

Support and Information



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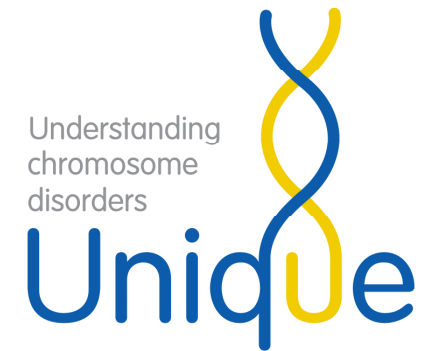
There is a Facebook group for 12q deletions at:
www.facebook.com/groups/190739047708306

Unique mentions other organisations' message boards and websites to help families looking for information. 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 Katherine Rauén, paediatric medical geneticist, University of California San Francisco Hospital, and by Unique's chief medical advisor, Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK. 2010 (PM)

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12q deletions



What is a 12q deletion?

A deletion from chromosome 12q is a rare genetic condition in which a part of one of the body's 46 chromosomes is missing. When material is missing from a chromosome, it is called a deletion.

What are chromosomes?

Chromosomes are the structures in each of the body's cells that carry genetic information telling 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. Additionally there is a pair of sex chromosomes, two named X in females, and one X and another named Y in males. Each chromosome has a short (p) arm and a long (q) arm.

Looking at chromosome 12

Chromosome analysis

You can't see chromosomes with the naked eye, but if you stain and magnify them many hundreds of times under a microscope, you can see that each one has a distinctive pattern of light and dark bands. In the diagram of the long arm of chromosome 12 on page 3 you can see the bands are numbered outwards starting from the point at the top of the diagram where the short and long arms meet (the centromere).

Molecular techniques

If you magnify chromosome 12 about 850 times, a small piece may be visibly missing. But sometimes the missing piece is so tiny that the chromosome looks normal through a microscope. The missing section can then only be found using more sensitive molecular techniques such as FISH (fluorescence in situ hybridisation, a technique that reveals the chromosomes in fluorescent colour), MLPA (multiplex ligation-dependent probe amplification) and/or array-CGH (microarrays), a technique that shows gains and losses of tiny amounts of DNA throughout all the chromosomes. These tiny losses and gains are called microdeletions and microduplications. Array-CGH is a new, particularly helpful technique in that it can show whether particular genes are present or not.

Sources and references

This leaflet tells you what is known about people described in articles in the medical literature and about *Unique*'s members with 12q deletions. When this information guide was compiled, *Unique* had 24 members with a 12q deletion. Some of these members have a change on another chromosome as well as the 12q deletion. The change on the other chromosome can alter the overall effects, so these members are not included in this guide.

Many articles in the medical literature are now quite old and were written when ways of looking at chromosomes were not as precise as they are today. Sometimes the articles only describe very young babies. All the same, you may wish to look at articles where a child is described with similar break points to your child. If you do this, it's vital to remember that people can be very differently affected by apparently the same or similar changes in their chromosomes: we are all individuals. But references are given to allow you to read for yourself. You will find key references on page 19; for the full list and most articles, ask *Unique*. Throughout the text, the first-named author and publication date for references are given to allow you to look for the abstracts or original articles on the internet in PubMed (at www.ncbi.nlm.nih.gov/pubmed).

In addition, some information is drawn from the Decipher database, a database of people diagnosed by molecular techniques (<https://decipher.sanger.ac.uk>).

whether they occur or not. No environmental, diet, workplace or lifestyle factors are known to cause them. The only problem is that when a parent with a balanced translocation has children, there is a possibility that the translocation will be unbalanced in the child. There are various types of balanced translocation but in the most typical one, the child with the unbalanced translocation will have a deletion on one chromosome and a duplication on another chromosome.

Whether the deletion is inherited or *de novo*, what is certain is that there is nothing you could have done to cause it and nothing you could have done would have prevented it occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. They are no-one's fault. There is nothing you can blame yourself for or feel guilty about.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 12q deletion or any other chromosome disorder. Where a parent has a balanced translocation or any chromosome change involving the part of 12q that is missing, the risk of having another affected child is much higher.

If they wish, parents should have the opportunity to meet a clinical geneticist or genetic counsellor to discuss their specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother's uterus.

If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is very accurate, although not all of these tests are available in all parts of the world.

Selected references

A full reference list and most of the articles are available from *Unique*.

Brady 1999: Clinical and molecular findings in a patient with a deletion on the long arm of chromosome 12 *Journal of Medical Genetics* 1999 36 pp939-41

James 2005: Another Case of Interstitial Del(12) Involving the Proposed Cardio-Facio-Cutaneous Candidate Region *American Journal of Medical Genetics* 2005 136A pp12-16

Klein 2005: Interstitial deletion of 12q: Genotype-Phenotype correlation of two patients utilizing array comparative genomic hybridization *American Journal of Medical Genetics* 2005 138A 349-354

Menten 2007: Osteopoikilosis, short stature and mental retardation as key features of a new microdeletion syndrome on 12q14 *Journal of Medical Genetics* 2007 44 pp264-8

Mikaye 2004: Phenotype-Genotype correlation in two patients with 12q proximal deletion *Journal of Human Genetics* 2004 49 pp282-284

Niyazov 2007: Genotype/Phenotype correlations in two patients with 12q subtelomere deletions *American Journal of Medical Genetics* 2007 143A pp2700-2705

Schluth 2008: New case of interstitial deletion 12(q15-q21.2) in a girl with facial dysmorphism and mental retardation *American Journal of Medical Genetics* 2008 146A pp93-96

(Niyazov 2007). Birth weights were normal and although both babies spent time in special care, they were discharged home within a few days of birth.

