Understanding chromosome disorders

Unique

10p proximal deletions from 10p11 & 10p12

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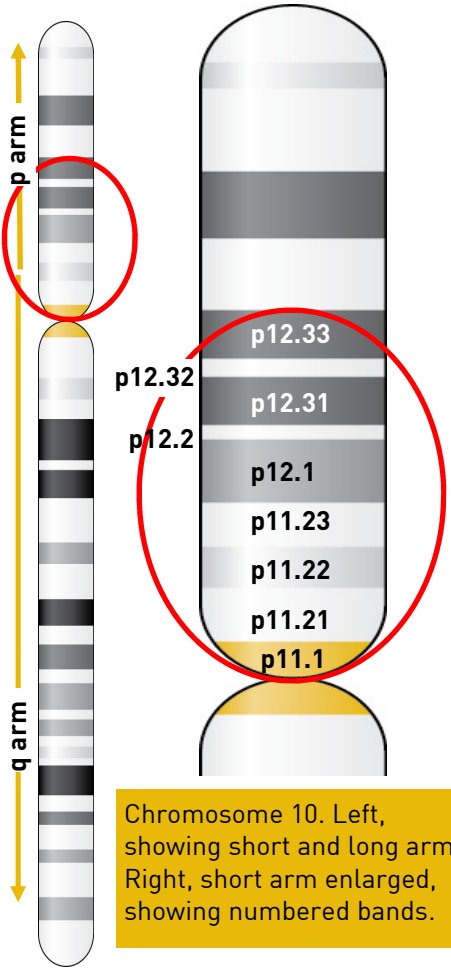
10p proximal deletions from 10p11 & 10p12

A chromosome 10p deletion means that part of one of the body's chromosomes (chromosome 10) has been lost or deleted. If the missing chromosome material contains important genes, learning disabilities, developmental delay and health problems may occur. How serious these problems are depends on how much of the chromosome has been deleted, which genes have been lost and where precisely the deletion is. 10p deletions are rare, with an incidence of less than 1 in a million.

Genes and chromosomes

Our bodies are made up of billions of cells. Most of these cells contain a complete set of thousands of genes that act as instructions, controlling our growth, development and how our bodies work. Inside human cells there is a nucleus where the genes are carried on microscopically small, thread-like structures called chromosomes which are made up of DNA.



Chromosome 10. Left, showing short and long arms. Right, short arm enlarged, showing numbered bands.

Chromosomes come in pairs and are numbered from largest to smallest, roughly according to their size, from number 1 to number 22. In addition to these so-called autosomal chromosomes there are the sex chromosomes, X and Y. So a human cell has 46 chromosomes: 23 inherited from the mother and 23 inherited from the father, making two sets of 23 chromosomes. A girl will have two X chromosomes (XX) while a boy will have one X and one Y chromosome (XY).

Each chromosome has a short (p) arm (at the top in the diagram left) and a long (q) arm (at the bottom of the diagram). In a 10p deletion, material has been lost from the short arm of one chromosome 10. The other chromosome 10 is usually intact.

You can't see chromosomes with the naked eye, but if you stain them and magnify their image with a computer or under a microscope, you can see that each one has a distinctive pattern of light and dark bands.

Starting from the point where the short (p) arm of chromosome 10 meets the long (q) arm, the band numbered p11 is divided into four smaller bands,

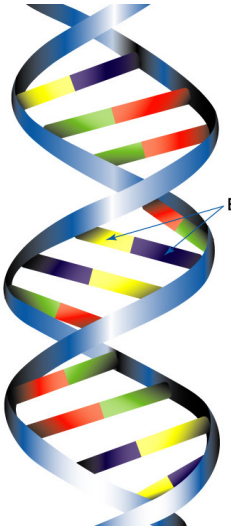
numbered p11.1, p11.21, p11.22, and p11.23. The band numbered p12 is divided into five smaller bands, numbered p12.1, p12.2, p12.31, p12.32, and p12.33.

A deletion from any of the p11 or p12 bands is called a proximal deletion. A small or very large piece of the chromosome can be missing. If the piece is visibly missing when the chromosomes are magnified and examined it is called a deletion.

If the missing piece is so small that the magnified chromosome looks normal, and it can only be found using enhanced techniques such as FISH or array CGH (microarrays), it is called a microdeletion. These techniques can be used to precisely map microdeletions, and are making it possible to find more precise genotype-phenotype correlations - that is, the link between a specific deletion and the clinical features observed.

You may see the missing piece called an interstitial deletion. This means that there are two breakpoints that have re-joined and the part of the chromosome between them is missing.

Each band of each chromosome contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. There are millions of base pairs in every chromosome. An array CGH test will show which base pairs and which genes are missing depending on the resolution of the microarray/ array CGH test.
Your geneticist or genetic counsellor can tell you more about the genes and chromosome material that have been lost. You will be given the results of your child's chromosome test, which will tell you what is missing.



DNA

Sources & references

The information in this guide is drawn partly from medical research papers. We have focused on articles describing people with a 'pure' proximal 10p deletion, without any other chromosome change, and on articles that include a review of 10p deletions.
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. Researchers have described around 50 people with a 10p deletion in medical publications, although there are certainly many more. Fourteen cases of deletions involving 10p11, 10p12 or overlapping 10p12p11 have been reported in the medical literature (Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Okamoto 2012; Mroczkowski 2014; Bosch 2015; DeSanto 2015; Sosoi 2015; Abdelhedi 2016). When Unique wrote this guide, we had details of 92 members with a 'pure' 10p deletion, without any other chromosome change, including 24 members with deletions involving 10p11 and/ or 10p12.

Genome Assemblies

The human genome project, an international effort to sequence the entire human genome and map all of its genes, was announced complete in 2003. However, there were many gaps in the sequence and mapping data, and scientists have since been working continuously to identify the missing information. When new sequence information is identified, the base pair numbers of each chromosome change slightly and hence the numbers for individual genes, deletions, and duplications and so on can shift. Sometimes they only shift very little; other times quite a lot.

Each new version of the genome is often referred to as an 'assembly' or a 'build'. Every few years a new assembly is released. The genetic information in this guide is based on the Genome Reference Consortium (GRC) human (h) genome assembly number 37 (GRCh37), which was released in 2009. Confusingly, you will often see the DNA sequence data for this assembly referred to as hg19 (human genome 19) on your/your child's genetic report.

The databases commonly used by clinical geneticists and Unique will soon move to a more recent assembly named GRCh38/hg38, which was released in 2014. Genetic reports will at some point also be altered, so genes and genetic changes may well have new base pair numbers.

