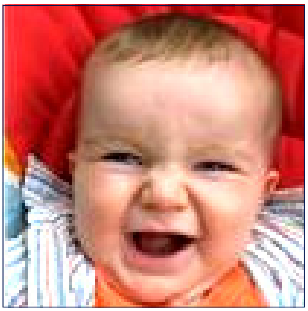
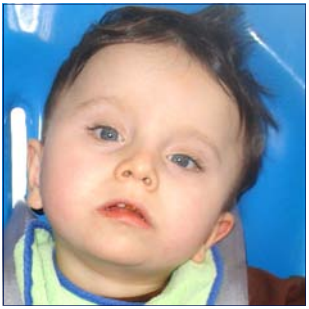
5q14.3 deletion syndrome



Sources & references

This guide tells you what is known about 21 people with a molecular diagnosis of a 5q14.3 deletion and recently described in the medical literature; about eight people with a molecular diagnosis on the Decipher database (https://decipher.sanger.ac.uk) and about *Unique*'s12 members with a 5q14.3 deletion.
The oldest person was just 17 years old when described so there is much still to learn.

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 full literature list is on page 21.

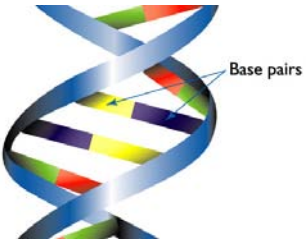
If you wish, you can obtain articles from *Unique*.
(Cardoso 2009; Engels 2009; Berland 2010; Ezugha 2010; Le Meur 2010; Marashly 2010; Novara 2010; Nowakowska 2010; Zweier 2010; Carr 2011; Decipher; *Unique*).

5q14.3 deletions

A 5q14.3 deletion is a rare genetic condition in which a piece is missing from one of the body's 46 chromosomes. The missing piece can be tiny or much larger but includes important genetic material. This material usually includes all or part of one or more genes that are important for normal development. Sometimes the missing piece does not include part of a gene but consists of material close to one.

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.

Research into 5q14.3 deletions is very active. The belief today is that a deletion involving the *MEF2C* gene in the q14.3 band of chromosome 5 causes the major features of the 5q14.3 deletion syndrome. The syndrome can also be caused by a point mutation involving the *MEF2C* gene. A point mutation occurs when a single base is replaced in the structure of DNA. Bases are the chemicals in DNA that are linked in pairs to form the ends of the 'rungs' of its ladder-like structure.



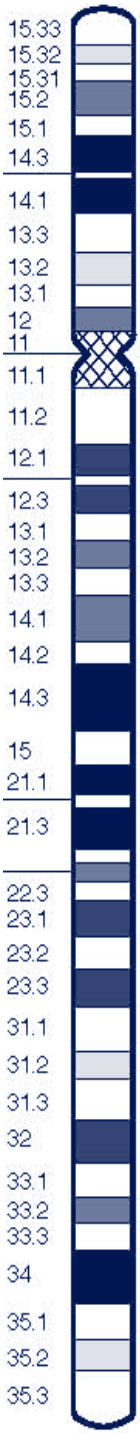
Looking at 5q14.3

Chromosome test

You can't see chromosomes with the 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 5 on page 3 you can see that the bands are numbered outwards starting from the point where the short and long arms meet (the centromere). Band 5q14.3 is roughly one third of the way down the long arm of the chromosome. If you magnify chromosome 5 many times, a small piece is sometimes visibly missing.

Molecular diagnosis

The missing piece can be so tiny that the chromosome looks normal down 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, a method of scanning the entire genome for extra or missing material.



Results of the chromosome test

Your geneticist or genetic counsellor will tell you the results of the molecular diagnosis or chromosome test. The result of a chromosome test is a karyotype, a way of describing chromosomes that shows the points where the chromosome has broken. It is likely to read something like this:

46,XY,del(5)(q14.3q15)dn

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
(5) = The deletion is from chromosome 5
(q14.3q15) = The chromosome has broken in two places, one in band 5q14.3 and the other in the next band 5q15
dn = Short for 'de novo', meaning a new event. The parents' chromosomes have been checked and no rearrangement found involving 5q14.3. The disorder is then very unlikely to be inherited and has occurred for the first time in this family with this child.

Comparing one 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 an individual child and others with apparently similar karyotypes. Your child is an individual.

The *MEF2C* gene is found between base pairs 88,051,922 and 88,214,780. It's currently believed that loss or point mutation of this gene causes the major features of the emerging 5q14.3 deletion syndrome. See also **Genes in 5q14.3**, page 19.

A molecular report is likely to read something like this:

arr 5q14.3(87,516,643-90,382,981)x1

arr = The analysis was by microarrays
5q14.3 = The analysis revealed a change in band 5q14.3
(87,516,643-90,382,981)x1 = The specific DNA base pairs that are missing. The first base pair shown to be missing is number 87,516,643 counting from the top of the chromosome. The last base pair shown to be missing is 90,382,981. Take the first number from the second number to get the number of base pairs missing. In this case, it is 2,866,338 base pairs. This can also be written as 2.9Mb.

Is there a 5q14.3 deletion syndrome?

At the moment, very few people have been reported with a molecular diagnosis of a 5q14.3 deletion. However, the reports that exist show remarkable similarities. These similarities are listed below and constitute an emerging syndrome.

