Understanding Chromosome & Gene Disorders

15q13.3 microdeletion

rarechromo.org

Sources and references

The information in this guide is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from a survey of members of Unique conducted in 2008/9 and 2012, referenced Unique. When this leaflet was updated in January 2013 Unique had 53 member families with a microdeletion at 15q13.3, ranging in age from a toddler to a 62-year-old adult.

15q13.3 microdeletion syndrome

A 15q13.3 microdeletion is a rare genetic condition caused by a tiny missing part of one of the body's 46 chromosomes – chromosome 15. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Even a tiny piece of missing material can disturb development, although it doesn't always do so.

Background on Chromosomes

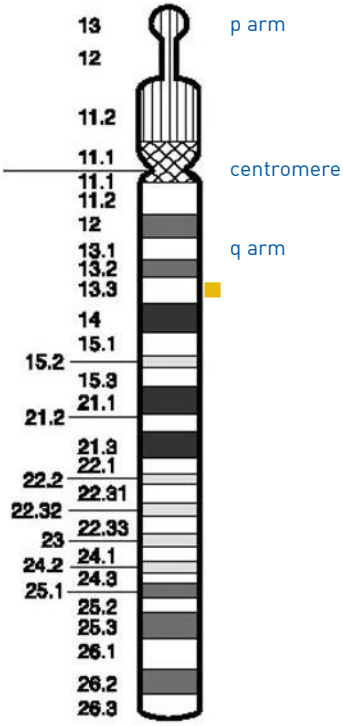
Chromosomes are structures found in the nucleus of the body's cells. Every chromosome contains thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information telling the body how to develop, grow and function. Chromosomes (and genes) usually come in pairs with one half of each chromosome pair being inherited from each parent. Humans have 23 pairs of chromosomes, giving a total of 46 individual chromosomes.

Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short or petit (p) arm (shown at the top in the diagram on page 3) and a long (q) arm (the bottom part of the chromosome).

Chromosome Deletions

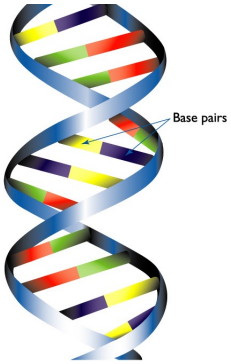
A sperm cell from the father and an egg cell from the mother each carries just one copy of each chromosome. When they join together they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes can break off or become arranged differently from usual. People with a 15q13.3 microdeletion have one intact chromosome 15, but a piece from the long arm of the other copy is missing. Although the exact numbers and types of genes that are affected by the deletion are not always known, since some genes are missing there can be effects on a person's learning and physical development. Therefore it is believed that most of the clinical difficulties are probably caused by having only one copy (instead of the usual two) of a number of genes. We are still learning the about the specific jobs or functions of the genes in this region. It is important to keep in mind that a child's other genes, environment and unique personality also help to determine future development, needs and achievements.

Looking at 15q13.3



You can't see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. You can see these bands in the diagram of the long arm of chromosome 15 on the right. The bands are numbered outwards starting from the point at the top of the diagram where the short and long arms meet (the centromere). A low number such as q11 is close to the centromere. You can see that q13.3 is quite close to the centromere.

Even if you magnify the chromosomes as much as possible, to about 850 times life size, a chromosome 15 with the microdeletion at q13.3 looks normal. People who have missing material on a chromosome are said to have a deletion but when the amount is so small that it can't be seen even under a high-powered microscope (known as karyotyping), it is called a microdeletion. The 15q13.3 microdeletion can only be found using molecular or DNA technology, in particular a technique using microarrays (array-CGH), that shows gains and losses of tiny amounts of DNA throughout the genome and can demonstrate whether particular genes are present or not. It is believed that the effects of the microdeletion are caused by the presence of only one copy of these genes instead of two, as expected.



1 base pair = bp
1,000 base pairs = 1kb
1,000,000 base pairs = 1Mb

Your geneticist or genetic counsellor will be able to tell you about the points where the chromosome has broken in your child. With a 15q13.3 microdeletion, the results are likely to read something like the following example:

46,XY.arr cgh 15q13.3q13.3 (RP11-126J1-)de novo

46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes: XY for males; XX for females
.arr cgh	The analysis was by array comparative genomic hybridization (array- CGH)
15q13.3q13.3	The deletion is on chromosome 15. There are two breakpoints in the chromosome, both in band 15q13.3, indicating a small deletion or microdeletion
(RP11-126J1-)	A DNA fragment of interest known as RP11-126JI has been found to be missing or deleted
de novo	The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 15q13.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

arr[hg19]15q13.2q13.3 (30,971,330-32,439,084)x1

arr	The analysis was by array (arr) comparative genomic hybridisation (cgh)
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted
15q13.2q13.3	The chromosome involved is 15. The chromosome has two breakpoints, one in band 15q13.2 and one in band 15q13.3, and material between these two breakpoints is missing
30,971,330-32,439,084	The base pairs between 30,971,330 (around 31Mb) and 32,439,084 (around 32Mb) have been shown to be deleted. Take the first long number from the second and you get 1,467,754 (1.5Mb). This is the number of base pairs that are deleted
x1	This means there is one copy of these base pairs, not two – one on each chromosome 15 – as you would normally expect