Medical conditions

One child had no medical conditions at all. The second baby had the kidney conditions mentioned above as well as one undescended testicle at birth and the possibility of a small pituitary adenoma (a tumour, almost always benign) detected by brain imaging when he was 11 years old.

Development

Both children grew normally in height but became seriously overweight, with a body mass index (BMI) at the top of the growth charts by the time they were 8 and 12 years old. Both boys had behavioural issues, including notable food seeking behaviour. One boy also had attention deficit hyperactivity disorder (ADHD) while the other had obsessions, a high tolerance for pain and showed some self harm.

In terms of their intellectual development, both boys were in the borderline to moderate range of difficulty, so one struggled in mainstream school and the other was in special education.

Mobility information is available for only one boy, for whom it was normal, with rolling at three months, sitting at six months and walking shortly after his first birthday.

Communication

Only one boy is reported, in whom there was some speech delay. He was able to talk in sentences from 3-4 years but retained a difficulty in understanding and following commands. The delay was attributed to his multiple episodes of glue ear and repeated ear infections as a child.

Why has this happened?

To answer this question both parents of a child with a 12q deletion should have their chromosomes tested. In most cases, both parents will have normal chromosomes. The chromosome break in the child is then said to have occurred out of the blue (*de novo*, meaning a new event). These *de novo* changes usually occurred well before the baby was conceived when the parents' sperm or egg cells were formed. They are not the fault of either of the parents. There is nothing a parent could have done to cause the chromosome change and nothing they could have done to prevent it occurring in their baby.



Unique has a separate guide to **Balanced Translocations**

Sometimes and in particular when the 12q deletions occurs together with a duplication of another chromosome, 12q deletions are the result of a change involving two chromosomes of one of the parents. This is usually a rearrangement known as a balanced translocation in which material has swapped places between two different chromosomes. As no genetically important material has been lost or gained, the parent usually has no health or development problems, although they may have experienced difficulties with fertility.

Everything that is known about balanced translocations suggests that it is chance

Are there any syndromes associated with 12q?

Yes, there is one. 12q14 microdeletion syndrome occurs when people lose a particular part of band 12q14. For more about 12q14 microdeletion syndrome, see page 7.

Results of the chromosome test

Your geneticist or genetic counsellor will probably give you your child's karyotype, a way of describing their chromosome make-up that shows where the chromosome has broken. It is likely to read something like this

46,XX,del(12)(q21.2q23.2)dn

46 The number of chromosomes in your child's cells

XX The sex chromosomes, XY for males; XX for females

del A deletion, or material is missing

(12) The deletion is from chromosome 12

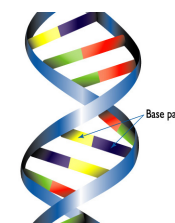
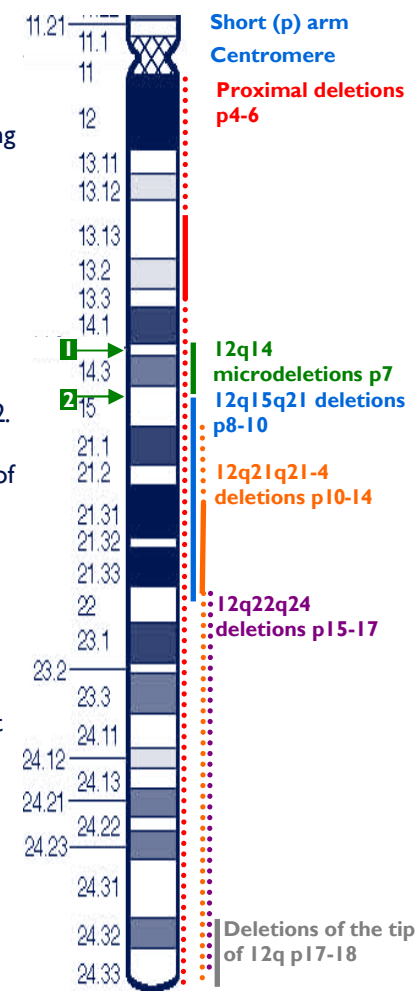
(q21.2q23.2) Chromosome 12 has broken in two places. The first break is in band 12q21.2. The second break is in band 12q23.2. You can see these bands on the image of chromosome 12 (right). The material between is missing

dn A short way of writing *de novo*. This means that the parents' chromosomes have been checked and no change found involving chromosome 12q. The deletion is then very unlikely to be inherited and has occurred for the first time in this family with this child.

Comparing your child's karyotype with others helps to build up a general picture of what to expect. But there will still be differences between your child and others with apparently similar karyotypes. Your child is an individual.

Molecular analysis

If your child's chromosomes are analysed using the array-CGH technique (microarrays), the report usually contains two very long numbers. These numbers, usually in hundreds of millions, refer to the base pairs in the chromosome. Chromosome 12 has around 132 million base pairs. The base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. The first number is the start of the deletion; the second is the end of the deletion, the difference between them is the number of base pairs missing. In a 12q14 microdeletion, this might be between 6335000 (at **1** on the image) and 6695000(at **2**).



Proximal deletions from close to the centromere: first break point in 12q11, q12 or q13

There are nine reports in all. Six cases and a possible seventh have been reported in the medical literature and *Unique* has two members. But none has precisely the same break points, so we can only make general remarks. The cases in the medical literature are as follows: a q11q13 deletion in Gallego 2000 and Mikaye 2004; a q11q13.11 deletion in Rapley 2001; a q12q13.2 deletion in Tonoki 1998 and Mikaye 2004; a q13q15 deletion in a pregnancy that was terminated in Pérez Sánchez 2004; a q13.3q21.1 deletion in Meinecke 1987; a deletion of the end of chromosome 12 from band q13 in some but not all cells of the tissues looked at in Donti 1979; a deletion of the end of chromosome 12 from band q13 in some but not all cells in the tissues looked at, with a break point at a fragile site, in Morič-Petrovič 1984. One *Unique* member has a deletion between band q11 and band q13.11; another has a microdeletion between bands q13.3 and q14.2, diagnosed using microarrays with precise base pair designation.