Most likely features

- Early and severe hypotonia [low muscle tone]
- Marked developmental delay
- Epilepsy
- Marked learning disability and need for special support
- Marked delay in learning to sit and move
- Marked language delay. Most children do not speak but communicate in other ways
- Delay in making eye contact
- Stereotypic or unusual movements
- Some unusual facial features
- Brain abnormalities on magnetic resonance imaging [MRI]

(Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Nowakowska 2010; Zweier 2010; Decipher; *Unique*)

Early and severe hypotonia

Babies and children with a 5q14.3 deletion typically have marked hypotonia from an early age. Hypotonia means that the muscles have low tone so a baby feels very floppy to hold. The most common pattern is either general hypotonia affecting all the body or marked hypotonia in the trunk area, with normal, raised [hypertonia] or abnormal tone [dystonia] in the limbs, especially the legs. When tone is raised, there is an abnormal increase in muscle tension and reduced ability of muscle to stretch, leading to increased stiffness or tightness. Some babies and children also have a tendency to throw their head back and arch their back and one *Unique* child used this posture to move around. Although most children have a very marked degree of hypotonia, others are somewhat more mildly affected. (Berland 2010; Nowakowska 2010; *Unique*)

2 years old, with older brother

❝ There is still a very considerable head lag when pulled to sit and when held in a sitting position, his head is not steady yet. His trunk is getting stronger – his legs are bearing his weight well. As his hands are still very alien to him it is difficult without support to find his balance. The Bumbo chair with tray really supports him well - *7-8 months*

❝ Tone has improved as she has become a lot stronger. She enjoys sitting in the Bumbo seat and sitting upright with assistance - *13 months*

❝ He was very hypotonic from the trunk. His floppy neck was a real problem with laryngomalacia as it compromised his swallowing and airway. Lying him on my tummy gave him a secure, soft environment to try to use his neck muscles. He is now much improved but still does not have full neck control. His shoulders and upper arms are getting stronger but his pelvis is still very weak - *19 months*

❝ He now has steady head control and his back is starting to show strength. But his resting muscle tone is still very low and he has very little musculature - *2 years 6 months*

❝ She was like a rag doll at birth and made very little improvement in the first year but now has improved a lot but still needs chairs with head support - *4 years 4 months*

❝ He has hypotonia with dystonia: at birth he was not just floppy, he used to push back, looking at the ceiling. Now he has better head control, can weight bear on his legs and can sit unaided for longer. Leg gaiters helped strengthen his legs - *4 years 8 months*

Developmental delay

It is usually obvious when a baby is only weeks or a few months old that they are not reaching their developmental milestones as expected. Delay is usually also obvious in making eye contact, tracking a moving object, smiling, swiping at toys and holding them. Communication and language are also affected so when you talk to your baby he or she doesn't pay attention or 'talk back' to you.

At this stage families usually consult their doctor in search of a diagnosis. Even before a diagnosis is made, you can expect to be referred for physiotherapy and occupational therapy and families typically do all they can themselves to promote their baby's development.

Toys that *Unique* families have found especially helpful in promoting their baby's early development include maracas, bells on or off a stick, bangles, cellophane, ping pong balls on a resonance board, lights, bright musical objects and toys to encourage reaching, shiny objects such as a big spoon [particularly helpful for improving grasping skills]; small bricks; and rusks or rusk-sized toys.

Babies' development remains slow but with time and practice, they generally make progress. Eye contact gradually becomes more constant; muscles strengthen; they become more responsive and communicative and in time they start moving around and enjoying life.

Epilepsy

Most babies and children with a 5q14.3 deletion have seizures but in many the seizures improve and in some they stop altogether. Out of 20 children with a 5q14.3 deletion that includes the entire *MEF2C* gene, all bar one 18-month-old child have had seizures and he was found to have an abnormal EEG [electroencephalogram recording of the wave patterns from the continuous tiny electrical signals coming from the brain].
In most children, seizures start in the first year, often before six months; in one baby they started on the first day of life and in another at 16 months. One child has only had febrile seizures [see page 6], has not been diagnosed with epilepsy and at the age of 4 is not taking anti-epileptic drugs [AEDs]. Another 13-month-old girl with a history of an abnormal EEG and seizure-like episodes which appear as an involuntary upward eye gaze is being investigated for the possibility that these are not in fact seizures.

Among three children with a partial deletion of the *MEF2C* gene, two have seizures, while a three-year-old boy has no seizures and a normal EEG. Among nine children with a 5q14.3 deletion, the oldest 15, but where the *MEF2C* gene is preserved intact, five have not had seizures. Among the four who have seizures, they started later in one child – at 4 years 9 months – than is typical in children who have lost the *MEF2C* gene (Cardoso 2009; Engels 2009; Le Meur 2010; Marashly 2010; Decipher; *Unique*).

Many different types of seizure have been reported and many babies have more than one type of seizure or start with one type that evolves into others. Seizure types include:

Febrile seizure Episodes only occur when the child has a high temperature

Absence seizure A change in behaviour as if the child 'switches off', sometimes with staring, eyelid flickering or lip smacking. Absences are very brief often lasting less than half a minute

Atypical absence seizure Child may appear confused and unresponsive for minutes, very different from a typical absence seizure

Infantile spasm Type of seizure usually occurring in clusters in babies between 3-10 months. Seen most often when a baby wakes and may be obvious, or subtle.

Generalised tonic clonic At the onset of a seizure, the abnormal electrical activity involves both sides of the brain. The seizure involves a phase of stiffening followed by jerking.

Myoclonic Generalised seizure involving jerky or shock-like contraction of different muscles anywhere in the body but usually the arms or legs. Each myoclonic seizure lasts for a fraction of a second or a second at most.

Myotonic Seizure involving stiffening of the muscles

Myoclonic-atonic Seizure involving jerky or shock-like contraction of muscles, followed by a loss of tone so someone standing up falls to the ground.

Families can expect their baby to be under the care of a paediatric neurologist. Once a diagnosis of epilepsy has been made, a child will be given anti-epileptic drugs [AEDs] which can control seizures well. The AEDs may be changed to improve control, to lessen any side effects such as drowsiness, appetite increase and weight gain or constipation or if seizure types change. In some children, seizures are hard to control with AEDs and the ketogenic diet has been tried alongside AEDs.

In a few cases, children do appear to outgrow their epilepsy or seizures can reduce. However, seizures can also become more intrusive and difficult to control.