Normal variant

Some people have been found with a tiny amount of missing material slightly closer to the centromere, often where both breakpoints are within the 15q13.2 band but sometimes where both breakpoints are within the 15q13.3 band. Some of them are unaffected by this, others have some developmental difficulties. It is not yet known whether losing a very tiny amount of material from this region is a harmless variant or a variant which can disturb development in some people but not in others (Sharp 2008).

15q13.3 microdeletion syndrome

The first published description of a person with a 15q13.3 microdeletion was in 2008. There have since been over 150 cases reported in the medical literature worldwide. When a particular set of developmental features occurs in a recognisable and consistent pattern in enough people with, as a result of a single cause, the condition is called a syndrome. The features of a 15q13.3 microdeletion do occur in this way, so the disorder is often known as 15q13.3 microdeletion syndrome. The deletion occurs equally often in males and females (Sharp 2008).

How much do we know?

Comparing different children and adults with 15q13.3 deletions shows that some effects seem to be very broadly similar. This information guide tells you what is known about those effects. Comparing your child's array results with others, both in the medical literature and within Unique, can help to build up a general picture of what to expect. But there will still be differences, sometimes quite marked, between your child and others with an apparently similar array result. In families where more than one member has the 15q13.3 microdeletion, the specific effects can sometimes be quite different. It is very important to see your child as an individual and not to make direct comparisons with others with the same chromosome test results. After all, each of us is unique.

How common is it?

It is surprisingly common— almost certainly found as often as much better known syndromes such as Prader-Willi, Angelman and Williams syndromes. It has been estimated that one person in every 30,000 to 40,000 in the general population has a 15q13.3 microdeletion although others have suggested that it might be even more common than that (Sharp 2008; van Bon 2009; LePichon 2010; Liao 2011).

Most common features

Every person with a 15q13.3 microdeletion is unique and so each person will have different medical and developmental concerns. Additionally, no one person will have all of the features listed in this information guide. However, a number of common features have emerged:

- Generally no obvious birth defects
- Children are likely to need support with learning. The amount of support needed by each child will vary
- Seizures or abnormal results on EEG (electroencephalogram), but not in all children
- Behavioural difficulties such as autistic spectrum disorder or attention deficit hyperactivity disorder. Some adults and children, but not all, have aggressive behaviour and rage
- Subtly unusual facial features. Families may notice similarities between their own child and others with the deletion
- Otherwise generally healthy

Are there people with a 15q13.3 microdeletion who are healthy, have no major birth defects and have developed normally?

There are many individuals with the microdeletion who appear normal and have no major birth defects, all of whom only discovered they had the deletion when it was detected in their children. Both fathers and mothers have passed a microdeletion on to their children (Sharp 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Hoppman-Chaney 2012; Unique).

If one person in a family with the 15q13.3 microdeletion is mildly affected, will others in the same family also be mildly affected?

Not necessarily. There is a lot of variation between different members of the same family who have the same microdeletion. We know that if one person is mildly affected or unaffected, others may be more severely and obviously affected (Sharp 2008; Miller 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Le Pichon 2010; Masurel-Paulet 2010; Liao 2011; Muhle 2011; Spielman 2011; Hoppman-Chaney 2012; Unique).

What is the outlook?

We can't be certain yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan and there are a number of adults both at Unique and

in the published medical literature (See section on Adults with 15q13.3 microdeletion syndrome on page 15).

Pregnancy and birth

Most pregnancies were uncomplicated and babies were born at or near their expected due date

The majority of mothers carrying babies with a 15q13.3 microdeletion experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, pregnancy complications in mothers carrying a baby with a 15q13.3 microdeletion have been reported. Three babies were described as having intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed, resulting in babies that are smaller than expected for the number of weeks of pregnancy. Two babies showed less fetal movement than expected while in the womb, and one baby had regular ultrasound scans after concerns about growth and low fetal movement in the womb. One Unique baby showed enlarged kidneys detected at the 20-week ultrasound scan and thereafter had regular scans for the remainder of the pregnancy. The baby was induced at 36 weeks due to the mother's pre-eclampsia (a sudden increase in blood pressure and the presence of excess protein in the urine. If left untreated, pre-eclampsia can have serious complications for both the mother and the baby). There is also a case in the published medical literature where a heart anomaly was detected on prenatal scans. One baby was delivered early due to deterioration of the baby's heart-rate. Three mothers had gestational diabetes, and in one of these mothers the placenta partially detached (Sharp 2008; van Bon 2009; Endris 2010; Liao 2011; Muhle 2011; Spielman 2011; Unique).

