Understanding Chromosome & Gene Disorders

# 15q13.3 microduplications

rarechromo.org

## Sources

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 (www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from Unique. In addition, this guide draws on information from a survey of members of Unique conducted in mid 2012, referenced Unique. When this guide was written, Unique had 13 members (seven female, six male) with a pure 15q13.3 microduplication (no other chromosome involved). These members ranged in age from a child of 3 years to an adult of 48 years. There are 10 people described in the medical literature, ranging in age from 3-20 years at the time of publication of the paper. The Decipher database decipher.sanger.ac.uk also lists approximately 40 people aged 1-20 with the 15q13.3 microduplication (although the information listed for each of these people is limited). The ECARUCA database also has several people listed (www.ecaruca.net).

## 15q13.3 microduplications

A 15q13.3 microduplication is a very rare genetic condition in which there is a tiny extra piece of one of the 46 chromosomes – chromosome 15. The extra piece is from the region known as q13.3 on chromosome 15 (see diagram). The extra piece of chromosome is very small and therefore is called a microduplication.

Much of what is known about 15q13.3 microduplications comes from studying people who have been referred for genetic testing. This may have been due to developmental delay, unusual behaviour or a health problem; sometimes the 15q13.3 microduplication has been identified in someone else in the family. This gives us a biased sample. If we looked for the 15q13.3 microduplication in the general population, we would have an unbiased sample but it is very difficult to do so. This means that we can't be certain about the cause and effects of 15q13.3 microduplications. There is still a lot to learn but this guide contains the best information available to date.

## Genes and chromosomes

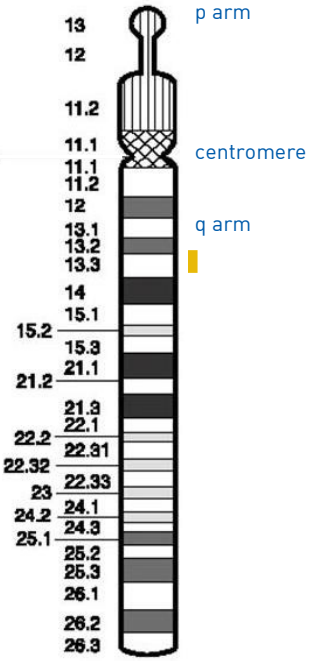
The human body is made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes; this genetic information tells the body how to develop, grow and function. Genes are carried on structures called chromosomes, which carry the genetic material, or DNA, that makes up our genes.

Chromosomes usually come in pairs: one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: XX (a pair of X chromosomes) in females and XY (one X chromosome and one Y chromosome) in males. The remaining 44 chromosomes are grouped into 22 pairs and are number 1 to 22 approximately from the largest to the smallest. Each chromosome has a short (p) arm, (from the French for small, petit) and a long (q) arm (see diagram of chromosome 15 below).

In general, the right amount of genetic material is needed for correct development – not too little or not too much. How an individual develops, his/her personality, needs and achievements, is influenced by both the genetic material he or she has and the environment in which he or she lives.

## Looking at chromosome 15q13.3

Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. In the diagram of chromosome 15, the chromosome bands are numbered outwards from the point where the long arm meets the short arm. A duplication occurs when an extra copy of a segment of a chromosome is present. In individuals with a 15q13.3 duplication, a small amount within the long arm (q) of chromosome 15 is repeated. People with a duplication of band 15q13.3 typically have approximately 1.5 million base pairs (Mb) duplicated (shown by the yellow bar on the diagram on the right). This sounds like a lot, but is actually quite small and accounts for less than 0.1 per cent of the total DNA in each cell.




## Genetic testing

Looking at chromosomes under a microscope, it is sometime possible to see the genetic material that has been duplicated, but only if the extra piece is large enough. A 15q13.3 microduplication is likely to be too small to be detected in this way. Molecular DNA technology gives a more precise understanding of the size and position of the duplication. This is important as scientists identify genes and pinpoint their location on chromosomes.

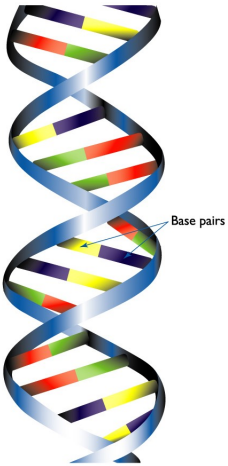
## Genetic testing

Techniques that are commonly used include FISH and microarrays:

- Fluorescence *in situ* hybridisation (FISH) uses fluorescent dyes to visualise under a microscope the number of copies of small sections of chromosomes. Unique publishes a separate guide to FISH

However, rare chromosome disorders may be caused by subtle changes in the chromosomes that are too small to see using a microscope.

