Support and Information

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There is a Facebook group for chromosome 10 disorders at www.facebook.com/groups/chromosome10disorder

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.
This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. It was compiled by Unique and reviewed by Dr Kavita Reddy, Genetics Department, Kaiser Permanente of Southern California, USA and by Unique's chief medical advisor, Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK. 2011 (PM)

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10q22q24 deletions

Sources and references

Information has been drawn from 50 cases: 30 in the published medical literature, 14 from *Unique*'s database; and 6 unpublished cases from the Decipher database (http://decipher.sanger.ac.uk). Information varies from full developmental and medical data to a handful of salient features. So it's possible that some important information has been missed out, especially as regards development after babyhood and early childhood. The cases in the medical literature published before 2006 were generally not examined using array-CGH so the given breakpoints may not be as accurate as they would be today. 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 [http://www.ncbi.nlm.nih.gov/pubmed]. [Davis 1982; Morey 1985; Glover 1987; Mori 1988; Farrell 1993; Arch 1997; Doheny 1997; Jacoby 1997; Tsuchiya 1998; Cook 1999; Delnatte 2006; Salviati 2006; Sanlaville 2006; Tzschach 2006; Balciuniene 2007; Alliman 2010; Babovic 2010; Tzschach 2010; Reddy 2011; van Bon 2011; Decipher; *Unique*].

10q22 to 10q24 deletions

People with a deletion between 10q22 and 10q24 have lost a small piece from one of their 46 chromosomes. This piece is missing from all the cells in the body that are needed for growth and development. For correct development, the right amount of genetic material is needed – not too little and not too much. Missing a piece of a chromosome makes it likely that there will be some difficulties with development, health, behaviour or learning. But *Unique*'s experience is that despite the challenges, children are generally happy and sociable and can surpass expectations in their achievements.

Unique families say what is special about their child

" Her dancing is wonderful: she picks up a routine instantly. She is a joy to watch and really enjoys doing it which makes it even better. She is loving and thoughtful and very helpful. She has achieved far more than we believed she would when first diagnosed. Her progress may be slower but she has got there in the end. I think help, encouragement and support along the way have helped her immensely - 16 years

" He can be very lovely when he wants - 16 years

" Despite all of his challenges he has given so much meaning to our lives. As his mother I have become so much more assertive and much more clear about how I want to spend my time. He has a real joy and zest for life and he brings such enthusiasm to even the most mundane experience! - 8 years

" She is a bundle of joy: though she's got a disability, that does not stop her from being a pleasant child with a radiant smile who never ceases to amaze us. In her own way she is very intelligent - 3½ years

" He is a beautiful boy. He has taught us to accept children of all needs. We have made lots of new friends through portage and *Unique*. He is affectionate and funny - 3 years

Looking at 10q

Chromosomes are the structures inside the body's cells that carry DNA, the genetic information that tells the body how to develop and function. They come in pairs, one from each parent, and are numbered 1 to 22, approximately from largest to smallest. Each chromosome has a short [p] arm and a long [q] arm. A 10q deletion means that material is missing from the long arm of one of the chromosome 10s.

How did the piece of chromosome 10 go missing?

A blood test to check both parents' chromosomes will be offered to find out how the piece of chromosome got lost in the child. Whatever the reason, as a parent you certainly did nothing to cause it and nothing you could have done would have

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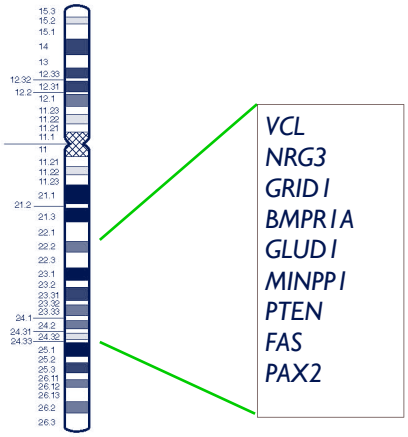
Some genes in 10q22-10q24

People with a 10q deletion between 10q22 and 10q24 can be missing anything from a handful of genes to more than 100. The function of many of the genes is not yet known, but losing one copy of some of these genes has been suggested as the possible cause for certain symptoms [Balciuniene 2007; Vasan 2009; van Bon 2011; Reddy 2011].

Identifying the gene or genes responsible for certain features of a 10q deletion may be valuable as doing so may help to guide future studies, but this does not currently lead directly to immediate improved treatment. Even if one copy of the supposedly responsible gene is missing, the associated feature[s] will not necessarily be present. Other genetic and environmental factors are often important as well.



VCL 10q22.2 Mutations associated with dilated cardiomyopathy. See page 14.

NRG3 10q23.1 Known to be involved in early breast development in mice. Could be responsible for failure of breast to grow. Important in neurobehavioural development and function [Balciuniene 2007; van Bon 2011].

GRID1 10q23.1 Important in neurobehavioural development and function [Balciuniene 2007]. Proposed as candidate gene for left ventricle wall thickness [Vasan 2009]. Absence could cause cardiac defects [van Bon 2011]. Also proposed as causative gene for schizophrenia [several studies cited by van Bon 2011].

BMPR1A 10q23.2 Tumour suppression gene; also associated with cardiac structure and function; also important in neurobehavioural development and function; associated with juvenile polyposis syndrome [Balciuniene 2007; Reddy 2011].

GLUD1 Important in neurobehavioural development and function [Balciuniene 2007].

MINPP1 10q23.2 Important in neurobehavioural development and function [Balciuniene 2007].

PTEN 10q23.31 Tumour suppression gene; also important in neurobehavioural development and function [Balciuniene 2007].

FAS 10q23.31 a gene with a pivotal role in regulating apoptosis [programmed cell death].

