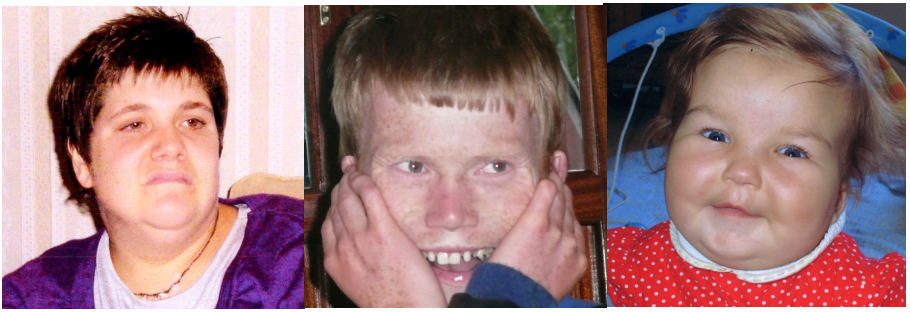
Understanding chromosome disorders

Unique

Duplications of 2p



rarechromo.org

❝ She made me re-evaluate my life. Nearly losing her made me realise how important my kids and family are. I stopped work. I do not want to miss a minute of my kids' lives.

❝ He has a lovely smile and has taught us not to be selfish and to count our blessings.

Duplications of chromosome 2p

A duplication of 2p means that the cells of the body have extra genetic material from one of their 46 chromosomes – chromosome 2. For healthy development, chromosomes should contain just the right amount of genetic material (DNA) – not too much and not too little. Like most other chromosome disorders, having extra material from chromosome 2 can increase the risk of birth defects, developmental delay and learning difficulties. But the problems vary and depend very much on what extra genetic material is present and how much.

Chromosomes and genes

Chromosomes are structures found in the nucleus of the body's cells. They contain thousands of genes which themselves contain all the genetic information the body needs to develop, grow and function. Chromosomes (and genes) usually come in pairs, with one chromosome from each pair inherited from each parent. Humans have 23 pairs of chromosomes, giving a total of 46 individual chromosomes.

Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest, so chromosome 2 is the largest chromosome but one. Each chromosome has a short or petit (p) arm (shown at the top in the diagram on page 3) which is joined to a long (q) arm (the bottom part of the chromosome) at a point known as the centromere.

People with a duplication of 2p have one intact chromosome 2, but there is an extra piece of the other chromosome 2. The piece can be added to the short arm of chromosome 2 or to a completely different chromosome. If it's on chromosome 2, the chromosome has often broken in two places and the extra piece has inserted itself into the gap before the 'sticky' broken ends have rejoined. Sometimes there is only one break, with the extra bit of chromosome 2 added onto the end of the chromosome. Having the extra bit of the chromosome means that extra numbers of some genes are present, giving a third copy instead of the normal two copies. It is believed that most people's clinical difficulties are probably caused by having this third copy of a number of genes. But a child's other genes, environment and unique personality also help to determine their future development, needs and achievements.

If the extra piece is material closer to the centromere, the duplication is called proximal. If it is closer to the tip of the short arm of the chromosome, it is called distal. Occasionally the extra piece is present in some cells, while others have normal chromosomes. It is then called mosaic.

The first published report of a person with a pure duplication of 2p - that is, without any other chromosome change - was in 1973. There have since been only around 25 cases reported in the medical literature worldwide, so reported cases are very rare. Naturally many people have duplications that go unreported.

Looking at the short arm of chromosome 2 (2p)

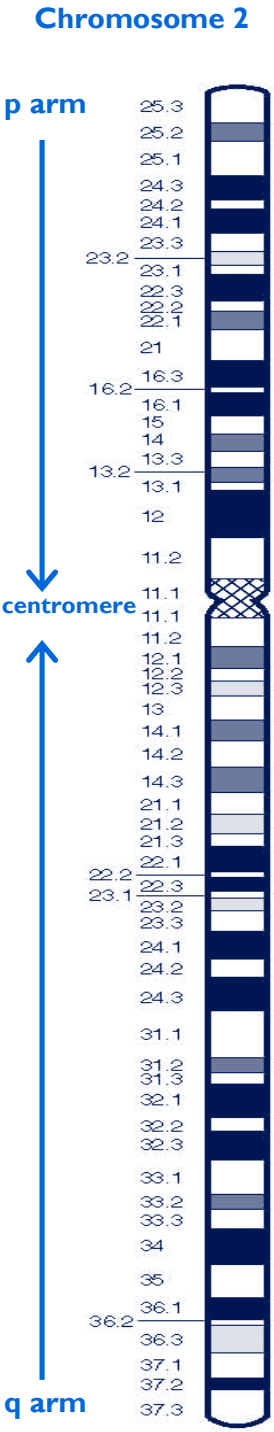
Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, it is possible to see that each one has a pattern of light and dark bands. In the diagram on the right you can see that the bands are numbered outwards from the centromere.

By looking at your child's chromosomes in this way, it is possible to see the point (or points) where the chromosome has broken and to see what extra material there is, if the extra piece is large enough. If the amount of extra material is quite small, this type of routine analysis will not show it or it will not be clear which chromosome the extra material is from or where the chromosome has broken. A duplication so small that it can't be seen down a microscope is known as a microduplication.

New, more sensitive molecular techniques such as fluorescent *in situ* hybridisation (FISH) or array comparative genome hybridisation (array-CGH, also known as microarrays) may be needed to confirm or detect the 2p duplication. These techniques may also be needed to detect another chromosome change such as a small 2p deletion occurring close to the duplication.

Sources and references

The information in this leaflet is drawn from what is known about around 43 babies, pregnancies, children and adults with a duplication of chromosome 2p. Knowledge is still limited, as overall numbers are very small, most reports are of individuals each with different and sometimes uncertain breakpoints and the oldest individuals were in their thirties when described. Around 25 people have been now been described in the medical literature with a pure duplication of material from 2p without loss or gain of material from any other chromosome arm or with the change known as an inverted duplication with deletion of 2p (inv dup del 2p, see page 5). The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (at www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain most articles from *Unique*. The leaflet also draws on *Unique*'s database. When this leaflet was written, *Unique* had 11 members with a pure duplication of 2p or inv dup del 2p.



The karyotype

Your genetic specialist can tell you more about the extra chromosome material. You will almost certainly be given a karyotype, a way of describing how chromosomes look. This usually shows the bands where the chromosome has broken and rejoined. Depending on the technique used to find your child's chromosome duplication, the karyotype sometimes shows whether particular genes are present in extra numbers.

46,XX,dir dup(2)(p25.1p25.3)dn

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XX for females; XY for males
dir dup	A direct duplication, or there is extra material running in the same direction as the rest of the chromosome arm
(2)	The duplicated material comes from chromosome 2
(p25.1p25.3)	The chromosome has broken in two places. The first break is at p25.1 and the second at p25.3 so these are the ends of the extra section
dn	The duplication has occurred de novo or as a 'new event'. The parents' chromosomes have been checked and no duplication or other chromosome change found at 2p25. The duplication is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child (see page 19)

As well as a karyotype or instead of one, you may be given the results of a molecular test such as array-CGH for your child. The results are likely to read something like the following example.

