



Understanding Chromosome & Gene Disorders

2q33.1 deletions and other deletions between 2q31 and 2q33



rarechromo.org

Deletions between 2q31 and 2q33

A chromosome deletion means that a part of one of the body's chromosomes has been lost or deleted. If the missing chromosome material contains important genes, developmental delay, some learning difficulties and health problems may occur. How important these problems are depends mostly on how much of the chromosome has been lost and where the deletion is.

Genes and chromosomes

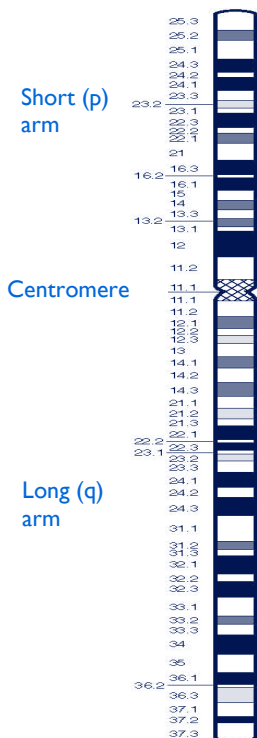
Our bodies are made up of billions of cells. Most of the cells contain a complete set of 20-25,000 genes. Genes act like a set of instructions, controlling our growth and development and how our bodies work.

Genes are carried on microscopically small, thread-like structures called chromosomes. There are usually 46 chromosomes, 23 inherited from our mother and 23 inherited from our father, so we have two sets of 23 chromosomes in 'pairs'.

Apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy), the chromosomes are numbered 1 to 22, generally from largest to smallest. Chromosome 2 is almost the largest chromosome and contains nearly 1400 known genes.

Each chromosome has a short arm (at the top in the diagram below) called **p** from *petit*, the French word for small, and a long arm called **q** (at the bottom). In a 2q deletion, material has been lost from the long arm of one of the two chromosome 2s.

Looking at 2q31 to 2q33



You cannot see chromosomes with the naked eye, but if you stain them and enlarge their image many hundreds of times using a high-powered microscope, you can see that each one has a pattern of light and dark bands.

In the diagram on the left you can see the bands are numbered outwards from the point where the long arm meets the short arm (the **centromere**). The three 2q31-3 bands are part way down the long arm and, as you can see, each band is subdivided into three more bands, making nine bands in all.

In a 2q31-3 deletion, the chromosome has usually broken in two places and the 'sticky' broken ends have rejoined, leaving out the chromosome material between them. You will sometimes see this type of deletion called **interstitial**.

The missing piece of chromosome can be tiny or much larger. If it is large enough to be visible when magnified under a microscope, it is called a **deletion**. Sometimes it is so tiny that it can only be identified using new technology with tests such as FISH or array-CGH. It is then called a **microdeletion**.

Smaller deletions generally remove fewer genes and newer techniques can usually show whether particular genes or parts of genes are present or not. These techniques are more precise than a traditional chromosome analysis.

Families say: What is special about my child

“ The most special thing she does is when we are quiet and alone. She can solicit my attention, through grabbing my finger or calling out for me from her bedroom with a grunt. I will either snuggle her in bed or hold her in my lap in my bedroom window and just quietly melt with her. It is then that we are most at peace, most in tune. All too frequently throughout our day, her disability is raw and in conflict with daily life. It is in these times of natural quiet peace that we are a typical mother loving her child. ”

“ Very sweet, almost always happy and smiling. Has a great sense of humor! ”

“ He has made me very humble. ”

“ He is a sweet boy who usually does his best to help accommodate you. He loves his baby brother and sister more than we realise. He is great with computers. Because he is non-verbal, he can feel when you are sad or tired, or just in pain, and he comforts you, acts very mature and tries to make you feel better. ”

“ She often makes us laugh, has a beautiful personality, can be cheeky and is great company. Mostly, she has caused me to grow in patience and understanding, which has lead me into a career in counseling, disability and behavioural management. ”

Families say: I wish I'd known

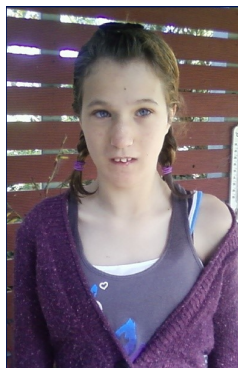
“ She has pushed my patience to a level I thought was never possible, and frequently beyond! Her deletion has caused me to completely redefine my role in this world, to a position of advocate/inquirer in an area where I never expected to have expertise. Her disability has caused me to view every wrong, error or inaccuracy with a far more forgiving filter. I have changed the lens on my life to see, hopefully, what is more important, and yet I also feel I have more to learn to keep patient for the long haul. ”

“ We have learned to honor who the child is, as a person, and to treat with a reasonable therapy load but be realistic. We were led to believe that if we tried or followed every therapy out there, it would somehow make her 'better'. No. Now, as she is 6 years of age, I am coming to terms with the reality of her potential, willing to cut off some therapy in exchange for getting some of our lives back, financially investing in my other children's futures. I would also have loved for someone to tell me that she would be non-verbal. That would have saved a lot of speech therapy time. ”

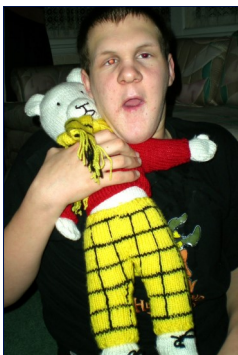
“ It is a heck of a time to go through the day and help your kiddo, especially when you have other kids. It breaks my heart that he is different, and my other two kids are normal. It breaks my heart that I may never hear him say 'mom' or 'dad' or 'I love you'... ”



7 years old



14 years old



19 years old

“ It breaks my heart that I cannot help him more. But at the end of the day he is my sweetest kid, my first child, always special in my heart. He may not talk or do normal stuff that other kids do at the same age but he makes you feel a whole lot better with just a smile. I cannot say I wouldn't change a thing; I would if I could, but he is healthy, he can walk and eat by himself, and he is making progress. That's all that counts. ”

“ I really was blind to any type of disability. Perhaps emotional support for the parents when given diagnosis, accompanied with information, would be great. Sibling support at diagnosis to help their understanding as well would have helped. ”

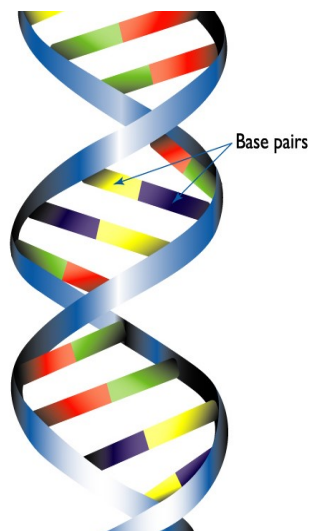
“ Enjoy and celebrate small positive changes. Embrace challenges. Consistency and hope. ”

The genetic test

Your genetic specialist can tell you more about what chromosome material has been lost. If the genetic test used traditional chromosome analysis, the report will show the bands in chromosome 2 where the breaks have occurred. This is an example of a report, known as a **karyotype**.

46,XX,del(2)(q31.3q33.1)

This karyotype shows that chromosome 2 broke in bands 2q31.3 and 2q33.1 and that the genes and other chromosome material between the breaks is missing.



Here is an example of an array-CGH report.

arr cgh 2q33.1(195,489,638-202,632,106) x1

This report shows that two breaks occurred in the same band, 2q33.1. The long numbers show the ‘base pairs’ that are known to be missing (x1 instead of x2, as normally expected). Each base pair represents the ends of one ‘rung’ of the DNA ladder. Take the first long number from the second to find out how many base pairs are missing, in this case 7,142,468. Since base pair numbers are very long, they are often shortened like this: 1 base pair = bp 1000 base pairs = 1kb 1,000,000 base pairs = 1Mb

A single band in a chromosome can contain many of the genes that direct development and each gene can contain many thousands of base pairs. The break in the chromosome can occur within a gene. Depending on the technology used, your geneticist can tell you which genes or parts of genes are missing.