Two mothers in the published medical literature had an amniocentesis (a test during pregnancy where a needle is used to extract a sample of amniotic fluid, the fluid that surrounds the developing baby in the womb) followed by conventional karyotyping; one after anomalies were seen on a prenatal ultrasound scan. In both cases the results were interpreted as normal (due to the small size of the microdeletion) despite their babies later being diagnosed a 15q13.3 microdeletion (van Bon 2009).

Feeding and growth

Feeding and growth can be affected in children with 15q13.3 microdeletion syndrome

Some babies are born small and light for dates. Intrauterine growth retardation (IUGR) was observed for two babies, although the size at birth was within normal limits. Most babies and children identified so far have shown a normal growth rate before and after birth and family influences on weight, height and head circumference appeared more marked than any effect of the microdeletion. However, three babies were described as failure to thrive (van Bon 2009; Hoppman-Chaney 2012).

Two adults and two children were described as 'short', although four others are described as tall (van Bon 2009; Unique).

Of those for whom birth weights are known the average was 3.24 kilos (7lb 2oz), with most babies on the small side of average and a minority being quite heavy (Sharp 2008; van Bon 2009; Unique).

Range of birth weights (at or near term):

2 kg (4lb 6oz) to 4.4 kg (9lb 11oz)

Two babies were tube fed in the early newborn period because of low muscle tone

(floppiness) and weight loss. Two babies had problems swallowing as babies; one at aged 3 years prefers to eat soft food and does not like to chew; the other has a limited food repertoire at aged 5 years and has difficulty manoeuvring food in his mouth. Another Unique baby who was unable to latch on to the breast was bottle-fed expressed breast-milk for three months. He was unable to tolerate dairy formula milk and was given a soy-based formula instead. Two babies in the medical literature and two babies at Unique had feeding difficulties as newborns; one of whom went on to have a feeding tube (Sharp 2008, Spielman 2011; Hoppman-Chaney 2012; Unique).

One girl developed an increased appetite, eating large quantities and leading to being overweight, which also affected her mother who has the same microdeletion. She developed Type 2 diabetes. However, her half sister who inherited the same deletion was not overweight. Another child did not seem to know when he was full. A 5-year-old and a 12-year-old in the medical literature have been described with hyperphagia (an increased appetite for and consumption of food). A 17-year-old boy, a 12-year-old girl and a 14-year -old girl were described as obese and two others were described as overweight (Sharp 2008; van Bon 2009; Hoppman-Chaney 2012; Unique).

"He prefers soft, slimy foods. He will eat pears, peaches and mandarin oranges, pancakes and yoghurt. He seems not like to chew hard textures" – 3 years

Learning

Some children with 15q13.3 microdeletion syndrome have a learning disability; most often mild.

Around half of those with 15q13.3 microdeletion syndrome have no learning (intellectual) disabilities. For those who have been observed to have a learning disability, it is generally a mild or at most a moderate level of learning disability. Out of 26 people with a known level of learning difficulty, sixteen were described as having a mild level of difficulty while seven faced moderate challenges and three have severe learning difficulties. Where an IQ has been assigned, it was over 70 (borderline to normal) for four individuals, between 50 and 70 (mild learning difficulties) for six individuals, 35-50 (moderate learning difficulties) for one and 27 (severe) for one child. One child with a mild level of learning difficulty appeared to be struggling harder by adolescence as his IQ showed a decline from 62 at 4 years to 44 at 15 years. This was also true of another boy whose IQ showed a decline from 74 at 5 years to 64 at 15 years. Among adults, assigned IQs varied between 34 at 23 years and 46 at 28 years, and an IQ of 52 for a 33-year-old. One child has dyslexia and a number of children are hyperactive or described as being easily distractible or having a poor concentration span, which can make learning more of a challenge (see Behaviour). A child with a learning disability is likely to need some learning support and many children benefit from attending a special educational school (Sharp 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Masurel-Paulet 2010; Muhle 2011; Hoppman-Chaney 2012; Unique).

