

Support and Information



Understanding Chromosome & Gene Disorders

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This guide is dedicated to the memory of Lucy Chadwick

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 has been verified by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick and by Dr Saskia Maas, clinical geneticist, Academic Medical Centre, University of Amsterdam.

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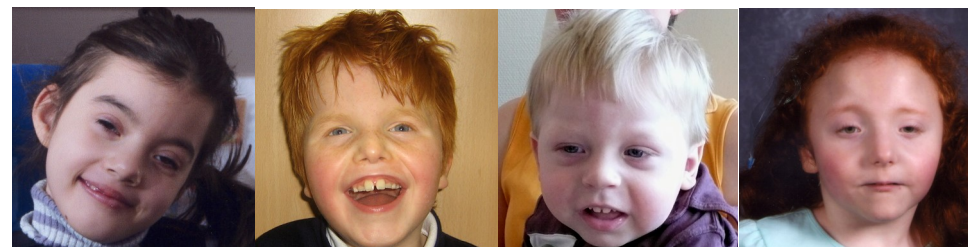
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Understanding Chromosome & Gene Disorders

2q24.3 microdeletions



rarechromo.org

“ Everything he does is special. He has taught me so much I couldn’t write it all down! - 4 years

“ We love his personality and his delightful laugh. We find he is a great blessing in our lives despite the challenges - 5 years

“ She is the light of my life - 6 years

“ Seeing her smile each day is very special - 8 years

What is a 2q24.3 deletion?

A 2q24.3 deletion is a rare genetic condition in which a small piece is missing from one of the body’s 46 chromosomes. The missing material includes genes which are important for normal development. Their absence is believed to cause the major features of a 2q24.3 deletion.

What are chromosomes?

Chromosomes are the structures in each of the body’s cells that carry the genetic information that tells the body how to develop and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. Each chromosome has a short (p) arm and a long (q) arm.

Looking at 2q24.3

Chromosome analysis

You can’t see chromosomes with a naked eye, but if you stain them 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 chromosome 2 on page 3 you can see the bands are numbered outwards starting from the point where the short and long arms meet (the centromere). Band 2q24.3 is roughly in the middle of the long arm of the chromosome.

Molecular techniques

If you magnify chromosome 2 about 850 times, a small piece may be visibly missing. 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 microarrays such as array CGH, a method of scanning all the chromosomes for extra or missing material.

Sources and references

This guide tells you what is known about people described in the medical literature - around 17 by 2009 - about three additional people on the Decipher database (<https://decipher.sanger.ac.uk>) and about *Unique*’s 16 members with a 2q24.3 deletion. Knowledge is still limited, as the oldest person was just 20 years old when described.

The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (at www.ncbi.nlm.nih.gov/pubmed) and a selected literature list is on page 19. If you wish, you can obtain articles from *Unique*.

(Pescucci 2007; Svensson 2007; Bijlsma 2005; Dimitrov 2005; Maas 2000; Slavotinek 1999; McMilin 1998; Nixon 1997; Chinen 1996; Boles 1995; Wamsler 1991; Bernar 1985; Moller 1984C; Shabtai 1982; McConnell 1980; Decipher; *Unique*).

Why has this happened?

To answer this question both parents of a child with a 2q24.3 deletion should have their chromosomes tested. In most cases, both parents will have normal chromosomes. The chromosome break is then said to have occurred out of the blue (de novo, meaning a new event). De novo changes are caused by a change that occurred when the parents’ sperm or egg cells were formed. What is certain is that there is nothing you could have done to cause the break to occur and nothing you could have done would have prevented it occurring in your baby. No environmental, workplace, dietary or lifestyle factors are known to cause these chromosome changes. They are no-one’s fault.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 2q24.3 microdeletion 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 2q24.3 microdeletion. 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 2q24.3 microdeletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 2q24.3 microdeletion 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.

Selected references

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

Bernar 1985: Interstitial deletion 2q24.3: case report with high resolution banding *Journal of Medical Genetics* 22 pp 226-228

Bijlsma 2005: Increased nuchal translucency and split-hand/foot malformation in a fetus with an interstitial deletion of chromosome 2q that removes the SHFM5 locus *Prenatal Diagnosis* 25 pp 39-44

Boles 1995: Deletion of Chromosome 2q24-31 Causes Characteristic Digital Anomalies: Case Report and Review *American Journal of Medical Genetics* 55 pp 155-160

Maas 2000: Interstitial deletion of the long arm of chromosome 2: a clinically recognizable microdeletion syndrome? *Clinical Dysmorphology* 2000 9 pp 47-53

McMilin 1998: Clinical Outcomes of Four Patients With Microdeletion in the Long Arm of Chromosome 2 *American Journal of Medical Genetics* 78 pp 36-43

Nixon 1997: Interstitial Deletion of 2q Associated with Craniosynostosis, Ocular Coloboma, and Limb Abnormalities: Cytogenetic and Molecular Investigation *American Journal of Medical Genetics* 70 pp 324-327

Pescucci 2007: 2q24-q31 Deletion: Report of a case and review of the literature *European Journal of Medical Genetics* 50 pp 21-32

Slavotinek 1999: Two Cases With Interstitial Deletions of Chromosome 2 and Sex Reversal in One *American Journal of Medical Genetics* 86 pp 75-81

Svensson 2007: Detection of a de novo Interstitial 2q Microdeletion by CGH Microarray Analysis in a Patient with Limb Malformations, Microcephaly and Mental Retardation 143A pp 1348-1353

holding out an arm for a sleeve, for example. One family commented that motivation is the key to acquiring personal care skills.

Personal care skills generally go hand in hand with the ability to grasp, hold onto and manipulate objects and toys and again there is some variation, but generally children depend entirely on their family and carers. Toilet training is also delayed and may not be achievable.