46,XY,add(2)(p16.2p12).arr cgh 2p16.2p13.1(RP11-652E20->RP11-16E12)x3dn

46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes, XX for females; XY for males
add	There is additional material
(2)	The additional material comes from chromosome 2
(p16.2p12)	The chromosome has broken in bands 2p12 and 2p16.2
.arr cgh	The analysis was by array comparative genome hybridisation (CGH)
(2p16.2p13.1)	This more precise analysis showed two breaks, one in band 2p16.2 and the other in band 2p13.1
(RP11-652E20->RP11-16E12)x3dn	This shows the part of the chromosome that is present in three copies instead of the usual two. The extra part includes two DNA markers, RP11-16E12 and RP11-652E20

Is there a 2p duplication syndrome?

There are many references in the medical literature to a 2p duplication syndrome or trisomy 2p syndrome but it is uncertain that this syndrome actually exists. It was first described in 1978 and summarised again in 1995 but was based almost entirely on descriptions of mostly babies and young children with other chromosome changes as well as the 2p duplication (Francke 1978; Lurie 1995). The first child with a pure 2p duplication was described in 1973 but pure duplications are still much rarer than duplications of 2p together with a deletion from a different chromosome arm.

One reason for this rarity is that before the mid-1990s, chromosome changes could only be identified by magnifying pre-stained chromosomes under a microscope and

looking for alterations in size and the expected banding pattern. This was inexact and missed small and subtle changes. Today's more sensitive molecular genetic techniques including FISH and microarrays give a more precise diagnosis. But so far, no paper has summarised features of a 2p duplication syndrome based on people diagnosed using these new techniques. All the same, in 2000, Aviram-Goldring tabulated the features found in 17 people with a pure 2p duplication. The age range is narrow, only up to seven years old. But the most common features found were: a low birth weight; developmental delay; unusual facial features; some visual disturbance. Minor genital anomalies were common in boys; around half the babies had a hole in the heart and one in three had some unusual feature of the lungs. In people with a tiny duplication near the end of the short arm taking in only the 2p25 bands, difficulties are more likely to be limited to developmental delay and typically long, thin fingers that may become more obvious with time (Stalker 2000; Roggenbuck 2001).

Inverted duplication of 2p with deletion of the tip of the short arm

Recently a very small number of children and an adult have been described with a specific rearrangement of their changed chromosome 2 that is known as inverted duplication and deletion of 2p, or inv dup del 2p. The extra part of 2p runs in the opposite direction to the rest of the chromosome, so it is called inverted. There are only five reports of children, one of an adult and two from *Unique*, so very few in all. On pages 17-18, you will find a summary of what is known about this disorder (Aviram-Golding 2000; Thangavelu 2004; Gruchy 2007; Bonaglia 2008; Kochilas 2008; *Unique*).

How many people have a 2p duplication?

No one really knows. The small number of reports in the medical literature suggests that 2p duplications are very rare but it's likely that many people are not diagnosed and many cases go unreported.

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

The first signs vary considerably depending on the impact of the duplication on the baby's development. In a few cases, the duplication appears to affect the development of the brain and nervous system and the first signs are a high alpha-fetoprotein (AFP) level at 15-20 weeks of pregnancy (Thangavelu 2004). In other cases an early pregnancy scan shows an increase in the pad at the back of the neck (Aviram-Golding 2000). Other babies don't grow well in the womb and sometimes an ultrasound scan reveals further problems (Siffroi 1994; Pipiras 2004). Among *Unique* babies, many families knew immediately from birth that something wasn't quite right. Some babies have an obvious birth defect, such as a cleft palate, a hernia or a heart problem, but others just found feeding and breathing difficult. Facially, some babies also looked a little unusual. In some children the disorder did not become apparent until later when developmental milestones were missed.

❝ She looked premature. Her voice was so small, you could hardly hear her cry.

❝ Within 36 hours her rapid breathing, weak sucking, cyanosis and failure to feed were noted.

❝ As our fourth child, we knew immediately at birth all was not right, even when the medical people said otherwise. But it still took until he was three to get a diagnosis.

❝ Our health visitor noticed she wasn't focusing properly when she was six weeks old.

Pregnancy

In around half of the 17 pregnancies described in the medical literature or to *Unique*, everything went normally. Common pregnancy complications such as spotting in the first three months were observed in three pregnancies and one mother noticed less fetal movement as the pregnancy progressed. Premature contractions threatened one pregnancy but only one baby was born early, at 37 weeks. One mother developed pre-eclampsia and was carrying a very large quantity of amniotic fluid. *Unique* mothers reported that their dates were frequently queried as the baby seemed unexpectedly small. In one case the placenta was also noted to be small (Say 1980; Fineman 1983; Fryns 1989; Al-Saffar 2000; Ishikawa 2002; *Unique*).

Your baby at birth

Some babies - but certainly not all - were small and light for dates, looking like a premature baby despite their maturity. The average birth weight at term of 22 babies was 2.727kg (6lb), the smallest weighing 1.45 kg (3lb 3oz) and the largest 3.45 kg (7lb 10oz).

A baby's condition at birth is determined largely by their underlying problems. Some babies have good Apgar scores – the Apgar score is a measure of wellbeing on a scale of 0 to 10. They may be a little quiet and sleep a lot but feed adequately. Other babies have much more marked feeding problems and those with a heart problem may turn breathless and blue as they try to feed. Some babies have difficulty breathing at a steady rate and they may well need to stay in special care for some days or weeks as do babies with additional problems (Say 1980; Fryns 1989; *Unique*).

Will my baby or child look different?

You may notice that your baby has some unusual facial features. You may notice some similarities with pictures in this leaflet. But any similarities can be quite subtle and overall your child will also look like other members of your family. Among the features that geneticists have commented on are a large, high or prominent forehead; widely spaced eyes; a low bridge to the nose; ears that are slanted backwards and set below the eye line on the side of the head; and a small, triangular mouth with a fine upper lip. Young babies sometimes have a very small chin and lower jaw but this tends to become less obvious with time (Aviram-Golding 2000; *Unique*).

Hands and feet

Your baby's hands and feet may look just like any other baby's. But you may also notice that they are rather short or that their thumbs are placed closer to the wrist than is usual, that the big toes are short and broad or there is some webbing between some of the toes. All of these features are more common when the duplicated part of chromosome 2p is proximal (nearer to the centromere) but they don't affect every baby. When the duplicated part is distal (nearer to the tip of the short arm), you may notice that your baby's fingers and toes are unusually long and thin. They may also be very flexible and one *Unique* family commented on slight dents in the middle of the nails (Aviram-Golding 2000; *Unique*).