PAX2 10q24.31 Mutations cause renal coloboma syndrome, renal dysplasia usually with coloboma. This is an eye and kidney disorder, but other body systems can also be involved [Reddy 2011].

prevented it. No environmental, workplace, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when they occur and nobody is at fault.

10q deletions sometimes occur out of the blue for no obvious reason or they can be inherited. If both parents have normal chromosomes, the deletion is almost certainly a new occurrence. The genetic term for this is de novo [dn].

When a sperm cell from the father and egg cell from the mother first join together, each typically carries just one copy of each chromosome. Together they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself [and all the chromosomes and genetic material] in order to make the trillions of cells that form into a human during 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. People with a 10q deletion have one intact chromosome 10, but a piece from the long arm of the other chromosome copy is missing. Since some genes are missing, it is believed that most of the clinical difficulties are probably caused by having only one copy [instead of the usual two] of a number of genes. But a child's other genes, environment and unique personality are also important in determining their future development, needs and achievements.

Can a 10q deletion happen again?

When a blood test shows that both parents have normal chromosomes , it is unlikely that another child will be born with a 10q deletion. When a parent has a rearrangement of their chromosomes with a break at 10q22-q24, the risk of having another affected child is higher and in the very unusual situation where a parent has the same deletion as the child, the risk can be as high as 50 per cent.

Could my child with a 10q deletion pass it on?

Adults with a 10q deletion may form close relationships and want to have children. Assuming that fertility is normal, in any pregnancy, someone with the deletion is likely to have a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the deletion. Their ability to look after a child is very likely to be closely related to their own degree of learning difficulty.

Unique families say what they wish they had known earlier

❝ I wish that I had let other people take my daughter as they found her instead of advising people first of her chromosome abnormality and secondly her autism. We as a family may have made her stand out for her difference and not her exceptional personality.

❝ I wish I'd known what hard work it would be to fight to get the right placement for school and adult life.

❝ It took us a long time to find the right people to help us develop a home program which was right for our son. I now wish I had had this information to use at each stage of the journey: for mobility – use chiropractic, and the program developed by the Institutes for the Achievement of Human Potential. For speech – PROMPT [www.promptinstitute.com] & The Affect-Based Language Curriculum, developed by Diane Lewis and Stanley Greenspan. For reading – the program Teach Your Child to

Read in 100 Easy Lessons. For behavior – Autism Partnership [www.autismpartnership.com]. For nutrition – high protein, gluten free, organic, lots of essential fatty acids - *family of a boy, 8 years, with a 10q22.1 deletion.*

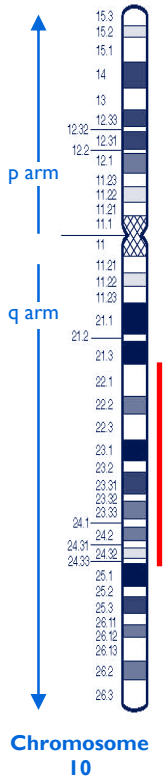
Please note that while encouraging stimulation and early intervention with individually-tailored therapies, Unique does not endorse any particular developmental programmes used for children with chromosome disorders.

Chromosome analysis

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a high-powered microscope, you can see that each one has a distinctive pattern of light and dark bands. You can see these bands in the diagram of chromosome 10 on the right. The bands are numbered outwards starting from the point where the short arm meets the long arm [the centromere]. A low number such as q11 is close to the centromere. A high number such as q24 is further down the chromosome.

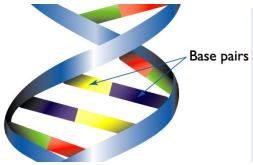
If you magnify chromosomes to hundreds of times life size and look at them down a microscope, the missing piece of chromosome 10q may be visible. A visible missing piece is often called a deletion.

The banding pattern on chromosome 10 makes it very hard to distinguish under a microscope missing bits at 10q23.2 to q24.1 from bits missing at 10q22.3 to q23.2. Newer ways of examining chromosomes such as array-CGH [microarrays] and the FISH technique using fluorescent DNA probes targeted to gene markers within the relevant 10q region give a more accurate diagnosis as well as showing whether important genes are missing or not. Some people diagnosed on conventional chromosome analysis with a 10q23q24 deletion or a 10q23 deletion have been found using array-CGH to have a 10q22q23 deletion and some people with apparently normal chromosomes even at high resolution have been found to be missing important genes. Since this region of 10q is particularly rich in genes, it is helpful to use the most precise technology available [Delnatte 2006; Salviati 2006; Balciuniene 2007; Reddy 2011].



Array-CGH [microarrays]

Array-CGH shows gains and losses of tiny amounts of DNA throughout the chromosomes. DNA has a ladder-like structure where each 'rung' in the ladder links a pair of chemicals known as bases. The size of small deletions and microdeletions, detectable only by array-CGH and similar techniques, is often measured in pairs of bases, called base pairs. You will sometimes see base pairs referred to as nucleotides or the 'building blocks' of DNA. Each chromosome has millions of base pairs – chromosome 10 alone has about 135 million. So chromosome 10 is about 135Mb long.



Bases are the chemicals in DNA that are linked in pairs to form the ends of the 'rungs' of its ladder-like structure. One thousand base pairs is often written as 1 kb. One million base pairs is often written as 1Mb.

is unusually short for his age, as are many youngsters with pieces extra or missing from any of the chromosomes.

Of the two children with much larger deletions, a toddler of 16 months with a deletion of around 8.25Mb from 94.89-103.14Mb at 10q23.33 to 10q24.32 had, in addition to the kidney problems just mentioned, a number of features that are relatively common among youngsters with a chromosome disorder, such as a squint [strabismus], low muscle tone making her floppy, incurving fifth fingers and some delay in learning to sit, walk and talk. She was also born with a moderate enlargement of the part of her heart responsible for pumping blood around the body [left ventricular hypertrophy], although this was seemingly not a concern by the time she was 16 months old.