New and emerging syndromes

There are a number of new and emerging syndromes caused by deletions close to bands 2q31 to 2q33. In many cases, the features of one syndrome overlap with another syndrome. They include:

2q24.3 deletions

Unique publishes a separate guide to 2q24.3 deletions

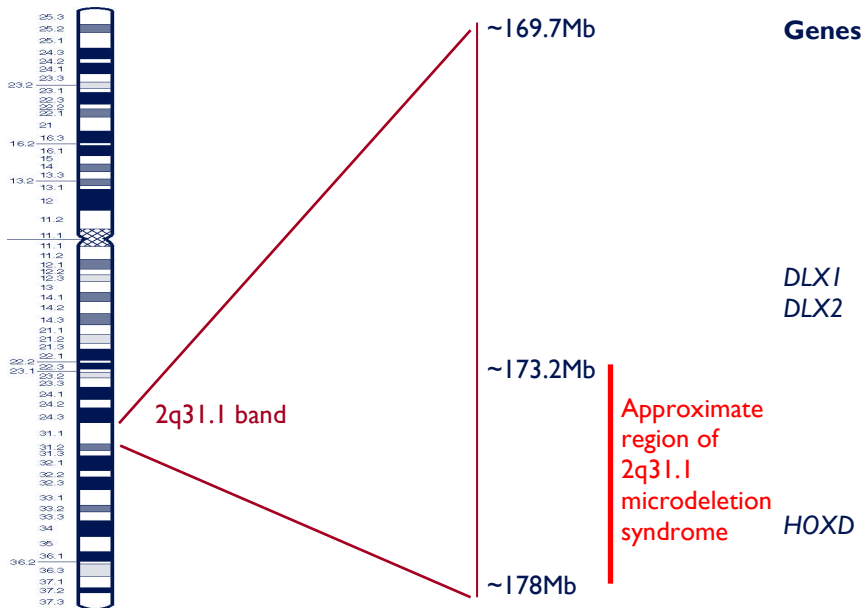
2q31.1 microdeletion syndrome see pages 5-7

2q31.2q32.3 microdeletions see pages 7-9

2q33.1 deletion syndrome also referred to as 2q32.2q33 microdeletion syndrome see pages 9-27

2q31.1 microdeletion syndrome

It has been suggested that when part of the 2q31.1 band between around 173.2Mb and 178Mb is deleted, a clinically recognisable syndrome is seen. One obvious feature of this syndrome is abnormalities of the hands and feet, which can be very minor or much more obvious. People with this deletion may also look facially like each other.



Sources and references

Four scientific articles have focused on the 2q31.1 microdeletion syndrome. Boyan Dimitrov and his colleagues examined five children and concluded that losing part of the 2q31.1 band between around 173.4Mb and around 175.8Mb causes the typical 'look' and that losing the next part of the 2q31.1 band between around 175.6Mb and 178Mb causes the hand and foot abnormalities. L-P Tsai and colleagues found hand and foot anomalies in three generations of one family who had lost part of the 2q31.1-q31.2 bands between around 175.4–178.8Mb. They only found developmental delay and learning difficulties in the youngest generation; the parents and grandparents had normal intelligence and social functioning. Diana Mitter and her colleagues examined eight patients with overlapping deletions in 2q31.1. The only deleted gene shared by all eight patients was *WIPF1*, situated at 175.4–175.5Mb, but Dr Mitter pointed out that this deleted gene does not explain patients' symptoms. Instead, she suggested that individuals differ from each other because each has a different deletion extent. DRH de Bruijn investigated a very severely affected 19-year-old girl who had lost part of the 2q31.1 band between 172Mb and 174.6Mb. She also had an apparently unrelated balanced translocation and de Bruijn suggested that this translocation may have unexpectedly intensified the impact of the 2q31.1 deletion. *Unique* has one member with a 'pure' 2q31 deletion without involvement of other chromosomes (Tsai 2009; de Bruijn 2010; Mitter 2010; Dimitrov 2011; *Unique*).

Most likely features of 2q31.1 microdeletion syndrome

- Most but not all children experience developmental delay. The degree of delay is individual and can be mild, moderate or significant
- Unusual feet and/or hands
- An unusually small head (microcephaly)
- Short stature and feeding problems
- Low muscle tone (hypotonia)
- Possibly, a typical facial appearance

Less likely features

- Heart problems, such as holes between the upper or lower chambers (atrial/ventricular septal defects)
- Eye problems, most commonly strabismus (squint) and a drooping upper eyelid (ptosis)
- Structural anomalies of the brain such as enlarged ventricles (fluid-filled spaces)
- Problems of the urinary or genital systems
- Cleft palate and/or lip
- Spinal curvature (scoliosis)
- Unusual formation of bones in the spine
- Seizures

Unusual feet and/or hands

The unusual features may be scarcely noticeable or much more obvious. Foot features seen so far include a long big toe, short toes with only one joint, underdeveloped nails, webbed toes (especially toes 2-3), a sixth toe, short bones in the feet, bones that are fused together and a large gap between the big toe and the second toe. Hand features seen so far include clenched hands, bent fingers, short bones in the hands, short middle joints in the fingers, incurved little fingers, webbed fingers, tapered fingers, a sixth finger, short fingers and split hand with a single finger.

A typical facial appearance

A child with any chromosome disorder often resembles the rest of their family. But they may also resemble other children with their particular syndrome. In a 2q31.1 microdeletion, some typical features are a narrow forehead, broad eyebrows that flare at the sides, a small nose with a bulbous tip, narrow eyes that slant downwards, a thin upper lip and thicker lower lip, ears set low on the sides of the head, and a small lower jaw and chin. Around half of people with the syndrome have an unusually small head.

Genes that may be involved

There is a cluster of genes called *HOXD* in 2q31.1 that play a key role in the formation of the arms and legs in embryonic life and are believed to lie at the root of the more obviously unusual feet and hands seen in people with a 2q31.1 microdeletion. Some of the chromosome material on either side of this cluster of *HOXD* genes is thought to regulate these genes and so losing this chromosome material can also cause the foot or hand features. It is possible that two genes known as *DLX1* and *DLX2* may also be involved in hand and foot formation but this is less certain. It has also been suggested that the *HOXD* gene cluster underlies the genital anomalies seen in some people with the deletion (Svensson 2007; Tsai 2009; Mitter 2010; Dimitrov 2011).

Scientific articles

Svensson 2007: Detection of a de novo Interstitial 2q Microdeletion by CGH Microarray Analysis in a Patient With Limb Malformations, Microcephaly and Mental Retardation *American Journal of Medical Genetics Part A* Volume 143A pages 1348-1353

Tsai 2009: A novel microdeletion at chromosome 2q31.1-31.2 in a three-generation family presenting duplication of great toes with clinodactyly *Clinical Genetics* Volume 75 pages 449-456

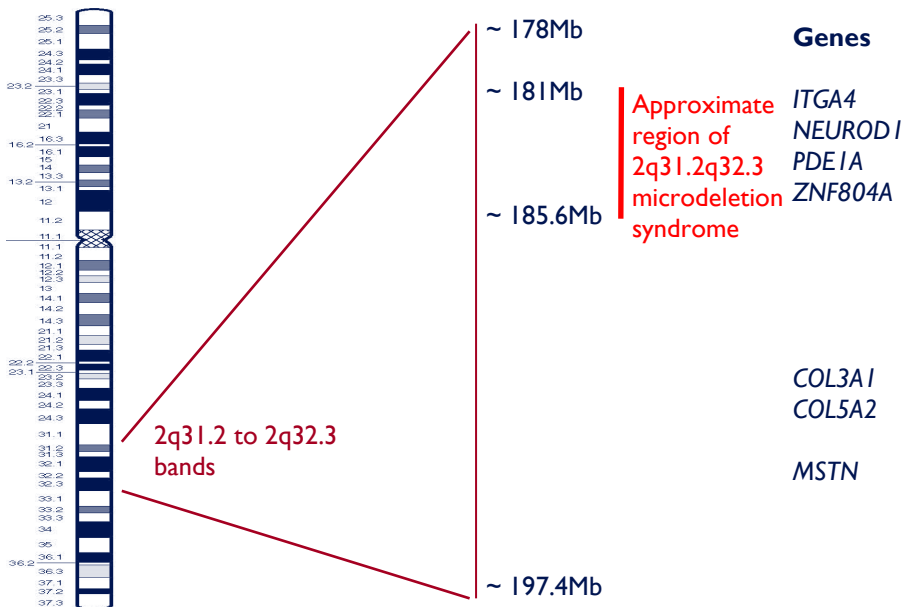
De Bruijn 2010: Severe Progressive Autism Associated with Two de novo Changes: A 2.6-Mb 2q31.1 Deletion and a Balanced t(14;21)(q21.1;p11.2) Translocation with Long-Range Epigenetic Silencing of *LRFN5* Expression *Molecular Syndromology* Volume 1 pages 46-57

Mitter 2010: Genotype-phenotype correlation in eight new patients with a deletion encompassing 2q31.1 *American Journal of Medical Genetics Part A* Volume 152A pages 1213-24

Dimitrov 2011: 2q31.1 microdeletion syndrome: redefining the associated clinical phenotype *Journal of Medical Genetics* Volume 48 pages 98-104

2q31.2q32.3 microdeletions

It's been suggested that when there is a deletion between around 181Mb and 185.6Mb in bands 2q31.2q32.3, a distinct syndrome can be recognised. So far two adults and a teenager have been described in the medical literature. *Unique* does not yet have any members with a diagnosis of this syndrome confirmed by microarray or FISH technology.