"He gets distracted easily" – 3 years

"His cognition is within normal limits. However, he struggles with visual motor tasks. He

has trouble self-regulating and is very easily distracted. When he is focused he can count, spell his name etc. When he is not focused he counts '1, 2, 3, 17, 17, 20'" – 5½ years

"He has dyslexia and dysgraphia [writing difficulties]. He likes science. He has difficulty with concentration. When he is doing his homework he can concentrate for about 45 seconds at a time. He needs constant redirection to stay on task. He can read but does not read for enjoyment" – 10 years

"He is good at mathematics. He is unable to attend discussions for longer than 25-30 minutes and cannot comprehend reading passages unless they are broken down into smaller parts. He reads comic books, books on superheroes, and monthly magazines for children" – 15 years

"He has a moderate learning disability. He attended mainstream school and had extra help in English and maths. He also has extra help in college. He reads Harry Potter books, Sarah Jayne Adventures and Dr Who books" – 20 years

"He was in mainstream school but had extra help in English and maths. He likes to read military books" – 22 years

"He has a severe learning disability and was in special education for all of his education. He doesn't read but enjoys looking at books" – 24 years

Speech and communication delay

Speech and language delay is common in children with a 15q13.3 microdeletion

Speech and language development was delayed in many, but not all, children but it is not known whether the delay was in line with the child's cognitive abilities. However, two children had no speech. Expressive language appears to be more delayed than receptive language: children are able to understand more than they are able to express. Many children have articulation difficulties. Speech therapy has proved extremely beneficial to many children. One woman who had speech delay and poor expressive language as a child spoke well as an adult. Two teenagers and one 11-year-old have nasal speech (Sharp 2008; Miller 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Masurel-Paulet 2010; Unique).

"He is great at communicating. He knows around 50 words. He does some signing for 'eat', 'down', 'biscuit' and 'dirty nappy'. He does a lot of pointing" – 20 months

"He is very verbal, but has significant articulation issues. He uses words to communicate, but will add signs, gestures, point and context clues to help make his thoughts clearer. He leaves out things like 'is' ('The boy eating ice cream. Why Daddy doing that?'). He mixes and substitutes sounds all of the time. He has a lot of trouble with more difficult sounds such as 'L' and 'S' – 5½ years

"The sound of his voice is higher than a typical child. It is also more staccato" – 7 years

"No communication issues" – 10 years

"He is verbal and speaks fluently although he can be difficult to understand at times" – 15 years

"He has no communication problems" – 22 years

Behaviour

Some children with 15q13.3 microdeletion syndrome have behavioural difficulties such as autistic spectrum disorder or attention hyperactivity deficit disorder

Out of 74 children whose behaviour has been described, 22 have been described with autistic spectrum disorder (ASD) and 20 with attention deficit hyperactivity disorder (ADHD), hyperactivity or attention problems. In two studies looking at the behavioural issues of 25 individuals with a 15q13.3 microdeletion, eight had some degree of difficulty with mood regulation and impulsive behaviours.

Self-injurious behaviour has also been described in three children in a separate study and anxiety has been described in seven people. A boy with autism is described as being easy-going and affectionate. At least eight people with a 15q13.3 microdeletion have aggressive behaviour and rages. One boy, who had mild autism, showed aggressive behaviour and rage. A 38-year-old man with ADHD has severe rages and aggression and has been diagnosed with schizophrenia (a brain disorder in which there is distortion in the perception or expression of reality). Schizophrenia has also been described in the published medical literature. Two fathers described in the medical literature had bipolar disorder but no other behavioural problems. Bipolar disorder, previously called manic depression, is a condition that affects a person's moods, which can swing from one extreme to another. Someone who has bipolar disorder will have periods or episodes of depression and mania. The two extremes are characterised as depression where the person feels very low, and mania where the person will feel very high (International Schizophrenia Consortium 2008; Miller 2008; Sharp 2008; Stefansson 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Masurel-Paulet 2010; Muhle 2011; Hoppman-Chaney 2012; Unique).

"He is a pretty normal toddler – plenty of energy and always on the go, jumping from one toy to the next and not concentrating on anything for more than a few minutes. He is a happy smiley baby. He can be clingy when other kids are around; wants me to be close. When out in the playground he is confident to be further away but as soon as another child comes near him he will race to me and just watch the other kids. He is more of a watcher than a doer. He is loving and affectionate" – 20 months

"He loves playing with children and adults. He is great at imaginary play and loves all sports. He loves playing cars and has loved music since he was very young. He loves animals. He is very active and needs lots of opportunities to move. He is usually good

about following directions and can be redirected with simple prompting. However, there are also days where he is very impulsive and makes poor choice after poor choice (always apologising sincerely). He can be very emotional and will sometimes laugh inappropriately. He has ADHD with impulsive behaviours and high distractibility. We work on calming his sensory system in therapy and he is on medication. He is very friendly and is a people pleaser. He thrives on praise and loves to be a helper" – 5½ years

"He loves animals and being in nature. He is very active and driven. He wants what he wants when he wants it and is impatient and needy. He will get angry and aggressive if he does not get his way" – 10 years

"He loves hanging out with his friends and camping. He has a great sense of humour and loves to entertain. He attends a drama club once a week. However, he can interrupt, be rude and use unkind words and he has a behavioural specialist and art therapist to reduce these behaviours. Treatment is on-going. He also attends a social skills group once a week" – 15 years

"On a normal day he has normal behaviour but he can get agitated very easily" – 20 years

"He has normal behaviour" – 22 years

"On a typical day his behaviour can change. He can be calm one moment, be aggressive the next and fly into a violent rage" – 24 years

Motor skills (sitting, moving, walking)

Children with 15q13.3 microdeletion syndrome are often delayed in learning to sit and walk.