- Microarray comparative genomic hybridisation (array CGH) is a sensitive technique which shows gains (and losses) of tiny amounts of DNA throughout the chromosomes. Array CGH identifies duplicated, disrupted or absent DNA. Unique publishes a separate guide to array CGH.




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

Modern genetic testing can reveal the precise nature of the duplicated genetic material. A microarray genetic report will tell you the size of the duplication:

### arr[hg19] 15q13.3(30,960,781-32,444,196)x3 pat

| | |
|---|---|
| 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 |
| 15q13.3 | The chromosome involved is 15, band 15q13.3 |
| 30,960,781-32,444,196 | The long arm (q) segment from 30,960,781-32,444,196 has been duplicated. An extra piece of DNA, between the base pairs 30,960,781 and 32,444,196 (around 31 and 32.4 Mega base (Mb) respectively from the top of the long arm where it starts counting from 0 Mb), has been found. By deducting the first number from the second, you get 1,483,415. This is the number of base pairs that are duplicated (approximately 1.48 Mb) |
| x3 | Three copies of this segment of band 15q13.3, not two – one on each chromosome 15 – as you would normally expect |
| pat | Some genetic reports will say 'pat' or 'mat' at the end, showing that the microduplication is inherited from the father (paternal) or mother (maternal). Other cases of microduplication are not inherited and arise dn (*de novo*), meaning that the microduplication has occurred for the first time in that individual. |

## Emerging phenotype: what to expect

The features of a 15q13.3 duplication were first described in 2009 in four individuals (van Bon 2009). Small numbers of people with a 15q13.3 microduplication have been identified and of these only ten cases are described in any detail in the medical literature. Therefore, it is not certain what the full range of possible effects of the microduplication is. In addition the features vary, even between members of the same family. Some cases of 15q13.3 microduplication are inherited but not all. The presence of a 15q13.3 microduplication does not affect everyone and in any individual the features can be more or less obvious.

The most commons features are:

- Feeding and growth – infant feeding problems and/or overeating in some older children. Growth may be affected.
- Delayed development – occupational therapy can help with difficulties with motor skills; not all children are affected and fine motor skills (handling objects etc) may be more impaired than gross motor skills (walking etc)
- Learning (intellectual) disabilities – learning support may be necessary in some children, with a range of support needed depending on the level of learning disability.
- Communication difficulties with speech delay in some children - speech and occupational therapy are beneficial.
- Behavioural/emotional disorders – Autistic spectrum disorders, emotional instability and/or sensory processing disorder are described in some children, requiring extra support at home and school.
- Sleep – Insomnia is common and often quite severe, requiring medication and/or

sleep training.

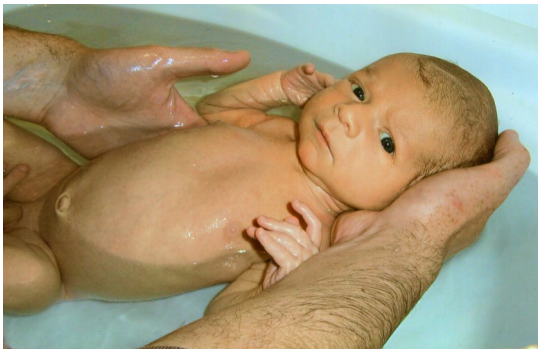
- Epilepsy – seizures can be a feature requiring regular brain monitoring and medication.

These features are discussed in more detail below. The number of children with any particular feature is given as, for example, five out of ten published cases (5/10) or six out of thirteen Unique members (6/13). Detailed information is not always available on all the known cases and therefore the numbers may reflect this. For example four may have a particular characteristic out of nine Unique members who have provided information (4/9).

## Pregnancy

**Most pregnancies were uncomplicated and carried to term with birth by vaginal delivery at 38-40 weeks.**

Most mothers carrying babies with a 15q13.3 microduplication experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. There is information available on eleven pregnancies, eight of which are reported as being uneventful. Two babies were born at 38.5 weeks; one of these mothers had had early labour contractions and was put on bed rest. One mother took progesterone supplements to retain the pregnancy after repeat miscarriages. Another mother experienced a lack of fetal movement, a large amount of amniotic fluid, a skin rash called PUPPS (pruritic urticarial papules and plaques of pregnancy) and high blood pressure; the baby was delivered by emergency caesarean section (van Bon 2009, Unique).



## Feeding and growth

**Feeding difficulties – including infant feeding problems and overeating in some older children – appear to be quite common in children with a 15q13.3 microduplication. Growth may be affected.**

The medical literature does not detail feeding and growth but nine Unique members have provided information. One child had no feeding problems. Another couldn't eat food with texture at 12 months. Two babies could not latch onto the breast to feed; one of these was reported as taking a bottle. Several Unique members reported breastfeeding until their babies were 18 months old.