“She is very delayed and does not grab or hold anything. She has almost no conscious movements. We use a lot of different textures, sounds etc to stimulate her development - 14 months

“She is adjusting to holding items in her hands but prefers someone to do it for her (we don't allow this) - 4 years

“He can hold a spoon and manipulate toys but does not pick up small objects or use a pincer grasp. He needs to be dressed but is co-operative, raising each arm in turn to put on a shirt - 5 years

“She has trouble holding anything between her thumb and index finger but can mark with crayons holding with her second finger and with both small fingers crooked. We have tried many splints but she removed them, even in her sleep. We are now working on picking up objects and putting them in containers, pushing buttons on toys or putting balls in toys. She is potty responsive but not yet timed or trained. She knows to put an arm in a sleeve and a leg in pants. Her left side is always somewhat stiff, so she needs help - 6 years

“He has achieved thumb and first finger opposition with a pincer grip and learned to clap his hands. For meals he uses ‘caring cutlery’ and suction dishes as well as a beaker with a spouted lid. He needs full assistance with personal care though we attempt to encourage him to complete parts of the tasks independently - 10 years

Therapies



8 years

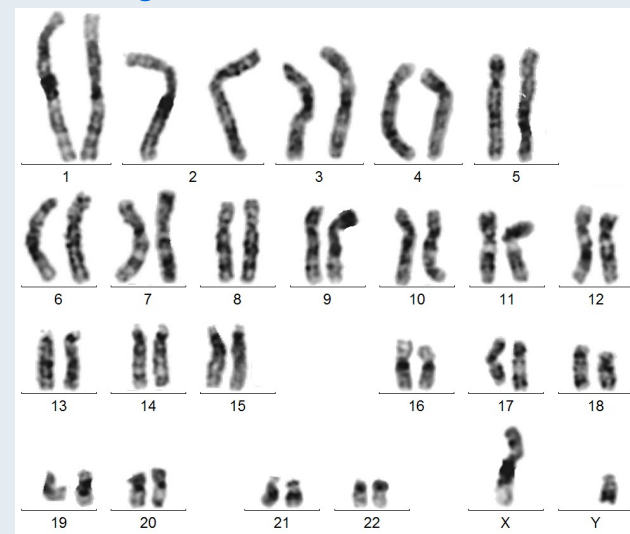
Families can expect their children to be assessed for the standard trio of therapies – physical (physio), occupational and speech, as well as early intervention play and learning therapies. All children qualify for the full range of therapies and generally make some progress towards appropriate targets. Children with vision difficulties should generally also qualify for specialist sensory teaching. Families have tried a range of other therapies including music, hippotherapy (riding for the disabled), cranial osteopathy and water therapies, all with some success. One family reported real improvements in epilepsy control, digestion and alertness with the Scotson technique, designed to improve breathing and oxygenation.

“Physiotherapy has eliminated his stiffness and with speech therapy, he now allows his mouth and face to be touched. We have seen many small developments with early intervention teaching - 3 years

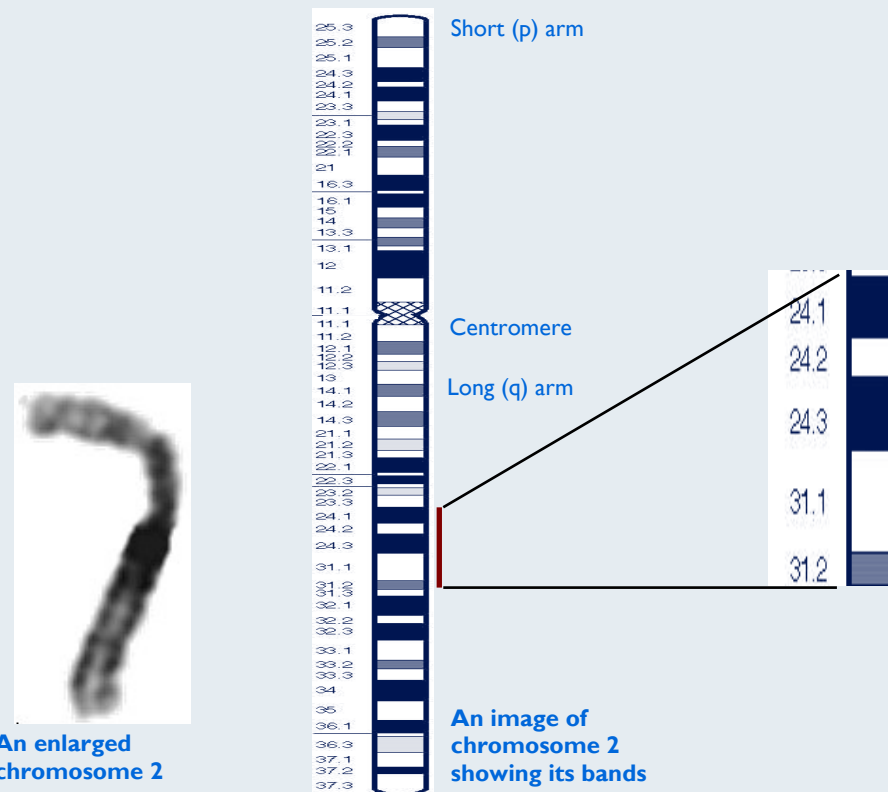
“She has been enrolled in hippotherapy and private water classes. Both modes of therapy are a tremendous benefit - 4 years

“Speech therapy for oral stimulation successfully stopped tooth grinding - 4 years

Looking at chromosomes and chromosome 2



A karyotype for a man or boy. All the chromosomes in a cell, arranged in their pairs. The two chromosomes 2 are on the top line, second from the left