Test results

Your child's test results are likely to look like one of these:

46,XY,del(10)(p11.2p12.2) de novo This result shows that the expected number of chromosomes [**46**] were found. It also shows that one X chromosome and one Y chromosome were found, so this is a boy or a man. **del(10)** means there is a deletion from chromosome 10. **(p11.2p12.2)** shows the bands in the chromosome where the missing material starts and finishes; in this case, the DNA is missing between one of the three p11.2 bands and band p12.2 (see diagram, page 2).

de novo means that the parents' chromosomes have been checked, and this chromosome change is a new occurrence [de novo] and has not been inherited from either the father or the mother. de novo is often shorted to **dn**.

arr[hg19] 10p11.22p11.21(33598125-35480937)x1 mat

arr The analysis was by array (**arr**) comparative genomic hybridisation (**cgh**) [**hg19**] Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. See box at the top of this page.

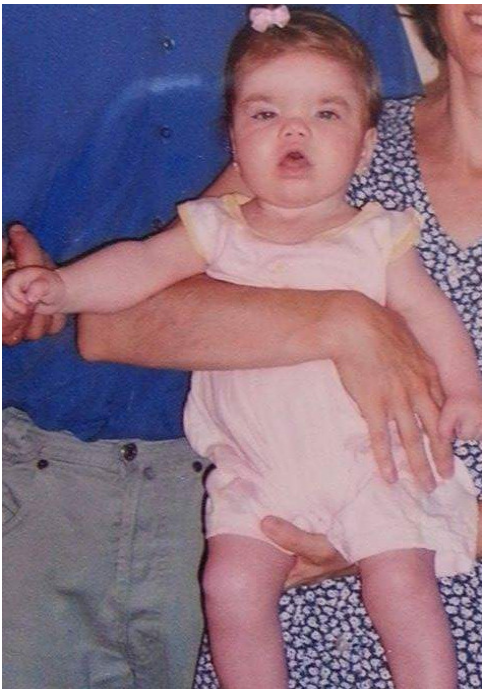
10p11.22p11.21 The chromosome involved is 10 and the deletion starts in band p11.22 and ends in band p11.21

(33598125-35480937) The base pairs between **33598125** and **35480937** have been shown to be deleted. Take the first long number from the second and you get 1,882,812 (1.88Mb). This is the number of base pairs that are deleted.

x1 means there is one copy of these base pairs, not two – one on each chromosome 14 – as you would normally expect.

mat means that the deletion has been inherited from the mother; **pat** means that it has been inherited from the father.

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



Deletion in 10p11.22-p11.23

Why did the 10p deletion occur?

A blood test to check the parents' chromosomes is usually the first step in trying to discover why the deletion occurred. However, most 10p deletions occur when both parents have normal chromosomes (Bosch 2015; Wenzel 2011; Shahdadpuri 2008). The term that geneticists use for this is de novo (dn). De novo 10p deletions are caused by a change that has usually occurred when the parents' sperm or egg cells were formed or, less commonly, around the time of conception. When the sperm and egg cells join they form a single cell and this cell must continuously make copies of itself (and all its genetic material) in order to produce the billions of cells that form during human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated replication process, parts of a chromosome are lost, leaving a deletion.

A minority of 10p deletions are the result of a rearrangement in one parent's chromosomes. This is usually a balanced translocation in which material has changed places between chromosomes but no material has been lost or gained and the parent usually has no difficulties with health or development. Occasionally, when the deletion is relatively small, one parent has the same deletion as the child.

Children from all parts of the world and from all types of background have proximal 10p deletions. No environmental, dietary, workplace or lifestyle factors are known to cause them. There is nothing that either parent did before or during pregnancy that can be shown to have caused the deletion and equally nothing could have been done to prevent it. So no one is to blame or at fault.

Can it happen again?

In families where both parents have been tested and have normal chromosomes, the extremely unusual sequence of events that led to a baby with a 10p deletion is very unlikely to happen again.

There is however a remote possibility that both parents have normal chromosomes on a blood test, but a few of their egg or sperm cells nonetheless carry the 10p deletion. Geneticists call this germline mosaicism. It means that parents whose chromosomes are normal when their blood is tested can have more than one child with the deletion.

If a blood test showed that either of the parents has a 10p microdeletion, there is a 50 per cent chance of passing it on and a 50 per cent chance of passing on normal chromosome 10s. 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; 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, testing a small sample of the cells that will become the baby's placenta) and amniocentesis (testing a small amount of the amniotic fluid in the womb that contains cells from the baby) to check the baby's chromosomes. Testing is generally very accurate, although not all these tests are available worldwide.

Deletion in 10p11.22-p11.23

Can a 10p deletion be detected in pregnancy?

It is possible to examine the chromosomes of a developing baby during pregnancy, either by chorionic villus sampling (CVS) or by amniocentesis. Until recently a baby's chromosomes were checked by imaging the chromosomes, which could only reveal relatively large deletions. Recently, the first use of array CGH was reported after risk factors were found on an early pregnancy dating scan at 12 weeks. Imaging studies after amniocentesis at 16 weeks suggested a 10p deletion, and an ultrasound scan showed unusual features including a flat face and short bones in the arms and legs. Array CGH was used after a second amniocentesis at 22 weeks to accurately map the deleted region to 10p11.22 – p12.31 (Sosoi 2015; Unique).

What are the common difficulties of people with proximal 10p deletions?

In general, clinical descriptions highlight problems rather than areas of normality or strength. The most common developmental and health problems are:

- Some degree of developmental delay and/or learning difficulties – pages 10 and 11-12
- Language delay – page 13
- Difficulty speaking clearly – page 13
- Low muscle tone – page 11
- Feeding difficulties – pages 8-9
- Heart conditions – page 14
- Eye and eyesight problems – page 15
- Undescended testicles at birth and other genital anomalies – pages 15-16
- People also have some characteristic facial features – page 17 (Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Okamoto 2012; Mroczkowski 2014; Bosch 2015; Sosoi 2015; Abdelhedi 2016; Unique)

Common features are marked in the guide with a grey square ■

Pregnancy/at birth

Most pregnancies described in the medical literature and at Unique were uncomplicated and went to term. Early pregnancy screening tests and dating scans raised concerns in two pregnancies, and in one case the 10p deletion was diagnosed during the pregnancy after amniocentesis. In the other case the baby's complex heart problems were correctly identified and monitored (see **Can a 10p deletion be detected in pregnancy?** page 6) (Sosoi 2015; Unique). Third trimester ultrasound scanning found enlarged ventricles (fluid-filled spaces) in the brain and a heart problem in one baby (Wentzel 2011).