A question that families will ask is whether their child's functioning will deteriorate if their epilepsy is not controlled. It's hard to answer for each case but in one child moving was affected when epilepsy was difficult to control at 2 years. This child was not able to walk at 14 years. (Cardoso 2009; Engels 2009; Berland 2010; Marashly 2010; Novara 2010; Nowakowska 2010; *Unique*)

❝ She has a history of seizures with one abnormal EEG although a repeat EEG showed generalised irregular spike and wave patterns but no clear seizure activity. She has had no seizure like episodes in over six months. The seizures are questionable as a neurologist was never present – a further EEG is now scheduled. Meanwhile she is taking Zonegran [zonisamide] until seizures are ruled out completely. The episodes appeared as involuntary upward eye gaze and the paediatric neurologist is looking at the possibility of paroxysmal tonic upgaze associated with nystagmus - *13 months*

❝ She has multiple forms of epilepsy including febrile seizures, absences and myoclonus, with no change of seizure type over time. She is currently taking Topamax [topiramate], Rivotril [clonazepam] and Tegretol [carbamazepine] - *1 year 10 months*

❝ His seizures started at 6 months but as he has got older, they have become more marked. He has tried lots of different medications and if the latest one had not worked he was to start steroids - *2 years 6 months*

❝ He has sudden drops of his head which medication helps to control some of the time. The head drops have declined but in the last six months he started to have regular seizures. Steroids worked briefly but the seizures returned and are proving difficult to control with sodium valproate and nitrazepam - *4 years 8 months*

Learning difficulty or disability

3 years

Children will need special support with their learning although how much support is needed will only become clear over time. Most children appear to have a level of difficulty with learning that would be described as severe or profound. As toddlers and early school age children, they may only be able to do what babies of a few months can do. However, children do learn and those of school age have been described enjoying - and learning from - activities such as touch screen computer games.

Early home-based learning schemes such as portage are helpful as are opportunity [special needs] playgroups. In time it is likely that the most appropriate level of support can be given at a special school. (Berland 2010; *Unique*)

❝ It is difficult to judge his level of learning difficulty. Since we have had a diagnosis and have started therapies he is making progress - *8 months*

❝ At 20 months she could point to all her body parts. She loved musical toys and could push or press buttons to make them work. She had good eye contact and could wave 'bye-bye' - *4 years 4 months*

Delayed motor development

4 years 2 months

Information in the medical literature and at *Unique* shows that babies and children are usually very slow to reach their milestones of head control, sitting and becoming mobile. As babies they may move their arms and legs but are typically very floppy due to their low muscle tone [hypotonia].

The most useful approaches suggested by families with a child with a 5q14.3 deletion are constant work with 'tummy time' and rolling on the floor and involving professionals at the earliest stage, typically by five months. Some babies dislike lying on their tummy and since this can be made worse by constipation, it's worth sorting out any constipation. Occupational therapists and physiotherapists will not only be able to work with your child directly but also to suggest exercises and games for you to do with them yourself. Therapists will help you to get the right equipment for your child; one family found physiotherapy with a bench, bolsters and swing particularly helpful. One family found a hydrotherapist and a chiropractor useful as extra sources of help. Equipment that families have found helpful for their child includes: a standing frame [Jenx and brand-free]; a supine stander; a Bumbo chair with tray; a Bee chair [Jenx]; a Tumble Form chair; a Jenx carrier chair; buggies and pushchairs.

Head control

When you hold a typical healthy baby's hands and pull him or her to sitting, by six weeks they can often hold their head steady for a second. Babies with a 5q14.3 deletion will reach this stage much later. They will also be late to turn or lift their head from lying and to hold their head still without wobbling when cradled in a sitting position. If you hold your baby tummy down on your forearm, their head will drop forward for longer than in a typically-developing baby. Just when a baby with a 5q14.3 deletion will acquire head control will depend partly on their innate abilities but also on the amount of 'tummy time' and therapy they receive. *Unique* families tell us that individual babies have been able to hold their head steady in a supported sitting position and lift it from the floor when lying prone from around 18-20 months, though these abilities may emerge somewhat later – and occasionally much earlier. Head control will continue to improve month by month and year by year, so control will often still be improving in children of primary school age.

Rolling

A typically-developing baby will often have discovered how to roll from his tummy to his back during his fifth month and from back to tummy a month or so later. In a baby with a 5q14.3 deletion, these rolling skills will develop later and often need help and lots of practice. *Unique* families' experience shows that there is quite a wide age range: babies first rolled from front to back between 5-6 months and two years, while they first rolled back to front between 10 months and three years and some babies in their third year had not yet rolled back to front.

Rolling is an important skill for a baby with a 5q14.3 deletion, since he may use it later on to make himself mobile, rolling continuously to move from one spot to another.

Sitting

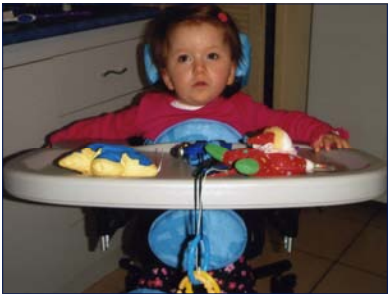
While a typically-developing baby can usually sit unsupported for a few seconds by four months, babies with a 5q14.3 deletion are unlikely to be able to sit alone before their second year at the earliest, although there are exceptions. One *Unique* baby learned to sit at eight months 'but collapses forward, sideways after 20 seconds or so, as his hands are still so alien to him.' Babies and toddlers will enjoy sitting in a suitably supportive chair before this. Models mentioned by *Unique* families include a Bumbo chair with tray; a Bee chair [Jenx]; a Tumble Form chair; and a Jenx carrier chair. Apart from the exception mentioned already, the youngest age at which a baby sat alone was 13 months ('occasionally, when focused') and the oldest was five years, although there are a number of younger children who have yet to learn to sit without help.

Almost 12 months old: sitting supported in a laundry basket

3 years

Moving around

While a typically-developing baby will often be on all fours ready to crawl by six months, some babies with a 5q14.3 deletion may not reach this stage. Some crawl later, others find other ways to move and others become mobile in a wheelchair. Among *Unique* members, a 13-month-old became mobile by rolling, a 14-month-old was almost at crawling stage, a 2-year-old moved across the floor on his head and heels, arching his back, and a 2-year-old (whose deletion includes only part of the *MEF2C* gene) started crawling. A child of five years couldn't move without help but could use a wheelchair with skill.



18 months old

❝ She's almost crawling! - *14 months*

Standing

If you hold a typically-developing newborn baby upright, they can usually take their weight on their feet, straightening their legs somewhat at the same time. Newborn babies with a 5q14.3 deletion do not have this skill and it may be months or years before they do, if ever. Having said this, a 3-year-old and a 4-year-old were both on their feet and cruising around furniture and the 4-year-old went on to walk independently. Meanwhile standers are extremely helpful, as are gaiters and other orthotic supports to strengthen the legs.