Four babies were underweight at birth, weighing around two kilograms (4lb 7oz) at term or one kilogram (2lb 3oz) at 35 weeks, and a fifth was undersized at 22 weeks of pregnancy, with short thigh lengths, while two others had normal birth weights of 2.66 and 3.4 kilograms (5lb 14oz; 7lb 8oz). It has been suggested that a possible cause of the growth delay is a gene known as *YAF2*, which may also be involved in low muscle tone (Mikaye 2004). All four small babies had feeding difficulties, one repeatedly bringing back feeds, another taking only small feeds, while a third was still on milk only at 3½ years due to chewing difficulties. Four children were small for their age, another was of normal height but underweight and one (with a small microdeletion) was of average height and neither underweight nor overweight (Gallego 2000; Pérez Sánchez 2004; *Unique*).

Unusual features at birth

Two babies (but neither of the *Unique* babies) were born with a cleft palate (split in the roof of the mouth), one of them also with a cleft lip (Meinecke 1987). A split in the roof of the mouth is common in children with and without a chromosome disorder. The hard palate at the front of the mouth may be split or the split may be found further back in the soft, fleshy tissue at the back of the top of the mouth. Occasionally the split is only seen in the tissue that hangs down above the tongue at the very back of the mouth (uvula, known as a bifid uvula when it is split). A cleft palate causes difficulties both in feeding and in speech. Surgical repair of the palate eases these difficulties and may eliminate them altogether.

Other unusual features were only seen in individual babies. One was born with a Sprengel malformation, a complex birth defect in which the shoulder blade (scapula) is small and displaced upwards, limiting shoulder movement. One had clubfeet, where the feet are unusually positioned, although these were only noticed when he was 3½ years old. He also had a shield-shaped, hollowed chest and widely spaced nipples and small hands. Two other babies had long fingers and toes, while another was born with slightly short fingers, in another the fingers overlapped each other and in another the fourth fingers were bent and the fifth fingers curved inwards towards the hand. In another

the muscles and nerves that control the legs, feet, bowel and bladder. If necessary the cord can be surgically released so that it can hang freely.

Two children developed a squint, which was corrected surgically and the boy with a 12q24.31q24.33 deletion had increased retinal pigmentation of unknown significance. The boy with a 12q.31q24.32 deletion had no eyesight or hearing problems.

One child had abnormal auditory brainstem evoked potentials as a baby and later developed a hearing loss due to glue ear so that grommets (tubes) were inserted into the eardrums to improve hearing. At six months of age, the boy with the 12q22q24.1 deletion had a hearing threshold of 80 decibels in the right ear and no hearing in his left ear but achieved good functional hearing with aids in both ears. In this child, the hearing loss was attributed to loss of genes from a region of band q24 on chromosome 12 known as *DFNA25* (Petek 2003).

Development

All children showed developmental delay but were walking within their second or third year, although the boy with a 12q.31q24.32 deletion was diagnosed with club foot when he was 18 months old and at 20 months was cruising along furniture but not yet walking independently. One child had tight heel cords; the child with a 12q24.31q24.33 deletion had low muscle tone initially but this improved greatly with maturity and physiotherapy. The boy with the 12q22q24.1 deletion was able to walk a few steps at 18 months and had an overall delay of around two to three years in both movement and using his hands at the age of five years. His IQ was estimated at 60.

Communication

All children showed speech delay but apart from the boy born deaf (see above) were able to speak a handful of words by the age of three and used additional communication means such as signing to express their needs and feelings. The boy with a 12q.31q24.32 deletion was using several words by 20 months but no two-word sentences yet.

Deletions of the tip of the long arm of 12q

When this guide was written, *Unique* had no members with a deletion that included the tip of 12q and no other chromosome changes. Three people with a microdeletion of the tip of the chromosome with a break point in the subtelomere have been reported in the medical literature (Niyazov 2007; van Karnebeek 2002). Conventional karyotyping gave normal results in all cases and the small deletions were only detected using FISH. In one child, the deletion includes about 1.6 Mb of chromosome material and 14 known genes. In the second, the deletion includes the last 4.5Mb of the chromosome and includes 22 known genes. The precise deletion extent of the third child (van Karnebeek 2002) has not been reported.

Possible implicated genes in the region include *P2RX2* and *ULK1*, both possibly involved in the learning difficulties and behaviour problems. *RAN* and *FZD10* genes could also contribute to intellectual difficulties.

Unusual features at birth

Pregnancy and birth were normal in two cases, although one child was found on prenatal ultrasound screening to have one polycystic kidney and one unusually placed kidney. This was confirmed at birth, but no details of further implications were given

unusual breathing pattern of shallow, rapid breathing followed by sighs. His windpipe was found to be unusually soft and floppy (laryngotracheomalacia). In time, he outgrew these episodes without harm.

This child was born with a small foramen ovale and a moderate persistent ductus arteriosus (PDA). A foramen ovale is a connection between the two upper chambers of the heart that is open in the unborn baby and normally closes during the first year of life but occasionally stays open. During childhood, this is not of any significance. A PDA is a channel between the aorta and the pulmonary artery that takes blood to the lungs which usually closes shortly after birth. When it stays open, the lungs receive more blood than they should and the heart has to work too hard. It can be closed using minimally invasive surgery by inserting a coil via an artery in the thigh. Tissue grows around the coil, closing the gap.