Results of the chromosome test

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

46,XY,del(2)(q24.2q24.3)de novo

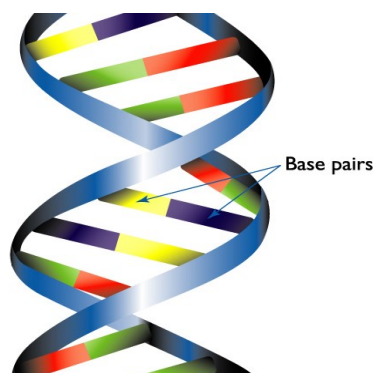
- 46 The total number of chromosomes in your child's cells
- XY The two sex chromosomes, XY for males; XX for females
- del A deletion, or material is missing
- (2) The deletion is from chromosome 2
- (q24.2q24.3) The chromosome has broken in two places, one in band 2q24.2 and the other in 2q24.3
- de novo The parents' chromosomes have been checked and no change found involving 2q24.3. 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, both in the medical literature and within *Unique*, will help 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!

You may be given a molecular report, which may read something like this:

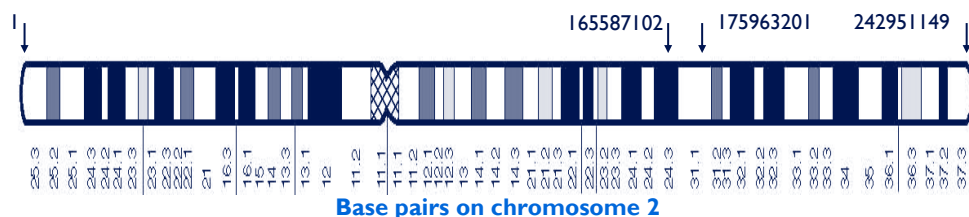
46,XX,arr 2q24.3q31.1(165,587,102-175,963,201)x1

- 46 The total number of chromosomes in your child's cells
- XX The two sex chromosomes, XY for males; XX for females
- .arr The analysis was by microarrays
- 2q24.3q31.1 The analysis revealed changes in bands 2q24.3 and 2q31.1
- (165,587,102-175,963,201)x1 Only one copy of the piece of the chromosome between base pair 165,587,102 (in 2q24.3) and base pair 175,963,201 (in 2q31.1) has been found instead of the expected two copies. 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.



Only one copy of the piece of the chromosome between base pair 165,587,102 (in 2q24.3) and base pair 175,963,201 (in 2q31.1) has been found instead of the expected two copies. 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.

Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. Chromosome 2 has around 243 million (243 Mb) in total and band 2q24.3 alone contains around 6 million (6 Mb).



Sleep

Sleep disorders do occur, but with no consistent pattern. Some children sleep without problems especially when they are well, but others experience major disruptions, particularly persistent night-waking. Common infections including ear infections frequently disrupt sleep in children who otherwise sleep well and it can take many months to re-establish clear sleep routines. Others wake in discomfort or pain, if for example their pads are wet, or if they are uncovered. Weighted blankets can help in this circumstance. Children with reflux may sleep better with the head end of the mattress raised. One child with reflux in this group had longstanding sleep difficulties until dairy and gluten-containing foods which made him hyperactive were removed from his diet. He also takes melatonin. Families should however only make changes to their child's diet with professional medical advice. Occasional children have been diagnosed with sleep apnoea - periods during sleep when the flow of air to the lungs is obstructed - and in some of these children removing enlarged tonsils and/or adenoids may prove helpful.

Some families seek to achieve a regular sleep routine by using medication. Melatonin is popular and some families believe it is at least partly effective but quite a few children have used other prescribed medication to ensure they stay asleep, generally with only partial success. (*Unique*).

- " Her sleep is very variable. She will sometimes sleep all day and night, and sometimes stay awake all day and all night. Everything is related to the status of her epilepsy. We give her melatonin from time to time—14 months
- " She had a horrible sleep study so we had her tonsils and adenoids removed. We also have her on a sleep aid. She takes Seroquel (quetiapine) at night for sleep disturbance. If she does not take this medicine, she will only sleep about 4 hours at night - 4 years
- " He has had problems since birth. We tried chloral hydrate, triclofos and melatonin but all upset his stomach - 4 years
- " She usually sleeps well but has occasional sleepless nights when she wakes and sits up in bed. We just lay her down and make sure she is dry and the right temperature. She likes covers no matter what the temperature - 6 years
- " She will fall asleep and then start to cry. We have no explanation for this - 8 years

Fine motor skills and personal care

Weakness, low muscle tone and coordination difficulties mean that children are likely to experience very considerable delay in learning to use their hands. The extent of the delay varies somewhat between individuals. Some children can hold a spoon or favourite toys by the age of four or five, while others do not consistently acquire this ability. Others can pick objects up but not hold them for long. This means that those children who take solid foods are likely to need to be fed. It seems that they are also likely to need a lot of help with other personal care skills such as dressing and undressing, although they can be co-operative by



9 years

- “ His motor skills are reasonably good and he needs no support although he does have episodes of loss of balance (vertigo, possibly related to viral infections) and apparent problems with depth perception. He is very careful when climbing and a bit clumsy - 9 years
- “ His balance is poor and he has difficulty changing directions and isn't able to manage on uneven surfaces. He isn't able to manage stairs so we have installed a stairlift - 10 years

Behaviour



8 years

It is not yet known whether there is a typical behaviour pattern for children and adults with a 2q24.3 deletion but children are generally described by their families as happy, laughing and smiling and mostly sociable, particularly with familiar people. Children prefer generally to relate to adults who can meet their needs than other children. Problem behaviours seem to be quite uncommon and episodes of agitation can be related to discomfort or pain. Some children have a well-developed sense of empathy with others. (Unique)