Another baby couldn't keep formula milk down and at six weeks was diagnosed with pyloric stenosis (a narrowed outlet of the stomach, with persistent vomiting as the main symptom), which was corrected with surgery. This child and five other Unique members had acid reflux, particularly as babies. This is when acid from the stomach leaks up into the feeding tube (oesophagus), causing heartburn and other symptoms. Keeping feeds small and medication, which reduces the amount of acid made in the stomach, can be beneficial.

“ She vomits more than a normal child of her age. Vomiting is brought on by a prominent gag reflex while eating, or simply coughing or laughing too hard ” – 3 years

Five children, aged 6-11, have ongoing problems with constipation. Dietary changes and daily medication were beneficial.

“ She had feeding issues as a teen – constipation, bloating and vomiting. Her gallbladder and appendix were removed at 18. Enemas were offered as a treatment for the constipation. She is frail, weak and anaemic and has to eat several low fat meals a day ” – 23 years old.

Several children were described as ‘failure to thrive’, a phrase which describes children whose current weight or rate of weight gain is significantly lower than that of other children of similar age and gender. Differences in height and weight may reflect the range seen in the population as a whole and individuals with the 15q13.3 microduplication can be within normal ranges. However, three individuals were reported as thin and tall for their age with, for example, weight measurements at 15-20 percent of the average and height at 80 percent (van Bon 2009, Unique).

“ He is tall for his age with thin to average build ” – nearly 6 years

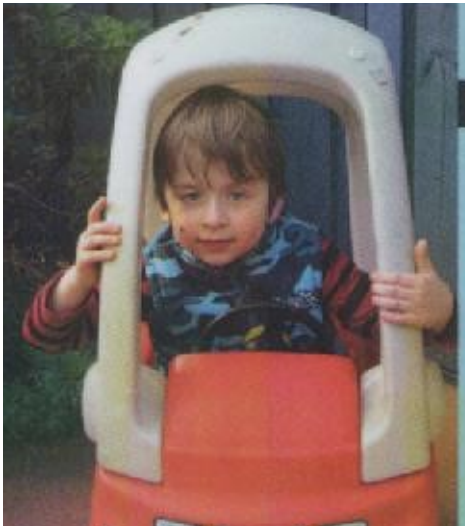
Two children had a short statue and, at 6 ½ years, one had a projected adult height of 1m 42cm (4’8”), whilst another child was of average height for his age but of above average weight (van Bon 2009, Unique). Two children in the medical literature, both aged 4, were reported as obese. Overeating is an issue for 3/9 Unique members (aged 6, 6½ and 11 years) and one case in the medical literature (van Bon 2009).

“ She has a tendency to overeat. If allowed she would eat constantly ” – 6½ years

## Development: sitting, moving, walking (gross motor skills)

**Gross motor skills may be affected with 5/13 Unique members reporting some developmental delay in these areas.**

Two adults, who appear unaffected by the 15q13.3 microduplication, demonstrated normal development as a child and six Unique members, who may be affected in other ways, do not have any impaired gross motor skills. For example, one child sat unaided at 8 months, crawled at 9 months and walked alone at 14 months (Unique). Five Unique members did have a developmental delay in acquiring gross motor skills. One member had a mild delay in walking but after exercises for lax ligaments and hip tendons was walking, within two weeks, at 18 months. One boy started to crawl at two years old and walking was also delayed; he walked



alone at 2 ½ years. Another boy, at aged nearly three, walks on tiptoes with his arms bent in front of him.

> “ At 1 year she is unable to sit and cannot bear weight very well ”

> “ Her legs appear normal, but she doesn't walk as smoothly as someone who doesn't have any disabilities. All of her therapists and doctors describe her movements as jerky and uncoordinated ” – 3 years

> “ She is a wonderful dancer and dances competitively ” – 6 ½ years

> “ He loves to swim and dive until his legs hurt and then he wants to go home immediately ” – 13 years

The medical literature does not provide any detail on gross motor skills but one child was described as moving in a stiff way at four years old, with hypermobile (lax) joints (van Bon 2009). A Unique member also has hypermobile joints caused by Ehlers Danlos syndrome III (a rare inherited condition that is not associated with the 15q13.3 microduplication). He also has hypotonia (low muscle tone) so he's very floppy. Despite the hypotonia/ hypermobility, his developmental milestones, sitting up, walking etc, were achieved at similar times to other unaffected children. Another Unique child also had hypotonia and doesn't have much muscle mass at 11 years old but enjoys Judo. He has double-jointed elbows but they don't affect him in any way. Two of the six cases described in one medical paper had hypotonia, at three years and ten years old (Szafranski 2010).