Sources and references

Three scientific articles have focused on 2q31.2q32.3 microdeletions. Alessandro Cocchella and his colleagues described a woman of 28 years with a 4.4Mb deletion between 181.3 and 185.6Mb and learning difficulties, no speech and an unusual facial appearance. Paolo Prontera and his colleagues found a 13.7Mb deletion between 177 and 191Mb in a 36-year-old man with significant learning disability, some behaviour difficulties, an unusual facial appearance, muscular build and anomalies of his hands and

feet. They concluded that the man's unusual development could be explained by the chromosome 2 deletion. Maria Mencarelli and her colleagues found a 13Mb deletion between 180 and 192 Mb in a 14-year-old boy with significant learning difficulties, no speech, sleep disturbance, some difficult behaviour and an unusual facial appearance (Mencarelli 2007; Prontera 2009; Cocchella 2010).

Most likely features of 2q31.2q32.3 microdeletions

- Need for significant support with learning
- Severe speech impairment; most likely no speech
- Behaviour difficulties which may improve with age
- Large head
- Specific facial features including a long face, small chin and receding jaw, tilted ears

Other likely features

- Premature birth
- Short stature
- Muscular build
- Epilepsy and/or abnormal findings on EEG. After 18 years, one adult had no further seizures
- High and narrow palate
- Split uvula or tip of the nose. The uvula is the extension of the soft palate (roof of the mouth) that hangs down above the back of the tongue
- Spinal curvature
- Inguinal hernia. This shows as a bulge in the area where the lower abdomen meets the upper thigh (the groin). It is caused when an opening in the lower part of the wall of the abdomen that is open during fetal life but closes before birth, fails to close. The remaining opening may be small, only allowing fluid through, or it may be large enough for something such as a loop of the intestine or another organ to get stuck in it. An inguinal hernia should always be assessed by a doctor and may need surgery.
- Minor anomalies of the hands and feet, including tapering fingers, bow legs, a wide gap between the big toe and the second toe.

Genes that may be involved

The *NEUROD1*, *ZNF804A*, *PDE1A* and *ITGA4* genes have been suggested as underlying the learning and behaviour difficulties as well as the speech delay (Cocchella 2010). *ITGA4* is a candidate gene for behaviour disturbances and speech disorder (Cocchella 2010).

NEUROD1 has been shown to be involved in the development of the cortex of the brain. But people who have lost this gene may still have structurally normal brains (Cocchella 2010).

ZNF804A is a candidate gene for learning difficulties and behaviour disturbances (Cocchella 2010).

COL3A1 and *COL5A2* code for collagen and may underlie the inguinal hernias seen quite often. When *COL3A1* is deleted, there may be a raised risk of swelling in the walls of the arteries and possible rupture (vascular aneurysm). Any high blood pressure should be treated promptly and effectively, other risk factors avoided and any relevant head, chest or abdominal pain appropriately investigated (Prontera 2009).

MSTN is a gene which controls muscle growth. When it's disrupted, muscles may be bulkier, so the suggestion is that people in whom the *MSTN* gene is missing may have a more muscular build (Prontera 2009).

Scientific articles

Mencarelli 2007: Clinical and Molecular Characterization of a Patient With a 2q31.2-32.3 Deletion Identified by Array-CGH *American Journal of Medical Genetics* Volume 143A pages 858-65
Prontera 2009: 2q31.232.3 Deletion Syndrome: Report of an Adult Patient *American Journal of Medical Genetics* Part A Volume 149A pages 706-712
Cocchella 2010: The Refinement of the Critical Region for the 2q31.2q32.3 Deletion Syndrome Indicates Candidate Genes for Mental Retardation and Speech Impairment *American Journal of Medical Genetics* Part B Volume 153B pages 1342-1346

2q33.1 deletion syndrome

Researchers have recently identified a new microdeletion syndrome among people with genes missing from bands 2q32 to 2q33. The emerging new syndrome is variously called the **2q33.1 deletion syndrome**, the **2q32.2q33 deletion syndrome** and **2q33 microdeletion syndrome** (van Buggenhout 2005; Balasubramanian 2011).

Sources and scientific articles

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. If you wish, you can obtain articles from *Unique*. The following references contain single or series of case reports of individuals with a deletion involving 2q32: Brewer 1999; van Buggenhout 2005; de Ravel 2009; Rifai 2009; Rosenfeld 2009; Tegay 2009; Urquhart 2009; Balasubramanian 2011. References to *Unique* are marked *Unique*.

How many people have a 2q33.1 deletion?

Although larger deletions have been reported for more than a quarter of a century, the technology for detecting microdeletions has not been widely available for long, so it's not yet known how common 2q33.1 deletions are. So far 20 people with the 2q33.1 deletion syndrome have been reported in the medical literature, but there are likely to be thousands more who remain undiagnosed. When this guide was written, *Unique* had 13 members with this deletion, aged between two and 20 years.

Does everybody with a 2q33.1 deletion have exactly the same amount of missing genetic material?

No. Some people have a deletion that is hundreds of times smaller than other people. Reported deletion sizes in the medical literature range from 35kb to 10.4Mb. Among *Unique* members, deletion sizes range from 3.59Mb to 8.35Mb. Some people have only lost part of one gene. Others have lost many genes.

Are there people with a 2q33.1 deletion who have developed normally and have no speech, behaviour, learning or health difficulties?

So far everyone who has come to the notice of doctors and been reported in the medical literature or who has joined *Unique* has some developmental delay. The degree of delay varies and some people have no behaviour or health problems.

Is there a 2q33.1 deletion syndrome?



A 2q33.1 deletion syndrome is emerging although numbers of people with the deletion remain quite small, so much more is to be learned.

Individuals will differ from each other in some ways, partly because of the extent and position of their deletion.

Most likely features of 2q33.1 deletion syndrome

- Developmental delay
- Significant speech delay with no speech in most cases
- A degree of learning difficulty or disability, usually severe
- Slow growth before and after birth
- Severe, persisting feeding difficulties, often requiring nasogastric tube feeding, and failure to thrive
- Recognisable facial similarities
- High or cleft (split) palate (roof of mouth) or bifid uvula
- Crowded teeth with abnormally shaped teeth and some missing teeth
- Typical behaviour pattern; this includes hyperactivity, chaotic behaviour and a happy personality with bouts of anxiety or aggression (van Buggenhout 2005; Balasubramanian 2011)

Possible other features

- Genital anomalies in boys
- Lipodystrophy-like phenotype around puberty. In lipodystrophy, the distribution of fat in the body changes, with increases in areas such as the chest, abdomen and neck, and loss of fat under the skin from other parts of the body such as the face, arms, buttocks and thighs
- Reminiscent of a condition known as Wrinkly Skin Syndrome, with thin sparse hair
- Small head (microcephaly)

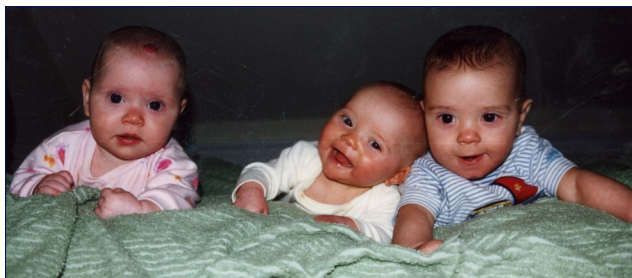
First signs

Among *Unique* members, the first sign that there was something amiss with their child was a cleft palate detected at birth in two, myelomeningocele (a type of spina bifida in which the backbone and spinal canal do not close before birth) detected antenatally in one, a neonatal seizure in one, a cluster of unusual findings (small genitals, hernia, small mouth) in one and delayed development by 18 months in one.

“ She wouldn’t smile at us by one month old, she avoided human faces as an infant, she had no innate desire to eat - let alone thrive! ”

Development

All babies and children known to *Unique* have shown some developmental delay and in some cases this, in addition to a birth anomaly such as a cleft palate, led to a genetic test. The degree of delay is quite variable, ranging from mild to more severe; one child, a triplet,



The triplet in the middle has a 2q33.1q33.2 deletion

achieves 50% of her triplet siblings' developmental level. It is better to let your child show his or her own pace of development than to try to predict it in advance. While delay is generally global, some children are more obviously affected in some areas. One family first noticed that their baby responded slowly to visual stimuli at one month, another noted slow acquisition of fine and gross motor skills, and another, delay in both speech and walking.