These differences are not serious and will not in themselves affect the way your child uses their hands or feet.

Is there a typical growth pattern?

Babies and children with proximal duplications appear likely to grow very slowly, so that they are among the shortest three per cent or even the shortest one per cent of the child population for height. Their slow growth may be so marked that growth hormone levels are checked but abnormalities have not been found. Despite this, some children have been treated with synthetic growth hormone. Despite treatment, short stature remains and they are likely to be much smaller as adults than the rest of their family.

Some children with distal duplications are also short, with a thin, frail physique. But this is not universal: other children grow slightly slower than others but achieve a normal adult height for their family.

There is no simple relationship between size at birth and growth afterwards: some babies are born small and remain short, while others catch up. Among babies who are born a normal weight and length, some continue to grow normally, while in others the growth rate drops off during childhood.

❝ He looks quite frail and very slim and is probably a little short for his age - *2p21p23 duplication, 13 years*

❝ Her height and weight as child were average. As an adult, she is a little shorter than her sister - *2p24p25 duplication, 30 years*

What about food and eating?

Early difficulties with both sucking and swallowing are common but do not affect every baby. In particular, babies with a distal duplication from 2p24 or 2p25 have been able to breastfeed well and to meet their own nutritional needs (Roggenbuck 2001; *Unique*). Other babies are likely to need feeding support. Some find breastfeeding too effortful and lose weight but suck well when given expressed breast milk from a bottle. Others take only small amounts from a bottle and need additional high calorie formula to promote growth.

Where feeding difficulties are severe, babies can be helped by direct feeding by tube through the nose or in some persistent cases by gastrostomy tube direct into the stomach. In *Unique*'s experience, this has been necessary where there is an additional problem such as cows' milk intolerance or a bowel problem (*Unique*).

Some babies also experience reflux, in which feeds and stomach contents return up the food passage (oesophagus) and may be vomited or inhaled, causing chest infections known as aspiration pneumonia.

Careful feeding and positioning both for feeds and sleeping, the use of feed thickeners and medications prescribed to inhibit gastric acid may control reflux. If these measures are not enough, an operation called a fundoplication can be performed to improve the function of the valve from the stomach to the food passage.

Weaning is likely to present a challenge to babies who found milk feeding hard work.

They may show little interest in solid food and need much longer than typically developing babies to learn new tastes and textures and to get used to chewing. Most children with chromosome disorders need their food puréed, mashed, chopped or cut up for longer than other children.

Constipation appears to occur more commonly than in other children and if it is not possible to give extra fluid or high fibre foods, prescribed medication may be needed.

Development

Most babies and children show a degree of developmental delay and benefit from early intervention with stimulation and play schemes. The extent of any delay varies from child to child and it is better to let your child show their own pace of development than to try to predict it in advance. Your children's centre, developmental paediatrician, opportunity playgroup, portage scheme and health visitor are resources you can turn to for ideas on suitable stimulation.

How will a child's ability to learn be affected?

Children with a 2p duplication can be expected to need support with their learning but the amount of support can't be predicted just from the karyotype. Information from the medical literature is sparse, but evidence from *Unique* suggests that while a few children start their education in a mainstream (regular) school with 1:1 help, most make better long term progress in an environment that caters for their special needs. Those with a proximal duplication are especially likely to need extensive support but even among children with a distal duplication there are some who need very considerable support as well.

In a few children, the ability to learn is affected to a more moderate degree and some children within this group will learn some academic skills such as drawing, reading or writing. For all children, however, the focus will be on learning the skills that will make their life richer and more enjoyable. Children often learn well through music and may retain a tune better than words or recall words within a tune. Some children have a better visual memory and remember faces well or familiar scenes in films or videos. Most enjoy social interaction and this can help their learning. As a broad generalisation - and there are exceptions - both children and adults enjoy looking at pictures and magazines and listening to music.

Some children will benefit from particular teaching programmes suitable for youngsters with learning difficulties and other conditions, such as autism. One family found the TEEACH system helpful; in other contexts, families have found Applied Behaviour Analysis (Lovaas); the Son-Rise programme; and EarlyBird programmes helpful. These programmes can call for a considerable commitment from families who are recommended to research them thoroughly in advance. (Stoll 1974; Sawyer 1994; *Unique*)

❝ She seems to be able to reason and do basic problem solving - *2p12p16.1 duplication, 2 years*

❝ She learns best when she's interested and by repetition and is good at remembering what happens next in videos - *2p21p24 duplication, 6 years*

❝ He has a very good long term memory and learns best in a small class with 1:1 teaching, a quiet room and no distractions - *2p21p23 duplication, 13 years*

❝ He's currently at a college for young people with profound communication disorders following programmes on living skills and communication. He recognises or remembers familiar people, places and situations but could not, for example, find his own way home. He enjoys people watching and travelling by car or bus - *mosaic 2p13p21 duplication, 22 years*

❝ She reads her name, advertisements and simple signs but doesn't write or draw. She knows a lot of songs and poems by heart – but has especial difficulty in understanding time - *2p24p25 duplication, 30 years*

How will communication be affected?

Children will generally be slower to understand and express themselves in speech than typically developing children. Instead, they communicate through vocal sounds, facial expressions, gestures and to some extent babble. It is *Unique*'s experience that most children, although not all, do acquire some speech although the range of eventual fluency is very broad, from limited words and phrases to speech in full, clear sentences. The age at which first words have emerged ranges from 1 to 4 years but in some children they may emerge even later. When words do emerge, they may not be clear because children can muddle or leave off certain sounds. Speech and language continue to develop with vocabulary widening into adulthood. Many children appear to understand language better than they can use it but in others, with more fluent speech, the reverse can be true. Two people with a small distal duplication have echolalia, where they repeat or echo what another person has said, immediately or hours, days or weeks after the words or phrases were originally heard.

Early speech and language intervention is very helpful and individual children have been greatly helped by learning to use objects of reference and picture exchange systems or mastering a signing system to express their wishes and needs (Fineman 1983; Fryns 1989; Roggenbuck 2001; *Unique*).

❝ She can laugh, use vowel sounds and some gestures, especially if she wants to be picked up - *2p12p16 duplication, 2 years*

❝ She understands most speech but can only say the odd word. She will say words and then not again for ages - *2p21p24 duplication, 6 years*

❝ His speech is good and clear and he speaks in full sentences but he can lack some understanding - *2p21p23 duplication, 13 years*

❝ We are certain she understands and knows more than she can express. She spoke her first words at three, and was using 2-3 word phrases by the time she was 10. As an adult she has acquired more speech - *2p24p25 duplication, 30 years*

Sitting, moving: gross motor skills

The milestones of gaining head control, rolling over, sitting and becoming mobile are very likely to be delayed, in some cases quite markedly so. This means that babies and young children will benefit from early physiotherapy to promote their body control and mobility. They will make progress, but it will be slower than in typically developing babies and crawling may not occur.