- “ She is in general a happy child, but is having a lot of seizures every day, making her tired or agitated or apathetic. It is different from day to day and from week to week - 14 months
- “ She is a very tolerant and loving child but

her behaviour gets wild and erratic in crowds. She is a social butterfly but unfortunately she does not talk so people, especially kids, overlook her. Her friends at school are great with her - 4 years

- “ Socially, he will approach familiar adults, climb on their laps and explore their face. He doesn't interact with other children. Generally he is in his own world of solitary play and exploration - 5 years
- “ She is very friendly especially with other children and very sympathetic – if a child cries, so will she - 6 years
- “ She's a very happy, laid back, relaxed, lovely natured girl. She's not really interested in people she doesn't know but once she knows them, she is full of smiles for them and claps her hands at them - 6 years
- “ She likes people to talk to her and give her kisses and makes noises to show she is happy - 8 years
- “ He is generally calm and happy but has a very limited range of things he likes to do. He is undersensitive to stimuli and seeks tactile sensations. Socially, he is curious and gentle but has no understanding of how to interact appropriately and usually ignores people he does not know or need. Until he was 2, he was very hyperactive, lacked the ability to concentrate and only ever slept for 2 hours at a time. Since then he has been on a gluten and casein free diet which gave immediate results - 9 years 11m
- “ He continues to mouth or eat anything, leading to concerns about safety - 10 years

Most likely features of a 2q24.3 deletion



- Developmental delay
- Learning difficulty or disability
- Seizures
- Unusual feet and/ or hands
- Severe growth failure after birth, possibly with low birth weight. A very small head
- A heart condition
- Some unusual facial features. These may include a cleft palate or lip (Pescucci 2007; Bijlsma 2005; Maas 2000; Boles 1995; Unique)

What are the first signs in a baby or child?

The first signs can be incredibly diverse. Out of a group of eight babies and children, only one was identified before birth because of severe hand and arm deformities. Five babies were identified at birth, four of them very floppy (hypotonic) but otherwise with quite different problems: two had a cleft palate (one of them a cleft lip as well), two had webbed toes and a small jaw, one had feeding difficulties and some unusual facial features, the fourth had episodes of stopping breathing (apnoea) and no sucking or crying reflex and a fifth also had a dimple at the base of the spine and club feet. Three babies were considered normal at birth and only diagnosed after their development showed delay. One of them also had digestive problems, frequently bringing feeds back (reflux) and another made no eye contact, did not respond to smiles and was very passive in general although investigations only began after epilepsy developed. (Bijlsma 2005; Bernar 1985; Unique)

- “ We were told that a chromosome disorder was highly unlikely as he had no visible malformations except his toes
- “ At seven weeks, a consultant said to check her chromosomes as he felt her hands were extremely small

Pregnancy and birth

For most of the seven pregnancies where we have any information, everything went normally. One mother noticed a lessening of fetal activity and one mother experienced leakage of amniotic fluid at seven months; another noticed all signs of pregnancy disappeared at 20 weeks. However, out of 13 pregnancies, seven babies were born before their due date of whom five were born at or before week 37, making them premature. The birth was generally easy, perhaps partly due to babies' relatively small size but one baby aspirated meconium and needed intubation and mechanical ventilation for five days. (Pescucci 2007; Svensson 2007; Slavotinek 1999; Nixon 1997; Bernar 1985; Unique)

Newborn

There isn't such a thing as a typical newborn baby with a 2q24.3 deletion. Babies vary in birth weight, with around half born well below the expected birth weight for gestation, while others are a normal weight at birth. The range of birth weights is between 4 kg

(8lb 13oz) and 2 kg (4lb 7oz) at term, from *Unique* records. Apgar scores (a measure of wellbeing at birth on a scale of 0-10) at one and five minutes after birth also range from 3 to 10, but are generally reasonable to high. After birth, some babies thrive and go home as expected while others need to spend time, generally a few days, in special care. A few babies have specific health concerns. These included a cleft palate (split in the roof of the mouth), a cleft lip and spells of turning blue or stopping breathing. Many babies struggle at first to feed and either show no sucking reflex or are too weak and sleepy to succeed in breastfeeding and are fed instead by spoon or tube. This is not true for all, however: a few babies breastfeed well from the start. Some babies - again, not all - are also very floppy, with low muscular tone. (Pescucci 2007; Slavotinek 1999; Nixon 1997; Decipher; *Unique*)



2 months

Will my baby look different?

You and the doctors may notice that your baby has a slightly unusual facial appearance. He or she may bear a resemblance to other babies and children with a 2q24.3 deletion in this guide as well as to your family. Young babies often have a head that is unexpectedly small. Their ears may be set a little lower on the side of the head than is usual and the lobes may be unusually fleshy. Their lower jaw and chin may be particularly small and their eyes may also be slightly small, with a downward slant. Occasionally their eyelashes will be noticeably long.

But while many researchers comment on these and other unusual facial features, most *Unique* families say that their child has a clear family resemblance and many have no unusual facial features at all. (Pescucci 2007; Maas 2000; Slavotinek 1999; McMilin 1998; Chinen 1996; Wamsler 1991; Bernar 1985; Boles 1995; Moller 1984; Shabtai 1982; McConnell 1980; Decipher; *Unique*)

“ She does look a little bit different to her brother and sister. She has small features (hands, feet, nose, ears and mouth). Her lips are a bright red that looks like lipstick
 “ The bridge of her nose is flat, so glasses flatten her very long eyelashes

Cleft palate or lip

In the medical literature and on the Decipher database, cleft palate is reported quite often, with half of babies (10/20) born with a split in the roof of their mouth and one born with a cleft upper lip. Four further babies were born with a high arched palate. The *Unique* experience suggests that a cleft palate is less common, with only three out of 15 members affected, one with a cleft lip as well.