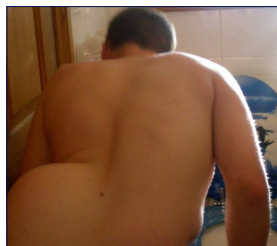
All children will benefit from early intervention with stimulation and play schemes. Your children's centre, developmental paediatrician, opportunity playgroup, portage scheme and health visitor are resources you can turn to for ideas on suitable stimulation.

Sitting, moving: gross motor skills

The major baby milestones of gaining head control, rolling over, sitting, becoming mobile and walking are very likely to be delayed. This means that early physiotherapy (physical therapy) and stimulation programmes should be made available to all children with this syndrome at the very least as a precautionary measure.

Many babies have a degree of low muscle tone (hypotonia, causing floppiness), but muscle tone may also be raised. Initially, gait may be broad-based and children may walk in short, unsteady steps. Any abnormalities of the angle of the foot, such as a 'banana foot' (metatarsus adductus) or club foot (talipes equinovarus) have an obvious impact on mobility, but once corrected by surgery or physiotherapy, a smooth walking style should become possible. Other youngsters have unusually flexible joints, making walking evenly difficult (Urquhart 2009; Balasubramanian 2011; *Unique*).

Among *Unique* babies, rolling emerged from around 8 months, sitting between 6 and 10 months, becoming mobile between 11 and 17 months and walking between 24 and 36 months. For many children the most obvious delay was in starting to walk but they did not need aids to do so; they were just a little late to get going. Children with high energy levels then progressed to walking a lot, and families report that any unusual walking style quickly evened out so their gait soon looked normal. They were generally climbing stairs by around three years. There are individual differences, but favourite physical activities include riding a ride-on toy, hiking, wrestling (6 years); riding a bike, playing with a ball (9 years); swinging (12 years); and swimming (water play), bike riding (with trainers), horse riding on a supported program, and any activity involving balls (14 years). One 6-year-old enjoys dancing and is learning to ski. However, a young man of 20 who had a severe spinal curvature corrected by surgery uses a wheelchair indoors and out.



Spinal curvature
corrected by surgery
at 18 years



“ She tends to ‘W’-sit to flex her joints or she may sit such that she can mouth her kneecap. If she’s restrained, as in a car seat, she often flexes against the belts, as she loves pressure. Her walk is ‘gawky’ and she can be floppy and is generally hypotonic. But she’s a stable walker and can walk for ever! Physical therapy provided her with great training and we used several tools (Pattibobs [arch-supporting

shoe inserts] and Theratogs [under-clothes support]) to help her ” 6 years

“ His progress has been somewhat slow, but steady, and his posture a bit hunched. His walking was somewhat abnormal but is now fine, and he loves running ” 7½ years

“ She is constantly on the move, even when eating or watching TV, though she is somewhat less steady than a typical child of her age ” 9 years

“ She walks anywhere and any distance. She is extremely active and has much energy and stamina ” 14 years

“ He always sits on his knees and lies in a fetal position, never flat. He only walks for transfers but is mobile in a wheelchair ” 20 years

Hand-eye coordination and fine motor skills



One year old

The evidence from *Unique* is that hand use and hand-eye coordination tend to be delayed, so that early play and occupational therapy intervention is important. Children are often late to grab and hold toys and late to develop a pincer grip. Holding cutlery and writing implements also tends to be late to develop. Low muscle tone plays some role in this delay, with children lacking the force needed to grasp and hold onto objects.

“ Her OT uses adaptive scissors that spring open so that she only has to motor plan the closure, not the opening of the scissors ” 6 years

“ He did have difficulty with fine motor skills: he couldn’t pinch, put a thread through holes, etc. He is now better: he can hold a fork or pencil and scribble but still needs hand over hand guidance most of the time ” 7½ years

“ Has a good grasp when writing and eating now ” 9 years

“ She has numerous fine and gross motor difficulties, such as with zippers and buttons, and an unusual pencil grasp ” 14 years

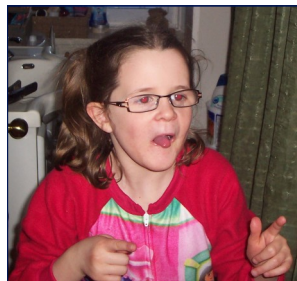
Personal care

Self care skills are late to develop, with some children able to cooperate with dressing and washing by six to nine years, pulling on and off clothes, zipping and unzipping and buttoning and unbuttoning. Toilet training is a slow process, and was successful at six years in only one child known to *Unique*, so may not be possible for all.

“ He washes his hands and face by himself, and helps with bathing ” 7½ years

“ She can dress and feed herself but cannot bathe herself completely and needs help in the bathroom. My advice to other families is to emphasise personal care skills at an early age! ” 9 years

“ She responds best to praise and reinforcement, patience, creativity, visual supports and small steps ” 14 years



10 years old

How will communication be affected?

Children will generally be slow to understand speech and express themselves, and may be helped by learning to sign their needs or by assistive communication systems and devices. In general, it appears that speech development is particularly delayed and most children do not acquire speech. The typical cleft or high palate also affects speech production. Researchers have commented on an unusual ‘Donald Duck’ speech style in two children (van Buggenhout 2005; Balasubramanian 2011; *Unique*).

Unique’s experience is that children understand some speech, particularly often-repeated short phrases. They may even learn to babble, to make word approximations and to use some single words of speech, but the sounds of speech are usually unclear and babbling or words may not be retained, so that alternative means of communication are more consistent and reliable. Overall, children and adults are largely non-verbal.

Early non-verbal communication is generally also delayed, with babies first smiling socially at around three to six months and any babbling sounds also emerging late before generally fading. Finding the right alternative communication method is individual: while some children learn to sign ably and to link signs into phrases, others struggle to do so. Early on, children can get their meaning across by using vocal sounds, pushing, pulling or pointing; as they mature, they may be able to learn picture symbols and use picture exchange systems. Hand-held communication devices have worked very successfully for some children, while others with fine motor difficulties have struggled to handle them. Families suggest that a combination of methods seems to work best, allowing the child different ways to reinforce their meaning.

“ She said her first words at 28 months but, they didn’t stay. She has learned several words but they fade away and she currently only has one phrase: ‘All done’. She has used communication devices (talking notepads, a TechTalk8 for school) but pointing and grunting are by far the most effective ” 6 years

“ He forms sentences with three to four words using signs and via his VantageLite device, and can make himself understood about 80 per cent of the time ” 7½ years

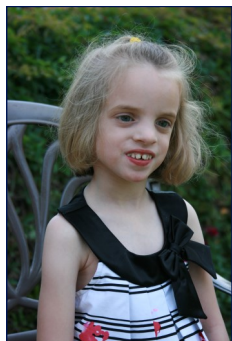
“ She is generally able to convey what she wants, though we sometimes misunderstand her gestures and signs. She uses a communication device at school and is getting more proficient at it, but signing is easiest and quickest, although not everyone understands sign language. My hope is that some day she will be able to read and write well enough to be able to type her thoughts into a device that will speak her exact thoughts for her! ” 9 years

“ She uses signing, picture exchange and a Tellus Smart, a palm-sized communication aid that combines text and symbols in the message window ” 12 years

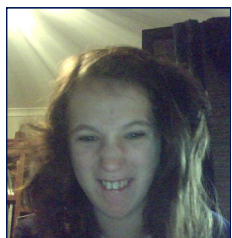
“ She has no language or speech, but makes sounds and babbles, with possibly recognisable words of *mama*, *bye* and *hello*. We trialled some electronic communication boards but they were cumbersome, difficult for her to operate, and constantly required reprogramming, so were not successful. Perhaps the combination of augmenting her limited speech in context with keyword signs, objects and visuals works best. She appears to be a here and now communicator ” 14 years

“ He understands basic speech but cannot respond ” 20 years

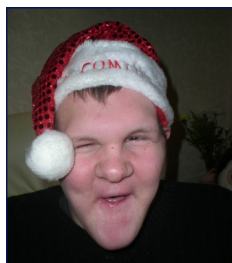
How will a child's ability to learn be affected?



5 years, 10 months old



14 years old



19 years old

Children with this deletion can be expected to need some support with their learning, but the amount of support needed can't be predicted just from the genetic test results.