One of the causes of the delay in mobility in children with a 15q13.3 microdeletion is low muscle tone (hypotonia), reported in a number of individuals. This makes a child or baby feel floppy to handle and generally improves and may disappear with physiotherapy and exercises. However, this means it may take a little longer for them to roll over, sit, crawl and walk. From the information that is available, sitting unaided is mastered between 4 months and 18 months (at an average of 8½ months) and walking is mastered between 12 months and 3 years (an average of 21½ months) (Sharp 2008; Miller 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Masurel-Paulet 2010; Unique).

Two children in the medical literature have difficulties with co-ordination and three Unique members are described as clumsy (Pagnamenta 2009; Unique).

"He has just in the last month started taking his first steps. He did not move until he was one year. At 1 year he moved by doing an asymmetrical bottom shuffle using his left hand to propel himself forward" – 20 months

"He has a lack of co-ordination and balance issues. He loves to walk outside but sometimes falls on uneven ground if he's not guarded. He can crawl up three steps without help but still cannot walk up or down steps without assistance" – 3 years

"He is fully mobile but quite clumsy. He is able to walk and run. He climbs holding on to a rail or person. He is starting to jump with both feet off the ground and is learning to pedal a bike" – 5½ years

"He is VERY active. He was riding a bike at age 2. He now skateboards, bikes and scoots and can throw hard and fast" – 10 years

"He moves around okay but can be really clumsy and unsteady on his feet. He falls quite easily" – 24 years

Fine motor skills and self care

Fine motor skills may be affected in children with 15q13.3 microdeletion syndrome

Very little is known about the fine motor skills of children with 15q13.3 microdeletion syndrome. Toilet training is only known for two children who achieved bladder and bowel control at 3 and 4 years. One child achieved bladder control but struggled with bowel control at age 7 years. A 5½-year-old is in nappies (diapers) at bedtime but is being potty-trained during the day. A 3-year-old is still in nappies but will brush his teeth (with assistance) and will lift and push his arms through sleeves when getting dressed. One Unique child developed good fine motor skills, but regressed and lost skills in handwriting, drawing and toileting at around the age of 10 when his seizures became difficult to control. He is currently undergoing occupational therapy to try to regain these skills with good progress (Sharp 2008; Unique).

"He is delayed with fine motor skills in his right hand. We have been working with this with the occupational therapist (OT). In the last month he is able to feed himself with a spoon" – 20 months

"He can do all personal care but likes to have help getting dressed on school days – 10 years

"He can wash, brush his teeth and can dress himself. He needs help at times to choose appropriate clothing" – 24 years

Facial appearance

Children with 15q13.3 microdeletion syndrome may have a subtle characteristic facial appearance.

Babies and children with this microdeletion may have subtly different facial features that would not, however, make them stand out from a crowd of other children. Geneticists trained to note unusual features may find features such as wide, deep set or upslanting eyes, a skinfold across the inner corner of the eye (an epicanthal fold), a prominent groove on the upper lip and full lips or an outturned upper lip. In one family, members with the deletion had a more gaunt appearance than those without (Sharp 2008; Ben-Shachar 2009; Unique).

Hands

People from two families and a number of other unrelated individuals with a 15q13.3

microdeletion have been described in detail in the medical literature. Certain unusual features of the hands appear to run in the affected families but the features are not seen regularly in other families or individuals. In one family the thumb joints are loose. In another family the fourth metacarpals (the bone in the hand that links the wrist with the ring finger) are unusually short, and this has also been described in one other unrelated individual. Two members of this family also have stiff fingers, one has a short fifth finger and another cannot fully open their elbows. Sixteen unrelated children have incurving little fingers (5th finger clinodactyly), a feature that is very common in people with a chromosome disorder and quite common in the general population. A further two have brachydactyly (short fingers). Five children have fingers that taper and another child is described as having very floppy hands. One child has 'fetal' fingers and toes (the pads of the digits are prominent as they are in the womb but they usually flatten out before birth). Overall, the pattern is of variable minor hand and arm anomalies (Sharp 2008; Ben-Shachar 2009; Masurel-Paulet 2010; Unique).