3 years

Walking

While typically-developing babies are walking in their second year, a baby with a 5q14.3 deletion may well not learn to walk but as mentioned already can be skilful in a wheelchair. The earliest age at which we are aware of a child with a 5q14.3 deletion walking with support is four years and it may be years before a child is able to walk unsupported. Of those aged 5 or over when this guide was written, 5/8 were not yet walking. A girl who walked supported at four was able to walk alone at 11 years. (Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Novara 2010; Zweier 2010; *Unique*)

❝ His trunk is getting stronger and his legs are bearing his weight well. As his hands are still very alien to him it is difficult without support to find his balance - *8 months*

❝ Although floppy she is in constant motion. Moves her arms and legs a lot and bats her toys but more in anger than fun - *9 months*

❝ Her arms and hands seemed foreign in the beginning but she is now reaching and grabbing for toys as well as applying her weight when sitting. Very close to crawling - *13 months*

❝ He is sitting with support and at tummy time is starting to push up with his arms - *2 years 6 months*

Absent or severely delayed speech

While a typically-developing baby usually coos and babbles by six months, produces speech-like noises in the next months and says understandable words around their first birthday, speech and language development in a baby with a 5q14.3 deletion is different. Overall, progress is slower but one *Unique* baby was cooing at eight months; another knew to ask or say baba when she was hungry at 14 months; others are making a range of vowel and consonant sounds or babbling [mama, baba, dada] by seven months to three years. One child is saying single words [no, bottle, mama, Elmo, yeah] by 20 months but others only use words years later, if at all.

Children with a 5q14.3 deletion draw on a rich variety of alternatives to speech and language. They may use subtle facial expressions, smile, cry, laugh or look sad, they may use modified signs, body language, pushing things away or pulling them close. They may shout or make vocal noises. They may mimic sounds but not in a meaningful context. As they mature, some children use alternative communication aids such as picture exchange systems or electronic speaking aids.

Once reasonably consistent eye contact has been established, babies can let you know when they have understood you – and by and large they understand better than they can speak. A baby who can hold his gaze can watch your mouth as you talk. All the same, children need time to process even one-word instructions like 'No' and their low muscle tone means that they have difficulty complying. One 22-month-old baby can, with time, show that he understands he should lift his legs up [nappy change]; arms up [dressing]; or open his mouth for medicine - but he cannot yet carry out the actions.

Children qualify for speech and language therapy but typically start in their second or third year and all families find it helpful. (Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Novara 2010; Nowakowska 2010; Zweier 2010; Decipher; *Unique*)

❝ He has twice chuckled out loud! - *8 months*

❝ Sometimes I think she's singing or humming, which I do a lot round her - *14 months*

❝ She knows a few signs and 11 words and can point to pictures. She is very vocal and tries constantly to communicate. Her receptive language is great but her expressive language is not as good. Since starting speech therapy at one year she tries to communicate and understands everything - *4 years 4 months*

❝ He doesn't know how to get across what he wants, so he vocalises - *4 years 8 months*

Delay in making eye contact

8 months.
This baby has a 5q14.3 deletion but has an intact *MEF2C* gene

Within days or weeks of birth, a typically-developing baby will gaze at you intently and make eye contact, often particularly when feeding. A baby of less than 8 weeks can slowly follow a bright moving toy held steadily around 20 centimetres from his face. In babies with a 5q14.3 deletion eye contact and tracking develops much more slowly. It may be many months before your baby with a 5q14.3 deletion can hold your gaze and years before he or she can hold it steadily. Reports in the medical literature and at *Unique* suggest that many babies typically look up at the ceiling. In time vision improves but eye

contact may remain transient; there are reports of children over 10 only occasionally making eye contact. Tracking too improves, sometimes more obviously than looking at faces. The visual delay means that babies will have thorough vision investigations and some will be considered partially sighted or blind and qualify for vision support and services.

From what we know today, the evidence is that vision matures considerably in all babies and most of them eventually see perfectly well. Babies initially prefer looking at objects rather than faces. As eye contact emerges it is transient at first but gradually strengthens. Nonetheless, no real eye contact may have been established by 18 months to 2 years. Tracking has been seen in quite young babies and was well developed in one child of almost 4.

Unique families have found many ways of stimulating eye contact, including choosing toys with lights and music or sounds; objects or toys with bold stripes or in bold, bright colours such as orange and purple or black, white and red; shiny, noisy materials such as cellophane; shiny objects such as big spoons, mirrors, an emergency blanket or old CDs; and sitting very close so you are directly in front of your child.

Suggested reasons for the delay in eye contact usually focus on a delay in development or in visual maturation, suggesting that in time the child will be able to see well. However, in some children the vision problem has been attributed to the brain's inability to process the information it receives from the eyes [cortical visual impairment], suggesting a permanent impairment. (Engels 2009; Berland 2010; Le Meur 2010; Novara 2010; Nowakowska 2010; Decipher; *Unique*)

❝ He started to make eye contact probably around 3 months, initially off and on. He is now reliably fixing and following a purely visual target but on occasions he still goes back in his own little world. We have to work hard to get his attention. He has now started to show an interest in black and white books and you can see him look from one picture to the other. He has started to pick up things from his tray - *8 months*

❝ Her ophthalmologist is very pleased with how her eyes have matured. She has been making eye contact from around 6-8 months, initially, off and on but now steady when she is interested. Currently, her vision problems have improved greatly. She enjoys Baby Einstein videos - *13 months*

❝ He is registered blind but can track something bold and bright to about 1 metre. TV and sensory rooms were very useful, especially very early on when he had virtually no sight at all - *19 months*

❝ Lacks interest with people but OK with objects - *22 months*

❝ His eyes did not start to work until he was 9 months old and even today eye contact is off and on. He continually looks up; and won't look for anything on his tray, for example, mainly feeling for things instead. Yet on all tests his eyes are normal - *2 years 6 months*

❝ She can have great eye contact but shows autistic traits of averting her eyes. She tracks well. She started to make eye contact at around a year old, initially on and off. Now she does not sustain eye contact for long periods but will glance quickly. She loves toys with lights and music and will look at them for long periods of time - *4 years 4 months*