The researchers who originally identified the emerging syndrome suggested that most children will need considerable support as they will have a severe learning disability. Among 24 children whose learning ability was graded, three had a mild level of disability; five had a moderate disability; in 15, it was severe; and in one, profound (van Buggenhout 2005; Balasubramanian 2011; *Unique*).

Below, families say what children can achieve despite these challenges.

“ She has an incredible memory for high motivators: we bought ice cream at the store, so she will ask incessantly for ice cream until it's all gone. She can't read, but knows the labels of certain products. Just a few months ago she learned the M&M's label and now finds them at the grocery store check-out. She can scribble, literally straight lines.

“ She's in a public (mainstream) school in a 'special day class' of eight children who require significant educational support. Her classroom has one teacher and six aides, so she shares an aide with another student.

“ We found the more autistic-based classrooms provide the visual supports, high schedule/routine, and Alternative and Augmentative Communication-trained teachers that work well with our daughter. We toured classrooms for other mentally impaired children (Down's syndrome) and found that our daughter was far behind them in terms of cognitive ability. She needed to be in a more 1:1 education setting ” 6 years

“ He is functioning cognitively and socially at a 4-year level and has been making real progress lately. He has a great visual memory, loves letters, puzzles and numbers and is getting those a lot quicker and better than some other things such as clothing or food types or names. He writes mostly hand over hand and can write his first name and a few other letters independently.

“ He is in a mainstream class as well as participating in a severe special needs (SSN) class due to his behavior.

“ I would say that the most important thing is the team who will work with your kid. Make sure the team or teacher is well qualified or certified in special education, as it makes all the difference. Get involved and try to be your kid’s best advocate! Work closely with the school, see what’s working at school and try to implement it at home, or the other way around ” 7½ years

“ She is at about a kindergarten level (age 5-6) academically. She can write her name and a few other words such as *Mom* and recognizes some sight words. She knows all the numbers and letters and can do simple addition. Her memory is OK, though she easily forgets what she has learned recently, unless it is done repeatedly. She likes it when learning is fun ” 9 years

“ She attends a normal school with a full time educational assistant, has a pretty good memory and recognizes certain words, ie *Barney, library, ice cream, Dora, Victoria, the Big comfy Couch, Zack and Cody, mommy, daddy, Shelby, Shania*. She can write the first three letters of her name ” 12 years

“ On the many levels of learning and understanding, her development appears to be between around four and eight years in most respects. Things that motivate her and gain her a reward are the most helpful. For example, she is able to put her shoes on, especially when she is aware of going shopping for grocery, and if she does ‘good listening’ she will usually receive a meal at McDonalds (her favorite food). She appears to generally want to help, and will learn your routine and then support you with this.

“ Academically, she is extremely delayed in most aspects, with some splinter skills, and has not shown any level of reading skills ” 14 years

“ His mental age is around two to four years; he doesn’t read or write ” 20 years

Is there a typical growth pattern?

Birthweight range at term 1.9kg (4lb 3oz) – 4.5kg (9lb 14oz)

Babies are often, but not always, on the small side at birth and continue to grow more slowly than other children, remaining short and thin despite an adequate food intake.

Slow growth has been seen in 21/31 children. There is some evidence from *Unique* that growth picks up in older children and adolescents. Many children have only a thin layer of fat beneath the skin, which contributes to their slim build, and this is sometimes the case even when their height is normal.

“ Wearing clothes for a 9-12 month baby ” 22 months

“ Her build is very slight, thin bones, very thin muscle bulk, very little body fat ” 6 years

“ She’s been on a fairly steady, slow growth curve ” 6 years

“ He was a big baby, 4.5 kilos at birth, but his rate of weight gain started dropping in his first year. This changed within the last year, in part due to the medication he is on for laughing seizures. He is tall now, nicely developed, with nice muscle tone ” 7½ years



Front: 3 years old, with same age sister

“ She has always been slow growing in every aspect, even her hair and nails. Adding cereal to high-calorie formula as an infant helped, as did sometimes giving her Pediasure (a nutritional drink) as a toddler. Nothing special lately, but she usually gets the extra slice of bacon! Today she is short and thin but proportionate, and not the shortest in her class. She looks more like a typical 6-year-old ” 9 years

“ From birth until about five years of age, she grew slowly and today is short for her age, despite eating constantly, with a protruding abdomen and long legs ” 12 years

“ She grew slowly until she was seven, but today is above average in height, with an elongated body. Both parents enjoy good height. She is also slight and slim ” 14 years

“ He grew slowly until he was 13. Now he is heavy on top, skinny below ” 20 years

What about food and eating?

Most babies have early difficulties with both sucking and swallowing, and need active support with feeding by tube through the nose or in some persistent cases by



Home made pizza:

3 years

gastrostomy tube direct into the stomach. With their low control over the muscles in the mouth area, feeding requires considerable effort for some babies, who fall asleep only a few minutes into their feed (Balasubramanian 2011; *Unique*). Babies with a cleft palate will experience particular feeding difficulties, but the problems are usually obvious even when the palate is intact. However, with teats and bottles adapted for babies with a cleft palate, it is possible to nourish a baby on breast milk or formula, frequently supplemented to promote growth.

Once children are feeding from a beaker, they may retain a tendency to choke on liquids and need careful supervision at mealtimes.

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

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

The good news is that the early feeding difficulties do resolve and by school age, children are generally eating family meals. Nonetheless, babies are generally late to learn to use a beaker and to feed themselves using cutlery, due to their delayed fine motor skills.

“ At one year old she was transitioned from formula to Pediasure (a nutritional drink). At some point shortly thereafter, we moved her to a more calorically rich supplement (Resource 1.5 by Novartis) which had 50 per cent more calories per ounce. It was her main source of calories, and she stayed on it until she weaned herself at around three years old. Around age three, she was also willing to drink Carnation Instant Breakfast and eat table foods. Today she eats solely table foods, and has no supplements ” 6 years

“ When learning to drink from a straw, her OT had us take a soft, plastic honey bear bottle with PVC tubing in the middle as the straw. That gave us the ability to help

squeeze the drink up the straw with her little sucking power. It was a great learning tool!" 6 years

"We tested many bottles to figure out which method would take the least amount of effort from her. We used the Haberman feeder for several months, then moved to a Dr Brown's bottle with a Y-cut nipple sliced even further open, and with added Duocal (a high-calorie nutritional supplement) to increase calories. All the same, it was a horribly long, tedious process to feed her. We counted milliliters and it took about eight hours per day to feed her.

"Our pediatrician really wanted to avoid a nasogastric tube, so we worked very hard with a nurse specialist, occupational therapist, adapted bottles and teats, and the gastrointestinal clinic to get enough calories in her. The lactation consultant who was also a specialist in adaptive bottles was the most helpful person for us, as well as a nurse coordinator at the craniofacial clinic" 6 years

"During his hospital stay, he was getting very hungry and used to get bluish around the mouth, as when he sucked on the bottle, he forgot to also breathe, so I had to remove the bottle every few seconds to remind him to breathe. Once solids were introduced, he only had a few favorites he would eat. This was a very difficult process, as we had to distract him so that he paid no attention to the food. We might go to a parking lot where he could watch the cars go by, or have a third person playing with him while I was feeding, or watch his favorite show on TV. We tried counseling and a feeding program, but it brought no progress. He favored soft-textured foods, and had difficulty chewing because of teeth issues; he loved cooked spinach and eggs, yogurt, cottage cheese, banana, and apple sauce. He took milk by bottle until the age of three and at first used a sippy cup for water. He didn't eat sweets, cookies, sugar or ice cream until he was about six to seven years old. He started getting better by himself, but it was a continuous struggle. By almost eight years, we had no issues whatsoever.

"There was no treatment, just numerous attempts to introduce different textures and flavors. Once he got used to something, cheese, for example, we tried various flavors such as mozzarella, cottage cheese and feta and saw what he liked. No matter how hard we tried, he was not too fond of fruit: the only fruit he would eat was banana.

"Now he eats almost everything, though there is still a bit of an issue with harder textures due to his teeth, but he likes crackers and pretzels, his fruit variety has increased and he will also eat peach, apple, grape, pear, orange and strawberry although not often or consistently. He still favors pasta, mac & cheese and pizza, but also likes soups and meat cooked in different ways such as meatballs, hamburgers, tacos, stuffed peppers or other veggies" 7½ years

"She wasn't able to breast feed due to her cleft, but had a feeding tube in the hospital and we used a Haberman feeder bottle at home. The most helpful thing, with three babies, was



Honey bear bottle



In this family, the girl in the front on the right has a 2q33.1 deletion

friends and family offering to feed her. Today, in spite of her low weight and stature, she loves to eat and eats a lot!" 9 years

"She has a preference for soft and cooler foods, and needs foods cut into smaller pieces to aid chewing and swallowing. If not prompted, she will swallow foods whole and has had many near choking events" 14 years

"He eats a normal diet but is not good at chewing due to his poor teeth. Perseverance helps!" 20 years

Will my baby or child look different?