The child with a 12q24.31q24.32 deletion was born with holes between the two upper chambers of the heart (atrial septal defect, ASD) and the two lower chambers (ventricular septal defect, VSD). With an ASD some blood flows through from the left to the right side of the heart, increasing the amount of blood flowing to the lungs. Treatment depends on whether the ASD closes spontaneously and its size and can include medical management, taking medications to help the heart to work better, control of potential infection to the inner surfaces of the heart and surgical repair with stitches or a special patch.

A VSD allows blood to flow from the left to the right chamber of the heart, increasing the blood flow to the lungs. Specific treatment for VSD is determined individually and a baby with a VSD will be evaluated periodically. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from exposure to extra blood flow.

The child with a 12q22q23 deletion was born with an unusual formation of the valve in the heart that regulates blood flow from the heart into the blood vessel that supplies the rest of the body. This valve normally has three flaps or valves, but in this case, it had only two. This is known as a bicuspid valve. In many cases no treatment is needed but a valve replacement may sometimes be necessary.

On imaging, the boy with the 12q22q24.1 deletion had some unusual formations of the brain. These included a partial developmental failure of the broad band of nerve fibres that connects the two hemispheres of the brain (agenesis of the corpus callosum, ACC). He also had a variety of different types of seizure from the age of six months but these were well controlled with medication, which was stopped at the age of one year, with no return of the seizures by the age of six years (Petek 2003).

The child with a 12q22q23 deletion also had some spinal problems. She had mild spina bifida, a fault in the development of the spinal cord and surrounding bones (vertebrae) that leaves a gap or split in the spine. The spinal cord has not formed properly and may be damaged. She also had a tethered spinal cord, a condition in which there is restricted movement of the spinal cord which lies within the spine, surrounded by the vertebrae. The bottom end of the spinal cord is usually free within the spinal column but occasionally it becomes attached to one of the surrounding structures. A tethered cord can be put under tension as a child grows and moves and this can cause damage to

baby, the fingers were short and the fifth fingers which had very tiny nails curved inwards, while the big toes were broad and the second and third toes were joined by skin and tissue (Gallego 2000; *Unique*).

Facially, babies had some unusual features but were not like each other in appearance. Six babies had ears set low on the side of the head, two had widely spaced eyes but while in two babies they slanted upwards, in another they slanted down. Two babies also had a broad bridge to the nose, and one a large mouth and two a recessed jaw. Another had bright blue irises, long eyelashes, a short nose, a double crown and a frontal hair whorl. Another had hooded eyelids, which became much less obvious with time, a short upturned nose, a long philtrum (the space between the nose and upper lip), crooked teeth, a small jaw, thin hair and a short webbed neck. Yet another had a receding forehead and her tongue generally protruded by the age of eight months. Another had a ridge down the middle of his forehead where the plates of the skull had joined, a high forehead, a short, upturned nose, a short philtrum and downturned mouth corners (Pérez Sánchez 2004; Gallego 2000; Tonoki 1998; Meinecke 1987; Donti 1979; *Unique*).

Medical conditions

Two babies had a heart problem, but the problems were very different. One baby had holes between both the upper and lower heart chambers (atrial septal defect, ventricular septal defect) (Meinecke 1987). Treatment of septal defects depends on the size and effect and can range from careful monitoring as the hole closes naturally over time to open heart surgery to close the hole. The other baby had slight narrowing of the vessel that takes blood to the lungs to pick up oxygen, but this needed no treatment.

One baby had a horseshoe shaped kidney, where the bottom points of the two usually separate kidneys are joined, creating a U (horseshoe) shape. In itself this is not harmful. However, one third of people with horseshoe kidney have another anomaly or complication which may need supportive treatment (Pérez Sánchez 2004). Another baby had a Wilms' tumour (a type of kidney cancer that is very treatable if caught early) and lost his other kidney at the age of 14 months (Rapley 2001). This baby and one other had an inguinal hernia, causing a bulge in the area where the lower abdomen meets the upper thigh (the groin). The cause of inguinal hernia is that an opening in the lower part of the wall of the abdomen that is open during fetal life but closes before birth does not in fact close. The remaining opening may be small, only allowing fluid to pass 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 always be assessed by your child's doctors and your child may need surgery to repair it. This baby's inguinal hernia was repaired at 4 months.

The other baby with an inguinal hernia was also born with undescended testes. If they do not descend naturally in time, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy. He also had a squint (strabismus), as did one further child. 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.

Development

All children showed a degree of developmental delay, being slow to show interest in their surroundings and to reach baby milestones such as grasping objects and picking up things between thumb and forefinger. One boy uses different hands for different tasks, such as pointing with his left hand and picking things up with his right hand. He has benefited from lots of practice and sensory objects.

Both *Unique* children and another child in the medical literature have low muscle tone but despite this and despite their delays in getting mobile, both walk. They sat around 11 months, crawled at 15 to 23 months and started to walk between 23 months and three years. However, while one does not walk far and uses a buggy for long distances, the other walks, runs, jumps, climbs and swims at 6 years of age. But he can't yet clap his hands or ride a bike. He benefited from a standing frame in his second year to strengthen his legs and to encourage him to play with his hands. He also wore special boots with ankle supports to the age of three years. A third child described in the medical literature learned to roll over at two years and to sit at the age of 3½ years; he had the mobility skills of an eight-month-old baby at 3½ years. Another child mastered head control at 7 months, was sitting at 13 months and walking with help at 18 months. His fine motor skills were adequate for his age at 20 months (Gallego 2000; Tonoki 1998; *Unique*).

Communication

Both *Unique* children were late to talk, one saying his first words shortly before his third birthday, the other using vocal noises, pushing and pulling, gestures and visual aids such as picture exchanges and photographs to communicate his wants and needs. He has a good understanding of vocabulary and commands and at the age of six years understands the present but not the past or future. A third child in the medical literature had a 90 decibel hearing loss (left) and a 50 decibel loss (right). Another child was babbling at 18 months and responding to his name at 20 months (Gallego 2000; Tonoki 1998; *Unique*).