❝ He had very poor eye contact at 3 months. He always seemed to look away, to avoid making eye contact, and never smiled, but with time he is making more eye contact. He started at 3 years 9 months and was initially transient; now it is still off and on but has definitely improved: he holds your gaze for longer periods of time - *4 years 8 months*

Stereotypic or unusual movements

Some babies and children but by no means all make unusual repetitive movements. Repetitive hand movements mean that in some children, the first diagnosis suspected was Rett syndrome, an entirely different disorder. The hand movements can include flapping, clapping, hand washing, hand-to-mouth movements and 'an unusual up and down motion with the right arm, especially when holding a toy, and always rubbing her ear or eye with her left arm even when not tired'. Other repeated movements include finger sucking, head rocking, hip rocking to get to sleep and chin rubbing. The movements have been seen in children aged between 22 months and 11 years and may change over time: in one girl handwashing evolved into flipping. Additionally, a number of children grind their teeth. (Engels 2009; Berland 2010; Le Meur 2010; Novara 2010; Nowakowska 2010; Zweier 2010; Decipher; *Unique*)

Other aspects of behaviour

Information on other aspects of children's behaviour is more limited than we would wish. *Unique* families have contributed helpful descriptions of young children; these are supplemented by an upbeat report in the medical literature of an 11-year-old girl with improved social skills who is 'normally happy and joyful'. The reports indicate that babies and young children tend to be placid and passive but at the same time are quite demanding, needing high levels of attention to be happy.

Socially, not all children interact actively. At 8 months, one baby is cooing and smiling, even at strangers; at 13 months, one baby does not always interact well, displaying autistic type characteristics; at 21 months, a toddler doesn't interact very well but is used to people being around and handling him; at 4 years 8 months, a child reaches for faces with his hand and sometimes makes eye contact or smiles.

The *Unique* reports show that constipation and wind are frequent causes of discomfort with a big impact on behaviour. Babies can have screaming attacks, sometimes triggered by discomfort, sometimes by noise, sometimes with no known trigger.

In front, 4 years 2 months

What makes children happy? Some families are not sure; others say cuddles and being talked to; funny noises, rough and tumble play; lying on his back on a wooden floor; having lots of attention; watching favourite videos; listening to music; being outdoors; music and lights; swimming and water; bubbles; books; and unusual sounds and

patterns. What makes them unhappy? Too much noise; particular noises; tummy time and bath time; being in pain; being unwell; having tummy ache; being tired; not having their mother.

The activities that children most enjoy include 'lying on his back on your legs and doing funny things with his arms and legs while smiling and making funny sounds' [8 months]; Baby-Art and music videos and toys that make silly sounds and/or light up [13 months]; TV, a bouncy hammock, baby gym and a lightshow in his cot [19 months]; playing with maracas, a net bag with bells and cellophane [21 months]; playgym [2 years 6 months]; toys with lights and music and videos [4 years 4 months]; touch screen computer/ In the Night Garden TV programme, music and swimming [4 years 8 months]. (Engels 2009; Berland 2010; Nowakowska; Decipher; *Unique*)

❝ Normally a very happy, smiley baby who will be quite passive but really enjoys being played with and stimulated - *8 months*

❝ Very active, thrives with constant stimulation. Fussy without. Sometimes very challenging when fatigued - *13 months*

❝ When unhappy or unwell a screaming episode can start very quickly; it's like a panic attack and there is very little you can do about it. Some noises trigger them. When he's well, he's happy if he has my total attention but can quickly get stressed. When he's unwell he needs constant reassurance and gets very upset if left - *19 months*

❝ She is placid and very passive. Sometimes she interacts socially, actually makes eye contact and stills to listen when people talk - *21 months*

❝ At daycare, a little girl sits and plays beside him all day - *2 years 6 months*

❝ She does well so long as acid, gas and digestion are under control - *4 years 4 months*

❝ He is fairly happy if he is amused but needs to be entertained or he will become upset or bored. He does get frustrated - *4 years 8 months*

Some unusual facial features

Your child may have some slight differences about their face but these are likely to be subtle. Overall, babies and children with a 5q14.3 deletion do not look particularly like each other and most resemble their own family. The facial differences seen most often affect the forehead [high/wide/prominent]; the ears [prominent/simply formed/lowset/ large/with prominent/upturned lobes/asymmetric/with a notch in the edge]; the nose [broad, flat or deep nasal bridge/upturned nostrils/short/small and hooked/thin/broad]; the eyes [set wide apart or close/up- or downslanting/deepset/small skinfolds across the inner corners/hooded upper lids]; the mouth [a pronounced 'Cupid's bow' on the upper lip/thin or full lips or prominent bottom lip/downturned/small] and the groove between the nose and the upper lip known as the philtrum [short and prominent/long/ effaced/ a haemangioma].

A number of children also tend to keep their mouth open, probably as a result of low facial muscle tone. These children will be especially prone to dribbling [drooling]. If children do not outgrow dribbling, hyoscine patches or a medicine called glycopyrrolate can be given by mouth. Botox [botulinum] injections can also be given into the salivary glands in a specialist centre or some of the salivary ducts in the mouth can be tied off. (Cardoso 2009; Engels 2009; Berland 2010; Marashly 2010; Novara 2010; Nowakowska 2010; Zweier 2010; Decipher; *Unique*)

Brain malformations

Under magnetic resonance imaging [MRI], the brains of most babies and children show some structural abnormalities but these are quite variable and can be subtle. However, some children with the typical features of a 5q14.3 deletion have apparently perfectly normal brains under MRI. Because of the known association between 5q14.3 deletions and structural brain abnormality, MRI scans are usually offered.

Among the many different abnormalities noted are:

Cerebral atrophy Loss of nerve cells in the brain and the connections between them. Generalised atrophy means the brain has shrunk. Atrophy in a particular area [focal] means that the functions that area of the brain controls will be diminished.

Colpocephaly A congenital brain abnormality in which the back part of the lateral ventricles of the brain [occipital horns] are larger than normal because white matter in the posterior cerebrum has failed to develop or thicken. Children with colpocephaly have an unusually small head [microcephaly] and need extra support with learning. Other features can include movement abnormalities, muscle spasms and seizures.