Feet

Foot problems appear not to be common in 15q13.3 microdeletion syndrome, although three people are described as being flat footed; one with the arch of the foot located on the outside of the foot rather than the inside as is usual and one has fallen arches. Another child has large toes, another has a bunion and another's littlest toe does not touch the ground. A 2 ½-year-old has brachydactyly (short toes) and a 5½-year-old has toes that curve towards his big toe and a weak ankle that pronates (turns or rotates). Specialist footwear and insoles have helped some children (Sharp 2008; van Bon 2009; Masurel-Paulet 2010; Unique).

Health matters

Seizures or abnormal EEG patterns

Children with 15q13.3 microdeletion syndrome have an increased risk of seizures

Around a quarter (20/86) children and adults with a 15q13.3 microdeletion have seizures and a further two have had a single seizure. The age of onset of seizures is variable: some developed seizures in infancy; others throughout childhood and two adults started to have seizures in their forties. The seizure types are also varied and there are only three reports of the seizures being resistant to control with medication. One Unique child had seizures that began at 34 months and were well-controlled. At the age of 10 years the seizures become harder to control and he had vagus nerve stimulation (VNS) therapy. VNS is a treatment for epilepsy where a small generator is implanted under the skin below the left collar bone. This is connected to a lead with three coils at one end. These coils are wrapped around the vagus nerve in the left side of the neck in a small operation. The VNS stimulates the vagus nerve at intervals to reduce the frequency and intensity of seizures. Other methods that his family utilise to help control his seizures are frequent snacks, a high carbohydrate diet, plenty of rest and elimination of foods with artificial sweeteners or colouring. His seizures are now under control (Sharp 2008; Ben-Shachar

2009; Pagnamenta 2009; van Bon 2009; Masurel-Paulet 2010; Muhle 2011; Hoppman-Chaney 2012; Unique).

Among 16 people who have had an electroencephalographm (EEG: a test that records brain activity), including five with diagnosed epilepsy, an abnormal EEG pattern was found in 11 people. A 19-year-old woman had absence seizures at aged 5 years which were well controlled with medication. At 8 years the medication was withdrawn but she had a relapse of seizures at puberty and an abnormal EEG pattern was found at age 14. At age 19 years she has no seizures and a normal EEG pattern. Another child who has had a normal EEG and has not had a seizure has periods of staring off into space, and is currently being monitored (Miller 2008; Sharp 2008; Mulley 2009; Masurel-Paulet 2010; Muhle 2011; Unique).

One gene within the missing region, known as *CHRNA7*, is thought to be responsible for the frequent seizures (see Research involving 15q13.3 on page 15). A recent study suggested that one per cent of people with epilepsy have a 15q13.3 microdeletion encompassing the *CHRNA7* gene, making this microdeletion the most common identified genetic cause of epilepsy to date (Helbig 2009). However, while identifying the responsible gene is interesting, it does not lead directly to improved treatment or seizure control. It is, however, helpful to know whether in your child this gene is missing or not as the likelihood of seizures may be higher if it is (Sharp 2008; Unique).

Brain

A number of individuals have had brain imaging and abnormalities were found in seven. In one a patchy change in the white matter by the left ventricle (the fluid-filled space in the brain) was found. A second child had areas of the brain where the white matter was thinner than expected. A third child had a less developed myelin sheath than expected at the age of 5 years but imaging at 13 years was normal. Two people had hydrocephalus (excess fluid in the brain) and two had an arachnoid cyst (fluid filled sacs located in the brain) (Sharp 2008; Ben-Shachar 2009; van Bon 2009; Masurel-Paulet 2010; Hoppman-Chaney 2012; Unique).

Heart

Cardiac problems have been rarely reported although in one study three out 18 had a cardiac defect. One had tetralogy of Fallot (a complex cardiac condition where the artery that takes the blood to the lungs has an unusually narrow entrance [pulmonary stenosis] coupled with a hole in the heart); one had a mitral valve prolapse (the valve between the upper and lower chambers of the left side of the heart is unusually thick and one of the heart valve flaps [also known as a leaflet] moves back into the upper chamber when the heart beats) and one baby had hypoplasia (underdevelopment) of the right side of the heart. All three were missing the *KLF13* (Kruppel-like transcription factor 13) gene which has recently been reported to be involved in cardiac development (van Bon 2009).

One Unique member has a leaky heart valve with shortness of breath and high blood pressure (Unique).