The birth weight of most babies was in the small normal range: the average weight among 19 babies was 2.878kg (6lb 6oz), in the lowest 10-25 per cent of newborn babies. The smallest baby weighed 1.92kg (4lb 4oz), in the bottom 3 per cent, and the largest weighed 3.645kg (8lb 1oz), in the top 60 per cent.

Many babies raised no particular concern as newborns, had reasonable Apgar scores (a measure of wellbeing at birth on a scale of 0-10), and were able to stay with their mother.

Microdeletion in 10p11.21

A few babies had difficulty getting feeding established, and had episodes of a low blood sugar (hypoglycaemia). Four babies had breathing problems, one because of small upper airways, and another because the pressure in the blood vessels to the lungs was too high (pulmonary hypertension). Two babies lost too much body heat (hypothermia). In one, the cord had only one artery, instead of two; another baby had a high temperature whose cause was never found. At least three babies needed to stay in hospital, but all recovered and did well later. One baby with a complex heart condition was acutely unwell and needed oxygen. In terms of appearance, most babies looked like other newborns, but doctors noticed unusual facial features - including deep-set eyes and abnormalities of the ears - in a few (Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Okamoto 2012; Mroczkowski 2014; Bosch 2015; Sosoi 2015; Unique).

Feeding

Deletion in 10p11.22-p11.23

Many babies, both those with a heart problem (see pages 12-13) and those without, have early feeding difficulties. They may find it hard to coordinate sucking with swallowing, be reluctant to suck or get tired very easily. If specialist feeding support, adapted teats and enriched milks are not enough to ensure proper weight gain, babies may benefit from temporary feeding direct into the stomach through a nasogastric tube. Occasionally, babies and older children are most appropriately fed for some time through a gastrostomy tube directly into the stomach.

A few babies have quite severe and long lasting gastro-oesophageal reflux, where the stomach contents flush back up the food passage to a significant degree. Babies are then at risk of choking or of inhaling part of their feeds or stomach secretions, setting the scene for respiratory infections. Feed thickeners can be added to milk to lessen reflux and propping a baby up after a feed can help. Eventually, some babies outgrow the tendency to bring milk back, but if reflux is severe and persistent, a surgical operation known as a fundoplication can resolve it.

Some babies find it hard to move on to solids or chew and in general self-feeding skills can be late to develop. Older children may continue to find it hard to chew foods and prefer a soft or mashed diet, but Unique's experience is that most of those who have not needed a gastrostomy or other surgical intervention are eating family foods and feeding themselves by school age (Wentzel 2011; Mroczkowski 2014; Sosoi 2015; Unique).

❝ He was unable to nurse because he couldn't latch on, and we had to use a nipple with a larger hole in it so the formulas would run in his mouth. He couldn't suck, but around the age of 2 he was able to use a straw so he figured it out.❞ 5 years
❝ He had a history of choking as a baby and needed feeding therapy. He also had difficulties swallowing and used to pocket his food as a toddler. He was a picky eater then and only liked smooth foods. These days he has food allergies including milk, eggs, fish and oats, so avoiding large quantities of these helps.❞ 7 years
❝ She is the best eater of our three children, though she is very sugar driven. She loves ice cream, and gets stuck on particular favourite foods. If we sit next to her, she can feed herself.❞ 13 years
❝ He has always been a good eater and enjoys all his food; his grandma says she loves cooking for him as he is not fussy and will always eat whatever she puts in front of him. ❞ 17 years

For most children, long term constipation is not an issue, but it does affect a minority of babies and children. In one child a channel [fistula] between the vagina and the anus and the anus being placed unusually far forward exacerbated the problem. If it is not possible to add fluid or fibre to the child's diet, or to introduce more exercise into their day, it can almost always be managed with prescribed medication such as stool softeners (Wentzel 2011; Unique).

❝ Constipation resolved with a change of diet.❞ 7 years
❝ Constipation has been an ongoing issue. It affects her mood and everything, and there is a psychological component: when we gave her ice cream she went more frequently.❞ 13 years
❝ He had constipation especially as a child. He has unusually large stools and still only goes to the loo every 2-3 days. Lactulose was prescribed and his paediatrician suggested prune juice to help things along.❞ 17 years

Growth

Growth in babies and children is usually measured in terms of height, weight and head circumference (HC). These measurements are compared with other children of the same age and sex. Centile charts use lines (centiles) showing average measurements for these characteristics. The centile predicts the percentage of children who are below or above a given measurement for height, weight or HC at a given age; for example, the 25th centile means that 25% of children of the same sex and age will be smaller and 75% bigger.

Using these parameters, growth in babies and children varied widely, with some children significantly short for their age, most short, some of a normal height and two at the upper limit of normal. Many children were tested for growth hormone deficiency, but it was only shown in two children: a boy with a 10p12.1-11.23 deletion, and a girl with a 10p11.23p11.22 deletion. In four children the head was large compared with height, but two children had an obviously small head, and one was diagnosed with microcephaly (a very small head and brain).

Growth accelerated or stabilised in some babies once their feeding was regular, but this was not always the case. One baby was a normal weight at birth, but then grew very slowly. In one baby, growth speeded up once her complex heart problems were surgically corrected (Yatsenko 2004; Wenzel 2011; Okamoto 2012; Mroczkowski 2014; Bosch 2015; Unique).

❝ From a normal birth weight, she fell off the charts at 2-3 months and never went back. She is 112 cm (4'4") tall, and weighs 20 kg (3 stone 2 lb). ❞ 11 years

❝ She is only slightly smaller than other children her age – about 150cm (4' 11"). She has very slim legs but is built like a rugby player with very strong stomach muscles. She has a slight spinal curvature which makes her look a little smaller.❞ 13 years

Development – sitting, moving, walking

Being late to roll over, sit or become mobile is often the first sign of the chromosome disorder, but babies vary a lot, and at least four children showed no delay at all (Yatsenko 2004; Bosch 2015; Unique).

The children we know about learned to roll over between 4 and 12 months. They first sat up without support between 6 months and 3 years, at an average age of 14 months. They crawled between 8 and 27 months, at an average age of 16 months; and they learned to walk between the ages of 14 months and 7½ years, with an average age of 2 years 4 months.

Children gradually learned to climb stairs and to run, albeit in some cases with a clumsy style, a stiff or awkward gait, feet placed wide apart or with a poor sense of balance.