Cortical dysplasia The brain cells [neurons] arise during development in the innermost part of the brain near the ventricles. As they develop they travel outwards to the cerebral cortex [the outermost grey matter of the brain]. Normally the cortex has a precise complex structure with six layers of neurons. When this process of development does not occur properly in some parts of the brain, the cortex in that area develops abnormally. The cortex then often lacks the normal layers, structure and connections needed for the brain to work normally.

Delayed myelination Nerve fibres are protected with a layer of insulation, called myelination. Myelinated nerves conduct impulses more rapidly than non-myelinated nerves.

Enlarged ventricles The fluid-filled spaces within the brain are larger than normal

Gyration, abnormal The pattern of humps and grooves on the brain's surface is different from normal

Leucencephalopathy White matter disease of the brain

Periventricular heterotopia A disorder characterised by abnormal clumps of nerve cells [grey matter] around fluid-filled cavities near the centre of the brain

Periventricular leucomalacia White matter injury around the ventricles. People with periventricular white matter injury generally have developmental delay and motor control problems.

Short, underdeveloped or thin corpus callosum The corpus callosum is the largest connective pathway in the brain, linking its two hemispheres in a broad band of nervous tissue containing about 300 million nerve fibres. When the corpus callosum is missing or undeveloped, the two sides of the brain are poorly connected. Each hemisphere of the brain is specialised to control movement and feeling in the opposite half of the body, and each hemisphere specialises in processing certain types of information (such as language or spatial patterns). Thus, to coordinate movement or to think about complex information, the hemispheres must communicate with each other. The corpus callosum is the main, although not the only connector that allows that communication. The *splenium* is the back end of the corpus callosum. (Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Marashly 2010; Novara 2010; Nowakowska 2010; Decipher; *Unique*)

Suprasternal/ jugular pit
Two children have been described with an unusual pit [hollow] at the bottom of the front of the neck. It isn't known yet whether this is typical of people with a 5q14.3 deletion. (Berland 2010; Le Meur 2010)

Pregnancy and newborn
In most of the 14 pregnancies where we have any information, everything went normally and babies were generally born at or near term. In two pregnancies there was concern about increased nuchal thickness at the early pregnancy scan and in one of these there was later concern over scans showing an echogenic bowel [bright bowel, the cause usually never determined and it disappears before birth but echogenic bowel can be due to a chromosome condition] and enlarged kidneys, with a postnatal scan confirming slightly large kidneys. Two mothers noted little fetal activity, one only noting movements from 23 weeks.

The birth was generally easy and most babies were considered normal at birth with normal birth weights and good Apgar scores [measure of wellbeing on a scale of 0-10] of 8-10. In most babies, the low muscle tone was not picked up at birth but one baby was obviously limp and also arched her back very noticeably. Only 3/22 babies were identified because of concerns at birth. One had a club foot, one had an extra toe on the right foot and another was very floppy, had rapid breathing and a type of epileptic seizure known as infantile spasms.

Some babies fed well while others had a weak suck and brought feeds back readily [gastro-oesophageal reflux]. One baby showed a tremor from time to time and had abnormal arm movements; another had a seizure on the first day. Two *Unique* families noted that their babies were unsettled, hard to console and cried a lot. (Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Marashly 2010; Novara 2010; Nowakowska 2010; *Unique*)

❝ She was extremely limp at birth. Her eyes were closed and she had a poor suck. At two months she had ptosis [drooping upper eyelids], low muscle tone and failure to thrive - *Unique parent*

❝ From birth he had poor weight gain, was crying and unhappy - *Unique parent*

❝ At a routine check up at four months we mentioned to the paediatrician that she was not tracking with her eyes and not yet reaching for objects - *Unique parent*

❝ As a newborn he didn't feed, was very sickly, unsettled, rarely slept, and was difficult to comfort, crying most of the time - *Unique parent*

❝ The first 6 weeks were no problem at all, he slept and fed well. From around 6 weeks of age he developed a pattern of recurrent episodic screaming, arching his back and screaming inconsolably. He would only settle when swinging in his cot or passively making cycling movements with his legs. Normally he would have 6 or more such episodes lasting for around half an hour until he would be exhausted from the crying and fall asleep - *Unique parent*

What about food and eating?
Most babies with a 5q14.3 deletion have initial difficulty taking enough milk to support their growth. Typical problems include pharyngomalacia and laryngomalacia [the

cartilage supporting the back of the nose and throat is soft and limp, potentially collapsing inwards and causing feeding difficulties]; low tone in the muscles needed for effective sucking and swallowing; difficulties sucking; frequent vomiting and gastrooesophageal reflux [feeds and stomach contents return up the food passage]. Some newborn babies, but not all, succeed in breastfeeding but often fail to gain enough weight and switch within weeks to formula, energy-enriched formula or expressed breast milk. Bottles are often given at frequent intervals, so that feeding becomes a major activity of each day. Weaning to solid foods typically occurs late with babies and children able to suck puréed or mashed food off a spoon but only later to chew or handle finger foods.

The degree of feeding difficulty varies and while some babies manage to get adequate nourishment, others need tube feeding. Initially this may be via a nasogastric tube threaded up the nose and down the throat but some babies need a gastrostomy tube fitted so they can be fed directly into their stomach.

Constipation is fairly common among children with chromosome disorders and can be related to low muscle tone, little exercise, a low-bulk diet and small fluid intake. It is seen quite often among babies and children with a 5q14.3 deletion and appears to cause considerable discomfort. Discuss the possible causes with your health visitor or doctor before adapting your child's diet or giving any medicines.

Longer term outlook on feeding suggests that children generally have a good appetite and eat a wide range of foods but some children continue to eat purées and mashed foods to the age of 6 or 7.