Learning

Both *Unique* children have a degree of learning difficulty. One learns best with visual aids, photographs, books, a computer, TV and with repetition. At 6, he cannot read but loves books and will point to writing for a story and knows if you are not telling it right. He enjoys 'word' books and books with flaps and points to a picture at your request. He doesn't really enjoy creative activities; but will allow hand over hand activities with an adult. He has a statement of special educational need and has 1:1 support in a class of eight at a special needs school. It has been suggested that one gene underlying the learning difficulties is a gene known as *MIGO2*, which is important for the development of the nervous system and plays a role in maturation of the nerve pathways (Mikaye 2004).

Behaviour, sleep

Both *Unique* children are sociable and loving, especially with adults. One has no sense of danger and enough autistic features to be assessed for autistic spectrum disorder. The other is generally well behaved but shouts or cries if you stop him doing what he wants, take him somewhere he doesn't like or make him do an activity he doesn't want to do.

One *Unique* child sleeps well, the other has disturbed sleep, waking most nights repeatedly, needing to be consoled and given a drink but unable to say what upset him.

Deletions with two break points closer to the tip of the chromosome than band 12q21

Four children have been described. *Unique* has had two members with deletions nearer the tip of the chromosome, one with break points in 12q22 and 12q23 and the other with both break points in bands of 12q24. One of these children, with a 12q24.31q24.33 deletion, has been reported in the medical literature. Another child with an overlapping deletion at 12q.24.31q24.32 has also been reported. A third child with break points at 12q22 and 12q24.1 has also been reported (Petek 2003; Plotner 2003; Sathya 1999; *Unique*).

Unusual features at birth

Two pregnancies were entirely normal; a third was affected by excess amniotic fluid. Two babies were small at birth, weighing around 2.5 kg (5lb 8oz); a third was of normal birth weight. All four babies had some feeding difficulties, such as uncoordinated sucking and swallowing made worse by a large tongue, and two were notably small for their age. Another baby was born a normal length and weight although his head was unusually small (microcephaly) and he then grew very slowly, so by the age of 20 months he was short for his age. A fourth baby was also born a normal size and weight but again grew very slowly, so by the age of five, he was in the smallest three per cent of the population for size, with his head being particularly small.

One baby had long fingers and thumbs and upturned big toes; the boy with a 12q.31q24.32 deletion was born with tapering fingers and both he and the boy with the 12q22q24.1 deletion had fifth fingers that curved inwards towards his hands (clinodactyly).

Facially, some features were somewhat unusual: the boy with a 12q.31q24.32 deletion was born with a large, bulbous, upturned nose, a smooth groove between the nose and upper lip (philtrum) and large ears. He also had a sacral pit, a small pit or hole at the end of the spine. The boy with a 12q24.31q24.33 deletion had eyes that were short and one eyelid was hooded; his nose was short and upturned. The boy with the 12q22q24.1 deletion had subtly unusual facial features, including wide set eyes, small skinfolds across the inner corners of the eyes (epicanthic folds), a broad nasal bridge and a bulbous tipped nose, a somewhat receding jaw and lowset ears.

Medical conditions

All children apart from the boy with the 12q22q24.1 deletion had unusual genital features, although there was a wide range of severity. The boy with a 12q.31q24.32 deletion was born with a large pubic fat pad; the girl was born with fused labia. The boy with a 12q24.31q24.33 deletion was born with undescended testicles and hypospadias, where the hole normally situated at the end of the penis lies on the underside instead. If necessary, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy and hypospadias can be corrected surgically. As other babies and children with chromosome changes involving the 12q24 band have been reported with unusual genital features, it has been suggested that a gene or genes within 12q24 may play a role in the normal development of genitalia (Sathya 1999).

One baby, with a 12q24.31q24.33 deletion, had unusual episodes of stopping breathing in his first weeks of life, triggered by feeding or moving his airways. He also had an

Learning

All children known to *Unique* need some support with their learning and generally speaking they need quite considerable help. Typically they are characterised as having severe difficulties but in two children the difficulties are described as moderate. An eight-year-old has a very short attention span and learns best with repetition and visual prompts and support. She enjoys outdoor activities at school and has 1:1 support. She is not reading, drawing or writing.

A nine-year-old attends a mainstream school with a teacher's aide most of the day and is three to four years behind his peers. His strengths are his personality, his memory (other than academic) and his love of music. He learns best in a happy environment and is particularly good at puzzles and reading. He can read 5 to 80 words. His writing is very messy and only legible when he takes his time.

Eyesight

One child with a q21.2q22 deletion was found to have marked long sight at eight months and was given corrective lenses. Another wore glasses for strabismus and astigmatism to the age of eight.

Behaviour

Five children are described as having quite marked behaviour difficulties even in early childhood and potentially continuing into adulthood, making behaviour problems the most consistent feature of this chromosome deletion. However, the girl with a 12q21.1q21.3 deletion is only noted to have 'preschool' behaviour at the age of 14. Three children have marked temper outbursts. Two children have a diagnosis of an autism related disorder. Parents report that their children have temper tantrums, kicking, banging and shouting (24 years); attention deficit and autism (11 years); destructive outbursts in response to frustration as well as obsessions (9 years); violent reactions to displeasing situations head banging and self injury as well as sensory abnormalities, sleeping and eating disturbances, temper tantrums, impulsivity, over-activity, aggression and autism (8 years).