A cleft palate causes difficulties both in feeding and in speech production. Surgical repair of the palate eases these difficulties and may eliminate them altogether. (Pescucci 2007; Svensson 2007; Dimitrov 2005; Maas 2000; Nixon 1997; Chinen 1996; Boles 1995; Wamsler 1991; Shabtai 1982; McConnell 1980; Decipher; *Unique*)

Sitting, moving: gross motor skills

Most children achieve some degree of mobility. While many need persistence, practice, physiotherapy and special exercise programmes, a few are walking well by their second year.

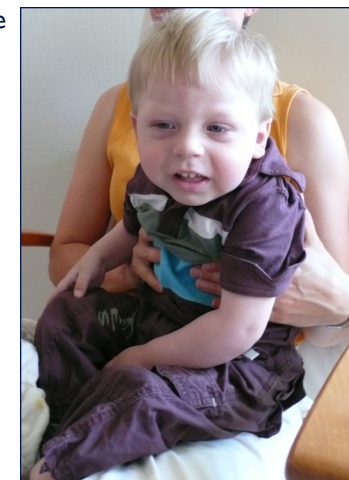
Babies are typically unusually floppy (hypotonic) and acquire head control late. In addition to regular physiotherapy and sometimes special clothing to support the upper body, families of other hypotonic babies have experimented with taping the trunk to promote stability.

Most babies reach their early milestones, although later than other typically developing babies. Early developers may learn to roll from around nine months but others are unable to roll over until their third year or even later. Sitting – at first in a slumped position – typically emerges from around 18 months, although it can be much later - though one baby was sitting at eight months. Supportive clothing helps to counteract upper body floppiness. Once sitting independently, babies may lack a ‘save’ reflex, so need seating in safe surroundings. Children may become mobile, some by conventional crawling but others using ingenious alternatives including commando crawling (creeping), bottom shuffling (scooting), spinning or continuous rolling in their second or third year, but this is not possible for all. First supported or unsupported steps may be possible in a very few children as early as 18 months but usually emerge much later, most typically between 4 and 8 years, and may follow years of persistent practice. Some children need walking aids and supportive footwear.

Problems with balance can persist although climbing stairs may be possible by 4 years. In general, most children will use a wheelchair outdoors and may need one indoors as well.

The family observations below show that while mobility always appears to be affected, individual abilities can vary a lot. (Pescucci 2007; Slavotinek 1999; Nixon 1997; *Unique*)

- “ She does not move around by herself - 14 months
- “ He turns from back to side and vice versa. He supports his head well and if well placed can sit unaided for 2-5 seconds - 3 years
- “ She gets around fastest and most steadily by crawling. Her walking is improving greatly. She doesn't use any supports (walker, wheelchair) - 4 years
- “ She uses a wheelchair with maximum support, a maximum support high chair and a support wedge in bed - 4 years
- “ He likes to explore far and wide – crawling (including in, under, through and around objects). He likes climbing, particularly in the local playground and loves playing at the beach, eating and exploring the sand and water - 5 years
- “ She started walking with a gait trainer, advanced to a walker and recently to swivel wheels; she uses it better at school because of the long halls there. She also has a wheelchair - 6 years
- “ She needs to be lifted. She has a wheelchair and a standing frame - 8 years



2 years

- “ She learns best by repetition. Circle time is her best time, playing games and being with other children. She especially enjoys animal books with sounds being read to her - 6 years
- “ He enjoys tactile play with toys, balls, sand, fabrics and found objects; infant programmes on TV; travelling in the car and walks - 9 years

How can communication be affected?



8 years

Eye contact is typically delayed so babies do not always look into their mother's eyes and first smiles arrive late. Babies communicate their needs by crying and facial expression and, as they mature, by body language and gestures. Intonation, vocal noises, approximations and even recognisable words may emerge in some children, but in others may not emerge at all. Communication is supported by children's generally sociable temperament but some children scarcely seem to make eye contact or communicate their needs.

Children usually understand more than they can express, especially when they are given maximum help using focused attention, short phrases and words are supplemented by body language and physical manipulation.

A few children learn a useful single word signing vocabulary. Others use actions to signal their needs and wishes.

Since the temporary hearing loss that accompanies glue ear is quite common, babies and young children should be regularly screened. (Pescucci 2007; Slavotinek 1999; Nixon 1997; Decipher; Unique)

- “ He kicks a lot and brushes his eyes when he's unhappy or tired. When he's very unwell he yells, but extremely rarely. It's difficult to judge his level of comprehension: he seems to listen very carefully to what is happening around him - 3 years
- “ Her speech is extremely delayed. I don't know if the palate made the delay worse. She uses signs, vocal noises and one-syllable vocalisations. She understands more than she can express - it is very frustrating for her - 4 years
- “ We are trying to use requesting for whatever she wants – the remote for TV; a CD or a book; or going to door to go outside - 6 years
- “ She communicates with vocal noises. When she goes to school and hears voices she smiles; and she reacts to our voices when we talk to her - 8 years
- “ He takes us to the things he wants such as food, or TV and places our hands on them. We started a picture exchange system several times but it was not sustainable due to motivational issues - 9 years 11m
- “ His range of sounds is increasing. He has receptive problems but we feel he can understand simple instructions - 10 years

Hands



2 years

In around two babies out of three, the hands are unusual in some way. Unusual features vary quite a lot, and are often just cosmetic – a single crease across the palm, an incurving fifth finger or unusually long and perhaps tapering fingers. Other features that are sometimes seen may affect function, such as clenched fingers or rather short and stubby fingers some of which may be joined by a web of skin or tissue; and very tiny hands. Occasionally, the hands may be even more obviously affected, with fused joints in the fingers so they cannot be bent or missing bones in either the fingers, the hand or even the lower arm.