Information from *Unique* suggests that milk protein and other intolerances and food allergies are common, affecting three out of seven children. (Engels 2009; Berland 2010; Le Meur 2010; Nowakowska 2010; *Unique*)

❝ He breastfed well but because of screaming I went dairy, nut and soya free. He eats three servings of puréed stage 2 baby foods per day and will try to suck or munch on a rusk which, with guidance, he is able to hold on his own when he is in the mood - *8 months*

❝ Pharyngomalacia and laryngomalacia made feeding very hard. He had a nasogastric tube in hospital but hated it, as it further restricted an already compromised upper airway - *19 months*

❝ She still has poor suction for feeding and is unable to chew effectively so eats puréed food - *22 months*

❝ He has been on medication for reflux since he was six weeks old. He takes mashed foods and thickened formula. A speech therapist advised us from six months; she was most useful in positioning for feeding to ensure he is safe - *2 years 6 months*

❝ She eats puréed foods and drinks Neocate [hypoallergenic] formula; due to her food intolerances her diet is dairy-free, sugar-free and gluten-free - *4 years 4 months*

❝ Major feeding problems: tried to breastfeed for three weeks but he couldn't latch on. Then bottle fed but he still had difficulty sucking and had severe reflux - *4 years 8 months*

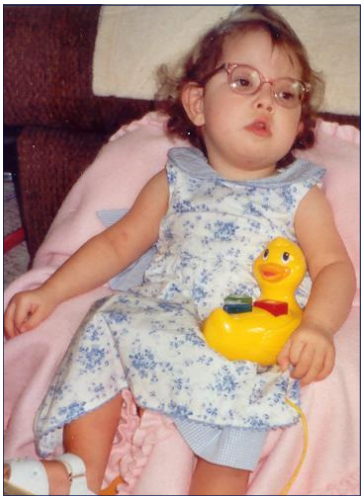
Is there a typical growth pattern?

Babies and children generally grow at a normal rate for their family whether the *MEF2C* gene is involved or not. All the same, children gain weight more slowly than they gain height when the *MEF2C* gene has been deleted or mutated. The difficulties in gaining weight are very likely due to the feeding difficulties that many children experience. As a result, children tend to be lean or frankly thin for their height. In children in whom *MEF2C* has not been deleted, weight gain may be faster than height, resulting in a plump body build. We don't have information yet on adult height, but growth rates were normal in an 11-year-old and a 14-year-old. (Engels 2009; Berland 2010; Le Meur 2010; Novara 2010; Nowakowska 2010; Zweier 2010; Decipher; *Unique*)

Will my baby be healthy?

Young babies and children do seem to be unwell more than other children of the same age, catching frequent colds that take weeks to clear and turn readily into chest infections. Once ill, children tend to be more unwell than children without a chromosome disorder and are more likely to need hospital treatment. However, health varies a lot between individuals and it isn't easy to see a general picture. Some children are quite healthy, especially those where the *MEF2C* gene is not deleted and older children. There is no evidence among *Unique* members of higher than average rates of urinary infections, hernias or breathing disorders.

There is a report of a 12-year-old child with a 5q14.3 deletion and a mitochondrial disorder due to complex IV and I deficiencies but this was not found in any *Unique* children. There is a report on the Decipher database of an individual with a germinoma but no further information. A germinoma is a germ cell tumour that arises from the cells that produce eggs or sperm. A germ cell tumour can be benign or cancerous. No *Unique* members have had a germinoma and there are no reports of one in the medical literature.



2 years

❝ Generally up till now has been a healthy baby - *8 months*

❝ Very prone to colds which can last from 4-14 weeks. Problems breathing, especially at night, high fevers and febrile convulsions - *19 months*

❝ She gets sick easily - *21 months*

❝ He is constantly sick with colds, chest and ear infections and has been in hospital for RSV [respiratory syncytial virus] infection, pneumonia, asthma and croup - *2 years 6 months*

❝ She has PFAPA [periodic fever, aphthous stomatitis, pharyngitis and adenitis] causing fever and stomach pain every month until she outgrows it - *4 years 4 months*

❝ Overall he has been healthy though he had 2 chest infections in the first 2 years - *4 years 8 months*

Sleep

Babies and young children frequently have disturbed sleep and families will benefit from specialist sleep advice and training. Reports from *Unique* families suggest a variable pattern of sleep disturbance, with babies initially waking at night but sleeping better from 6 to 18 months of age and gradually learning to amuse themselves. Some children are woken by night seizures. An 11-year-old girl had a normal sleep pattern. Families have found that treating problems such as gastrooesophageal reflux helps sleep; also using a sleeping bag or wrapping an older child like a newborn baby. (Berland 2010; Le Meur 2010; Nowakowska 2010; *Unique*)

❝ From 6 months he has been in a much better sleep routine both during the night and day. He does need a completely dark room and will not sleep well in a car or pram - *8 months*

❝ She is starting to sleep in her crib, will sleep through the night several times a week and is starting to put herself back to sleep - *13 months*

❝ He wakes every night for 2 to 3 hours, normally between 1 and 4 am. Nothing has worked and we are trying melatonin but it's not working yet - *19 months*

❝ Wrapping him like a newborn baby helps - *2 years 6 months*

❝ She doesn't sleep a lot. An elevated bed is most helpful - *4 years 4 months*

❝ He never slept when he was younger. He still wakes in the night and is up early but is happy to amuse himself. We found a sleeping bag and sorting out other problems such as reflux most helpful - *4 years 8 months*

Undescended testicles

Boys with a 5q14.3 deletion are occasionally born with undescended testicles. At first, they are usually monitored to see whether the testicles 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. (Le Meur 2010; Decipher; *Unique*)

Feet and hands

In most babies with a 5q14.3 deletion, the feet are not in any way unusual. Any abnormalities are usually minor and do not generally affect mobility. Occasionally the second and third toes on one foot or both may be joined with a bridge of skin or tissue or the big toes are short or broad. One child has unusually short, narrow feet. More seriously, one child was born with the last joint missing on four toes of the right foot and another with an extra little toe on one foot and two children were born with a type of club foot.

More commonly, the muscle tone in the legs and feet is altered and children need supportive footwear, gaiters or splints to help their mobility.

The only unusual hand features noted have been irregular palm creases. (Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Decipher; *Unique*)

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. Babies and children with a 5q14.3 deletion 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. (Berland 2010; Nowakowska 2010; *Unique*)

❝ Multiple ear infections and perforated ear drums but hearing is fine - *19 months*

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 5q14.3 deletions, the only problem seen by *Unique* families is late appearance of baby teeth (first teeth at 12 months; only six teeth at 21 months). There is a report in the medical literature of a teenager with very large teeth. (Novara 2010; *Unique*)

Therapies

Families can expect their children to be assessed for the standard trio of therapies – physical (physiotherapy), 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 conductive education and cranial osteopathy, with a measure of success.