## Development: hand-eye coordination and dexterity (fine motor skills) and self care

**Fine motor skills may be affected, with 5/13 Unique members reporting some degree of difficulty, ranging from mild to severe.**

Children may have trouble handling objects, taking longer to reach for and grab toys and hold a bottle or cup. Gross motor skills may be further ahead of fine motor skills. At one year old, one chid is described as having severe developmental delay; she cannot focus on objects and does not hold toys or a bottle. One three year old child is functioning at about the 18 month level. Most Unique members do not report difficulties with fine motor skills; those that do describe their children's experiences:

> “ She has trouble using her hands and tends to use her raking grasp to pick things up. She is unable to isolate or separate fingers and she does not point to objects or people. She can hold a cup on her own or bring a fork or spoon to her mouth, but she has trouble putting food on a fork or spoon on her own. She can manipulate infant-type toys: she put rings on a ring-stacker and is working on stringing chunky beads on a string (with help). She struggles greatly to draw/colour. She only makes light markings on the paper and holds the crayon/her hand upside down to do so ” – 3 years

> “ He couldn't hold a spoon until nearly two years old. I just worked with him over and over again...The doctors thought it was because people were doing things for him but my gut instinct told me something was wrong ” – 13 years

Personal care may be delayed for a small number of children.

> “ She is still in diapers [nappies] and is totally dependent on us taking care of her. She can help us put on her clothes, but she cannot do this on her own ” – 3 years

> “ He's in nappies at night and was only toilet trained in the day at five years old. He needs assistance with dressing; he does try though and can brush his teeth/hair ” – 6 years

> “ He can look after himself; he showers, gets dressed etc. He's fine now, but as a toddler he was delayed in this area ” – 13 years

## Speech and language development

**Some, although not all, children with a 15q13.3 microduplication have a delay in acquiring speech and language skills.**

Seven of eleven Unique members who detail language, and two cases in the medical literature, have reported delayed speech and/or speech that is hard to understand (Szafranski 2010, Unique).

> “ He does not understand everything that is said to him. He does not talk except for a few words like 'mum', 'dad', 'bye bye', 'no' and 'hiya' that he has picked up from his younger sister ” – 33 months

One child began saying words at four years and at six years old language was developing with the use of small phrases. One child started speaking around 2 years but the development of language has been slow:

> “ She has limited language and her speech is very hard to understand. She has probably 20-50 word approximations, with a few intelligible words like: backpack, purple, cracker, apple, bubble etc. Most words are just a few consonants or vowels and may sound the same (Blueberry and Ball sound similar – Buh or Bah Bah). We are working with therapists who provide exercises for her mouth to increase her ability to produce sounds ” – 3 years.

Another at two years had a vocabulary of about 10 words:

> “ He didn't talk on schedule and we began to worry. Six ear infections during his third year made us think it was hearing – related. He had myringotomy (ear tubes for the treatment of ear infections) in both ears. His speech still did not progress and I began to work with him daily doing sentences. He finally began speaking at age five. His language to this day is delayed and he struggles to formulate sentence structure or find the correct word for what he is trying to describe or tell me ” – 13 years

Picture exchange communication (PEC) methods are helpful, including those on devices such as the iPAD. Online resources that focus on children with autistic spectrum disorders are also relevant here to the development of language, for example, the ZAC Browser website (this is an internet search engine developed specifically for children with autism and other special needs). Sign language may be useful; basic sign language was started at around 15 months with one child and this is still used at aged three years with signs for 'more', 'mine' and 'please' etc. Speech therapy is regularly used to develop more language (Unique).

“ I just worked one-to-one with him daily to build speech and vocabulary. Now we use a phonics-based approach to reading and that has helped quite a bit ”– 13 years

“ She was delayed in her use of language but is fine now; she uses proper grammar, words etc ” – 23 years

Other children have no apparent speech or communication problems (Unique).

“ She started speaking at 9 months and now has good communication skills. She has no problems making the sounds of speech clearly ” – 6 ½ years

## Learning

**Some children with a 15q13.3 microduplication have a learning disability. Although this covers a wide range from mild to severe, children are more commonly at the milder end of the spectrum. In addition, there are Unique members, and several cases in the medical literature, who have no learning disabilities.**

Some Unique members are too young to determine whether learning (intellectual) disabilities are present or, if so, their precise nature. Five Unique members describe learning disabilities which require learning support. In the milder cases, this is provided in a mainstream school. More severely affected individuals are educated in a special school; none of the current Unique members have a severe learning disability but two cases are mentioned in the medical literature (van Bon 2009, Unique).

Behavioural issues (see page 10) are sometimes found which may affect a child's learning: difficulty concentrating, inability to sit still, anxiety and frustration are reported by six Unique members. Three children have been diagnosed with an autistic spectrum disorder and others show possible symptoms. Some individuals are particularly talented in art or music (Unique).