- “ An extremely happy and caring child with many friends. However, he is a challenge every day with his behaviours but he always feels bad after they happen - 9 years
- “ Interacts with me using special vocal noises, finding this ritual reassuring and calming. Lately has become very affectionate, although over the top - 8 years

Typical features of 12q21.2q22 deletion

It has been suggested that the features of people with a 12q21.2q22 deletion are similar enough to warrant separate mention (Klein 2005). These features include: typical facial features, including a prominent forehead, short, upturned nose and low ears; keratosis pilaris (see above); sparse hair; possibly heart and kidney problems. (Klein 2005; Rauen 2002; Rauen 2000; *Unique*)

Growing up with a proximal 12q deletion



Clockwise from top left:
1 day old
1 year old
6 years old
5 years old
4 years old

12q14 microdeletion syndrome

On the basis of three children with similar features and 12q14 microdeletions, a '12q14 microdeletion syndrome' has been suggested (Byusse 2009; Mari 2009; Spengler 2009; Menten 2007). The three children all had a mild degree of learning difficulty, low birth weight and failure to thrive as babies, were short but proportionate and had a condition known as osteopoikilosis which literally means 'spotted bones'. Osteopoikilosis is a benign, asymptomatic condition that can occur at any age, be inherited or occur spontaneously. On x-rays, circular or oval lesions appear near joints, usually in a symmetrical distribution. The lesions can increase, decrease and even disappear.

In 12q14 microdeletion syndrome, the amount of chromosome material lost between base pairs 63358186 and 66931792 can vary from 3.44 to 6Mb and typically includes a gene known as *LEMD3*, which is situated between 63849638 and 63928374. When the *LEMD3* gene isn't working, osteopoikilosis is likely to develop but doesn't always do so. Another condition affecting bone and soft tissue can also develop, known as melorheostosis. Melorheostosis is also benign but can cause pain, stiffness and even deformity (Decipher). *Unique* does not yet have any members with this microdeletion syndrome. Information on 12q14 microdeletion syndrome is available at Orphanet (www.orpha.net) and at Decipher (<https://decipher.sanger.ac.uk>).

Deletions with two break points, the first in 12q15, the second in 12q21

There are five reports in all. Two cases have been reported in the medical literature with a 12q15.2q21.2 deletion (Schluth 2008; Watson 1989). *Unique* has three members, aged 4 to 12 years, all with one break point at 12q15 and the second at 12q21 or 12q21.2.

Birth weights varied widely from one baby born weighing 1.7 kg (3lb 12oz) to two weighing around 3.3kg (7lb 4oz). At least two babies showed clear evidence of slow growth before birth, leading to low birth weight. Three babies are known to have had feeding difficulties, one sucking poorly and gaining weight slowly, the others needing to be fed by gastrostomy tube direct into the stomach, one of them to the age of 3½ years. Three babies had reflux, where feeds and stomach contents return into the food pipe and can be vomited or may be inhaled; one of these was treated with a Nissen fundoplication, in which the top of the stomach is wrapped around the bottom of the oesophagus (food passage) and stitched in place. This creates a one-way valve that allows food to enter the stomach but stops acid and stomach contents flushing back up to oesophagus. One baby had marked constipation. Two children grew very slowly, one being significantly short at five years of age.

Unusual features at birth

One baby was born with a cleft palate, a cleft lip and what is known as Pierre Robin sequence. Typical features of Pierre Robin sequence are a small or retracted lower jaw and a cleft palate, usually without cleft lip. Babies with breathing obstruction need expert urgent attention. Babies who cannot breastfeed due to the cleft need properly taught feeding through an adapted teat and may need tube feeding. Palate repair typically is carried out at 10-18 months. By 3 years, most children born with Pierre Robin sequence are taking food by mouth and do not have significant breathing obstruction. A multidisciplinary team is needed to deliver a full care plan.

One baby was born with joined second and third toes on the left foot, another with the same feature on both feet. This child also had remarkably short fingers, a tuft of hair near the base of the spine, and a somewhat sunken chest (pectus excavatum).

Facially, only two babies have been described in any detail. Unusual features in one were a broad, prominent forehead, a flat back of the head, small and sunken eyes, a slightly beaked nose, ears set low on the side of the head, a thin upper lip and sparse, fine hair. The other child showed a change in facial features with age: at six months, what was remarkable was her high forehead, wide-set and down-slanting eyes, upturned nose, long space between nose and upper lip (philtrum), downturned mouth corners, thin lips, small lower jaw (micrognathia) and ears placed low on the side of her head. By five years of age her remarkable features included a large forehead, upwards-slanting, crescent-shaped eyes with arched eyebrows and large mouth with thin lips.

Medical conditions

Three babies were born with a heart problem and one had a harmless heart murmur. One baby was born with a persistent ductus arteriosus. The ductus arteriosus is a channel between the aorta and the blood vessel that takes blood to the lungs that usually closes shortly after birth. When it stays open, the lungs receive more blood

Development

All children for whom records are held at *Unique* have shown some degree of developmental delay, but detailed information is held on only two children. In a few cases, the delay was the first sign of the chromosome disorder. In addition, helpful information is published on the development of a girl with a 12q21.1q21.3 deletion (James 2005). This girl was developmentally delayed, crawling at 16 months and walking at two years, three months; she was toilet trained at the age of five and by the age of 14 was starting to dress herself although still unable to manage buttons or zips.

At eight years, one child still needs considerable help with dressing and undressing and other personal care. She prefers to eat with her fingers, claps or rubs her hands together when happy and bites one particular finger when agitated. She is very talented at pouring liquids from container to bottle, very precise and finds water play very calming. She is unreliably toilet trained. A second child, aged nine, needs a moderate amount of help with personal care, can clean his own teeth and dress himself; and was toilet trained by the age of two.