The person with the largest amount of missing chromosome material – around 12.43Mb between around 89.14Mb at 10q23.2 and 101.57Mb at 10q24.2 – is reported with relatively few complaints: a delay in development and need for learning support, an unusually small head, a birthmark and low blood sugar.

Learning and development

Some children with very small microdeletions within the 10q23 band have ordinary levels of intelligence. Their deletions extended from 88.4 to 90.4Mb and from 88.5 to 90.6Mb [Delnatte 2006]. Others with slightly larger deletions from 87.8 to 92.5 Mb and from 82.1 to 94.4Mb have mild learning difficulties [Tsuchiya 1998; Salviati 2006].

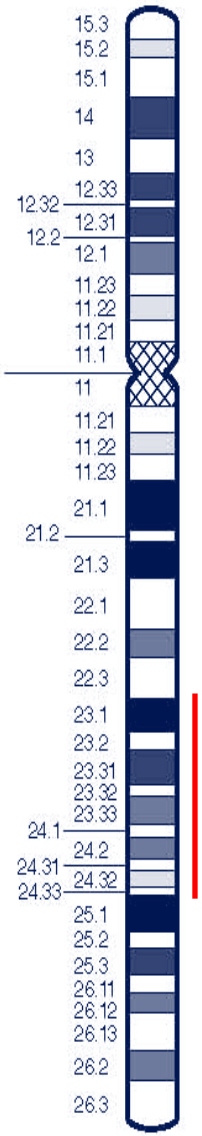
Polyposis syndromes

Children who have lost the *BMPR1A* gene at around 88.5-88.6Mb and possibly also the *PTEN* gene at around 89.6-89.7Mb in 10q23.2 may develop polyps in the gastrointestinal tract in childhood. Polyps are growths of tissue from the intestinal wall that protrude into the intestine. Usually, polyps are not cancerous but in some children, the polyps turn cancerous. Polyposis is a condition where there are a lot of polyps.

There are different types of polyposis, including one particularly severe form, known as juvenile polyposis of infancy [JPI]. Signs of JPI include onset before the age of 2, severe rectal bleeding, diarrhoea, protein-losing enteropathy [abnormal protein loss from digestive tract or inability of digestive tract to absorb protein], inanition [exhaustion from lack of nourishment] and rectal prolapse [tissue lining the rectum falls into the rectal opening]. JPI is associated with an increased risk of colon cancer. When two tumour suppressor genes in the 10q23 band known as *BMPR1A* and *PTEN* are missing, it has been suggested that JPI can sometimes be the consequence. The size of the deletion does not seem to be relevant; children with larger deletions can be more mildly affected than children with small deletions [Tsuchiya 1998; Delnatte 2006; Salviati 2006; Sanlaville 2006]. Children who have lost these genes may also be at risk of developing other types of tumour [Babovic 2010].

The precise role of the *BMPR1A* and *PTEN* genes in the development of polyposis is still a matter of debate but when one or both is lost, a child can expect to be monitored for rectal bleeding and early growth of polyps.

Flanking deletions: 10q23q24 deletions



Many people diagnosed by conventional chromosome analysis with a deletion between 10q23 and 10q24 may in fact have a deletion of a slightly different part of chromosome 10q. Here we have only included people with a diagnosis from microarrays or other molecular technology showing clearly that the deletion is from 10q23/10q24. There are many others in the medical literature diagnosed using conventional chromosome analysis [Jacoby 1997; Farrell 1993; Mori 1988; Maltby 1986; Morey 1985] but these are not included. The experience of the 9 *Unique* members diagnosed by traditional chromosome analysis is described separately on pages 5-10 in **The *Unique* experience**.

Four people have been described or reported in the medical literature with a molecular or microarray diagnosis: a toddler of 16 months [Reddy 2011] and three people on the Decipher database [Decipher]. In addition, six youngsters were diagnosed with a 10q23 deletion after developing a type of gastrointestinal polyposis [Tsuchiya 1998; Delnatte 2006; Salviati 2006; Sanlaville 2006].

The points at which chromosome 10 has broken and rejoined are different in each case as is the amount of deleted material and the number of missing genes.

A child with the smallest deletion, between around 91.59Mb and 91.97Mb in 10q23.31, inherited this from one of their parents who was unaffected. This raises a question as to whether the tiny amount of missing chromosome material is in fact responsible for the child's problems – hyperactivity and a short attention span, a delay in development, a need for support with learning and unusually bendy elbows and wrists.

A slightly larger deletion between around 102.9Mb and 103.45Mb from bands 10q24.31 to 10q24.32 was found in young man with kidney problems. The deletion was overlapped by a much larger one – 94.89Mb to 103.14Mb, from 10q23.33 to 10q24.32 - in a different young child who also had abnormal kidneys. It's been suggested that underlying the kidney problems in both young people is the absence of a gene known as *PAX2*. This is because it's already known that a change in a single base pair in *PAX2* can cause abnormal kidney development. So it seems that when the *PAX2* gene is missing, doctors should pay particular attention to a child's kidneys [Reddy 2011].