“ She is still cognitively behind, although it is hard to tell her skill level. This is because of her difficulty maintaining attention and her inability to speak, but I believe her cognition ranges between 12-24 months. She is in a mainstream preschool but attends special education classes with an individual education plan (IEP). Having no other distractions helps her to learn, no additional noise (other than background music), no additional people, toys, etc. She needs to focus in a quiet and clean room/ table ” - 3 years

“ He has a great memory and his computer skills are fantastic. He picks up other languages easily, for example, Spanish. He loves being read to. Although he can't read as yet, he recognizes lots of words and can write his name and draw faces

(started at age 5). He is at a mainstream school but we have 2 hours of learning support a week. Sitting still can be an issue. To help this, he has a 'Disco Sit' chair which helps him maintain movement whilst sitting at a table during therapy and classroom activities. Repetition, pictures, songs, quiet environments and a one-to-one approach all help him to learn" – 6 years

"No learning delays have been noted yet. She started drawing/writing at 2 years old and is now proficient at them. She has a good memory; repetitive teaching helps her to learn. She started to read at aged 6 and has no learning support" - 6½ years

"He is at a mainstream school but has a statement of special educational needs, with borderline learning disability in some areas, moderate in others. At aged 11, he gets mostly grade C's, sometimes F's. He started to read at 6 years and sometimes now reads books. He has a great memory; watching other people do activities helps him to learn" – 11 years

"He has a moderate learning disability. He doesn't like to study unless it's an area he likes. He is very impatient, aggressive at times; you have to know how to work with him to get him to focus. Although he can write letters, his penmanship is still crude. At 4 years old, he was starting to draw and write and was reading at 8 years old. Concentration can be an issue with schoolwork but not when he's playing games! He's homeschooled and we find a good diet, sleep and patience help him to learn" – 13 years

"She has a mild learning disability, with a statement of special educational needs. Her particular strengths are art, history and music; she can play the piano for hours. She has a good memory, except for mathematics, and loves to read. She learnt to read at 6 years old and started drawing and writing at 2 years old. A quiet and calm environment helps her concentration" – 17 years

## Behaviour

**Children with a 15q13.3 microduplication can be happy, sociable and affectionate. However, behavioural issues, often on the autistic spectrum of behaviour, are frequently reported. Socially, children may be behind in their development, relative to their peers, and be emotionally volatile.**

Amongst the 13 Unique members, there are two who carry the 15q13.3 microduplication who do not have any behavioural issues. In most other Unique members, several characteristics are reported, with all those members highlighting one or more of these as being of particular concern: frustration, anxiety, finding it hard to concentrate, an impulsive or restless nature, repetitive behaviour or play, putting objects in their mouths and an emotional temperament. Some features such as frustration and anxiety may be associated with communication difficulties and children's ability to learn may be affected by these behavioural issues (see 'learning' page 9).

The medical literature does not describe behaviour in any detail and may highlight only the more severe cases. One individual with a15q13.3 microduplication was reported as being aggressive from childhood onwards. At 17 years old, he was diagnosed with bipolar disorder (previously called manic depression – periods of overactive, excited, manic behaviour alternating with periods of depression) and Pervasive Developmental Disorder, Not Otherwise Specified (PDD – NOS). This is a condition in which some - but not all -

features of autism are observed. Autistic tendencies were also observed in a child who behaved in a distant manner at 4 years old, would rock repetitively and bang their head. Another child was described as being extremely talkative and preoccupied with food but did not have major behavioural problems (van Bon 2009).

Three individuals, of six described in another publication, were on the autistic spectrum; one of these also had an anxiety disorder and another had disruptive behaviour. Severe pica (persistent and compulsive cravings to eat non-food items, such as paper, dirt or sand) was noted in one case. Analysis of other family members showed that some, but not all, of the individuals with the same duplication were affected with disorders such as depression, bipolar disorder, anxiety and alcoholism (Szafranski 2010).

“ She is calmer than she was, although she is still in constant motion and loves to run around. She can ride in the car and not get upset now. She will sit with us and watch TV, which she wouldn't have done a year and a half ago. She does bang her head on the ground or on the wall from time to time but this behaviour peaked between 24-36 months; it is much less now. She is overly friendly with people. For example, she goes up to any adult and takes their belongings, looks through their bags etc ” – 3 years

“ He has a great capacity for finding joy and happiness in all he does. Always on the move, he dances and jumps constantly. He loves to kiss and hug and is always happy and upbeat, even when very sick. He is our little ray of sunshine ” – 6 years

“ She is a wonderful child, a very caring loving sister and daughter. She interacts well with other children but does have a tendency to repeat questions over and over ” – 7 years

“ He observes and remembers things very well. He has a great sense of humour and is very sensitive to others' feelings. He can be overly shy and anxious and has a tendency to talk non-stop ” – 11 years

“ He has little patience for himself when he fails at something. He tends to have obsessive compulsive tendencies when it comes to any interest he has. He is a very emotional child, with a sweet and loving personality, very loving to animals and others ” – 13 years

“ She has very fragile emotions that can be set off when others would not take any notice of a comment or action ” - 17 years

> “Mood swings are an issue. She enjoys socialising with the family, but finds making friends difficult. She is a loner, does not like to be in public or attend social events. She does love private family events, holidays etc.” – 23 years

Attention deficit hyperactivity disorder (ADHD) has been discussed as a possible diagnosis in one individual at Unique. A recent study found 37 people with ADHD who had a 15q13.3 microduplication, providing further evidence that duplications on chromosome 15q13.3 are a risk factor for ADHD. Three children have been diagnosed with an autistic spectrum disorder (Williams 2012; Unique).