Many babies have a degree of low muscle tone (hypotonia, causing floppiness), but muscle tone may also be raised and some joints may be contracted.

In *Unique*'s experience children with a proximal duplication become mobile in their second or third years and learn to sit unsupported at around this time, although it may be even longer before they master the technique of moving from a lying position to sitting up. They may at first move in unconventional ways, by 'barrel-rolling', scooting, shuffling on their bottom or by creeping on their stomach ('commando crawling'). Standing unsupported tends to develop later and some children need a standing frame to practise being upright and a walker while they learn to take steps.

One child, now an adult, learned to walk shortly before his fifth birthday and was climbing stairs soon after that, although he has not mastered climbing a straight ladder, for instance out of a swimming pool. He walks with his knees bent, due in part to tight hamstrings and tires quickly, so is inclined to drop to the floor after a short distance. Supports did not help to straighten his knees and he stopped wearing them without any harmful effects when he was 18. Today, as an adult, he walks indoors but uses a wheelchair out of doors (Fryns 1989; *Unique*).

Some children with a distal duplication developed more quickly in terms of body control and mobility, while in others the pattern was similar or occasionally even more markedly delayed than that seen in children with a proximal duplication. One child was sitting by 10 months and walking by 17 months and others also started walking around the middle of their second year or soon after.

Babies and children have had access to physiotherapy (physical therapy) but the level of provision did not meet all families' needs. At least one family found it necessary to enrol their child on an intensive private therapy programme before he started walking. In addition to regular physiotherapy, families of more mobile children found therapies such as horse riding and swimming helpful in improving balance, range of movement, strength and confidence. Families also had access to occupational therapy but some said that getting appropriate equipment was hard (Therkelsen 1973; Stoll 1974; Fineman 1983; Parruti 1989; Mégarbané 1997; Roggenbuck 2001; Ishikawa 2002; *Unique*).

❝ When she achieves something she is so pleased with herself, it makes us happy *- 6 years*

❝ He moves around like any other child but with poor coordination. He's especially good at swimming *- 13 years*

❝ She can throw a ball and catch one better than one would expect *- 2p24p25 duplication, adult*

Behaviour

Unique has fairly detailed information on the behaviour of six children or adults with a 2p duplication. There is also a brief description of one child in the medical literature (Sawyer1994; *Unique*). The number is too small for a definitive picture to emerge but the remarks that follow may give families helpful insights.

Families most often mention their child's friendly, outgoing disposition. Some children interact well with both children and adults, while others prefer adults and one teenager specifically prefers the company of children a year or two younger than himself. One young adult, by contrast, does not interact much with others unless he wants something. Although many children do show some aggressive behaviour typical of toddlers (biting, pinching, slapping, tantrums etc), this is usually a passing phase and can be minimised by avoiding frustrating situations and employing distraction techniques and controlled by clear, consistent discipline. However, challenging and obstinate behaviour emerged in one young man at puberty and a deterioration in behaviour marked the onset of puberty in another adult. One adult has a pattern of behaviour where she starts the day cheerful and friendly but later on becomes aggressive, loud, introverted or unresponsive. Her moods can change suddenly. One young child with a proximal duplication has an intense dislike and fear of crowded spaces and reacts by screaming or growling. When upset or frightened, she can hold her breath until she passes out.

In general, children are at risk for hard-to-handle behaviours and families should have early access to behavioural management or family therapy support.

Unique has no experience of children or adults with psychiatric disorders but an adult with a 2p21p22 duplication and a moderate learning disability described in the medical literature was prescribed methylphenidate (Ritalin) as a schoolboy for inattention and impulsive behaviour and as a 14-year-old had suicidal thoughts (Sawyer1994).

Children enjoy watching others play, playing with musical toys, favourite TV programmes and videos, going for rides and outdoor activities. Common interests frequently also include social activities.

Sleep problems are common but not universal: young children may find falling asleep difficult and need a parent to lie with them while they fall asleep. Sleep disturbance occurs and some children are light sleepers or wake at night after wetting the bed, having a bad dream or night terror or when their routine is disturbed and need firmly but carefully settling to sleep again. Others regularly stay awake for hours at night. *Unique*'s experience is that it is important for the family's wellbeing to seek a cause for sleep disturbance and have a staged management programme that includes support for the parents and respite care.

❝ Her behaviour is challenging: she throws a lot and kicks. She is then disciplined and told that she must go in the special chair to calm down - *2p21p24 duplication, 6 years*

❝ He loves to help other people to the best of his ability. A very loving child who likes watching TV, walking the dog with his dad, swimming, playing on his Nintendo and computer games. He likes board games but can't concentrate for too long - *2p21p23 duplication, 13 years*

❝ He is inclined to wake early from about 3.30am, especially if his routine is changed. He stays in his bedroom with the door closed and usually returns to bed and to sleep - *adult*

Personal care and skills for living

All children appear to experience some delay in controlling their hand use and this may be considerable. Recurring themes in parental reports are poor coordination, a weak hand grip and a delay in developing a pincer grip and holding objects. Small children find even manipulating toys a challenge but with consistent training, the right implements and prompting may achieve some feeding skills - such as holding a double-handed cup - and cooperation with dressing. Undressing comes before dressing and finger foods before the use of spoons and other cutlery. Progress is always possible: one youth learned to use a spoon at the age of 19. Individual children may well progress at a much faster rate, but in *Unique*'s experience, children continue to need very high levels of support in feeding, dressing and caring for themselves. This need for total or almost total care may continue into adulthood.

In terms of toileting, it is not appropriate for parents to expect this to occur at the same age as in unaffected children. Data from *Unique* suggest that while daytime bladder and bowel control may be achieved in occasional children with a slight to moderate delay, in others it occurs much later (12 years) and in others control may not prove consistently possible (*Unique*).

What's life like for adults?

Two of *Unique*'s members are adults, one 22 years old, the other 30 years old. The 22-year-old lives with his parents and outside college relies on them for his social life and friendship. He enjoys swimming, riding his tricycle and going for trips on a canal boat. He is generally healthy but specialist medical support should he need it is good. The 30-year-old regularly attends social events laid on for people with disabilities and enjoys a range of friendships among her family and those who care for her.

Medical matters

Heart

Regardless of which part of chromosome 2p is duplicated, around half of affected babies are born with a healthy heart and around half with a heart problem. In some babies, the problem is simple and may resolve naturally with time. In others, probably the majority, the problem is more complex and early corrective surgery is needed. Outcomes are determined in part by how severe and complex the problems are but *Unique*'s experience is that babies have generally thrived well after heart surgery, even when repeated surgical interventions have been needed.