A young man with a 102.9-103.45Mb deletion had quite a few other problems: he has a cleft lip and palate, a narrowing of the blood vessel that leads from the heart to the lungs [pulmonary stenosis], very small eyes and a hearing impairment. A heart problem was also seen in a 3-year-old child with a 12Mb deletion from 82.1Mb to 94.4Mb in 10q23.1q23.33 who had a small hole between the upper chambers of the heart [atrial septal defect] [Salviati 2006]. The young man has needed support with his learning and

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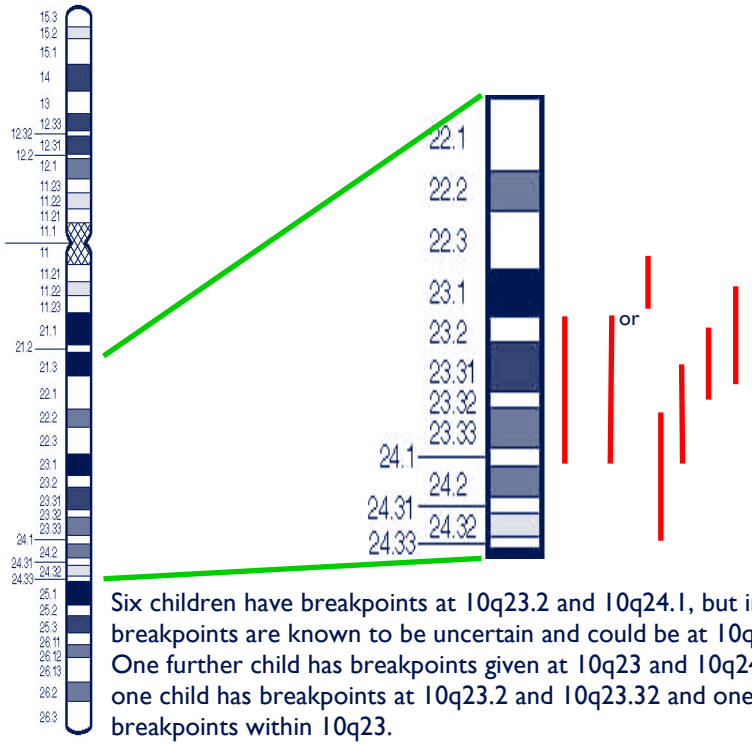
10q22q24 deletions: the *Unique* experience

Of *Unique*'s 10 members with a deletion between 10q22 and 10q24, nine were diagnosed using chromosome analysis, without microarrays. Five families completed a detailed survey about their child's progress in 2011; their children were then between 3 and 16 years old. The families' experiences are summarised here.

Where are the breakpoints in chromosome 10?



Six children have breakpoints at 10q23.2 and 10q24.1, but in two of them the breakpoints are known to be uncertain and could be at 10q22.3 and 10q23.2. One further child has breakpoints given at 10q23 and 10q24. Beyond these, one child has breakpoints at 10q23.2 and 10q23.32 and one has two breakpoints within 10q23.

Development

Some developmental delay was noticed in all children with full records; the delay was often a reason for seeking genetic advice. There is quite a wide range of severity, with marked differences between the two 16-year-olds, one of whom is significantly delayed while the other is 'very independent'. Generally, all areas of development are affected but some families say that learning to talk and moving around [motor skills] are most affected. Hand-eye coordination or using their hands [fine motor skills] is much more obviously affected in some children than others.

Learning

Families assess their child's need for support with learning as moderate. As you can read below, children with a moderate learning difficulty can make considerable achievements but there are significant differences between youngsters of the same age and with apparently very similar chromosome deletions.

❝ His memory is good. He likes routine and remembers where things are from one week to the next. Learning new skills takes some practice which is where portage [early intervention] helps. If he enjoys a particular task, he will concentrate to complete it. If he does not enjoy a task he lacks the patience to complete it. He enjoys playing, especially with cars, tractors and lorries. He likes books, especially books with varying textures. He is unable to read yet but if you ask him to point to particular items in a book he can do so. He can draw circles and is now learning to draw straight lines. He attempts to use a computer mouse at home/nursery - 3 years

❝ She has a good memory. Generally she is better at visual tasks and learns by persistence. She imitates reading and vocalises as she does so - 3½ years

She was reading and writing by 4 and recently did well in her GCSEs [UK exams taken at 16 years], getting a B in catering, a C in English and passing all subjects she took. She wasn't able to tackle maths: she is totally unable to recall mathematical sequences. She is helped by being very determined and independent; she also loves to please people. She writes a lot but her drawings are very child-like. 1:1 support seems to work best for her and visual teaching is also very successful - 16 years

❝ He writes own name but otherwise cannot write and hates drawing: his fine motor skills are very poor. He has a good long term memory, but poor short term. He attends a school for children with autistic spectrum disorders - 16 years

Speech and communication

A delay in learning to talk was evident in all children with full records. Children first smiled only a little late and their first words were heard between 2½ and 5 years. They are keen communicators, using a rich variety of ways to get their meaning across: vocal noises, gestures, signing, taking you to what they want, as well as more formal techniques such as picture exchange systems. There seems to be a link between early talking and eventual fluency, with early talkers more likely to be fluent later and later talkers more likely to need some support with their communication.

❝ He made noises as a baby but not normal babbling of babies his age. He can say 5 words and sign approximately 25 words. He understands everything that is said to him but has difficulty communicating back. He makes noises and points to what he wants or he takes the hand of the person he is talking to and shows them what he wants. He nods and shakes his head for Yes and No. He is very sociable and makes good eye contact - 3 years

❝ She uses signs to point what she needs or pulls you to where she wants you to help her. She taps you and points, making vocal noises. She can say No if you are doing the wrong thing until you guess right what she wants. She can say Mama, no [sounds like mo], Daddy and Dada. Otherwise she sings and dances to tunes that she understands or tries to imitate what she has heard - 3½ years

❝ She talks normally, using fluent conversation, though some sounds at the front of the mouth [sh, ch] can be pronounced incorrectly. She can have problems with understanding - 16 years

Other

Unique has four members with deletions within 10q21 and 10q22, aged between 8 and 35 years. Information from the group's database shows that developmental delay is consistent, with walking achieved from 18-28 months and first spoken words typically emerging in the third year of life but in one case not until 4½ years. Toilet training developed in the 2nd or 3rd years but in one case was not consistent at night until 7 years.