> “We are managing his mild Asperger’s syndrome with a strict diet, fish oil supplements and a good sleep pattern. His difficulties have improved with time. However I would say that he is mentally a few years behind his physical age but still continues to improve” – 13 years

Some children have sensory issues, with an increased sensitivity to noise and/or tactile sensitivity (4/9). Parents describe various treatments (Unique):

> “We’ve brushed the body, tried vibrating toys, pressure/massage, chewy tubes, bouncing on balls, playing with textured beads or gooey gel pack etc. She’s worn a ‘hug vest’ sometimes to give her extra input” – 3 years

> “Noise is an issue: he will say ‘no noisy, go away’, when he hears loud children in a shopping centre. We see an occupational therapist and are trying therapeutic listening – he won’t keep the headphones on, so we are currently trying surround sound speakers” – 6 years

> “We just keep noise as low as possible. She will get very emotionally upset, unable to study, read or do anything if it is too loud. This may be another reason why she doesn’t like going out and doing a lot of things in public” – 23 years

## Sleep

**Children with a15q13.3 microduplication are prone to difficulties falling or staying asleep.**

Although sleep is not discussed in the medical literature, insomnia is prevalent amongst Unique members with 8/9 reporting it as an issue. Sleep apnoea (a temporary cessation of breathing) occurs in two cases, one of whom also snores (Unique).

> “Sleep has got better, but she has had always had trouble sleeping the whole night through. She often rocks on all fours in the middle of the night for a while and then puts herself back to sleep. She has never taken long naps. She always wakes up crying from a nap, after about 30 minutes, and often cannot fall back to sleep” – 3 years

> “He has problems staying asleep. We use a night light or he’ll just sleep with us. He wakes very early at 4-5am (in bed at 7pm)” – 6 years

> “She has trouble going to sleep and takes melatonin” – 7 years

> “He has terrible problems going to sleep and wakes up a few times and walks around a little” – 11 years

“ He has severe insomnia that we have tried many things to resolve. Getting him to sleep has always been an issue since he was a baby ” – 13 years

“ She has a very hard time falling asleep. The insomnia is terrible and we have tried all kinds of things to cope with it ” – 17 years.

Melatonin has been prescribed for several children. This is a hormone which helps to regulate sleep. Other children may be part of a sleep study to try and identify ways to help them sleep better.

# Medical concerns

## Seizures

Epilepsy can be a feature of a 15q13.3 microduplication.

Epilepsy is a condition that affects the brain and causes repeated seizures, also known as fits. Epilepsy occurs when clusters of nerve cells in the brain sometimes signal abnormally. Brain electroencephalograms (EEGs) record brain activity and abnormal patterns of electrical activity may lead to a diagnosis of epilepsy or a predisposition to seizures. Six of thirteen Unique members describe seizures or suspected seizures. Three of these were related, suggesting a link with that particular length/type of 15q13.3 microduplication or another genetic component that the family share.

Having a seizure does not necessarily mean that a person has epilepsy. About one child in 30 in the general population will have at least one febrile convulsion (an epileptic-type seizure associated with a high temperature) before their fifth birthday. Epilepsy is usually diagnosed when someone has had two or more seizures.

In one Unique child, seizures were most apparent as an infant. Growth spurts and/or the onset of puberty were reported by two Unique member to be associated with the occurrence or reoccurence of seizures. There are several different forms of epilepsy. One Unique member has grand mal seizures. This is a form of epilepsy characterized by tonic-clonic seizures, involving two phases - the tonic phase, in which the body becomes rigid and the clonic phase, in which there is uncontrolled jerking.

“ At 12 months, she had infantile spasms and was treated. She also jerks her head, like a tick or tremor, which has been reduced since she has been on medication ” – 6 years

“ She has had many grand mals. The focal attacks (partial seizures) are getting better now but for about a year were recurring daily throughout the day ” – 17 years

In the more severe cases, the seizures may have an impact on day-to-day activities such as sleep, learning or ability to drive/work. One parent comments that with hindsight they realised that you can live a normal life with epilepsy, provided you adapt to it. Steps to control the seizures include appropriate medication, a good diet, rest and enough sleep.