You and the doctors may notice that your baby has an unusual facial appearance. He or she may look more like one or more of the babies and



3 years old

children in this guide with a 2q33 deletion than like other members of your family. Many children, although not all, are fair, and have thin, sparse hair, a long face with a high forehead, a small mouth, unusually positioned and formed teeth, unusually formed or positioned ears and a small lower jaw. Their eyes most typically slant downwards; the upper eyelid may be hooded. It's possible that there are two typical facial appearances, one with an upturned nose, the other with a prominent nose and eyes that slant downwards (Balasubramanian 2011).

Typically, skin is thin and transparent, with an abnormally thin layer of fat, allowing the blood vessels beneath to show through, and there have been reports of people with wrinkly skin over the abdomen and on the backs of the hands and feet as well as an increase in creases on the

palms of the hands and the soles of the feet. One child has developed vitiligo, a skin disorder with loss of brown colour from areas of skin, requiring careful protection from sunlight. Hair can be sparse and fine or, by contrast, unusually thick and coarse. These observations, together with the unusually formed teeth, suggest that genes in the deleted section of chromosome 2 are important for the normal formation of the skin (ectodermal) and the fat layers beneath (Balasubramanian 2011; *Unique*).

"He should have more hair than he has currently" 2 years

Cleft palate (split in the roof of the mouth)

Eighteen/31 babies were born with a cleft palate; 9/31 were born with an unusually high palate. Typically the palate is split (cleft) or it may be unusually high. 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). Loss of a gene known as *SATB2* from band 2q33.1 is the most likely cause of the palate anomalies (Brewer 1999; FitzPatrick 2003; van Buggenhout 2005; Balasubramanian 2011).

Both cleft and high palates can cause significant feeding difficulties and feeding support should be available. Surgical repair of the palate, usually in the second half of a baby's first year, eases these difficulties and may eliminate them altogether.

“ Figure out a great feeding method. If it’s a struggle, try another method. Be very realistic about providing breast milk. For me, it was not sustainable to pump, feed, clean equipment, and then repeat. The time and patience it took to feed a cleft palate baby was more than enough work alone. The soft palate cleft was surgically repaired in a double opposing Z-plasty at 10 months old ” 6 years

“ Bear with it until it can be repaired! Keep your baby sitting up after eating; add cereal to milk in older infants. We found the most helpful person was the craniofacial doctor. The cleft was repaired at eight months and nowadays has no effects at all ” 9 years

“ His palate is very high, so that food such as peas and sweetcorn comes down his nose. Our advice to other parents is: get answers, don’t ignore it! ” 20 years

Unusual dental development 19/27

In some children the teeth grow short, broad and oddly-shaped, or they may be very large and are frequently unusually crowded. Milk teeth may erupt late and fail to fall out to allow adult teeth through; the set of adult teeth may be incomplete. There may be a gap between the front top teeth or teeth may be fused together.

It has been suggested that the gene defect underlying children’s unusual skin and hair may also affect dental development. Whether that is true or not, children with a 2q33 deletion warrant specialist paediatric dentistry partly because of the genetic influences on their dental development but also because of their unusual early feeding difficulties which in turn can affect dental development (van Buggenhout 2005; Balasubramanian 2011; *Unique*).

“ Her baby teeth are unusually large for her mouth. I cannot imagine how she’s going to fit her adult teeth in her mouth! She has struggled with cavities and at this point has three fillings. We have also put sealants on all her baby molars. She is very resistant to brushing, but we restrain her once a day for a good brushing. She is not always compliant, but we do our best. Our best advice is to find a pediatric dentist who has a large number of special needs kids in their practice. To have a confident dentist puts the parents at ease ” 6 years

“ His teeth are very crowded. His four bottom front teeth were in parallel rows, the milk teeth in the rear row having to be extracted when he was three. The front upper teeth were chipped when he was one or two years old, and had to have crowns. We ended up extracting them at five years of age, and he is still without permanent teeth. The lack of teeth makes it difficult to chew harder textured foods ” 7½ years

“ Her teeth have come in and fallen out very late and in an unusual order. She cut her first baby tooth at about 12 months and lost her first tooth at eight. She grinds her teeth, so many surfaces are flat and the dentist has a hard time with her ” 9 years

“ She has large, misshapen teeth as well as missing teeth, and easily gets cavities. When her front top baby teeth were removed, the permanent teeth did not come down until the dentist cut her gums ” 12 years

“ She has had extensive dental treatment and checks and also excessive drooling throughout her life. However, drooling generally only occurs now when she is excited or concentrating, possibly as a result of OT oral exercises and use of an electric toothbrush ” 14 years

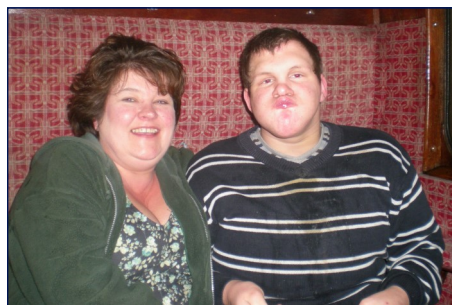
“ His teeth are peg-like and rotten ” 20 years

What about behaviour?

A typical pattern of behaviour has been described in some children with a deletion in this region. They have episodes of marked hyperactivity and restlessness, and can be chaotic. Although basically they are happy, they can have tantrums inappropriate to their age, outbursts of aggression and anxiety as well as sleep difficulties, and some self-harming (headbanging). Not all children are affected, and the challenging behaviour can develop at different ages, with 30 months the earliest age recorded (van Buggenhout 2005; Balasubramanian 2011; *Unique*).



Left, at 8½ years, enjoying harvest



Enjoying travelling by train, 18 years

Researchers have suggested that the underlying cause of the behaviour abnormalities is deletion of a gene in the 2q32.2 band known as *GLS*, which plays a role in the production of a neurotransmitter in the brain. This remains to be proven, particularly as children with the typical behaviour pattern have apparently had deletions that did not include this gene.

The *SATB2* gene has also been suggested as underlying behaviour difficulties, but not all the children with microdeletions within the *SATB2* gene have exhibited difficult behaviour. Further, children with non-overlapping deletions have behaviour difficulties, suggesting that more than one gene underlies the behaviour problems and that they may act cumulatively.

In the meantime, early intervention with behaviour management is strongly recommended for all families before any problems develop. The importance of early intervention is underlined by a description of a youngster with severe problems in the institution where he lives, but none at his own home, suggesting that a programme that can support families is important for these children's wellbeing (van Buggenhout 2005; Balasubramanian 2011).

Best advice to other families? A combination of consistent parenting, positive behaviour support and applied behavioural analysis (ABA) principles. ABA is a way of enabling learning and development. For more information, read about ABA on the www.autism.org.uk site.

One boy with a deletion within the 2q32 bands who stopped using previously acquired language at 30 months, and developed self injury, tantrums and a dislike of crowds was diagnosed with autism. Other children have been found to have autistic features (Gallagher 2003; Balasubramanian 2011).

“ He smiles to interact with other people. I would say he is borderline shy. He likes to look at new faces, and smiles at new people, but does not like them to carry him. He is also very restless and cannot sit still for more than a couple of minutes ” 22 months

“ Her difficult behaviours include: being restless, hyperactive behaviour, chaotic behaviour, anxiety, aggression. She can be fine, then turn on a dime. She can throw incredible tantrums that just spiral for a few hours. Taking her for a walk makes it all better. She has a very high energy output and is moving or flexing her body at all times. She stimulates incessantly, be it teeth grinding, flexing her joints, visually stimming, tapping her fingers, squeaking her fingers on the floors, squeezing her fingers into her pockets, etc. She is generally very stubborn.

“ With age and size, we have discontinued use of a stroller and often do not put her in a shopping cart. Now that she is more free rein, it can be difficult to control her in public. She can run away quickly, and has no separation fear or sense of danger. Obviously, with her being bigger and longer, she's more 'scrappy' to contend with if she pitches a fit. Our best control methods include time-outs. We now put her behind a puppy gate when she's pushed us too far.

“ Socially, there are certain adults and children that she is clearly comfortable with and actively solicits their friendship. Then there are those people she just ignores. Then there is our baby, who she adores to a point of constant irritation. We noticed about age four that she realized she was a child, and would actively separate herself to be near a group of children in parallel but not interactive play. That is still basically the case at age six. I do see some similarities with autistic behaviour.

