one third of the children were unusually short when measured between babyhood and 12 to 14 years of age and one family commented that their child's short stature was caused by having short limbs. Children showed a general tendency to be well-built, muscular and even overweight, with weights high relative to their heights that persisted into adulthood, although one child with a duplication of the tip of the chromosome was described as 'slight' (Segel 2006; Stengel-Rutkowski 1981; Uchida 1973; *Unique*).

“ Very stocky and solid ”

Health in childhood

■ Coughs and colds

There is a distinct possibility that the common cough-and-cold type infections of childhood are both more common and in some more severe in children with a 12p duplication. These upper respiratory tract infections appear to be more common and severe among children with any chromosome disorder, so this effect may not be specific to a 12p duplication. In one study, seven out of 16 young children had repeated coughs, colds and ear infections. Many needed fluid removed from the middle ear and grommets (tubes) inserted into the eardrum to aerate the middle ear (Segel 2006). In a few children common coughs and colds turned rapidly into emergencies needing hospitalisation, so that parents had to be constantly vigilant. *Unique* cases show that other infections were also common, including in individual cases urinary tract and eye infections. By mid-childhood, from around eight years, the frequency of infections lessened.

A small number of children (4 out of 20) developed more serious chest infections and in one or two children these were recurrent.

“ Frequent infections to the age of 22 but he is now like the rest of the family ”
- 28 years

“ Good immune system but can't blow her nose well so swallows phlegm and then vomits it back ” - 9 years

“ Generally happy and healthy other than the usual coughs, colds and tummy upsets ”- 3 years

■ Hypothyroidism

An underactive thyroid was found in 3/40 babies or children (Zelante 1994; *Unique*). The thyroid gland in the neck produces a hormone (chemical substance) called thyroxine needed for normal growth and development. If the thyroid gland does not produce enough thyroxine, hypothyroidism will result. It is treated by taking medication that replaces the thyroxine the body cannot produce.

■ Other conditions

Among the conditions that individual children developed, where it is uncertain whether or not they are related to the 12p duplication, are: diabetes insipidus, a condition in which large quantities of urine are passed because too little anti-