There is a cluster of children with more significantly delayed mobility who first sat unsupported at 2-3 years and took their first steps after the age of three years. While more of these children had a large deletion greater than 10Mb, some children with a smaller deletion had more delay in their mobility, and others with a large deletion had little or no delay (Wentzel 2011; Okamoto 2012; Unique).

Certain genes have been particularly implicated in the developmental delay, most specifically the WAC gene (see **Genes**, pages 22-23 and Unique's separate guide to Disorders of WAC). Support for an involvement of the WAC gene in causing development and intellectual delays comes from a review of six patients with mutations in this gene who all had developmental delay. However, other children in whom the WAC was intact still had significant developmental problems. Hopefully a clearer picture will emerge as more cases come to light (Wentzel 2011; Mroczkowski 2014; DeSanto 2015; Sosoi 2015; Abdelhedi 2016).

❝ Has a double patella on his right side; this knee can give him problems and sometimes the wrong movement will cause it to swell and be too painful to walk on. Thankfully this doesn't happen too often anymore. It is because of this knee that he doesn't stand straight and walking is sometimes difficult.❞ 17 years

Muscle tone – low, high or both

Altered muscle tone, usually low (hypotonia), but sometimes raised (hypertonia) is very common in children with a chromosome disorder. Among those with a proximal 10p deletion both types occur, sometimes in the same child. Low tone is common among Unique children, contributes a lot to their mobility difficulties, and can persist. But it is comparatively uncommon among 13 people reported in the medical literature, where only one child has low muscle tone persisting beyond age 6 and it is limited to the body, while the legs and forearms are affected by raised muscle tone (Wentzel 2011; Unique).

Low muscle tone (hypotonia) makes a baby feel floppy to hold, while hypertonia causes an abnormal increase in muscle tension and reduces the ability of muscles to stretch, making the affected areas stiff and rigid. A few children had evolving abnormalities of muscle tone, or showed high and low muscle tone in different parts of the body. Both conditions are caused by developmental damage to the motor pathways of the central nervous system and are helped by physiotherapy. Muscle tone changes impact on a child's mobility, making it harder and more tiring for them to crawl and walk. Some children needed leg supports or insoles while walking (Shahdadpuri 2008; Wentzel 2011; Mroczkowski 2014; Unique).

"He was diagnosed as an infant with low muscle tone and went to therapy 2 times a week. He sat up, crawled and walked late, crawling at 1 and not walking until he was 2 years old. He still tires out easily where there is a lot of walking or when using the stairs." 5 years

"When she started walking at about 3½ years, she was very stiff due to her raised muscle tone and her balance was poor. She had one operation at 3 to lengthen her Achilles tendons and to break and remould her ankles to improve her ankle mobility and stability. She had another operation at 11, and does exercises every day for her stiffness. She has always worn special footwear and insoles but has never needed a walking frame or any other mobility aid. Because it was hard for her to keep up on a long walk, we used first a pushchair, then a wheelchair until she was about 9 or 10. The hypertonia makes her stiff so when she falls, she falls stiffly and is more likely to hurt herself." 13 years

10p11.23 deletion
Starting school

Learning

Some children need help with their learning, others do not. Predicting which children will need learning support, and how much, is not however straightforward. Within Unique, the children who have needed no learning support have deletions that do not include the WAC gene. WAC has recently been a focus of research interest, and when changed (mutated) is thought responsible for learning difficulties that are generally mild but can be more pronounced (DeSanto 2015) (see **Genes**, pages 22-23). However some children with two intact copies of the WAC

gene still have difficulties with learning, and more research is needed. Within Unique the range of cognitive ability is from normal to a moderate or, less often, severe degree of disability, with most children mildly affected. Other difficulties also impact on learning, and one girl with an adult IQ in the mild to borderline range of disability had special education because of her poor eyesight. Another child of 6 had problems with visual perception, drawing mirror and upside down images. Poor concentration, low muscle tone and difficulties holding and handling objects similarly impact directly on school performance (Mroczkowski 2014; Bosch 2015; DeSanto 2015; Abdelhedi 2016; Unique).

❝ When he was evaluated for pre-school at age 4, they did not see anything cognitively 'wrong' with him and did not put him on any special education program. They said he was ready for preschool and would do fine; and he has.❞ 5 years

❝ An extremely bright boy. He is doing well at kindergarten and is reading. He loves science. But he struggles with time management.❞ 6 years

Microdeletion in 10p11.21
First grade: 6 years old

❝ She can read her name and recognises letters and numbers quite well, but is not yet reading or writing. She understands two languages and has learned the colours in English by herself from YouTube. She has a good memory and likes among other things mobile phones, tablets and computers. She has learnt a lot by herself. She is very good at jigsaw puzzles and doesn't need to look at the picture on the box.❞ 11 years

❝ The 'best fit' school here in Sweden for our daughter who is quite mobile but has a moderate to severe learning disability is a 'training school' for children with autism. The children do not follow the curriculum in any way and have a 1:1 staff: child ratio. She is making huge progress in life skills such as getting dressed and putting her shoes on, and even though she cannot read or write, she is incredibly good at finding her way around an iPad to the most disturbing videos. She has a good memory and a very good sense of musical rhythm, so singing is a good way to teach her and also to distract her. She is one of the most sociable children there, and is very empathetic and can read situations very well emotionally.❞ 13 years

❝ He is now able to read fairly well but is only just beginning to be able to tell the time, and is unable to use money. Moderate learning difficulties and dyspraxic.❞ 17 years

Speech

Some children with a proximal 10p deletion say their first words at the expected age and learn to speak as any other child would. Most, however, speak late, and in at least one child speech delay was the first sign of the chromosome deletion. Some children also have a persisting problem making the sounds of speech clearly.

Young children started to form words between the ages of 12 months and 4 years, with an average age of 2½ years. Most families reported that their child's understanding was ahead of their speech, as is usually the way, so a child of 27 months with a vocabulary of 15-20 words could point to all body parts and follow multi-part requests and instructions. A child of 3½ years from a bilingual home understood well in both languages and spoke two words in one. A second child from a bilingual home, this time 11 years old, again understood both languages but was not fluent or easy to understand in either. She spoke in short sentences, and could not yet hold a proper conversation in
either language. At the bilingual home of a third child, this time 13, the parents chose to use Swedish: the girl now speaks Swedish but understands English and can say one or two words in it.