“ Her favorite activity at home is a ride-on toy (Plasma Car) that requires no pedals or balance. She also loves to stare out of the window and watch the outside world. She loves to be outside, and go for endless walks. She loves to walk, unconstrained, anywhere ” 6 years

“ He has some moderate behaviour issues, such as outbursts. He can swing very quickly from hugging and kissing to slapping, especially if his younger siblings are around, but not when he is alone with a single adult. As he has matured, he understands more and you can talk things through with him, and make him realise what's good and not. He can be very OCD (obsessive-compulsive), and needs constant schedule; if he doesn't have anything to do, his behaviors tend to escalate. He is still a bit jealous of his siblings, but his aggressive behavior has decreased a lot! He now helps with their toys, cleaning, food, dressing etc. He also loves puzzles, Thomas the Tank Engine, cartoons, books and matching games ” 7½ years

“ She has a very sunny and friendly disposition, likes routine and has many OCD-type behaviours: she has to have two books at bedtime, her clothes set out for next day, her bike parked perfectly in a certain spot, a bagel with cream cheese for breakfast every day. Prozac helps her not to have a complete meltdown when one of these things is not just so. She did not care much for television until she was five, but at nine, she wants to watch her favourite films repeatedly. She is also hyperactive, with attention deficit, and



10 years old



2 years old

is on Concerta to help her focus at school. Socially, she is very friendly and loves to laugh with familiars. She can be shy, but not usually. She often puts herself right into another person's face to look at them!

" She loves animals, stuffed or live, but especially her dog, iCarly (a TV show), riding her bike, going to school, and dining at a restaurant. We have found school personnel and her psychiatrist the most helpful people " 9 years

" She loves music and watching Barney, has a

molly doll that she takes everywhere she goes, and loves to play on the computer. But she can be restless, hyperactive, has anxiety issues, and can become aggressive, and is currently on Risperidone. She smiles at people and has a fondness for males, but can change at a moment's notice and become aggressive. No autism " 12 years

" She is extremely sensory orientated with touch, taste and orally. She mouths and smells most objects. She also shows a self injurious type behaviour, picking her skin until she has open sores and will habitually pick her nose until it bleeds. She also has an extremely high pain tolerance. In the past she has been on Ritalin due to excessive activity and inattention. However, the sedating effect was concerning, and after about eight months she stopped taking it.

" On a normal day she can be very routine-orientated and becomes distressed with change. We are presently trying to reduce this. She can also experience extremes in moods and can be impulsive, repetitive and at times compulsive. Over time we have become better able to redirect her.

" Now she is into adolescence and appears to enjoy the same type of activities as others, although at a lower level, ie music, dance, shopping for clothes, and being with same age peers, especially within the school environment. Socially, she is a very jovial and social young lady, enjoys others' company and is very interactive, albeit quite tactile at times, polite and is known and accepted within the local community. She enjoys music, generally with movement (dance), interacting and engagement with other people, helping her parents generally, and has always been encouraged to participate in, for example, helping to prepare a meal, general chores or gardening etc " 14 years

" Since puberty, he has had major problems with aggression (spitting, hitting), so can't be taken out. He interacts well socially if he wants but is rough. His poor communication makes him very frustrated. He does have autistic tendencies " 20 years

Sleep disorder

Children with the syndrome are at risk of a sleep disorder with frequent awakenings (Balasubramanian 2011).

“ She sleeps with a puppy gate at her bedroom door, more necessary when training her to stay in bed, now it’s just routine ” 6 years

“ He has had difficulty sleeping due to laughing seizures. On treatment, this has improved a lot during the last few months ” 7½ years

“ She has problems falling asleep and will sometimes get up three times a night. When she was younger, she would wake up at night and stay up for three hours ” 12 years

“ She generally sleeps through, although at times will get up during the night to raid the fridge and pantry. She rises at 5-5.30 am, no matter what time she retired ” 14 years

“ He is given a 10ml dose of melatonin at night to help him sleep, but it doesn’t help too much ” 20 years

Minor anomalies of the genitals Found in 8/16 males

A range of minor anomalies of the genitals has been found in boys. This includes small genitals, hypospadias (where the hole usually at the end of the penis is on the underside instead) and undescended testicles, where the testes have not yet completed their natural descent from the abdomen into the scrotum. The approach to undescended testicles depends on the suspected cause, but whatever it is, treatment is usually needed if the testicles do not descend naturally in time. If a hormone problem is suspected, a short course of hormone treatment may be suggested. Otherwise, or if hormone treatment does not work, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy.

Additionally, inguinal hernias (in the groin) are reported to be relatively common. During fetal development, a boy’s testes descend into the scrotum through an opening in the lower part of the wall of the abdomen. The opening usually then closes, but if it fails to close or re-opens, fluid or even a loop of the intestine or another organ can pass through. This is an inguinal hernia and it usually appears as a bulge in the groin or as an enlargement of the scrotum. An inguinal hernia should always be assessed by your child’s doctors and your child may need surgery to repair it. Although inguinal hernias are more common in boys, they can also occur in girls (van Buggenhout 2005; Balasubramanian 2011; Unique)

Very small head (microcephaly) Seen in 10/26

In some children, the head is unusually small, taking age and sex into account. A small head indicates a small brain and while in some children this may not matter at all, in others the growth of the brain may have been affected. This is more likely if there is a genetic cause such as a chromosome disorder. Although a small head is typical, it is not universal, and some children appear to follow their familial pattern and have a normal or large head.

Hands and feet

In many babies and children, the hands and/or feet have at least some unusual features. The fingers may be clenched or very long and thin, the hands may be small, thumbs may be unusually broad or short, and the fifth fingers may curve inwards.

Typical features affecting the feet include long, slender toes, 'clawed' feet with a raised arch, overlapping toes, prominent heels, incurving little toes, clenched toes, club foot, short toes, broad first toes, broad, short nails, flat feet and a wide 'sandal' gap between the big toe and the second toe.



Children may need foot and/or ankle supports, shoe inserts or special boots to support them in the early stages of walking (Brewer 1999; van Buggenhout 2005; Rifai 2009; Rosenfeld 2009; Tegy 2009; Urquhart 2009; Balasubramanian 2011; *Unique*).

“ Her nails seem to grow really slowly, I almost never trim the nails! Her nails cover a wide area of her finger, more than the other members in our family. She has incredibly skinny, bony feet and tends to curl her toes ” 6 years

“ She flexes her toes rigidly and walks on them, or on some surfaces rises to them ” 14 years

Seizures Diagnosed in 7/29

Seizures are not a common feature of 2q33.1 microdeletion syndrome, but can occur. One child had several febrile seizures in her first two years. Another developed 'laughing seizures' at almost seven years: initially, these lasted for a few seconds to a few minutes, but they grew in duration and intensity and started to happen at night, rather than during the day. Once treated with oxcarbazepine (Trileptal), the seizures decreased. A baby of two weeks had an apparent seizure, initially diagnosed as gastroesophageal reflux, but eventually as epilepsy. She had no further seizures after the age of five.

Unfortunately, it is not possible to predict which children will develop seizures. Imaging of the brain in affected children may show anomalies such as enlargement of the fluid-filled ventricles within the brain, but may just as well reveal an entirely normal brain structure (van Buggenhout 2005; Urquhart 2009; *Unique*).

Eyesight Squint/strabismus seen in 7/26

The eyes and vision may be affected. A persistent squint (strabismus) needing surgical correction, and amblyopia, requiring strengthening of the weaker, 'lazy' eye, have been observed most commonly. A developmental defect of the eye known as a coloboma has occurred and underdevelopment of the optic nerve has also been found, leading to a variable degree of visual impairment. In one child, the vision in one eye is markedly reduced compared with the other eye and she is long-sighted.

In two cases, the tear ducts have been persistently blocked, requiring opening in a minor surgical operation. One child had a perforated keratoconus at the age of 16, requiring transplantation of a cornea. Keratoconus is a degenerative condition where the cornea thins and is pushed outwards, usually in the centre, by the internal pressure of the eye. It is a condition which requires to be regularly monitored. In mild cases, spectacles will offer correction of the refractive problems. Contact lenses may be required for more advanced cases or, as in this case, surgery (van Buggenhout 2005; Balasubramanian 2011; *Unique*).