The most common problems are holes between the upper or lower chambers of the heart or between both (atrial septal defect/ ASD; ventricular septal defect/ VSD). In a baby with a VSD, blood pressure is higher in the left heart chamber than in the right chamber so with every heart beat some oxygen-saturated blood flows from the left to the right heart and then through the lungs. The bigger the VSD, the more the lung is over perfused. A decision whether to close the hole and when is taken for every baby individually. In a baby with an ASD, oxygen-rich blood flows to the lungs and over perfuses them. Small ASDs may well close naturally and a decision to close one surgically, using minimally invasive surgery or a patch, depends on the size and position of the hole. ASDs and VSDs can cause pulmonary hypertension, where blood pressure in the arteries that take blood from the heart to the lungs is raised.

Other heart problems have included a persistent ductus arteriosus (PDA), where a channel that is open during fetal life fails to close just after birth; narrowing (coarctation) of the aorta that takes blood from the heart to the rest of the body; underdevelopment of the left side of the heart; and a condition known as AV canal where instead of separate valves between the left and right upper and lower heart chambers, there is a single common valve. One baby was born with a single lower chamber and transposed blood vessels leading from the left and right sides of the heart. (Therkelsen 1973; Say 1980; Heathcote 1991; Siffroi 1994; Lurie 1995; Mégarbané 1997; Magee 1998; Al-Saffar 2000; Aviram-Golding 2000; Gruchy 2007; *Unique*)

Lungs

In some babies, the 2p duplication appears to disrupt the development of the lungs, so that one lung or both is unusually small, the normal division of the lungs into two or three lobes is disrupted or, in one baby, only one lung is present. This effect on lung development has been observed in around one baby in three in the medical literature but it has not been observed among *Unique* members. Among those identified in the medical literature, all babies shared a duplication of the 2p21p22 section (Say 1980; Fryns 1986; Siffroi 1994; Lurie 1995; Winsor 1997; Aviram-Golding 2000).

Minor genital anomalies in boys

Minor genital anomalies are not uncommon in boys in the general population and seem to be somewhat more common in those with a chromosome disorder. They occur in boys with a 2p duplication both reported in the medical literature and within *Unique*. The genitals may be small and the hole usually situated at the end of the penis may be on the underside instead (hypospadias). This may not need treatment but if it does, it can be corrected in a straightforward surgical operation. The testicles usually complete their natural descent from the abdomen into the scrotum by the time a baby boy is

born but may not have done so (undescended testicles, cryptorchidism). If they do not descend naturally in time, they can be brought down in a short operation called an orchidopexy under general anaesthetic. A condition known as 'shawl scrotum' has been seen, where the scrotum surrounds the penis like a shawl (Yunis 1979; Fryns 1989; Heathcote 1991; Aviram-Golding 2000; *Unique*).

Respiratory complications

Breathing problems are common in babies and children with a 2p duplication. Children with a chromosome disorder have a high rate of respiratory infections and tend to be especially ill when they catch one; those with a 2p duplication are no exception. The breathing passages may be unusually floppy and limp and you may notice that your baby breathes noisily (stridor). Some children are prone to gastro oesophageal reflux (*see* Food and eating, page 7) which brings with it the possibility of inhaling part of a feed and causing an infection (aspiration pneumonia). In some children the tonsils and adenoids become enlarged in response to frequent infections. If it is shown that this plays a part in pauses in breathing while asleep, they can be removed (Stoll 1974; Yunis 1979; Say 1980; Fryns 1989; Heathcote 1991; Mégarbané 1997; *Unique*).

Hernias

It's been suggested that babies are at a raised risk of having a diaphragmatic hernia. This is a developmental defect in the muscular wall that separates the heart and lungs from the contents of the abdomen. It allows part of the abdominal contents to take up space in the chest, potentially depriving the lungs and heart of room to develop properly. This has been seen in one baby with a pure 2p duplication and three others with mixed deletion/ duplications; however, it has not been seen in *Unique* families (Heathcote 1991; Mégarbané 1997; *Unique*).

Umbilical hernias (at the navel) and inguinal hernias (in the groin) have also been seen. An umbilical hernia develops when a small opening in the abdominal muscles that allows the umbilical cord to pass through does not close after birth. Many umbilical hernias close naturally by the age of three or four but a very large hernia or one that stays open after this age can be closed surgically.

An inguinal hernia occurs when an opening in the lower part of the wall of the abdomen during fetal life fails to close before birth. The remaining opening may be small, only allowing fluid through, or it may be large enough to allow something such as a loop of the intestine through. An inguinal hernia is repaired in a small surgical operation.

One child had a hiatus hernia, where part of the stomach protrudes into the chest cavity through the hole for the food passage (Sawyer 1994; *Unique*).

Intestines

Three babies with a pure 2p duplication have been born with an intestinal problem. In one case, the bowel was much shorter than expected and a condition known as Meckel's diverticulum was found. This is a small pouch in the wall of the intestine near the junction of the small and large intestine consisting of a remnant of tissue from life before birth. Most people do not have any symptoms or problems but in

some cases the tissue can cause problems. If symptoms develop, the diverticulum can be removed with a surgical operation.

Two babies had a developmental anomaly of the digestive tract known as intestinal malrotation. Some babies with malrotation have no symptoms or problems but if the intestine is obstructed or twists, surgical repair is performed as soon as possible (Siffroi 1994; Aviram-Golding 2000; *Unique*).

Kidneys and urinary system

Most babies with a 2p duplication will be born with normally functioning kidneys. Out of 34 reports in the medical literature and *Unique,* four babies have had unusual kidneys: in two babies, they were unusually small; in another, the lower points of the kidneys had joined to create a horseshoe shape. In itself this is not harmful and around one third of children with a horseshoe kidney have no symptoms and may need no treatment. However, a horseshoe kidney can increase the risk of urinary tract infections and one third of people with horseshoe kidney have another anomaly or complication which may need supportive treatment. In a fourth case, the kidneys were slightly swollen during fetal life. Two further babies had kidney reflux, where urine from the bladder can flow back into the ureters and, depending on the severity, as far as the kidneys. The first line of treatment is usually low-dose antibiotic treatment, which can give a child the opportunity to outgrow the reflux (Stoll 1974; Siffroi 1994; Al-Saffar 2000; Aviram-Golding 2000; Pipiras 2004; *Unique*).

Eyes

Vision problems are very common: 16 out of 21 babies, children or young adults were affected. However, the problems are very varied, and the number of children with any one particular problem is quite small. Some children have also outgrown considerable visual problems.

By far the most common difficulty is a squint (strabismus), looking inwards, outwards, up or down. The main effect is that usually the child will have one eye which is stronger than the other. Treatment depends on the cause but can include patching the stronger eye, exercises, glasses to correct a refractive error such as long sight and surgery to realign the muscles that hold the eye in place.

Another frequent problem is obstruction or absence of the tear ducts. Tear ducts that remain obstructed can be gently teased open but a tendency to sticky eyes may remain, especially when a child has a cold.