If the hands are rather obviously affected, it may be possible to see them on a mid-pregnancy 3-D scan.

In many cases, the child's hands can be left to grow naturally. When the joints are clenched but can be opened, splinting may help to straighten them.

There is some uncertainty about the cause of the effects on the hands, but it has been suggested that the fingers are more likely to be bent when band 2q24.3 is missing and that deletions involving 2q31.1 can cause more major anomalies in some children. (Pescucci 2007; Svensson 2007; Bijlsma 2005; Slavotinek 1999; Boles 1995; Unique)

- “ Stubby fingers. He tends to splay his fingers between the middle and index, but this is less noticeable as he gets older - 5 years

- “ Some wasting of the intrinsic hand muscles is now evident - 10 years

Feet

In most but not all babies with a 2q24q31 deletion, the feet seem to be in some way unusual. Both feet may be equally affected, or one foot may be more obviously affected than the other. Like the unusual hand features, these differences can be scarcely noticeable and unimportant or they can be obvious and have an impact on the child's ability to walk. Cosmetic differences that are quite typical include an unusually long and broad big toe and a very wide 'sandal' gap between the first and second toes. Two or more toes may be joined by a web of skin or tissue; typically, the second and third toes are joined, but the fourth and fifth may also be involved. At the more severe end of the spectrum, one or more toes may be missing and others may be surprisingly small; the foot may even appear to be split. The feet may be held at an unusual angle to the legs and there may be club foot (talipes equinovarus).

To achieve the best position for walking and to prevent relapse, manipulation, taping, physiotherapy, splinting, bracing, casting or surgery can be used. Special support boots with adapted insoles can help.

It is suggested that feet are likely to be affected when the 2q31.1 band is missing. There is a cluster of genes known as *HOXD* that are known to be important for limb development and may underlie some of the hand and foot problems in people with a

2q24.3 deletion and other genes close by, such as *DLX1* and *DLX2*, that are also important. (Pescucci 2007; Svensson 2007; Bijlsma 2005; Boles 1995; *Unique*)

“ He was born with bilateral talipes bilaterally but after splints, casts and later surgery to lengthen his Achilles tendon, it is now fully corrected. The third toe on his right foot stands higher than the others - 9 years, 10 months

Do children with 2q24.3 deletion syndrome have epilepsy?

Some babies do not have seizures but most children (19/25) eventually do. Losing genes from the cluster known as *SCN* seems to be the cause of epilepsy in babies and children with a 2q24.3 deletion. There are a number of *SCN* genes in band 2q24.3, each involved in different types of epilepsy. In particular the *SCN1A* gene is involved in a type of epilepsy known as Dravet syndrome but it is not yet known whether there are other distinctive patterns and types of epilepsy associated with 2q24.3 deletions. For a baby or child who has had a microarray analysis, it should be possible to show which genes are missing and this information should be helpful in suggesting the likelihood of epilepsy developing.

Seizures can first develop within weeks of birth or even sooner or may not become apparent until years later in childhood. Seizures occasionally occur as a one-off event but it is more usual for them to recur. Various seizure types and degrees of severity have been seen and in some children they come in clusters. In one group of babies and children control is easily upset by even mild illness such as a cold or a slightly raised temperature. At the severe end of the spectrum, some babies and children have a hard-to-control severe type of epilepsy known as Dravet syndrome.

Medication can generally keep the seizures under control but the type, dose and combination may need regular review. Some families have tried a ketogenic diet but long-term control with this approach has not been achieved. Depending on local provision, families recommend a referral to a specialist epilepsy centre (rather than a general paediatric neurologist) for any child with hard-to-control seizures. (Pescucci 2007; Slavotinek 1999; *Unique*)

“ Seizures are a sign of ill health. When she was very ill for many months she had severe seizures, which stopped when she was better and on permanent oxygen. She now has behavioural seizures, caused by excitement when she has a bath or has her teeth brushed but we do not medicate for these - 6 years

“ She was first hospitalised at two months with seizures. Now she has seizures once a month or if she has a cold or is unwell she may have five to seven in one day - 8 years

“ He first had seizures from 6-7 years and has remained borderline for treatment and is being monitored now - 10 years

Will my baby have a heart condition?

Perhaps one third to a half of babies with a 2q24.3 deletion are born with a structural problem with their heart. It has been speculated that babies who are born with a heart defect have a deletion of either band 2q24.2, band 2q24.3 or possibly band 2q31-3 (Maas 2000; Del Campo 1999). The evidence from *Unique* suggests that band 2q24.3 is likely to be involved.

Teeth

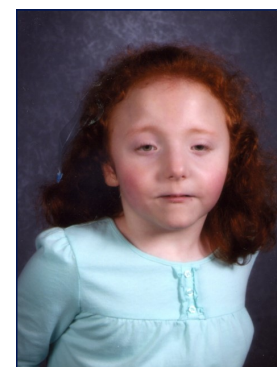
Generally speaking, children with chromosome disorders have a somewhat higher rate of dental problems than other children. At the same time, some children can be quite resistant to having their teeth cleaned; this can be an issue with children who take no food orally and do not strongly associate the mouthing experience with pleasure. Children may need specialist treatment in part because they can need general anaesthesia for dental procedures. Among children with 2q24.3 deletions, no characteristic problems are seen but *Unique* families report a variety of concerns: late appearance of baby teeth (front teeth in the second year of life, molars at the age of four); failure of baby teeth to fall out to allow adult teeth through; crooked teeth; enamel erosion; and gum overgrowth caused by the anti-epileptic drug phenytoin. (*Unique*)

“ Her mouth is very crowded, otherwise everything is normal - 4 years

“ Her teeth are still beautiful - 6 years

“ We find a battery toothbrush is good. She seems to like the vibration and it keeps her teeth cleaner than conventional brushing - 8 years

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



6 years

Children will need support with their learning, and the amount of support they need may be quite considerable. They benefit from early intervention programmes and from attending special pre-schools and schools where their individual needs can be met properly. It is to be expected that they will have a learning support statement or plan. Depending on local provision, this may be a school attended by other children with special learning or physical needs, a special unit for autism or in some cases a school for children with vision difficulties.