Some degree of speech delay remained for most children, with limited vocabulary and unclear speech obvious. The nature of children's unclear speech is unknown, but is commented on by many families and some researchers. Descriptions include: problems with pronunciation of most words and an unusual voice at 5 years; unintelligible speech at 5 years; persistent speech articulation problems at 6 years; an unusual voice; inability to say the unvoiced consonants k, t, s and f at 13 years; and struggling with pronunciation at 17.

Children used non-verbal communication - signing, pointing, gestures, facial expressions, taking by the hand, pictures, an iPad - to get over what they wanted to say while they acquired language. As they matured, some expressed frustration at being unable to communicate understandably. Speech therapy was important, and some children needed intensive courses to support their language development (Yatsenko 2004; Wentzel 2011; Okamoto 2012; Mroczkowski 2014; Unique).

" His speech and receptive language was also a big concern. His speech has improved with weekly intensive therapy but is still in the delayed range.**"** 5 years

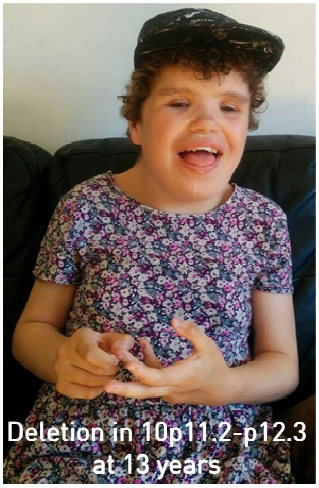
" She understands two languages, but is unable to hold a proper conversation and sometimes it is difficult to understand what she is saying. She can only make short sentences. She learnt the colours in English by herself watching YouTube, but cannot speak English.**"** 11 years

" She is learning new words all the time, and can put 3 words together, and even 4 in the phrase 'I want to have ice cream.' She does have problems with certain sounds of speech but makes sure we understand using her iPad.**"** 13 years

" Still struggles with pronunciation and will occasionally stutter.**"** 17 years

Heart

Heart problems are common, but they range from the trivial and unimportant to complex structural defects needing surgical correction.


Deletion in 10p11.2-p12.3 at 13 years

As far as health was concerned, the most common difficulty for as many as half the babies with a deletion involving 10p11 and/or 10p12 was a heart problem. Eight out of 13 of published cases in the medical literature reported some kind of heart abnormality. In Unique, 7/23 babies were known to have a heart problem (Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Okamoto 2012; Mroczkowski 2014; Bosch 2015; Sosoi 2015; Unique).

Two babies had heart murmurs that required nothing more than monitoring; a murmur in a third baby was caused by a small amount of backflow through the valves in the heart (Yatsenko 2004; Unique). Three babies had holes (ventricular septal defects/ VSDs) between the lower pumping chambers of the heart (ventricles) that started to close naturally and did not need any surgery. One of these babies also had a persistent ductus arteriosus (PDA) - a normal shortcut in the unborn baby's circulation that fails to close naturally soon after birth. A PDA can be closed surgically if necessary, but in another baby no surgery was needed. Another baby was born with a VSD that was still present at the age of 6 but had not needed surgical closing (Wentzel 2011; Unique).

Other babies needed surgery, or had more complex heart conditions, including multiple holes between the left and right heart chambers; a disorder similar to tetralogy of Fallot with multiple defects, narrowing of the aorta (the blood vessel leading from the heart to the rest of the body) and overgrowth of the heart muscle in the pumping chambers as well as overgrowth of the heart muscle in both ventricles and a two-leaf (instead of three) valve from the heart to the aorta; and a blockage of the valve to the blood vessel taking oxygen-depleted blood to the lungs (Shahdadpuri 2008; Wentzel 2011; Unique).
Unique's experience has been that children who need even complex surgery to correct heart conditions generally thrive afterwards. However, one baby with multiple heart problems died in infancy due to pulmonary hypertension (the pressure in the blood vessels to the lungs was too great).
Researchers believe that two genes in 10p11 contribute to these heart conditions: LYZL1 and SVIL (see **Genes**, pages 22-23).

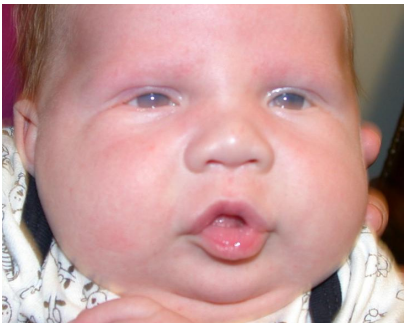
" She still has a small VSD and moderate aortic insufficiency, but so far doesn't need any medication.**"** 11 years

" When she was 3, she had 4 holes in her heart mended, and now is just monitored every 2 years. The only thing left is the narrowing of the aorta and the concern that it may not grow as she grows.**"** 13 years

Eyesight

Some difficulty with vision is common, affecting 8/13 children or adults reported in the medical literature and at least 6/15 children at Unique. Difficulties are extremely varied and include:

- astigmatism (an abnormal curvature of the cornea at the front of the eye);
- amblyopia (a 'lazy eye', where the brain prefers one eye to the other);
- strabismus (a squint);
- clouding of cornea at the front of the eye;
- long sight;
- short sight;
- differing visual acuity in each eye;
- a developmental defect affecting the light sensitive area at the back of the eye (retina);
- a drooping eyelid (ptosis);
- nystagmus (a wandering eye); and
- congenital hereditary epithelial dystrophy (CHED, see image above).



Deletion in 10p11.22-p11.23
Corneal transplants corrected CHED

One 6-year-old boy had problems with visual perception, drawing pictures upside down and in mirror image. In addition, some children have structurally problem-free eyes but impaired vision, because the vision part of the brain or the nerves connecting the brain with the eyes are immature, underdeveloped or do not function properly.

Most eye problems can be treated or corrected with glasses, surgery and sometimes patching or exercises as well. Where the problem originates in the brain rather than the eyes, early stimulation is important to maximise the child's visual potential (Shahdadpuri 2008; Wentzel 2011; Mroczkowski 2014; Bosch 2015; Unique).

"She has recurrent bacterial eye infections similar to conjunctivitis that go away with antibiotic cream. She also has strabismus and probably other eyesight issues but we could not check as she would not open her eyes." 11 years

"She does not respond to tests, but can if she is motivated. She wasn't cooperating with a test that involved distinguishing different shapes until we placed a brown chocolate on a brown teddy bear and offered her an ice cream." 13 years

Genital anomalies

Among baby boys minor genital anomalies are quite common, regardless of the breakpoint. At birth one or both testicles (testes) may not have descended from the abdomen, where they develop during fetal life, into the scrotum (cryptorchidism). Cryptorchidism is found in about three in 100 baby boys born at term regardless of whether they have a chromosome disorder or not, but by the

age of one year 80 per cent of undescended testes have come down naturally. This condition has been reported in four of seven boys with 10p12p11 deletions in the medical literature, and in 5 /15 boys in Unique. Treatment for undescended testicles depends on the suspected cause but is usually needed if the testicles do not descend naturally in time. None of the undescended testes reported in the medical literature descended naturally. 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 anaesthetic called an orchidopexy.