“ She has delayed visual maturation, originally thought to be cortical visual impairment, and is also treated for strabismus and amblyopia. This impacts on her very little, she has functional vision. She wears glasses currently, half the prescription estimated to be needed. She did not tolerate eye patching: instead we used dilation drops to weaken her strong eye in the hope of realigning her eye muscles, but it didn't work as she just swapped dominant eyes ” 6 years

“ No apparent response in her right eye. She appears to adapt by turning her head to the side with apparent better sight, but can appear clumsy and bump into objects even in familiar environments. She has been prescribed glasses but generally refuses to wear them ” 14 years



First glasses at
2½ years

General wellbeing

There is no firm evidence that children with this deletion will be any more unwell than children without a chromosome disorder. Like other young children, they have repeated coughs and colds and are prone to develop ear infections. Those with a cleft palate seem to be more prone to sinus infections. Moreover, with their precarious weight gain, they may be more likely to stop feeding and lose weight while ill than other children (*Unique*).

“ Generally, she's a healthy, small-framed child. She catches every virus that comes near her and takes much longer to clear a cold or stomach flu. Her sinuses tend to be her issue: she ends up with frequent sinus infections that knock her out. She is the weakest child in our house by far, but considering she's never been hospitalized for an illness, I shouldn't complain. I just keep her far away from anyone who's ill ” 6 years

“ Prone to sinus infections. Ear tubes placed to prevent ear infections ” 9 years

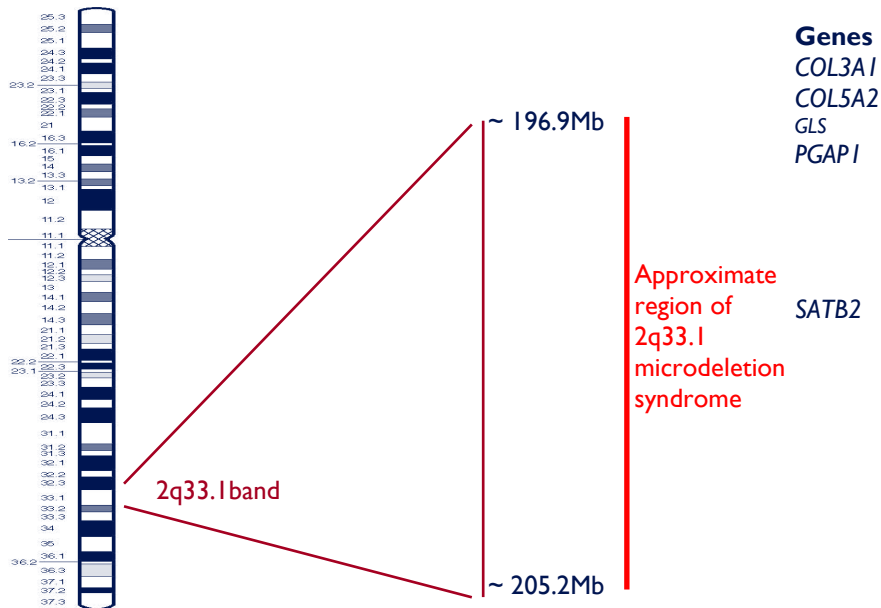
“ Usually healthy ” 12 years

“ She was twice hospitalised for pneumonia before four years of age, likely as a result of feeding difficulties and aspirating. We were advised of a weakness in her lungs, and she was prescribed a preventer and Ventolin. Today she is quite resilient to common ailments, and even when unwell is still extremely active ” 14 years

Genes that may be involved

It's likely that many genes within the lost chromosome material contribute to the features seen in any individual with the syndrome. However, the gene that's thought to underlie many of the features of the 2q33.1 microdeletion syndrome is called *SATB2*. Even when only part of the gene is missing, typical features of the syndrome are seen. The gene is expressed in the developing brain and so may underlie the developmental delay. It also plays an important role in craniofacial patterning and can cause a cleft palate and is believed to contribute to the tooth abnormalities when it is present in only one copy. It may possibly also underlie the facial features that people with the syndrome show (Fitzpatrick 2003; Rifai 2009; Rosenfeld 2009; Balasubramanian 2011). Another gene that's been suggested as important in facial formation is *PGAP1*, possibly acting together with the *SATB2* gene. *PGAP1* is found in the 2q33.1 band (Urquhart 2009).

Two genes that are close neighbours in 2q32.2 - *COL3A1* and *COL5A2* - have been suggested as underlying the thin, transparent skin and sparse, slow-growing hair that some people with the syndrome show. Both genes encode the instructions for the correct development of types of collagen. Mutations of the *COL3A1* or *COL5A2* genes cause some types of Ehlers-Danlos syndrome, marked by loose joints, very elastic skin and easily damaged blood vessels (van Buggenhout 2005; Rifai 2009).



Scientific articles

Balasubramanian 2011: Case series: 2q33.1 microdeletion syndrome – further delineation of the phenotype *Journal of Medical Genetics* Volume 48 Pages 290-298

de Ravel 2009: Another patient with a de novo deletion further delineates the 2q33.1 microdeletion syndrome *European Journal of Medical Genetics* Volume 52 Pages 120-122

Rifai 2009: Ectodermal Dysplasia-Like Syndrome With Mental Retardation Due to Contiguous Gene Deletion: Further Clinical and Molecular Delineation of del [2q32] Syndrome *American Journal of Medical Genetics* Volume 152[A] Pages 111-117

Rosenfeld 2009: Small Deletions of *SATB2* Cause Some of the Clinical Features of 2q33.1 Microdeletion Syndrome *PLOS ONE* Volume 4 Issue 8 e6568 **Free Access**

Tegay 2009: Toriello-Carey syndrome in a patient with a de novo balanced translocation [46,XY,t(2;14)((q33;q22)] interrupting *SATB2* *Clinical Genetics* Volume 75(3) Pages 259-264

Urquhart 2009: 4.5Mb microdeletion in chromosome band 2q33.1 associated with learning disability and cleft palate *European Journal of Medical Genetics* Volume 52 Pages 454-457

van Buggenhout 2005: The del(2)(q32.2q33) deletion syndrome defined by clinical and molecular characterization of four patients *European Journal of Medical Genetics* Volume 48 Pages 276-289

Brewer 1999: Locus for Isolated Cleft Palate, Located on Human Chromosome 2q32 *American Journal of Human Genetics* Volume 65 Pages 387-396 **Free Access**

Why did the deletion in chromosome 2 occur?

Deletions within chromosomes happen naturally and probably much more often than we realise. To find the cause of the 2q deletion in your family, your geneticist will offer to check the parents' chromosomes. A small blood sample is needed for the test. It will show whether the deletion is a new event, termed **de novo** (dn) by geneticists, or whether a change in one of the parent's chromosomes has caused it.

Most 2q deletions occur when both parents have normal chromosomes. New deletions occur when sperm or egg cells are forming or just after fertilisation during the copying of the early cells that will become an embryo, then a fetus and then a baby. No-one has ever watched a deletion happening during the formation of the eggs and sperm, but here is one idea of how it can occur: during the formation of the egg and sperm cells the two members of each pair of chromosomes normally line up together and then break and rejoin to create new chromosomes. These new chromosomes contain different combinations of the genes from the grandparents passed down by the parents to the child. It is believed that after the chromosomes break, the rejoining can take place between the wrong broken ends, and this can lead to a 2q deletion.

Some 2q deletions are the result of a rearrangement in one parent's chromosomes. This is usually an inversion in which material has switched directions on one chromosome 2 but no material has been lost or gained and the parent usually has no difficulties with health or development. Occasionally, when the deletion is very small, one parent has the same deletion as the child.

Whatever the explanation for your child's 2q deletion turns out to be, what is known is that as a parent you did nothing to cause the deletion and nothing you could have done would have prevented it from occurring in your child. No environmental, dietary, workplace or lifestyle factors are known to cause these chromosome changes. No one is to blame when they occur and nobody is at fault.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 2q deletion or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 2q deletion. This is called **germline mosaicism** and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the deletion.

In families where the 2q deletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 2q deletion rises to 50% in each pregnancy. However, the effect of the microdeletion on the child's development, health and behaviour cannot be reliably predicted.

Your genetics centre should be able to offer counselling before you have another pregnancy.

Will my child with a 2q deletion have similarly affected children?

Adults with small 2q microdeletions may form close relationships and want to have children. We have not known about the condition for long enough to be certain if it affects fertility but it is likely that in people with small microdeletions, fertility will be normal. In each pregnancy, someone with the deletion has a 50 per cent chance 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.

Support and Information



Understanding Chromosome & Gene Disorders

Rare Chromosome Disorder Support Group,

The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel/Fax: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org/donate Please help us to help you!

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 Meena Balasubramanian, Sheffield Clinical Genetics Service, UK and by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK. Version 1: 2011 (PM)

Copyright © Unique 2018