Medical problems differ between individuals. One girl is apparently healthy in early childhood, while a boy of 8 is generally healthy but takes or has regularly taken 25 different nutritional supplements. At birth a small lymphangioma (a small grape-like structure) was found under his tongue. This resolved spontaneously at 7 weeks of age. At birth he was noted to have a branchial cyst on his neck [a cyst that has arisen from embryonic remnants], which was repaired at 1 year. Although he was a good weight for his gestational age (8lb 2 oz/ 3.6 kilos at 41 weeks), he needed oxygen and suctioning to start breathing and low levels of oxygen were given for the first 12 hours. He was breastfed to 18 months and aside from being a noisy feeder, had no feeding problems and at 8½ years eats a normal diet using normal utensils, although he has a chair with a foot support to stop his feet from pronating. At 8½ years, he has teeth crowding especially in his lower jaw and unusual tooth positions in both jaws. Additionally, he has very challenging behaviour and needs a highly structured environment with constant 1:1 adult support. His difficult behaviours include aggressiveness – hitting, spitting, throwing heavy objects – and being destructive – throwing, tearing, scribbling on furniture. He is currently enrolled in a full time behavioural program. Having said this, he loves to engage with people. He has no inhibitions – he is very curious and will speak to or go with strangers.

One of his challenges is that he does not have many/ any age appropriate activities that he enjoys. He enjoys looking at pictures of airplanes on the computer, some DVDs (Stuart Little, Toy Story, cars). He loves travelling on airplanes and likes to buy airplanes and to look at airplane books. He is good at puzzles (vehicles, airplane puzzles). Overall he has always been a good sleeper.

Another young adult has chronic liver inflammation and primary immune deficiencies (IgA, IgG-2, and IgG-4) for which he is treated with regular intravenous gammaglobulin. Another adult has allergies affecting breathing [asthma] and skin [rashes]. She also experiences unexplained swollen, aching joints. She has had swollen lymph nodes excised.

Puberty

Information is available on only one woman for whom puberty proceeded normally, although breasts never fully developed.

It is of note that mutations in the vinculin gene, *VCL*, which is found in the 10q22.2 band between base pairs 75427878-75549916, have been associated with dilated cardiomyopathy in adults. It has been recommended therefore that adults with 10q22 deletions including the *VCL* gene should undergo regular cardiac examinations. Dilated cardiomyopathy is a condition where the heart becomes weakened and enlarged and cannot pump blood efficiently [Tzschach 2010].

- **Dental lamina cysts** 2/12

Whitish-yellow nodules on the gums and hard palate are seen in many newborn babies. No treatment is needed and the cysts usually disappear within a week or two of birth [Cook 1999; Tzschach 2010].

- **Short stature** 6/11

This may follow normal length and weight at birth or continue a pattern of slow growth that started before birth. Growth hormone treatment may be offered but outcomes are unknown.

❝ Four foot two inches – 75th percentile – and appropriate body build for age - 8½ years

- **Unusual facial features** 9/9

Among a variety of slightly unusual facial features, the most common are wideset eyes, a broad nasal root and unusually formed or positioned ears. A relatively large head was seen in two children [Tzschach 2010; Reddy 2011].

- **Hand abnormalities** 5/9

These are usually but not always cosmetic and include long thumbs that look more like fingers, incurving fifth [little] fingers, a single crease across the palms and fingers that curl in and will not straighten.

- **Squint [strabismus]** 3/8

The crossed eye can look inwards, outwards, up or down. The main effect of strabismus is that usually one eye is stronger than the other. This is because the brain has to give priority to one eye over the other with the result that the weaker one does not 'learn' to see. Treatment of strabismus 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.

- **Hearing loss** 2/9

One child had profound permanent hearing loss in one ear and a moderate loss in the other ear [Tzschach 2010].

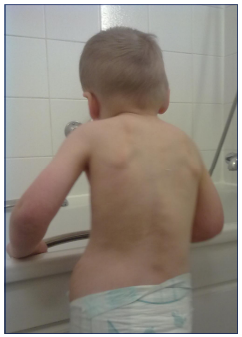
A *Unique* member has had 3 sets of bilateral ear tubes (age 1, 5, 6), adenoids removed at age 6 and wears hearing aids for mild to moderate hearing loss in one or both ears.

- **Minor genital anomalies** 4/9

Minor genital anomalies are not uncommon in children with a chromosome disorder. One girl had thin labia minora; another girl has underdeveloped external genitals; one boy had undescended testes and another had surgery to straighten a curvature of the penis [chordee] when he was a year old [Cook 1999; Reddy 2011; *Unique*].

Sitting, moving, walking

Everyone *Unique* knows about has had some delay in learning to sit, move and walk but was walking by 3 years. In the early stages of walking, children are liable to be unsteady, trip and fall. Some children have low muscle tone throughout their body or in some parts such as, in one child, in the upper body. Low muscle tone [hypotonia] makes a baby or child feel floppy and makes it more difficult and tiring for them to learn to move and walk. Physiotherapy [physical therapy] is very helpful both with low muscle tone and in helping children to get moving.



Two children have a curvature of their spine [scoliosis] that is significant enough for treatment to be considered. One child, 3 years old, currently wears a plaster jacket to straighten the spine but may need rods inserted into the spine later. He also wears a built-up shoe to correct the unequal leg lengths that have developed because of the spinal curve.

Babies learned to roll over between 8 and 12 months; to sit between 6 months and 2 years; to get mobile by crawling, bottom-shuffling or commando creeping between 19 and 29 months; and to walk between 13 months and 3 years. Children enjoy a wide range of physical activities including trampolining, swinging, playing, dancing and using an exercise bike. One youngster has a particular talent for dancing, can pick up a routine instantly and performs in public.