Other

Other health concerns which may or may not be linked with the microdeletion include

ureteral ectasia of right kidney (distension of the tube that carries urine from the right kidney to the bladder); hydronephrosis of one kidney (the kidney has become stretched, or swollen, due to a build-up of pressure when urine fails to drain out of the kidney); faecal incontinence (loss of control of the bowels) which was corrected by a surgical procedure; a hiatus hernia (the upper part of the stomach pushes upwards into the opening in the diaphragm) which was repaired in infancy, and enteritis (inflammation of the small intestine). Two boys had slight breast development and two children had excessive hair growth. One woman had hypothyroidism (the thyroid gland does not make enough thyroid hormone) (Sharp 2008; Pagnamenta 2009; van Bon 2009; Masurel-Paulet 2010; Unique).

Eyesight

A squint (strabismus), where one or both eyes can turn inwards, outwards or upwards, is the most common vision problem. Many squints are convergent (the eyes cross) and many children need surgery to re-align the eyes. At least three people have astigmatism, which is when the cornea (the clear cover over the iris and pupil) is abnormally curved. The effect on vision is to make objects appear blurred. Sometimes the brain can compensate for astigmatism, although it may be too strong for this to happen without glasses. A number of other vision problems have been reported more rarely.
One child had a small left eye; two have a coloboma (a developmental defect of the structure of the eye), another has a possible coloboma and two have nystagmus (rapid involuntary eye movements). Two adults are longsighted. A 38-year-old man has blurred and double vision (Sharp 2008; Ben-Shachar 2009; van Bon 2009; Masurel-Paulet 2010; Hoppman-Chaney 2012; Unique).

Hearing

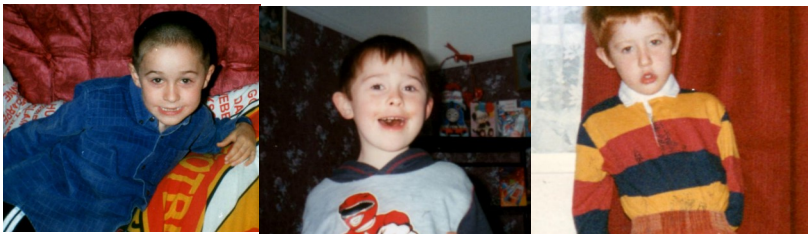
Generally speaking children have had normal hearing. Young children frequently have the fluctuating temporary hearing loss caused by a build-up of fluid behind the eardrum (glue ear) but they outgrow this naturally. If it is severe or persistent, tubes (grommets) may be inserted into the eardrum to aerate the space (the middle ear) behind it and improve hearing. One child within Unique has hearing tubes.

Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than others. In this group there were few difficulties, although four children were reported as having misalignment of the teeth (malocclusion) (Sharp 2008; Hoppman-Chaney 2012; Unique).

Genital anomalies

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. Three Unique boys have a large penis and one boy in the medical literature had a shawl scrotum (the scrotum surrounds the penis, resembling a 'shawl') (van Bon 2009; Unique).



Brother with 15q13.3 microdeletion syndrome

Puberty

There is limited information available on puberty in both males and females with 15q13.3 microdeletion syndrome. It seems that puberty is generally at the normal age and proceeds as expected. However, one woman had late puberty which otherwise proceeded as expected. One Unique child developed pubic hair at the age of 9 years and one boy had premature puberty due to an excess of the hormone testosterone (van Bon 2009; Unique).

Adults with 15q13.3 microdeletion syndrome

Several adults have been described in the literature and are members of Unique. At least 36 people have no major birth defects and appear healthy and only discovered the microdeletion after it was detected in their children. One passed the microdeletion on to five of her six children. A 35-year-old who passed the microdeletion on to her son had reading and writing difficulties and so attended a special school. She had raised two children and showed normal behaviour. A 33-year-old woman has learning difficulties and seizures which are under good control. A 44-year-old, who has passed the deletion on to three children, developed seizures at 43 years old and takes medication for depression. A 42-year-old woman has some slightly unusual facial features and mild delays and has recently developed seizures. Two fathers were healthy and had no learning difficulties but suffered from bipolar disorder. One father only discovered he had the microdeletion after his daughter was diagnosed but has developmental delay and mental health problems (Sharp 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Masural-Paulet 2010; Hoppman-Chaney 2012; Unique).