A degree of long sight has occurred, as also severe short sight with detachment of the retina in both eyes. The front part of the eye may be affected; one child had a cataract on one eye; another baby had a cloudy front part of the eye; another baby had a number of anomalies of the front part of the eye that are collectively known as Rieger malformations.

A small number of babies have been found to have immature or underdeveloped parts of the back of the eye, including the fovea, the area of the retina responsible for sharp vision, and the macula, the area on the retina designed for seeing detail. Others have been diagnosed with delayed visual maturation. In some of these babies from *Unique* families, visual outcomes have been very good, with natural resolution of the problem,

even when it was severe. In the meantime, babies and children whose vision is significantly affected can expect input from a visual impairment service.

It has been suggested that band 2p24 is usually duplicated in individuals with a vision problem (Aviram-Golding 2000) but when *Unique* cases are included, this is no longer true. Vision problems occur regardless of the position or extent of the duplication (Therkelsen 1973; Stoll 1974; Fineman 1983; Fryns 1989; Heathcote 1991; Sawyer 1994; Lurie 1995; Mégarbané 1997; Al-Saffar 2000; Aviram-Golding 2000; Wellesley 2000; Ishikawa 2002; Gruchy 2007; *Unique*).

Skin

Three *Unique* families commented on their child's dry skin or eczema, developing in one case at the age of 13. Families are recommended to moisturise their child's skin regularly with a simple emollient such as emulsifying ointment or aqueous cream and to seek medical advice if they can't keep the dryness under control.

Anus

In four babies with a 2p duplication, the anus was in a somewhat unusual position or was significantly narrowed. In each case, part or all of band 2p21 was duplicated (Say 1980; Siffroi 1994; Lurie 1995; Kubo 1999).

Head and brain

Some babies with a 2p duplication are born with a head that is unusually large or a slightly unusual shape. They may have a brain scan and in a few cases a build-up of fluid within the brain (hydrocephalus) has been found and a shunt placed to drain off the excess fluid. Other unusual formations of the brain have been observed in individual children. In two babies, the brain did not form completely and these cases, together with others where the 2p duplication was accompanied by a deletion from another chromosome, have led some researchers to wonder whether there is an association with neural tube defects in the developing baby and a duplication that includes bands 2p23-24. It is not at all certain that this association exists but if it does, not everyone is affected; on the contrary, most babies with a 2p23-24 duplication are born with an intact brain and spinal cord (Therkelsen 1973; Heathcote 1991; Siffroi 1994; Lurie 1995; Al-Saffar 2000; Ishikawa 2002; Thangavelu 2004; *Unique*).

Hearing

Hearing is generally unaffected by a 2p duplication. Young children are prone to a build-up of fluid behind the eardrum, known as 'glue ear', and may need aeration tubes ('grommets') in the eardrum to improve their hearing or hearing aids if the loss is severe. But there is no evidence that children with a 2p duplication are more likely to have this type of hearing reduction than children with no chromosome disorder. Children usually outgrow the tendency by the age of six or eight or sometimes earlier. There are two children in the medical literature with a permanent hearing loss, in one case affecting one side only (Therkelsen 1973; Parruti 1989; *Unique*).

❝ Extremely good hearing. More than normal ear wax - *adult*

Teeth

Children with chromosome disorders are more likely than other children to have dental problems. These do not affect everyone and many children have strong, healthy

teeth. Some problems occur during development and teeth can emerge small or with insufficient enamel. Milk teeth may fail to fall out and some permanent teeth may not emerge. Misalignment between the teeth in the upper and lower jaws occurs fairly commonly, especially in those conditions whether the lower jaw is small and set back. Other problems can be the result of difficulties with dental care.

Among children and adults with 2p duplications a number of varied problems have been seen: very small teeth in two children, misalignment and crowded teeth in two and failure of the milk eye teeth (canines) to fall out and be replaced by permanent teeth in one adult (Fryns 1989; Ishikawa 2002; *Unique*).

Happy and healthy?

There is no evidence that children or adults with this duplication will be any more unwell than those without a chromosome disorder. As children, they are likely to have repeated coughs and colds and may be more likely to develop ear or chest infections. Like other children, they will outgrow this tendency and almost all parents tell us that their children are currently healthy (*Unique*).

❝ After the age of 1 she has had reasonably good health, not needing hospitalisation. She does not seem to be prone to anything in particular - *2 years*

❝ She picks up a lot of colds, chest infections and stomach bugs - *6 years*

❝ He is now generally very healthy but when young caught lots of colds and bugs. He's been much better since starting on a multivitamin - *13 years*

❝ Her general health is good. Now and then she has urinary infections - *30 years*

Inverted duplication of 2p with loss of the tip of the short arm (Inv dup del 2p)

There are eight reports of children and one adult with an inverted duplication of 2p and a deletion of the tip of the short arm. The size of the extra and the missing pieces is different between individuals, with the proximal breakpoint ranging from band 2p21 to band 2p25.2. A father passed the smallest duplication-with-deletion on to two children, and all three have the same breakpoints. *See* also pages 5 and 21.

The karyotype

46,XX,inv dup(2)(p25.2p23)

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XX for females; XY for males
inv dup	An inverted duplication, or there is an extra piece of material running in the opposite direction to the rest of the chromosome arm
(2)	The duplicated material came from chromosome 2
(p25.2p23)	The extra material consists of the bands between 2p23 and 2p25.2

The absence of the tip of the short arm of chromosome 2 is not mentioned in the karyotype because it has not been demonstrated. An inverted duplication of bands close to the end of a chromosome is usually accompanied by a deletion of material from the tip but a sensitive molecular technique for examining chromosomes such as FISH or microarrays is usually needed to show the deletion.

The tiny number of reports of people with an inv dup del 2p makes it difficult to be certain about the effects of this chromosome disorder. All the same, these observations

can be made: everyone with the inv dup del 2p has shown some degree of developmental delay but the degree is variable with quite marked differences even between members of the same family with the same chromosome disorder. In at least three people, including two members of the same family, learning ability was only moderately reduced. In the others the effects on learning were more obvious. Speech is delayed as well but again there is quite a lot of variation, from a child who is able to sign 30-40 words at the age of two to an 8-year-old without any meaningful vocabulary. Sitting, becoming mobile and walking are generally delayed but again the range is wide, from only a slight delay at one end of the spectrum to a child who was sitting but not mobile at four years at the other. Coordination and hand use are also affected and it can be expected that milestones like toilet training will be delayed.

There is no agreement about the reported effects of inv dup del 2p on behaviour: one child was considered hyperactive, another has autistic-like tendencies, another passive and lacking initiative. But a *Unique* report on a child at the age of 2 is positive and upbeat.