❝ His posture is normal: he sits in a chair with side arms but at present is unsteady when sitting due to his plaster jacket. He can only sit on the floor for short periods due to the plaster jacket and hypotonia in his trunk. He walks independently around the house and outside although he is unsteady on ground that is uneven. He is prone to falling if the ground is unsteady. He cannot run yet but enjoys playing with a ball, going on a swing and playing hide and seek - 3 years

❝ He doesn't like sitting in chairs and sometimes squats on the floor. He can walk for miles but walks with his feet turned in and tends to shuffle, not picking his feet up. We get through shoes every 6 months as the heels are worn away - 16 years

❝ Her dancing is a joy to watch and she really enjoys doing it, which makes it even better. She walks stably for half a mile at a slow pace - 16 years

Behaviour

With only four detailed reports available, no specific pattern of behaviour is obvious. All four *Unique* members are considered sociable; one has a diagnosis of autism spectrum disorder. The snapshots below illustrate what families have said.

❝ He is a happy, sociable boy, shy around strangers and appropriately affectionate with people he knows. He plays well with his older brother and is confident in areas he is familiar with such as church, playgroup, nursery and friends' houses. He loves playing with cars and moves them appropriately for his age level and generally has good imaginative play. He does become quite obsessive about DVDs to the point where I have to unplug the DVD player at times. When he goes out or goes to bed he has to be carrying a car or DVD disc/case and gets quite upset if he doesn't have one. He also loves dancing, especially music with a good drum beat such as Queen! and enjoys being made to 'jump' ie "Boo!": the more frightened he is, the funnier he finds it - 3 years

❝ Her behaviour is quite normal. She makes friends easily, waves and smiles, drawing attention to herself, and enjoys playing with her dolls, doll's house and kitchen corner - 3½ years

❝ He can be good but also challenging and can run off. He hates bad, cold weather. Socially, he interacts with adults, carers and a few peers - 16 years

❝ She is normally very quiet, listening to music on her computer and iPod. She likes to go on the computer but it's difficult to get her off. She also talks to herself a lot. She interacts really well with other special needs children and OK with adults and younger children but is unable and unwilling to chat to others her age, probably because she is aware she is not 'the same' and this is a barrier. We sought professional help from the child and adolescent mental health services but she doesn't open up to doctors so this was not very helpful - 16 years

2 years old

Personal care

Records show that toilet training was achieved between 3 and 5 years but this may not be possible for all. Partly because of differences in fine motor skills - using their hands - some youngsters are much more independent in personal care than others.

A 3-year-old has good fine motor skills but not at his level for his age: so he can put coins in a moneybox but cannot undo buttons/poppers, peel a banana, open a yoghurt or crisps due to his hyperflexed fingers. Threading beads, cotton reels and wooden shapes onto a lace have helped to improve his fine motor skills but he needs full help with washing and dressing. He can hold a leg or foot up if he can hold onto something to help him balance but he cannot put socks or shoes on. He can unzip a coat but cannot take it off himself. If you give him a flannel he will attempt to wash his face and he can brush his teeth.

One 16-year-old is effectively independent while another cannot do up buttons or laces and needs help when dressing, for example, with socks, and uses an electric toothbrush but had problems with an electric razor.

Feeding and growth

Newborn babies are liable to have difficulties with sucking and for some the difficulty is enough to make breastfeeding unmanageable. One newborn baby also had gastro oesophageal reflux [bringing back feeds] for five days after birth. Once feeding has been established, babies seem to thrive well and move on to solid foods without great difficulty. One child had difficulty with hard and chewy foods and at 3 years, still has some difficulty with very chewy foods.

Delay in hand use means that children may be delayed in feeding themselves and particularly in using cutlery, especially a knife. Specially adapted, easy-to-handle cutlery may help but these children may pick up their food with their hands for longer than typically-developing children. The range and variety of foods that children eat is unaffected.

All *Unique* children have a slim build but despite prenatal concerns about the baby's size in 2/5 pregnancies, there appears to be no consistent effect on growth or height after birth: some children are short, like other family members, others are tall.

❝ In the first 9 months of his life he achieved only the developmental milestones of a 1.5 month old. He commando crawled at 13 months, crawled on all fours at 19 months, took his first steps at 28 months – and then ran a mile in 20 minutes at 3 yr 6 months and clearly said 'I love you' to his mother at 4 years, 10 months. At 8½ years, his fingers are at times clumsy. Fine motor activities such as opening jars, taking lids off plastic containers, tying shoe laces are challenging but he is independent with dressing although not yet able to do buttons or zippers. He can tie his own shoes using a modified shoe tying technique but cannot yet independently brush his teeth or hair effectively. He was toilet trained in the daytime at 4½ years and at night at 7 years. The night bed wetting alarm was really effective – it only went off twice.

As far as mobility is concerned, he was unable to weight bear or sit upright at 9 months but by 8½ years, having followed the intensive home program developed by the Institutes for the Achievement of Human Potential in Philadelphia*, he tests around a 5-6 year old. He has an upright posture but his gait is a little ungainly but otherwise looks normal. He is able to walk as far as a child of his age. When he runs, his arms flap. He wears ankle orthotics for plantar flexion and below knee splints at night. Physical activities are challenging for him, so are not his preferred activities. He enjoys riding his 2 platform scooter and his 2 wheeler bike without training wheels.

** Please note that while encouraging stimulation and early intervention with individually-tailored therapies, Unique does not endorse any particular developmental programmes used for children with chromosome disorders.*

Learning difficulties 10/10

The degree of difficulty is usually not characterised but ranges from moderate to profound. *Unique*'s experience is that its members typically develop speech but this is not always the case in young children reported in the medical literature. One child with a microdeletion within 10q22 was talking by 2½ years and another with a microdeletion within10q22.1 was forming sentences by four years.