15q13.3 microdeletion on both copies of chromosome 15

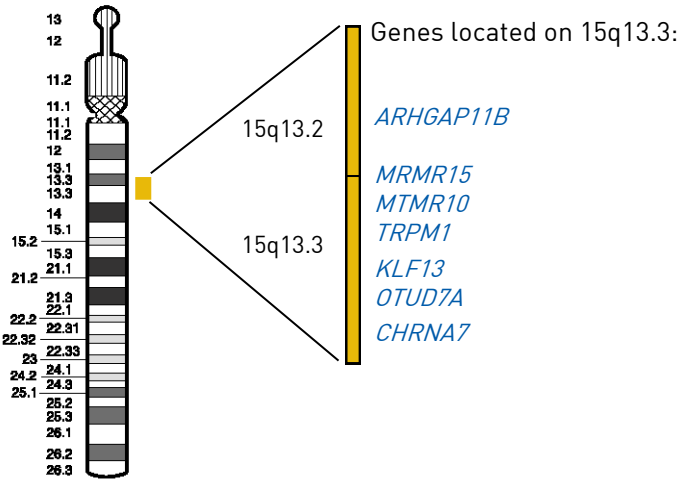
The vast majority of people with 15q13.3 microdeletion syndrome have one intact chromosome 15, but a piece from the long arm of the other copy is missing (see page 2). However, seven children have been described in the medical literature who are missing the 15q13.3 region from ***both*** copies of chromosome 15. This is called a homozygous deletion. At least four of these children have inherited the microdeletion from both of their parents, each of whom had the deletion on one chromosome. They are more severely affected than those with the only one chromosome affected: all seven have significant global developmental delay and severe hypotonia and none of them have any language skills or are able to walk, and all have seizures. At least three of them have severe visual impairment (Endris 2010; LePichon 2010; Masurel-Paulet 2010; Liao 2011; Spielman 2011).

Research involving 15q13.3

Most people have an approximately 1.5 to 2 Mb deletion, which contains seven genes: *ARHGAP11B*, *MRMR15*, *MTMR10*, *TRPM1*, *KLF13*, *OTUD7A* and *CHRNA7,* although the gene(s) responsible for the clinical features associated with 15q13.3 microdeletion syndrome have not been clearly defined. However, recently several people with very small deletions which contain only the *CHRNA7* gene have been described in the medical literature. These people all have a range of features similar to those who have larger deletions suggesting that the *CHRNA7* gene may be the gene responsible for these features (Shinawi 2009; Masurel-Paulet 2010; Liao 2011; Mikhal 2011; Hoppman-Chaney 2012).

The *TRPM1* gene has been suggested to be responsible for severe visual impairment (LePichon 2010; Spielman 2011).

The *KLF13* (Kruppel-like transcription factor 13) gene has recently been reported to be involved in cardiac development (van Bon 2009).



It is important to remember that while identifying the gene(s) responsible for certain features of 15q13.3 microdeletion syndrome is valuable and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is missing it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

How did this happen?

In many cases the 15q13.3 microdeletion was inherited from a parent (Sharp 2008; Ben-Shachar 2009; Pagnamenta 2009; van Bon 2009; Le Pichon 2010; Liao 2011; Muhle 2011; Spielman 2011; Hoppman-Chaney 2012; Unique).

In some cases the 15q13.3 microdeletion occurs out of the blue for no obvious reason. The genetic term for this is *de novo* (dn) and at first sight, both parents have normal chromosomes. *De novo* 15q13.3 microdeletions are caused by a mistake that is thought to occur when the parents' sperm or egg cells are formed. At one point in the formation, all the chromosomes including the two chromosome 15s pair up and swap segments. To pair up precisely, each chromosome 'recognises' matching or near-matching DNA sequences on its partner chromosome. However, throughout the chromosomes there are many DNA sequences that are so similar that it is thought that mispairing can occur. Although no-one has ever seen this happen, it is believed that when the exchange of genetic material - known as 'crossing over' - occurs after mismatching, it is unequal, looping out and excising a length of the chromosome.

What is certain is that as a parent there is nothing you could have done to prevent this from happening. No environmental, dietary or lifestyle factors are known to cause 15q13.3 microdeletions. There is nothing that either parent did before or during pregnancy that caused the microdeletion.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 15q13.3 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 15q13.3 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 15q13.3 microdeletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 15q13.3 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.

Could my child with a 15q13.3 microdeletion also have children with the microdeletion?

Yes, this is perfectly possible and has been seen repeatedly. The medical literature reports many parents who have passed the deletion on to their children. We have not known about the condition for long enough to be certain if it affects fertility but it is likely that fertility will be normal. In each pregnancy, someone with the deletion theoretically has a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the microdeletion. Their ability to look after a child is very likely to be closely related to any learning difficulty they may have themselves.

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Notes

Inform Network Support

Rare Chromosome Disorder Support Group,
The Stables, Station Rd West, Oxted, Surrey. RH8 9EE. UK
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

There is a Facebook group for families affected by 15q13.3 microdeletion syndrome at www.facebook.com

Join Unique for family links, information and support.

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

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This leaflet 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 Evan Eichler, Department of Genome Sciences, University of Washington, USA and by Professor Maj Hultén, Professor of Medical Genetics, University of Warwick, UK

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2009 Version 2.0 (SW)
2013 Version 2.1 (SW)