Genes in 5q14.3

Although a 5q14.3 deletion can remove many genes, it is currently believed that the *MEF2C* gene is responsible for most of the clinical features of the emerging syndrome. *MEF2C* is found between base pairs 88051922 and 88214780 within the 5q14.3 band. In most reports, the entire gene has been deleted, but in some, only part of the gene has been lost. In others, the *MEF2C* gene is intact but the deletion is very close to it. When the clinical features are the same although the gene has not been lost, it's believed that the cause is what is known as a 'position effect' – losing material close to the gene somehow switches it off. At this stage, a 'position effect' isn't certain for the *MEF2C* gene, but it looks likely.

MEF2C plays an important role in developing and maintaining multiple organs including the brain where one of its jobs is to create brain cells. The deletion of *MEF2C* is thought to underlie the learning disability, stereotypic movements and the epilepsy/ brain malformations and possibly also the slight facial differences. *MEF2C* also has a role in heart development but so far no-one has been found with a heart problem.

Some children with a 5q14.3 deletion have been found on brain imaging to have periventricular heterotopias [see page 14]. So far no one gene has been identified as causing this abnormal migration of nerve cells but at present *MEF2C* is not thought to be responsible (Berland 2010; Le Meur 2010; Nowakowska 2010; Stankiewicz *Personal communication*; Zweier 2010).

Why has this happened?

To answer this question both parents of a child with a 5q14.3 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 or very soon after fertilisation.

Some chromosome changes seem to occur partly because of the way the DNA is arranged at the break points. This does not seem to be the case with 5q14.3 deletions and a molecular diagnosis will show that the exact break points are not the same from individual to individual.

No environmental, workplace, dietary or lifestyle factors are known to cause these chromosome changes. What is certain is that there is nothing you as a parent could have done to cause the break to occur and nothing you could have done would have prevented it occurring in your baby. It is no-one's fault.

Can it happen again?

Where both parents have normal chromosomes, it is very unlikely that another child will be born with a 5q14.3 deletion or any other chromosome disorder. All the same, if they wish, parents should have the opportunity to meet a clinical geneticist or genetic counsellor to discuss their specific position and, if they are thinking about another pregnancy, to talk about options for prenatal diagnosis. Prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is very accurate, although tests are not available in all parts of the world.

Is there a 5q14.3 neurocutaneous syndrome?

Christopher Carr and his colleagues have described a boy with a 5q14.3 deletion that includes a gene known as *RASA1*. Mutations in the *RASA1* gene can cause a disorder known as CM-AVM, short for capillary malformation arteriovenous malformation. The CM part of the disorder shows as small flat pink-red birthmarks that may be obvious at birth but can also emerge later. The marks consist of an increase in the tiny blood vessels beneath the skin and/or a dilation of these vessels. The AVM part of the disorder consists of abnormal links between the arteries and the veins, typically in the head and neck region but potentially also within the spine. The boy described by Mr Carr has typical symptoms of a 5q14.3 deletion as well as capillary malformations, but no arteriovenous malformations were found. Mr Carr suggests that other people with a 5q14.3 disorder should be carefully screened for existing or emerging skin marks and malformations of the blood vessels (Carr 2011).

References

Berland 2010: Clinical Dysmorphology 2010 October Volume 19(4) pages 222-4: *Late-onset gain of skills and peculiar jugular pit in an 11-year-old girl with 5q14.3 microdeletion including MEF2C.*

Cardoso 2009: Neurology 2009 Volume 72(9) pages 784-92: *Periventricular heterotopia, mental retardation, and epilepsy associated with 5q14.3-q15 deletion.*

Carr 2011: American Journal of Medical Genetics 2011 Part A Volume 155 pages 1640-1645: 5q14.3 Neurocutaneous Syndrome: A Novel Contiguous Gene Syndrome Caused by Simultaneous Deletion of *RASA1* and *MEF2C*

Engels 2009: European Journal of Human Genetics 2009 December Volume 17(12) pages1592-9: *A novel microdeletion syndrome involving 5q14.3-q15: clinical and molecular cytogenetic characterization of three patients.*

Ezugha 2010: Journal of Child Neurology 2010 Volume 25(10) pages 1232-1235: *5q14.3 Deletion Manifesting as Mitochondrial Disease and Autism: Case Report.*

Le Meur 2010: Journal of Medical Genetics 2010 January Volume 47(1) pages 22-9: *MEF2C haploinsufficiency caused by either microdeletion of the 5q14.3 region or mutation is responsible for severe mental retardation with stereotypic movements, epilepsy and/or cerebral malformations.*

Marashly 2010: Journal of Louisiana State Medical Society 2010 July-August Volume 162 (4) pages 223-6: *Infantile spasms associated with 5q14.3 deletion.*

Novara 2010: Clinical Genetics Volume 78 pages 471-477: *Refining the phenotype associated with MEF2C haploinsufficiency.*

Nowakowska 2010: American Journal of Medical Genetics B Neuropsychiatric Genetics 2010 July Volume 153B (5) pages1042-51: *Severe mental retardation, seizures, and hypotonia due to deletions of MEF2C.*

Zweier 2010: Human Mutation 2010 June Volume 31(6) pages 722-33: *Mutations in MEF2C from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe mental retardation and diminish MECP2 and CDKL5 expression.*

Notes

Notes

Notes

Support and Information

Rare Chromosome Disorder Support Group,
PO Box 2189,
Caterham,
Surrey CR3 5GN,
UK
Tel/Fax: +44(0)1883 330766
info@rarechromo.org
www.rarechromo.org

***Unique* is a charity without government funding, existing entirely on donations and grants. If you are able to support our work in any way, however small, please make a donation via our website at http://www.rarechromo.org/html/MakingADonation.asp Please help us to help you!**

This 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. The information is believed to be the best available at the time of publication. It was compiled by *Unique* and reviewed by Dr Pawel Stankiewicz, assistant professor, Molecular and Human Genetics, Baylor College of Medicine, Texas, USA and by Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK. (PM) Version 2

Rare Chromosome Disorder Support Group
Registered in England and Wales

Charity Number 1110661
Company Number 5460413