In terms of growth, two children are described as short but within normal limits at the ages of 4 to 6. The finding of frequent eye problems in those with a pure duplication of 2p is echoed here: six out of seven individuals need some help with vision. Three are short sighted, two have a squint (strabismus), one has undeveloped optic nerves connecting the eye with the brain and one had transient cortical blindness, a temporary phase when she was unable to see because her brain failed to interpret the messages from the eye. Three out of five children developed a spinal curvature, but the adult was not affected and nor were children from *Unique*. Two children were born with a heart problem serious enough to need surgical correction, in one case a narrowing of the blood vessel that leads from the heart to the lungs and in the other case a large hole between the two lower chambers of the heart and partly fused and thickened valves at the outlet both to the lungs and to the rest of the body. Three children had a problem with their kidneys, in two cases relatively minor but a third child was born with one compromised kidney and one non-functioning one, but thrived after surgery.

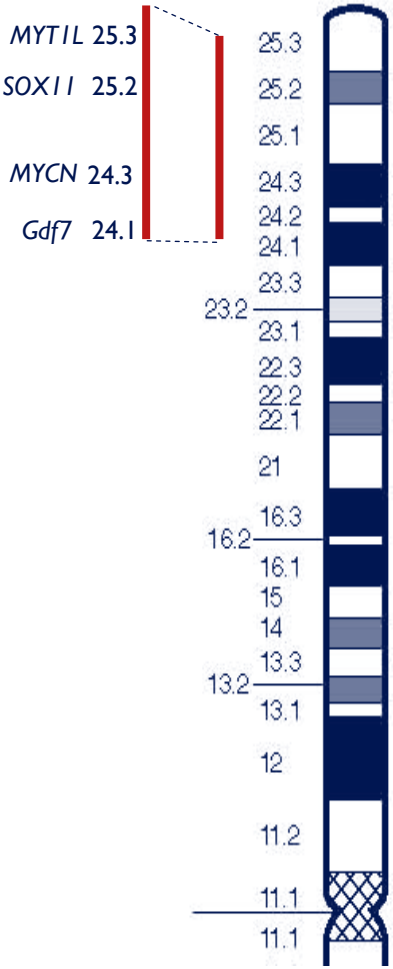
Babies were born without any neural tube defects but one baby was found early in the pregnancy to have little or no brain development and the pregnancy was terminated. Other problems have occurred in single cases and may not be linked with the chromosome disorder: one child was born with a cyst on the vocal cord as well as on the face, hands and feet; and one child had a small cleft in the soft palate at the back of the mouth (Aviram-Golding 2000; Thangavelu 2004; Gruchy 2007; Bonaglia 2008; Kochilas 2008; *Unique*).

Potential genes involved in duplications of 2p

We are still learning the about the specific jobs or functions of the genes in these regions. Genes at 2p24 have been suggested as essential for normal neural tube development. A gene known as *Gdf7* (growth differentiation factor 7) at 2p24.1 is one that has attracted interest. But additional factors may well be required as not everyone with a duplication of *Gdf7* has a neural tube defect (Singer 1987; Winsor 1997; Thangavelu 2004).

Genes known as *SOX11* at 2p25.2 and *MYT1L* (myelin transcription factor 1) at 2p25.3 are thought to play an important role in the developing central nervous system and so may play a role in the developmental delay and learning difficulties associated with a 2p duplication (Gruchy 2007; Bonaglia 2008).

A gene known as *MYCN* oncogene (also occasionally called N-MYC) is found on 2p at 2p24.3. This gene may possibly be involved in the development of a form of cancer that affects particular, immature nerve cells (neuroblastoma). However, the number of known cases is very small and some other factor may be needed, as many with a duplication of this region do not develop a neuroblastoma. No *Unique* members have developed a neuroblastoma (Nagano 1980; Say 1980; Patel 1997; Willatt 2001). Nonetheless, some clinicians have recommended regular screening with abdominal ultrasound as a precautionary measure (Roberts 2004).



How did the 2p duplication occur?

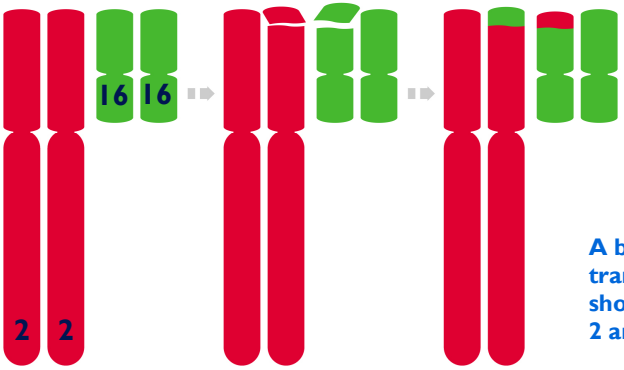
A blood test to check both parents' chromosomes is needed first. Many 2p duplications occur when both parents themselves have normal chromosomes. The term that geneticists use for this is de novo (dn) (see page 4). These duplications are caused by a change that has usually occurred when the parents' sperm or egg cells were formed or just after conception. When a sperm cell from the father and egg cell from the mother first join together, each carries just one chromosome from each pair. Together they form a single cell that now carries two chromosomes from each pair. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human development. Sometimes during the formation of the egg or sperm cells or during this complicated

copying and replication process, parts of the chromosomes can break off or become arranged differently than usual.

Here are some examples of changes that can happen. Your geneticist or genetic counsellor can tell you which the change is in your family.

Reciprocal translocation

Reciprocal translocations are rearrangements that result from a single break in each of two chromosomes (see diagram below). They are not rare – they affect one in 500 people. Someone with a balanced reciprocal translocation has chromosomes where some material has switched places between chromosomes but none has been lost or gained. People with a truly balanced reciprocal translocation are themselves usually symptomless although they may have difficulties with fertility and do have an increased risk of having a pregnancy affected by an unbalanced translocation. Many 2p duplications occur in this way.



A balanced reciprocal translocation between the short arms of chromosomes 2 and 16

The karyotype of someone with a balanced reciprocal translocation between 2p, with a breakpoint in band 2p24, and 16p, with a breakpoint in band 16p13.3, would look something like this

46,XY,t(2;16)(p24;p13.3)

46	the total number of chromosomes in your child's cells
XY	the two sex chromosomes. XY male; XX female
t	the chromosome rearrangement is a translocation
(2;16)	chromosomes involved in the translocation
(p24;p13.3)	chromosome 2 has broken in band p24; chromosome 16 has broken in band p13.3

Affected people with a balanced reciprocal translocation

Balanced or apparently balanced reciprocal translocations involving chromosome 2p have been reported in a very small number of people who do have symptoms. They may be *de novo* (Stoll 2003; Bocciardi 2005; Borsani 2008; Roohi 2008) or inherited (Lewanda 1993; Cargile 2000; Novelli 2004). In these cases it was supposed that the translocation must have interrupted a gene or genes that could potentially be responsible for any problems. Analysis of genes disrupted at the breakpoints will show this one way or the other.

People with an unbalanced reciprocal translocation

When a healthy carrier with a balanced translocation has children, they may have an unbalanced translocation. Typically, there will be a duplication of 2p, and a deletion from another chromosome (see diagram below). In general the features of affected people with an unbalanced translocation, whether *de novo* or inherited, depend on the size and gene content of both the 2p duplication and the deleted portion of the other chromosome.