A case in the medical literature had general myoclonic seizures (a fit characterized by jerking movements) (Szafranski 2010).

## General health

Children and adults with a 15q13.3 microduplication are generally healthy and do not see medical specialists regularly. Others are prone to chest and, in particular, ear infections; some individuals may see specialist doctors on a yearly or more regular basis (van Bon 2009, Unique).

> “ Her adenoids were removed and ear tubes (grommets) inserted at 30 months. This has greatly decreased the number of infections she has had and she is now able to clear the infections in a much shorter period of time ” – 3 years

> “ He had more than six ear infections by 2 years old. Ear tubes (myringotomy) were inserted at 2 years to help him. He also had regular visits to the doctor to manage any wax build up. Hearing tests were performed twice to make sure he wasn't having hearing difficulties when his speech was absent to minimal as a toddler. By age 5, he had outgrown his recurrent ear infections ” – 13 years

One Unique member describes a loss of hearing, which is managed without hearing aids at 6½ years. In the medical literature, a child had a transplant of the tympanic membrane in his right ear because of a cholesteatoma. This is a type of skin cyst located in the middle ear and skull bone, which causes hearing loss (van Bon 2009).

Seven Unique members mention seasonal and/or pet allergies, with regular use of anti-histamines. Another is allergic to milk and has lactose-free milk as a substitute. Four Unique members report asthma which is controlled with inhalers.

## Other medical concerns

Other medical concerns, which may or may not be linked with the microduplication, include the following:

### Heart

There is no particular heart problem that is associated with a 15q13.3 microduplication; although many individuals have had heart investigations, the majority do not reveal any abnormalities.

One Unique member mentions heart palpitations at 11 years old. Two members had a heart murmur (commonly heard in children's heartbeats as an extra or unusual sound), one of which resolved at six weeks old.

One individual has an atrial septal defect (ASD), also known as a 'hole in the heart' (Decipher). This is a type of congenital (present at birth) heart defect in which there is an abnormal opening in the dividing wall between the upper filling chambers of the heart. The hole may close on its own naturally, soon after a child is born, or be corrected surgically. One Unique member has a particular type of hole in the heart called a patent foramen ovale (PFO). Rest is necessary as she becomes tired very easily and at 17 years old she has repeat echocardiograms to see if is closing.

Another type of birth defect that has been observed, in one person, is an aortic coarctation, a narrowing of part of the aorta (the major artery leading out of the heart). This was combined with a hypoplastic left heart, in which the left side of the heart is underdeveloped (Szafranski 2010).

### Brain/Head

Two children have brain cysts (fluid-filled sacs that may produce symptoms with time eg. headache, nausea, vomiting seizures, balance difficulties etc) - in one child this was shrinking at 11 years old.
One child has a congenital Chiari malformation (defect in the back of the head where the brain and spinal cord connect), which has improved with time (Unique).
A Unique member has a small head, less than 10 per cent on the growth charts, at aged three years. This is being monitored by a paediatrician twice a year.

## Eyesight

Three Unique members wear glasses - one has been wearing them from aged seven and another has a substantially reduced field of vision, with severely impaired vision in her right eye.

## What were the first signs?

In some adults that are now known to carry the 15q13.3 microduplication, there were no obvious features. They had no idea they had a chromosome disorder until they were tested to determine whether their child's microduplication was inherited (Unique).
In newborn babies, that carry the microduplication and subsequently show some of the features described above, there were often no obvious signs.

Apgar scores are a system of evaluating a newborn's physical condition by monitoring heart rate, breathing, muscle tone, response to stimuli, and skin colour. Apgar scores were commonly high at birth and birth weights within the normal range. In addition, a 15q13.3 microduplication is not commonly associated with any particular facial features or congenital anomalies that would be evident at birth. One or two features are occasionally mentioned; for example three individuals have hypertelorism (eyes that are set wide apart) and two have microcephaly (a small head) (Szafranski 2010, Decipher, Unique).

In older children, failure to thrive, language and developmental delays and/or seizures may be the first indicators. Failure to thrive refers to a child whose growth is significantly less than that of their peers; one child was referred for genetic testing due to her short stature. In affected individuals, the age of diagnosis ranges from 14 months - 18 years.

> “ He was a little late on every developmental milestone by a month or two. He didn't talk on schedule and we began to worry ” - 13 years (diagnosed at 10)

## Growing up with a 15q13.3 microduplication

## Are there people with a 15q13.3 microduplication who have developed normally and have no speech, learning or health difficulties?

Yes, there are. The 15q13.3 microduplication can be silent. Some parents of children with a 15q13.3 microduplication have the same microduplication but do not have any obvious features (Unique). The effect on development, health and behaviour of some genetic disorders ranges from being barely perceptible to being obvious and more severe. The reasons for this are not clear but it seems that other factors influence the effects of having a 15q13.3 microduplication. For example, other genes that an individual carries may modify the expression of genes that are present within the 15q13.3 microduplication.