In common with others with a similar level of learning ability, children may well be late to show interest or curiosity in their surroundings, have a short attention span

and require longer than normal to process information and project a response. Families say that their children learn best by repetition and individualised teaching, with familiar routines and consistency. Some children have good social skills which can be put to their advantage in a classroom. Music, sensory play, and switch-operated and cause-and-effect toys are other important aids to learning.

From the information available at present, there is a range of learning disability, with most children not reading or writing and communicating most of their needs non-verbally, while others progress faster and further.

Children who do not read may well still enjoy books and being read to; other favourite activities noted by families include TV, playing with pets and siblings, musical instruments and tactile play. (*Unique*)

“ He likes to interact physically with his environment and loves musical activities.

He's best at exploring favourite and new experiences and materials. He loves picture story books and scans the pages but cannot read - 5 years

Eyesight

Quite a high proportion of babies and children - perhaps two in three - have some difficulty with their eyesight. This is more obvious within *Unique's* membership than among cases reported in the medical literature or on the Decipher database. The problems vary in type and severity and involve both the outside of the eye and its internal structures.

The most common problem (7/21) is strabismus (a squint) with the crossed eye looking in, out, up or down, due to weakness of the muscles that control eye movement. 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.

There are also three reports of coloboma, a developmental defect in part of the structures of the eye, usually caused in the womb when the cleft that forms to help the nourishment of the developing eye does not close properly. Coloboma commonly affects the iris when it makes the pupil look like a keyhole.

The small eyelid opening that can be a characteristic facial feature of a 2q24.3 deletion can itself cause vision problems when a child cannot open their eyes fully. There are also reports of children with a drooping eyelid (ptosis) which can interfere with vision and may need surgical correction and of cataracts (clouding of the lens).

Within *Unique's* membership there are five children with a very marked loss of vision, in which the inability or immaturity of the brain in interpreting what the eyes see plays a role rather than any structural abnormality of the eyes. This condition is known as cortical visual impairment. One of these children has underdeveloped optic nerves. (Svensson 2007; Nixon 1997; Boles 1995; Shabtai 1982; Decipher; *Unique*)

“ She attends the Indiana School for the Blind and Visually Impaired. Some days she can see well and other days she cannot, so we take a multi-system approach - 4 years

“ Her vision is +10 in both eyes - 6 years

Hearing

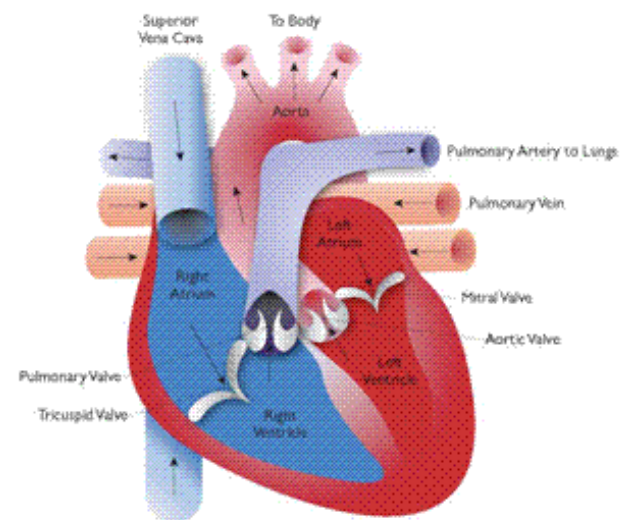
Children usually have normal hearing but the risk of a temporary hearing impairment is markedly increased. Some babies do not appear to respond to sound which may indicate delayed maturation of the hearing pathways. One child has hearing sensitivities to machinery and background noise in crowds. Babies and children with 2q24.3 deletions are also vulnerable to upper respiratory tract infections and may have a temporary conductive hearing loss that can be relieved by placing grommets (aeration tubes) in the eardrum. If this measure does not improve hearing to useful levels, hearing aids will be considered. (Svensson 2007; *Unique*)

“ She had moderate hearing loss for the first year of life. Her hearing is normal now. We don't know if it was because her ear canals were so tiny or if ear tubes helped - 4 years

“ Over the years she has had many hearing tests. Every test comes back with a different result. Some say she can hear high pitch noise, others only low pitch ... and vice versa. We decided in the end to stop the tests and let her be. She can hear something but also loves being signed to - 6 years



6 years



The heart

There is quite a variety of different problems, some needing surgical correction while in other cases they resolve naturally and do not affect the child's functioning. In general, babies with a heart condition will have significantly more ill health until their problem has been corrected than those born with a healthy heart.

The most common type of problem is either a hole between the upper (holding) chambers of the heart (atrial septal defect, ASD) or between the lower pumping chambers of the heart

(ventricular septal defect, VSD) or holes between both chambers. The holes may be an isolated problem or may be found with other concerns, including persistent ductus arteriosus (PDA), a persisting feature of the fetal circulation where a channel between the aorta and the pulmonary artery that usually closes shortly after birth fails to do so, supplying the lungs with more blood than they should have and making the heart work too hard.

In one child the aortic valve that regulates blood flow from the left ventricle into the aorta only had two flaps instead of the expected three. In one child, thickening of the heart wall was seen.