In terms of mobility, all children for whom *Unique* holds records were walking by the age of four years and one was walking alone at 20 months. *Unique* children achieved rolling between four and 26 months, sitting between seven and eighteen months and climbing stairs between two and five years. The child who was walking by 20 months had normal mobility at nine years. A child with balance and coordination problems (and a q21.2q22 deletion) needed to wear ankle-foot orthotic supports while learning to walk. One child is overactive, rarely sitting still for longer than a few minutes, running up and down rooms, touching walls with her hands or feet for confirmation and enjoying spinning, jumping and rocking. She needed a walking frame from two years and at the age of eight still goes outdoors in a wheelchair for safety as she has no sense of danger. One child has high muscle tone in one leg and walks on his toes on that side. A tendon stretch was not successful. One other child also has increased muscle tone and two children have low muscle tone.

Communication

There is considerable variation between individual children. One child with a 12q21.2q21.33 deletion has normal communication skills at the age of nine, speaking well and clearly in full sentences and understanding at the same level of complexity. He first spoke at 12 to 18 months of age. Another child with a similar but slightly smaller deletion only uses two words at the age of eight, communicating otherwise via picture exchanges, signing, pushing, pulling, facial gestures, vocal noises and stamping her feet. Her understanding is very limited and causes frequent behavioural problems due to her inability to express herself. A child with a q21.2q22 deletion was cooing by six months, babbling by 15 months, using words by 19 months and at 24 months had a 10-word vocabulary and good understanding of simple commands. Another child was putting two words together by three years. Another had no speech at three years. A second child with a q21.2q22 deletion was babbling by eight months but developed temporary hearing loss due to glue ear by 2. A further child had frequent ear infections with glue ear and had grommets inserted four times; she said her first words at the age of 3½ had a three to four word vocabulary at five and the understanding of an eight-year-old with expression somewhat more delayed by the time she was 14.

Medical conditions

A baby with a q21.2q22 deletion was born with one undescended testicle and this was removed when he was 14 months old as it had still not descended into the scrotum. This same baby had a swollen kidney before birth and this persisted, leaving only one third of normal function in the affected kidney. He was also born with two minor heart anomalies: a persistent ductus arteriosus (PDA) and a persistent foramen ovale (PFO). The ductus arteriosus is a channel between the aorta and the blood vessel that takes blood to the lungs that 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 does not close naturally, it can be closed, often using minimally invasive surgery by inserting a coil via an artery in the thigh. Tissue grows around the coil, closing the gap. The foramen ovale is an opening between the two upper chambers of the heart that usually closes in the first year of life. When it remains open, this allows extra blood to pass from the left to the right side of the heart. Treatment was not needed in this baby.

This baby developed pyloric stenosis, resulting in forceful vomiting as the passage between the stomach and the small intestine narrows so that feeds cannot get through. After treating dehydration and mineral imbalances caused by the vomiting, the tight pyloric muscle was repaired surgically (pylorotomy). Pyloric stenosis usually leaves no long term effects and the problem is unlikely to recur.

A second baby had the same combination of a small PFO and PDA, as well as an extra ureter (tube) leading down from the kidney to the bladder on one side and a swollen kidney; this baby was also born with hydroceles on both sides of the scrotum. A hydrocele is an accumulation of fluid round the testis in the scrotum and can develop when the passage through which the testicles descend into the scrotum fails to close. Fluid from the abdomen comes through the passage into the scrotum. A hydrocele at birth is usually fixed by a surgical operation in which the fluid is removed from the hydrocele and the passage between the abdomen and scrotum is sealed off.

This baby also had somewhat enlarged ventricles (fluid-filled spaces) within the brain. Four children were tested for possible epilepsy, in one case because of abnormal posturing and in another due to staring spells. Tests in the latter child were inconclusive but no problems in either were revealed on visual observation. A third child had absence seizures (a loss of consciousness that usually lasts 30 seconds or less) at the age of eight but these stopped or were completely controlled with anti-epileptic medication.

Three children had frequent respiratory infections, in one case croup from 18 months to 7 years of age which then became milder and less frequent. Another child also had croup as well as mild asthma and frequent respiratory infections in winter. A third child showed transient low levels of infection-fighting antibodies known as gammaglobulins while she had respiratory infections, but this normalised by the age of seven.

A baby with a q21.2q22 deletion developed an S-shaped spinal curve by the age of 15 months. One child had frequent nosebleeds at the age of eight, having her nose cauterised. One child experienced moderate environmental allergies. One child, a girl, showed signs of early puberty at the age of eight but another started her periods at 14 years.

than they should and the heart has to work too hard. If it does not close naturally, it can be closed, often using minimally invasive surgery by inserting a coil via an artery in the thigh. Tissue grows around the coil, closing the gap.

This baby also had an open foramen ovale. This is an opening between the two upper chambers of the heart that usually closes in the first year of life. When it remains open, this allows extra blood to pass from the left to the right side of the heart. Treatment may not be needed.

Another baby was born with a hole between the two upper chambers of the heart, known as an atrial septal defect (ASD). Some blood flows through from the left to the right side, increasing the amount of blood flowing to the lungs. Small ASDs can close naturally during the first year of life. Treatment depends on the type of defect, whether it closes spontaneously and its size. Treatment can include medical management, taking medications to help the heart to work better, control of potential infection to the inner surfaces of the heart and surgical repair with stitches or a special patch.

Another baby was born with a ventricular septal defect (VSD), where there is a hole in the wall between the two pumping chambers of the heart (ventricles). This allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Specific treatment for VSD is determined individually. A baby with a VSD will be evaluated periodically. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from exposure to extra blood flow.

One baby was born with a horseshoe kidney. The bottom points of the two usually separate kidneys are joined, creating a U (horseshoe) shape. In itself this is not harmful and around one third of children with horseshoe kidney have no symptoms and may need no treatment. However, a horseshoe kidney can increase the risk of urinary tract infections.