One research group has suggested that deletion of one copy of the MKX gene, which is located at 10p12.1 between base pairs 27961804-28034989, is a contributory factor, and the gene regulates the descent of the testes from the abdomen to the scrotum (see **Genes**, pages 22-23) (Wentzel 2011; Mroczkowski 2014; Sosoi 2015).

While undescended testes is the only genital anomaly reported in the medical literature, the range seen at Unique is a lot wider. Other problems include incorrect positioning of the opening (urethra) that is usually at the end of the penis. In one case, it was positioned on the top of the penis, in another it was on the underside (hypospadias), and in one boy there were two urethral openings, only one of which released urine. Apart from the most minor cases, hypospadias is treated using corrective surgery. An opening for the urethra is created at the tip of the penis which is straightened if necessary. As the foreskin may be used during surgery, boys with hypospadias should not be circumcised. Two boys had small genitalia, in one case just affecting the sac that holds the testes (the scrotum) (Unique).

One baby girl was born with underdeveloped (hypoplastic) genitalia; another with a channel linking the anus with the vagina (Unique).

Brain

After the 10p deletion has been diagnosed, children may be offered a brain scan. In some children, no abnormalities were found. In others, there was some unusual structure, including: two children had a thin or underdeveloped corpus callosum (the band of nerve fibres linking the two sides of the brain); three had somewhat enlarged fluid-filled spaces (ventricles) within the brain; two had underdevelopment of the cerebellum part of the brain important for motor control; one had mild hydrocephalus (accumulation of fluid) due to a blockage in the pathway for the fluid in the brain; one had underdeveloped optic nerves linking the brain with the eyes; and one had what was interpreted as a cyst (Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Okamoto 2012; Unique). The child's doctor will explain the results of an MRI brain scan.

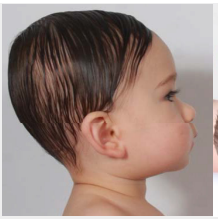
" He was seen by a neurologist at 3 and we were told that he has less grey matter in the brain and his brain is not as 'wrinkly' as they would normally see. They explained that it means that he will not be a genius but will be a normal, fully functioning child and adult. They were not concerned at all.**"** 5 years

Appearance

To parents, a baby with a proximal 10p deletion may look little different to other babies. Doctors trained to notice differences in children's faces have identified some characteristics as being more common when the child has a deletion involving chromosome 10p11 and/or 10p12. These include: a monobrow (eyebrows that join in the middle); a prominent forehead (frontal bossing); downslanting eyes; an unusual ear shape or small ears; deep set eyes; a wide, low or flat nasal bridge; and a downturned mouth. Additional features observed in more than one person include a short, possibly upturned nose; a bulbous tip to the nose; wide set eyes; skin folds covering the inner corner of the eye; a wide mouth without a Cupid's bow and with more than usual of the red part of the upper lip showing; unusual ears; a short neck; and the upper jaw and cheekbones being set further back than normal (midface retrusion) (Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Okamoto 2012; Mroczkowski 2014; Bosch 2015; Sosoi 2015; Abdelhedi 2016; Unique).

"He looks like his paternal grandma." 5 years

"Very cute." 13 years



The photographs in this guide show that children with proximal 10p deletions look quite different from each other. The photos above show (left) a boy with a 10p11.22-p11.23 deletion, and (right) a boy with a microdeletion in 10p11.21 whose natural head shape is what a geneticist would call brachycephaly.

Minor hand and foot abnormalities

Minor anomalies are common and varied and most do not have any impact on the child. Families report many fewer anomalies than doctors. The feature observed most often is a single or abnormal crease across the palm. Other features include: incurved fingers and toes; tapered, thick or short fingers; a short bone linking the wrist and the fifth fingers; short hands and feet; flat feet; under-developed nails; 'puffy' backs of the hands and feet; and toes that are bent and cannot be straightened (camptodactyly) (Shahdadpuri 2008; Wentzel 2011; Bosch 2015; Sosoi 2015; Unique).

Repeated chest infections

7/22 Unique children had repeated chest infections as babies and young children. Only two of these children also had a history of reflux, so inhaling part of their feeds was probably not playing a role in the repeated bouts of illness. One baby of two months needed mucus frequently suctioned from the airways to

improve breathing, and another had noisy breathing (stridor) caused by a collapse of the structure of the voicebox (laryngomalacia) to the age of 3; one child suffered a collapsed lung (pneumothorax); and two were diagnosed with asthma. In general, these children caught more colds than their brothers and sisters; the colds turned more often to chest infections; they were more ill; and they were more likely to be taken to hospital. Children generally outgrew the tendency to chest infections, but despite improvement, one girl of 13 still had colds lasting for 3-4 weeks with copious productive coughing and vomiting of mucus; testing showed that she was not immunodeficient. Sadly, two children died as a consequence of their chest infections (Sosoi 2015; Unique).

Hearing

All babies have their hearing tested at birth, and many of those with a proximal 10p deletion will pass this test and have no problems with hearing. However, seven children are known to have had some degree of hearing loss, and in a few the deafness was permanent. In five children the hearing impairment was caused at least partly by glue ear, the fluctuating, temporary hearing loss common in babies and young children, caused by a build-up of fluid behind the eardrum, and treatable by inserting aeration tubes (grommets) into the eardrum.

In two children, the glue ear combined with a permanent nerve deafness, and in one teenager hearing got progressively worse until she was profoundly deaf. In one child, the hearing loss was caused by a narrow ear canal (Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Unique).

“ He has 80% hearing loss in his under-developed ear. This is due to the narrow ear canal rather than any actual ‘loss’. Investigations have shown that the internal workings of the ear are normal.” 17 years

Other medical concerns

- Four Unique children have had a kidney problem or urinary reflux. Problems include: renal cysts which cleared naturally without causing further concern; enlarged kidneys joined at the bottom to form a horseshoe shape.
- Three Unique children were diagnosed with low thyroid levels and two were treated with thyroid hormone.
- Three babies, including two at Unique, were born with inguinal (groin) hernias. In one of them, the hernia re-appeared in adult life. This type of hernia shows as a bulge in the area where the lower abdomen meets the upper thigh (the groin). An opening in the lower part of the wall of the abdomen during fetal life has failed to close as normal before birth. The remaining opening may be small, only allowing fluid through, or it may be large enough for something such as a loop of the intestine or another organ to get stuck in it. An inguinal hernia should be assessed by a doctor and the child may need surgery to repair it. One baby had an umbilical hernia (at or near the belly button). This may close on its own or need surgical repair.