In some babies, the heart condition has no obvious effect, while other babies may tend to get blue or breathless while feeding. Mild cases may well need no treatment, especially if the defect improves over time. When surgical intervention is needed, it may be possible to use a minimally invasive technique, such as catheterisation. Surgery can often eliminate the problem. (Bijlsma 2005; Maas 2000; Del Campo 1999; Boles 1995; *Unique*)

Respiratory infections

Generally speaking, babies are particularly vulnerable to respiratory infections in their early months and years and those with a 2q24.3 deletion are no different. They do have an additional risk factor if they are taking food by mouth in that they may swallow incorrectly and inhale some feed into their lungs. With prompt treatment children generally outgrow this vulnerability although a number develop asthma symptoms and need additional treatment with bronchodilators and sometimes steroids. Children who also have obstructive sleep apnoea, where the upper airway collapses intermittently during sleep, may benefit from enlarged tonsils and adenoids being removed. *Unique* also has experience of one child who developed long term lung problems after frequent episodes of aspiration pneumonia. (Bernar 1985; *Unique*)

Undescended testicles

Boys are occasionally born with undescended testicles. At first, they are usually monitored to see whether they descend naturally in time. If they do not, they can be brought down into the scrotum and fixed there in a small operation known as orchidopexy. Other anomalies in the genital area have not been seen in this group apart from unusual placement of the anus in one child and a possible hydrocele (fluid accumulation around testis) that resolved naturally in another. (Slavotinek 1999; Nixon 1997; Bernar 1985; Decipher; *Unique*)

Will my baby be healthy?



6 years

Babies' and children's health varies a lot between individuals and it isn't easy to see a general picture. Many babies are frequently ill, with the risk of aspiration pneumonia adding to the infections common in all young children. Some babies then do well and by pre-school age are as healthy as their brothers and sisters. Others continue to get respiratory infections during the winter especially in early childhood and can become very ill. In this group of 32 babies and children, three are known to have died as young children, two of respiratory infections, and one *Unique* child has palliative care.

Other individual complaints mentioned by families include a kidney infection (with normal kidneys);

allergies including eggs, nuts and soy and milk intolerance; hypothyroidism; asthma; frequent upset stomachs. A child in *Unique* and one in Decipher have a curvature of the spine (scoliosis); in the child in *Unique* it is severe. This same child started puberty early, with breast development starting at the age of seven.

Many families give their children food supplements in an attempt to improve their general health. In some cases these are prescribed, in others not. *Unique* strongly recommends that all families check first with their child's doctor before giving any food supplements. In this group the supplements given by families include iron and vitamin D; carnitine; slippery elm food and probiotics; omega 3 fish oils; multivitamins; lipoic acid; liver herbs; folic acid and coenzyme Q10. (Bernar 1985; *Unique*)

Is there a typical growth pattern?

Around half of babies are small at birth, with a head measurement that is smaller than expected (microcephaly). Postnatally, there is frequently a drop-off in growth rate, and this may be made worse in some cases by feeding difficulties and a heart condition. As a result, the curve on a growth chart for a child with a 2q24.3 deletion is usually in the lower bands and in some cases it tracks below the lowest printed curve on the chart. However, some *Unique* members grow at a perfectly normal rate and may even be tall for their age, although in childhood there is a tendency to be thin and even skinny. The growth rate for the head has been shown in some cases to tail off in the first year of life due to early fusion of the bone plates in the skull (craniosynostosis). Parents and clinicians will decide whether to release the joints to allow further growth. (Svensson 2007; Slavotinek 1999; Nixon 1997; Decipher; *Unique*)

“ Despite being gastrostomy-fed, she was very overweight as a baby for no obvious reason but she did grow into it by the age of 2

“ He is slightly above average height for his age and a little underweight - 3 years

“ At the age of seven, he's the height of a 3-year-old - 7 years



Overweight at 11 months

What about food and eating?

Feeding and eating problems occur in some (but not all) babies and children. A few babies breastfeed successfully but others do not succeed in sucking and/or swallowing effectively. In some cases any feeding problems ease after the neonatal period but other babies benefit from a period of feeding via a nasogastric tube threaded up the nose and down the throat. The onset of seizures and other conditions including asthma can set feeding back. Some babies later do well when they have a gastrostomy tube fitted so they can be fed directly through it into their stomach.



14 months

Hypotonia also affects chewing so while some children move on to solids at the expected age, most are late in weaning and need their food cutting up small or processing for a long time. Even then, they may continue to gag on solid foods.

Children should be able to eat a normal range of foods and textures. Some families try a ketogenic diet for their child's epilepsy, if control is otherwise hard to achieve.

Feeding and eating delays can be quite persistent and severe with some school-age children still fed by nasogastric tube or gastrostomy with very limited intake by mouth and others still on an entirely or mostly liquid diet. Input from a speech therapist expert in feeding and possibly from a psychologist with experience of feeding

difficulties can help to overcome longstanding problems.

Gastro-oesophageal reflux and vomiting are common and can be severe from the earliest days, with a risk of aspiration pneumonia. Reflux may resolve once milk feeding is over or may persist. Careful feeding, using feed thickeners and medications prescribed to inhibit gastric acid have controlled reflux in most *Unique* babies. If not, an operation called a fundoplication can improve the function of the valve from the stomach to the food passage. Babies may need to be fed by tube when they are ill and it is sometimes necessary to insert a gastrostomy tube for direct feeding to the stomach.

“ His reflux was exacerbated considerably by his epilepsy medications, especially valproic acid and lamotrigine

Constipation is common in children with chromosome disorders and is significant in this group. Most babies and children take prescribed stool softening medications, sometimes together with glycerin suppositories and some also eat dried fruits and take linseed oil. One family has found probiotics particularly helpful. (Slavotinek 1999; Bernar 1985; *Unique*)