This is just an example. Any of the chromosomes can be involved in the translocation with chromosome 2.

The child has inherited two normal chromosomes 2 and one normal chromosome 16. The other chromosome 16 was involved in the translocation: its tip now carries extra material from chromosome 2

The karyotype of someone with an unbalanced reciprocal translocation between 2p with a breakpoint in band p24 and 16p with a breakpoint in band p13 would be like this

46,XY,der(16)t(2;16)(p24;p13)pat

46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes: XX female; XY male
der(16)	A derivative or abnormal chromosome 16
t	The abnormal chromosome 16 is the product of a translocation (t)
(2;16)	The chromosomes involved in the translocation are 2 and 16
(p24;p13)	Chromosome 2 has broken in band p24; chromosome 16 in band p13
pat	Paternal: the translocation is inherited from the father who carries a balanced reciprocal translocation. If the translocation is inherited from the mother, mat is written

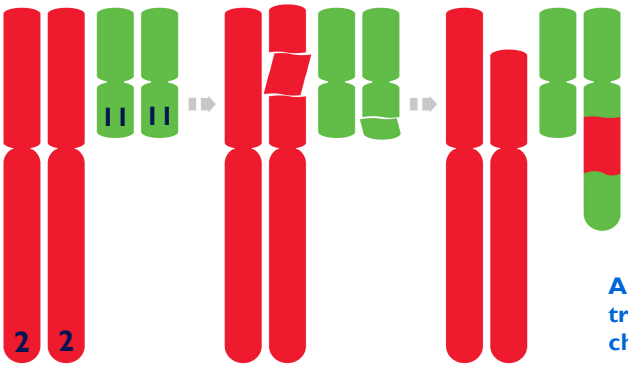
Duplication with deletion of 2p

Chromosome duplications can either follow the same direction as the rest of the chromosome arm (dir dup) or be inverted (inv dup). Inverted duplications are usually associated with a missing (deleted) portion involving the most distal part of the chromosome next to the duplicated portion. This type of arrangement is known as an inverted duplication with deletion or inv dup del (see pages 5 and 17-18). The features found in people with an inv dup del will depend on the size of both the duplicated and deleted segments of 2p.

In both direct duplications and inv dup del, the rearrangements are first identified by chromosome analysis finding a chromosome 2 with a 2p arm that is longer than normal. Only further molecular investigation (using FISH, array-CGH) allows the true nature of the rearrangement (dir dup 2p or inv dup del 2p) and the exact size of the duplicated segment to be defined.

Insertion

An insertion is a type of translocation. It can be *de novo* or inherited from a parent with a balanced insertional translocation (see diagram below). Insertional translocations are rare chromosomal rearrangements found in only one in 80,000 newborn babies (Van Hemel and Eussein, 2000).



This is just an example. Any of the chromosomes can be involved in the translocation with chromosome 2.

A balanced insertional translocation between chromosomes 2 and 11

The karyotype of someone with a balanced insertional translocation between 2p and 11q, with a segment of the short arm of chromosome 2 between bands 2p21 and 2p22.2 inserted into the short arm of chromosome 11 at band 11q14.1, would look something like this

46,XX,ins(11;2)(q14.1;p21p22.2)

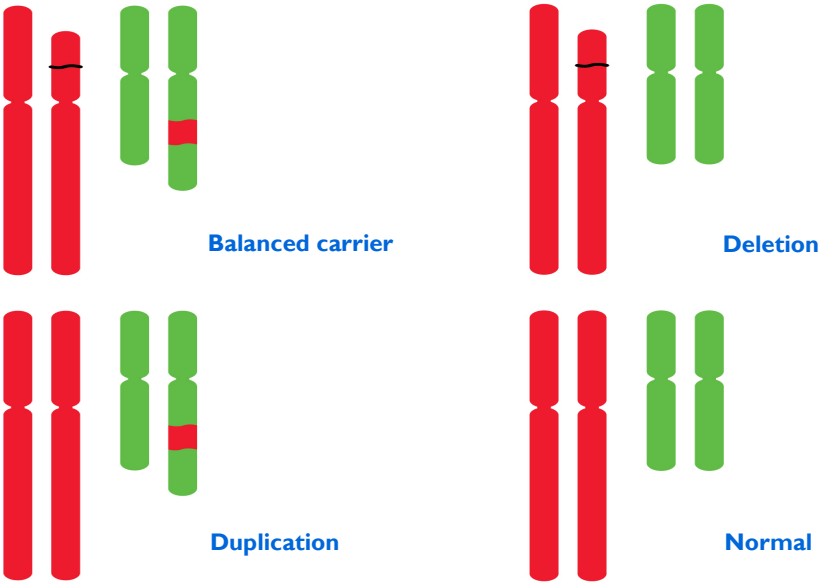
46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes. XX female; XY male
ins	Insertion
(11;2)	Chromosomes involved in the translocation
(q14.1;p21p22.2)	The insertion has occurred at 11q14.1; the inserted material consists of bands p21 to p22.2 of chromosome 2

From the diagram on page 23, you can see that for a parent with a balanced insertion there are four possible outcomes when they have children. Children can have a balanced insertion like the parent; a duplication; a deletion; or normal chromosomes. Data from a large number of families show that around one third of the children will have normal chromosomes; around one third will have a balanced insertion like their parent; and around one third will have either a duplication or a deletion. These proportions vary with the size of the duplication. If the duplication is small, the possibility of having an affected child increases and in theory could be as high as 50 per cent (Van Hemel and Eussein, 2000). Every case is individual and you should discuss your family's situation with your geneticist or genetic counsellor.

The karyotype of someone with a duplication due to an unbalanced insertional translocation between 2p and 11q, with a segment of the short arm of chromosome 2 between bands 2p21 and 2p22.2 inserted into the short arm of chromosome 11 at band 11q14.1, would look something like this

46,XY,der(11)ins(11;2)(q14.1;p21p22.2)

Possible outcomes when a parent with a balanced insertion has children



Can it happen again?

The possibility of having another pregnancy with a 2p duplication depends on the parents' chromosomes. If a blood test shows that both parents have normal chromosomes, the 2p duplication is very unlikely to happen again in another child.

If a blood test shows that either parent has a chromosome change involving 2p, the possibility is increased of having other pregnancies with chromosome changes. If they wish, parents should have the opportunity to meet a genetic counsellor to discuss their 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) or 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.

Discussing the chromosome change with other family members gives them the opportunity to have a blood test to see if they too carry it.

Will my child with a 2p duplication have similarly affected children?

Adults with small 2p duplications may form close relationships and want to have children. In one case a father with inv dup del 2p passed this on to two of his children (Bonaglia 2008).

Support and Information

Rare Chromosome Disorder Support Group,
G1, The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom
Tel/Fax: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

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