- Two girls aged 11 and 13 have a spinal curvature
- At 2 and 3 years, one child responded to infection with a drop (instead of a rise) in body temperature, acute lethargy and dehydration. The cause of this unusual response was never found, but he responded well to intravenous fluids
- An adult had repeated bouts of acute pancreatitis
- The collar bone failed to form properly in one child
- One child has coeliac disease
- One child has an extra rib
- One baby was born with a blocked nose on one side and an asymmetric chest wall and pigeon chest (pectus carinatum) on the left side

(Yatsenko 2004; Shahdadpuri 2008; Wentzel 2011; Bosch 2015; Unique).

Behaviour

Ask a family about behaviour and they are likely to tell you that their child is loving, friendly and happy. 'The most loving person you could hope to meet' said the family of a boy of 17; 'Very happy, great sense of humour, endears herself to people because she is so smiley, very giving, wants to share' – a girl of 13; 'very cuddly and affectionate'- a girl of 9; 'very loving and smiles a lot'; a 'baby who loves kisses and body contact'. Socially interactive, 'very sociable' is how parents described their child's attitude to others. 'A loving little boy, giving kisses and fistbumps to everyone' one family said of their 2-year-old son. At college, the tutors of the 17-year-old say he is a good friend and tries to make sure everyone is included in activities. Children are happy, even bubbly. They make others laugh. 'He has the most amazing sense of humour, he makes us laugh every single day and is good company.'. Youngsters are also described as caring, 'kind and thoughtful', empathetic; loving animals and babies; emotionally intelligent; generous and happy to share.

Music can be important in children's lives.

Any difficulties need to be seen against this background. The difficulties are there: short attention span; an unusually high level of activity, even in a baby, and hyperactivity; harmful responses (self, others) to frustration or fear; separation anxiety; delay in engaging with others socially and remaining socially disengaged; dislike of changes of activity or place, new places, noisy places or busy places; some obsessive behaviours; and in a few, autistic features (repetitive behaviours such as rocking, narrow interests).

Families generally cope without professional help, setting boundaries, allowing gradual adaptations to change, making allowances for sensory processing disorders, ignoring bad behaviour, using distraction, creating a structured environment, heaping on praise, finding creative ways to communicate.

One or two children can be aggressive, with an explosive temper, attacking family and classmates. Many families of children with chromosome disorders including a few of those with proximal 10p deletions need professional help, and behaviour problems are often discussed on Unique's Facebook pages.

Where children have been medicated for their difficult behaviours, most but not all have responded well. One family described their daughter's response to two days of methylphenidate (Ritalin) as 'horrible: she went crazy'.
The PIP5K2A gene in 10p12has been linked to psychiatric disorders and might play a role in the observed behaviour difficulties (see **Genes**, pages 22-23). However at least one child with an intact PIP5K2A gene had behaviour difficulties (Wentzel 2011; Bosch 2015; Abdelhedi 2016; Unique).

❝ The biggest thing now is her challenging behaviour. She is very hyperactive, just can't stay still, so is a danger to herself and others. You can't leave her alone for one second. She used to hit her head: we ignored it, and it's gone. Spitting was a big thing from the age of 5 or 6 when people got too close to her on a tram or bus. We couldn't ignore it, and it has persisted. She can't control her excitement. If you tell her something exciting at table, she can't hold back: she will clear the table and throw her plate across the room. So you have to tell her in a safe place.❞ 13 years

Sleeping

Problems with disturbed sleep have been noted in four children. One girl needed very little sleep while another would cry out and scream at night. Medications such as melatonin and clonidine have been used to treat those with disturbed sleep patterns (Wentzel 2011; Unique).

❝ Her sleep is much better now she is no longer on oxygen at night. She goes to bed early, lights out by 20.30. She used to wake constantly at 4am but now she is locked into her bed. When she wakes now, sometimes she falls asleep again, sometimes she tries to be so noisy that she wakes us. But this has improved too: 4 to 6 days a week she is OK unless she has a cold.❞ 13 years

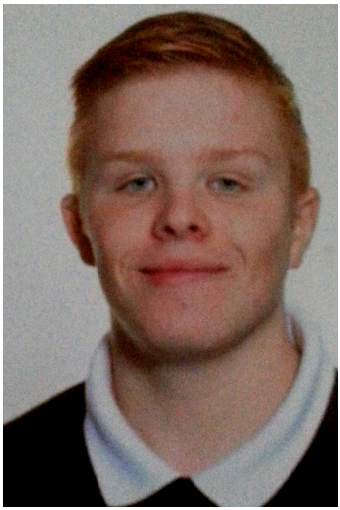
❝ There was a time between the ages of 1 and 3 when he wouldn't settle and kept waking up. However, this followed three serious chest infections in his first year that seriously disrupted his routine.❞ 17 years

Puberty

A girl with a 10p12 deletion had her first menstrual period relatively late at the age of 17. She also had underdeveloped breasts and subsequently underwent a breast augmentation. Another girl had her first menstrual period early at the age of 8 and her periods have subsequently always been irregular. Another girl had her first period at 13. She was more whiney and irritable beforehand (Wentzel 2011; Bosch 2015; Unique).

Families say what is special about their child

Children with different deletions from proximal 10p can be very different from each other. But each one is special.