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

Not necessarily. There can be a lot of variation between different members of the same family who have the same microduplication. One person can be mildly affected or unaffected whilst others may have more obvious affects. As with unaffected carriers of the microduplication, there are likely to be other factors that influence how severely a 15q13.3 microduplication affects someone.

## What is the outlook?

We can't be sure yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan. Unique has two adult members who carry the 15q13.3 duplication but were unaware of this until well into adulthood. Similarly, there are people in the medical literature who do not show any effects. Many children, who have learning and developmental disabilities that are associated with a 15q13.3 microduplication, do not appear to have major health problems.

## Puberty and fertility

Most of the children who are Unique members have not been through puberty yet. The adult members, who do not show any developmental/health affects from the microduplication, do not report any problems at puberty. In one Unique member, puberty was late at 17 years old; behavioural difficulties and the onset of epilepsy were linked to the influence of changing hormones.

Three Unique members, one of whom is affected by the microduplication, have had children. One member did have several miscarriages but it's not known whether this is associated with the microduplication and she went on to carry other babies to term.

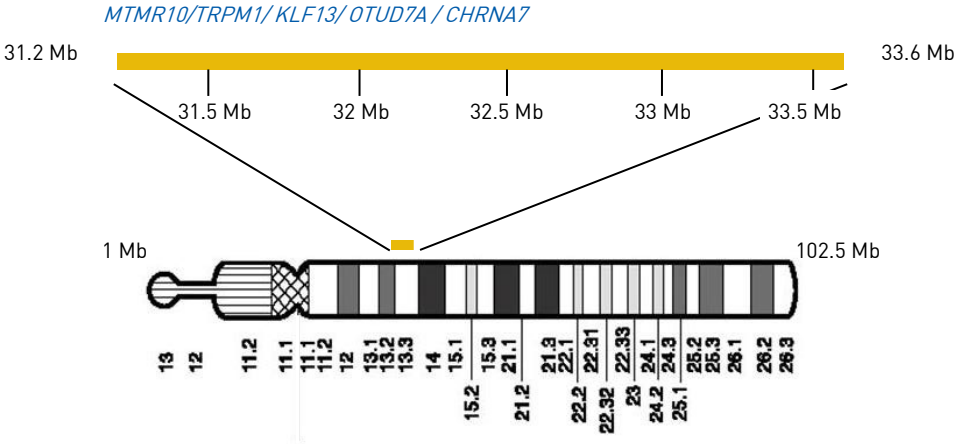
With her new baby

## Ongoing research involving 15q13.3

The exact size of the duplicated region of 15q13.3 varies from approximately 0.5Mb to 2.5Mb (see diagram below), but it is likely to contain at least six genes (including *MTMR10*, *TRPM1, KlF13*, *TUD7A* and *CHRNA7*). It is thought that the effects are caused by the presence of three copies of the genes in this region, instead of the normal two copies. However, it is unclear which genes contribute to the specific features of the disorder.

As some people with a 15q13.3 microdeletion have no obvious signs or symptoms, researchers believe that other factors, genetic or environmental, may also play a role. For example, one study has found a possible link between a 420 kb 15q13.3 duplication which includes the *CHRNA7* gene (involved in nerve cell signalling in the brain), ADHD and a conduct disorder (a group of behavioural problems where a child is aggressive, antisocial and defiant to a much greater degree than expected for the child's age) (Williams 2012).

Genes located on 15q13.3:




Although identifying the genes that are responsible for the features of a 15q13.3 microduplication is interesting and is likely to guide future studies, it may not lead directly to improved treatment. This is particularly relevant when the varying affects of a 15q1.3 microduplication are taken into account.

## Why did this happen?

A blood test to check both parents' chromosomes allows parents to find out how the 15q13.3 microduplication occurred. Several Unique members have inherited the microduplication from either a father or a mother. However, in some cases the microduplication occurred when both parents have normal chromosomes. Geneticists call this '*de novo*', which means 'new'. *De novo* 15q13.3 microduplications are caused by a change that occurred when the parents' sperm or egg cells formed, or possibly during formation and copying of the early cells after the egg and sperm joined.

In either inherited or de novo cases, there is nothing that you, as a parent, did to cause the microduplication, either before or during the pregnancy. Parents should feel reassured that no lifestyle change - environmental or dietary - would have prevented it from occurring.

## Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 15q13.3 microduplication 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 microduplication. 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 duplication.

In families where the 15q13.3 microduplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 15q13.3 microduplication rises to 50% in each pregnancy. However, the effect of the microduplication 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.

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## Siblings with a 15q13.3 duplication:

## 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

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2013 Version 1 (CW)