❝ He tests around a 5 year old level today. He did not babble and at 3½ years did not have any recognizable words. By 4 years, 7 months he was able to say 'I love you, Mum!' and communicate verbally. Today, at 8½, he is a verbal child although it is more challenging for him to speak than to understand what is said. He uses conversation, but is not yet fluent and has difficulty saying *r* and *th*, especially at the end of a word. Educationally, he is around 2-2½ years behind his age level in reading, writing and math. He reads at a 6 year old level and can write sentences, writing in printing form and larger than for a similar-aged well child. He is learning to touch type and is educated in a special education classroom, 2nd grade - 8½ years

Hypotonia [low muscle tone, floppiness] 6/10

Low muscle tone unavoidably impacts on motor skill acquisition and means that children become mobile later than children without hypotonia.

Heart murmur or other heart condition 4/13

Three children have been identified with a heart murmur and an adult with a prolapse of the mitral valve in the heart [MVP]. In MVP the flaps of the mitral valve allow blood from the left ventricle to flow back into the left atrium. There are various types of MVP, mostly relatively benign. MVP occurs in 1:30-50 people.

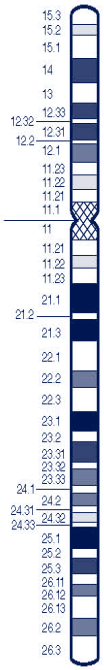
How did the 10q22.3q23.2 microdeletion happen?

One way that deletions are caused is by a mistake that occurred when the parents' sperm or egg cells were formed or in the very earliest days after fertilisation. At one point in the creation of sperm and egg cells, all the chromosomes including the two chromosome 10s pair up and swap segments. To pair up precisely, each chromosome 'recognises' matching or near-matching DNA sequences on its partner chromosome. However, throughout the chromosomes there are many DNA sequences that are so similar that it is thought that mispairing can occur.

Within the 10q22.3q23.2 region there are two blocks of DNA that are between 91 and almost 100 per cent the same as each other. It is quite likely that these very similar blocks have caused a mismatch. When researchers examined the break points in the chromosome in individual people, they found that in many of them, the break points fell within these near-matching DNA sequences [Reddy 2011; van Bon 2011].

Although no-one has ever seen this happen, it is believed that when the exchange of genetic material known as 'crossing over' occurs after mismatching, it is unequal, looping and cutting out a short length of the chromosome and so creating the deletion.

Flanking deletions: between 10q21 and 10q22.3



Very few people have been described in the medical literature with deletions from bands 10q21 and 10q22: just four babies and toddlers, aged 8, 9, 16 and 20 months [Davis 1982; Glover 1987; Doheny 1997; Cook 1999], three children of 2, 3 and 4 years recently reported by a team from Germany [Tzschach 2010; Tzschach 2006] and a 3-year-old girl reported from the US [Reddy 2011]. Additionally, two people have been described very briefly on the Decipher database [http://decipher.sanger.ac.uk]. Additionally, *Unique* has four members, aged 8, 9, 26 and 35 years old. This makes a total of 14 people aged from newborn to 35 years old.

The cases in the medical literature published before 2006 were not examined using array-CGH or FISH so the given break points may not be as accurate as they would be today. Additionally, reports come from different sources and deletion sizes are probably unique to each individual, it is not always possible to discern features that are 'typical'. Information varies from full developmental and medical data to a handful of salient features. So it's possible that some important information has been missed out, especially as regards development after babyhood and early childhood. Apart from the two adults on *Unique*'s database, no one has been followed up long term, so it is not yet possible to describe the natural history of this chromosome deletion.

Nonetheless, certain features are common. These are:

Developmental delay 10/10

Evidence from *Unique* shows that motor skills are often affected but delay in learning to sit and walk can be no more than slight. One child ran a mile in 20 minutes at 3½ years old and another was running and riding a bicycle by 7 years. Another child reported in the medical literature was not walking at 3 years, 9 months.

Heart problems

Seven/8 *Unique* babies were born with a significant heart problem. There is a range of specific heart problems: some heal spontaneously but three babies or children have had or will have surgery to correct the problem; some others are followed up regularly by a cardiologist. The problems include: pulmonary stenosis [the entrance to the artery and usually the valve that takes blood to the lungs is unusually narrow]; a persistent ductus arteriosus [a channel between the aorta and the pulmonary artery that takes blood to the lungs which usually closes shortly after birth. When it stays open, the lungs receive more blood than they should and the heart has to work too hard. If it doesn't close eventually, it can be closed using minimally invasive surgery]; multiple holes in the heart; subaortic stenosis [narrowing of the area below the valve in the aorta that regulates blood flow from the heart to the rest of the body]; a bicuspid aortic valve [the valve in the aorta regulating blood flow to the rest of the body usually has three flaps – a bicuspid valve only has two] and a degree of cardiomyopathy, disease of the heart muscle, making it harder for the heart to pump blood efficiently round the body; atrioventricular septal defect [AVSD/ a large hole in the middle of the heart caused by failure of the wall between the two sides of the heart and valves between the upper and lower chambers to form properly].