10p11.23 deletion
Teenager

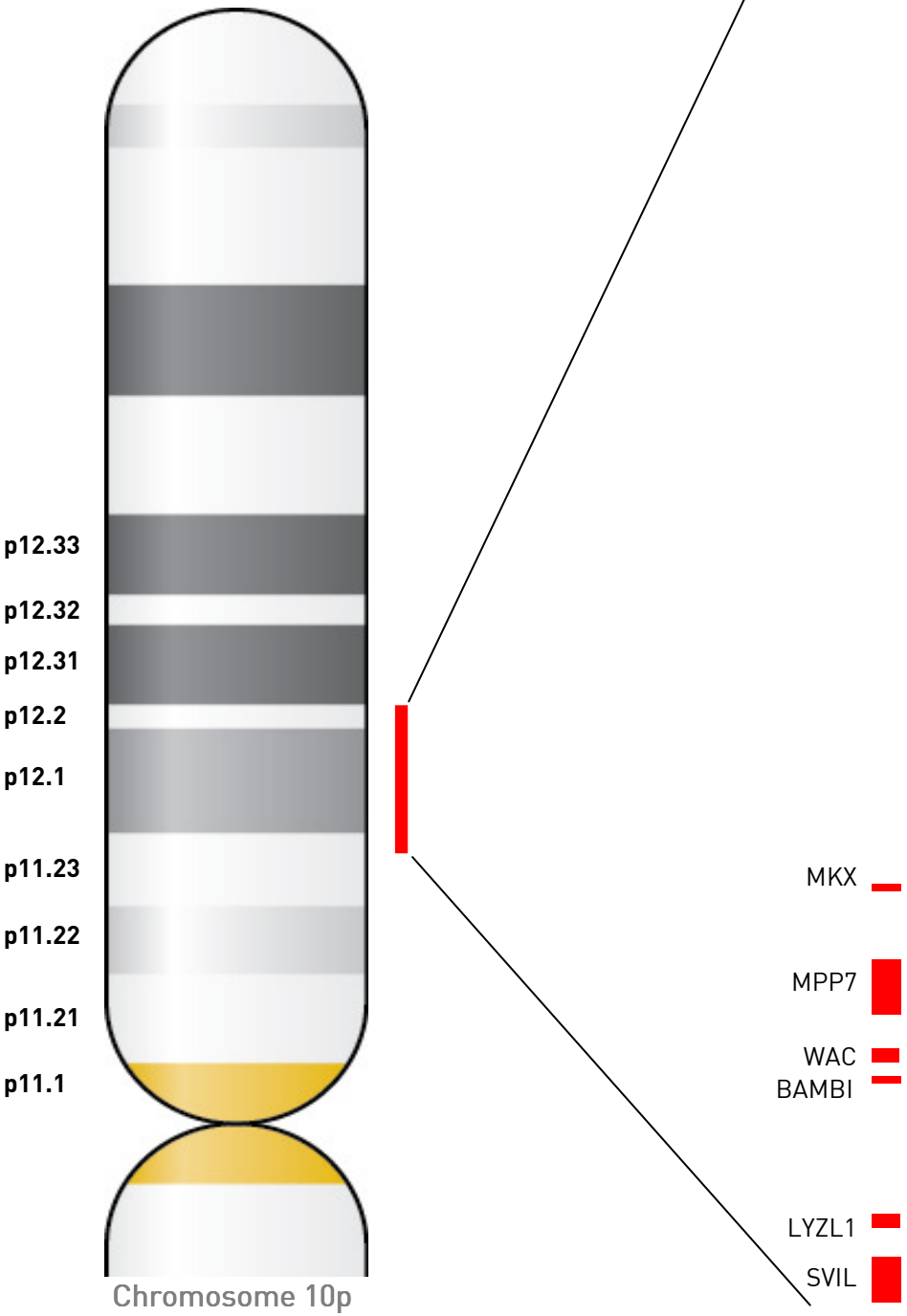
“ For my son, developmental delay and learning difficulties are what having his 10p deletion means. He's been through special schools since he was 6 (year 2) and now is at college doing a transition course. Obviously his physical appearance differs - he's short and stocky and very strong, and is still very heavy as well as looking young for his age. The autistic traits he shows also mark him out as a bit different. That being said, he has always been popular at school and college and never thinks of himself as 'special'. He has the most amazing sense of humour, makes us laugh every single day and is good company. He is kind and thoughtful and at college his tutors say he is a good friend and tries to make sure everyone is included. He is also the biggest football fan and loves Liverpool FC. ” 17 years

“ She loves animals, babies and music and likes to play outdoors. She is very cuddly and affectionate. Very generous, likes sharing, has a good sense of humour and a musical ear, and good comprehension for languages. ” 11 years

“ He knows how to make every one happy. He can bring a smile to your face even on a bad day. He loves to play pretend and has the biggest and most wild imagination. He is very mature (he has 8 older siblings) and can hold his own as the baby of the family. He would like to be a doctor when he grows up, but some days he says he wants to be a garbage man! He makes friends wherever he goes! He is very musically inclined and loves his guitar, drums and harmonica. He has been such an amazing blessing to our family and makes us all thankful that there are people out there that have chosen to be organ donors. Without new cornea tissue, he wouldn't be able to see.” 5 years

“ He loves to laugh, and gives the best hugs.” 5 years

Genes



Chromosome 10p

PIP5K2A

Also called PIP4K2A

The PIP5K2A gene in 10p12.2 at 22,823,778-23,003,484 is responsible for producing a protein that appears to be active in red blood cells. The gene has been linked to psychiatric disorders and might play a role in behaviour difficulties (Wentzel 2011; Bosch 2015).

MKX

The MKX gene in 10p12.1 at 27961804-28034989 is responsible for producing a protein has been found in mice in the earliest days after conception in a wide variety of parts of the body: the face, the top of the mouth [palate], some muscles, parts of the kidney, the bones, limbs and the structures that will become the male genitalia. One research group has suggested that losing one copy of the MKX gene plays a role in undescended testes, as one of the gene's many roles is to regulate the descent of the testes from the abdomen to the scrotum (Mroskowski 2014; Sosoi 2015).

MPP7

The MPP7 gene in 10p12.1 at 28,339,922-28,623,415 is responsible for producing a 'Stardust' protein that joins with two other proteins including one called DLG1. As a group these are then important in the skin.

WAC

The WAC gene in 10p12.1 at 10: 28,821,422-28,912,041 is responsible for producing a protein that is known to be important in a wide variety of processes within the cells of the body. These include different stages of the actual process of converting DNA [the gene] into protein – the fundamental principal function of genes. Although much remains to be explained about what WAC does, this means that it is likely to be at least partly responsible for a wide range of anomalies and developmental problems in people in whom WAC is altered [mutated] or deleted.

BAMBI

The BAMBI gene in 10p12.1 at 10:28,966,271-28,971,868 is responsible for producing a protein that is found in the placenta, the spleen and parts of the kidney but not in the lungs, skin, or muscles.

LYZL1

The LYZL1 gene in 10p11.3p12.1 at 29,577,990-29,607,257 is thought to play a role in heart conditions.

SVIL

The SVIL gene in 10p11.23p12.1 at 29,746,267-30,025,710 is thought to play a role in heart conditions.

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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Please help us to help you!

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