Two babies are known to have some structural brain anomaly. In one baby, the broad band of nerve fibres that connects the two sides of the brain known as the corpus callosum was mildly overgrown. In another, the fluid-filled spaces within the brain were larger than usual and the part of the brain known as the cerebellum was underdeveloped.

One child also had an outward squint (divergent strabismus). The main effects of a strabismus are that usually the person will have one eye which 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 as well as the stronger one. 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.

Development

From the very little information available, it seems that developmental delay is common and perhaps universal. But the degree of delay is not known, although in one child it was severe. Another child, who had low muscle tone, did not start walking until she was three years old.

Communication

We only have information on two youngsters. While one was not talking at six years, the other had a vocabulary of 30 words by the age of two and a half. So there is clearly the possibility of wide variety.

Learning

Youngsters show a range of learning difficulty, with one needing considerable support for his significant delays, while the other reads and writes and is 'quite clever' by the teenage years.

Behaviour

Information is available on only one youngster. By adolescence, he needed considerable support for his behavioural issues, which included anxiety disorder, bipolar disorder and an autistic spectrum disorder.

Deletions with two break points, the first in 12q21, the second between 12q21 and 12q24



Twelve cases have been reported in all. Six cases have been reported in the medical literature, one with a 12q21.1q21.3 deletion, three with a 12q21.2q22 deletion, one with a 12q21.2q23.2 deletion, the other with a 12q21.33q24.1 deletion. *Unique* has four members with a deletion within band 12q21. Two of these are microdeletions, one diagnosed by array-CGH. *Unique* has two further members with one breakpoint at 12q21 and the second breakpoint at 12q22 or 12q24, making for a somewhat larger deletion (Brady 1999; Rauen 2000; Rauen 2002; James 2005; Klein 2005; *Unique*).

Most pregnancies were uneventful but during pregnancy, one mother noticed a lack of fetal movement and another had a severe attack of influenza at 7 to 8 months of pregnancy. In a pregnancy where the baby had a q21.2q22 deletion there were no problems until seven months when too much amniotic fluid was found and the baby was found on ultrasound to have a swollen kidney. Later on, the level of amniotic fluid became unusually low and delivery was induced at term when the baby's movements in the womb lessened. Delivery of the babies was uneventful except for one baby who required an emergency Caesarean after developing fetal distress in labour at term. Birth weights varied somewhat from one baby born weighing 2.86 kg (6lb 5oz) to two weighing around 3.5 kg (7lb 11oz). From the information held at *Unique*, these babies did not have low muscle tone (making them feel floppy to hold) at birth, although low muscle tone was noted in one of the babies with a q21.2q22 deletion when he was four months old. One baby needed warming after birth. Another leaned her head towards her right shoulder, a sign in her case of a spinal curvature, scoliosis. She also made an unusual continuous 'ugh' sound rather than a cry at birth, held herself very still and rarely cried. Other babies were healthy at birth and as newborns.

Information on five babies shows that one breastfed for 10 months and could be settled with small feeds. He continued to eat well and was consuming adult quantities at the

age of nine. Four babies had feeding problems, one unable to breastfeed and sticking to a very narrow diet to around the age of seven and at eight still preferring cold food. This child likes to mouth everything, even soil. Another baby with a q21.2q22 deletion fed so indifferently that he had a gastrostomy tube fitted for direct feeding to the stomach at the age of four months. After the gastrostomy was fitted, he put on weight and grew at a normal rate. Another baby had what is termed failure to thrive, where weight gain is well below what is expected.

In terms of growth, two children are short, one below the lowest curve on the growth chart. At the age of 12, this child was diagnosed with growth hormone deficiency, treated with growth hormone and grew well for the next three years. The other children are tall or of average height or slightly below. They are not overweight. One child was an average weight and length at birth but then grew very slowly, following the lowest curve on growth charts, until she was five. Her growth rate then picked up and by the age of 11 she was again of average weight and height.

Unusual features at birth

As mentioned above, one child was born with a curved spine, possibly influenced by the loss of two genes called *MYF5* and *MYF6*.

She has twice had a brace cast under general anaesthetic and at the age of eight her family is considering alternatives to surgery such as further bracing or monitoring. Two babies were born with unusually long, thin fingers and toes but another baby with a very similar deletion had normal fingers and toes and another had entirely normal if narrowed hands and feet. One baby with a q21.2q22 deletion had single creases across the palms of his hands and skin webbing between the second and third toes on each foot.

Facially, only six children have been described, all with quite different features. However, a group of children with a 12q21.2q22 deletion shared facial similarities: a prominent forehead, a short, upturned nose and low-set ears. Other unusual facial features noted include: blue eyes, unlike the rest of the family who have who have brown eyes; a relatively small head (microcephaly); uneven front teeth; sparse eyebrows and hair; a small pit in front of one ear; widely spaced eyes; narrowly spaced eyes that slope slightly downwards; hooded eyelids and a very narrow opening for the eye; prominent eyes; a small mouth with full lips and a 'tentled' upper lip; a long groove between the nose and upper lip; an extra bridge of skin and tissue (frenulum) between the upper gum and inside of the mouth; an extra tooth; a slightly small lower jaw and chin; loose skin around the back of the neck.

Three children with a q21.2q22 deletion and one with a 12q21.1q21.3 deletion were described with the skin condition known as keratosis pilaris, causing rough, goose-flesh like skin on the forehead, eyebrow and cheek areas and on the arms and thighs from the age of three weeks. These children also had sparse and fine or thin hair and thinned eyebrows. Keratosis pilaris usually starts in childhood and often worsens in adolescence but usually improves in time. A particular gene known as *SCF* may underlie the development of this skin condition (Rauen 2000; Rauen 2002; James 2005; Klein 2005; *Unique*).

“ Extra pretty

“ His face is normal (beautiful)!!