❝ He does have cold extremities most of the time and his lips appear cyanosed when he is cold. He does get short of breath on exertion - *3 years, with two holes between the upper chambers of the heart*

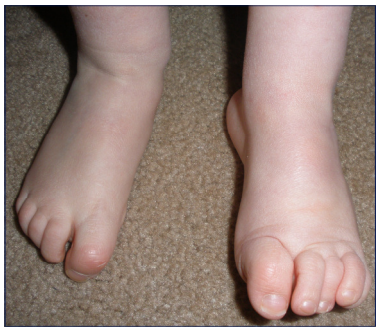
❝ She now has a 1st/2nd degree intermittent heart block [where electrical impulses from the upper heart chambers to the lower chambers don't get through and the ventricles can contract at a slow rate]. This generally doesn't affect her unless she is unwell with a cold, when she is quite poorly - *16 years, after surgical correction of AVSD*

Other problems from birth

Head and brain

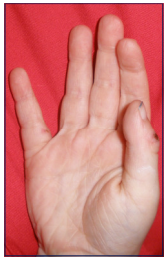
Other problems affect only one, two or at most three children. Three babies were born with a very small head. By contrast, a large head is typical for babies and children with the 10q22.3q23.3 microdeletion syndrome [see pages 11-12], and in one child the front part of the skull is unusually large. In this child an MRI scan [a scan that can show the structure of the brain] has shown a degree of wasting of the front of the brain, which has not been shown in the 10q22.3q23.3 microdeletion syndrome.

Feet



Two babies were born with one club foot [talipes equinovarus]; the other foot was normally positioned. One of these children has been treated using the non-surgical Ponsetti method and at 3 years wears special boots and a bar at night. This child also has 'clawed' big toes on both feet, which are not treated. As he walks, he 'grips' the floor with his toes.

Other



Hyperflexible fingers & a single palm crease

One child has a very short bottom pair of ribs.
One child has had two surgical corrections of an inguinal hernia, where 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 for something such as a loop of the intestine or another organ to pass through.
One baby had pyloric stenosis, where the passage between the stomach and the small intestine narrows so that feeds cannot get through. This affects young babies usually between two and eight weeks old and causes forceful vomiting. It is corrected by surgery.
One baby was also born with a split thumb and fingers connected by a 'web' of skin. They were corrected surgically.

Illnesses

Four/5 children have had troublesome respiratory infections especially during the winter that have landed them in hospital and one takes asthma medication but hasn't been diagnosed with asthma. He has a condition known as 'tracheal tug' [a downward displacement of the windpipe] which is expected to improve as his muscles strengthen.
One child who had kidney reflux, with urine backing up from the bladder into the kidneys, was successfully treated with the Sting procedure, where the valve between the bladder and the tube from the kidneys is strengthened by injecting a special gel called Deflux.

Skin

Most children have normal skin. One child has eczema and another has a fatty lump on his chin. Fatty lumps, or lipomas, are associated with Bannayan-Riley-Ruvalcaba syndrome [BRRS].

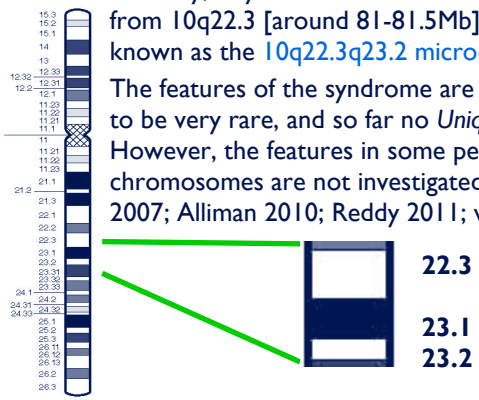
Hearing

Most children have normal hearing or at most glue ear, the temporary intermittent hearing loss that is common in all young children and is caused by a build-up of fluid behind the eardrum within the middle ear. One child has a permanent hearing loss and has had cochlear implants inserted in both ears; the hearing loss was the first sign of her chromosome disorder.

Eyesight

One child appeared to have a squint [strabismus] at times although this improved as he got older. No treatment has been needed, just monitoring.

An emerging 10q22.3q23.2 microdeletion syndrome



Recently, a syndrome has been identified in 9 people with a piece missing from 10q22.3 [around 81-81.5Mb] and 10q23.2 [around 89Mb]. This is known as the 10q22.3q23.2 microdeletion syndrome.

The features of the syndrome are emerging now but this syndrome appears to be very rare, and so far no *Unique* members have been diagnosed with it. However, the features in some people may be so mild that their chromosomes are not investigated, so they are never diagnosed [Balciuniene 2007; Alliman 2010; Reddy 2011; van Bon 2011].

Common features

- Speech and language problems
- Mild to moderate developmental delay

Other features

- In around half of those affected, an unusually large head [macrocephaly].
- Delay in learning to sit, move and walk.
- In somewhat less than half of those affected, a range of behavioural problems, including autism and hyperactivity.
- Slightly unusual facial features. Low set ears, widely spaced eyes and a flat nasal bridge seem especially common.
- In somewhat less than half of those affected, a heart problem. Persistent ductus arteriosus has occurred, a fairly common condition where a channel linking the main blood vessels leaving the heart fails to close as usual shortly after birth. When it stays open, the lungs receive more blood than they should and the heart has to work too hard. If the channel does not close naturally in time, it can be closed using minimally invasive surgery. Heart problems were also found in 2 people who have other chromosome disorders as well as the 10q deletion and in one person with a tiny microdeletion smaller than the typical 10q22.3q23.3 microdeletion. These other heart problems include an atrioventricular septal defect [AVSD], where a large hole is found in the middle of the heart caused by a failure of the heart to develop properly into four separate chambers. Babies with an AVSD tend to grow poorly, to tire easily and to have frequent respiratory infections. Generally speaking, early surgery is needed but exactly what repair is needed and at what age depends on the symptoms and how serious the problem is.
- In 2 babies, anomalies of the part of the brain known as the cerebellum. The cerebellum is at the back and base of the brain and is important for motor and cognitive functions, including time perception, precise movement and learning, particularly unconscious motor tasks like riding a bicycle.
- In 2, epilepsy. Seizures were found in one child with the full 10q22.3q23.3 microdeletion and in another with a smaller microdeletion.
- In 1, failure of one breast to grow.