



Understanding Chromosome & Gene Disorders

3q13 deletions and microdeletions



rarechromo.org

Sources

The information in this guide is drawn partly from 35 people reported in the medical literature [McMorrow 1986; Okada 1987; Fujita 1992; Genuardi 1994; Ogilvie 1998; Hou 2004; Kosaki 2005; Lawson-Yuen 2006; Sato 2007; Simovich 2008; Shimojima 2009; Malan 2010; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Wisniewiecka-Kowalik 2013]. 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 on Decipher (<https://decipher.sanger.ac.uk>); and on a survey of members of Unique conducted in 2013, referenced Unique. When this guide was compiled, Unique had 11 members with a pure 3q13 deletion.

A 3q13 deletion is a genetic condition that occurs when there is a small piece of genetic material (DNA) missing from one of the 46 chromosomes – chromosome 3.

The genetic change usually affects development, and sometimes health and behaviour as well. But how much it affects individuals, and the ways in which it affects them can vary a lot.

Genes and chromosomes

Our bodies are 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. Chromosomes usually come in pairs, one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: two Xs for a girl and an X and a Y for a boy. The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22, approximately from largest to smallest, so chromosome 3 is a relatively large chromosome. Each chromosome has a short (p) arm (petit, French for small) and a long (q) arm.

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

We wish we'd known ...

"I wish I had known to push them harder when they were younger. The taller and heavier they get, the harder it gets as a parent." - 6 years

"Everything has gone much better than we envisaged when we got the diagnosis, and she's a lovely girl we would never exchange. She has developed little by little, so I still think it is exciting to see how far she can go." - 8 years

3q13.31 deletion syndrome

When a particular set of developmental features occurs in a recognisable and consistent pattern in enough people, as a result of a single cause, the condition is called a syndrome. The essential features of a 3q13 deletion can occur in this way, and when they do, the disorder is known as **3q13.31 deletion syndrome**. This is an 'emerging' syndrome, first identified in 2012, so much remains to be learnt.



10 years



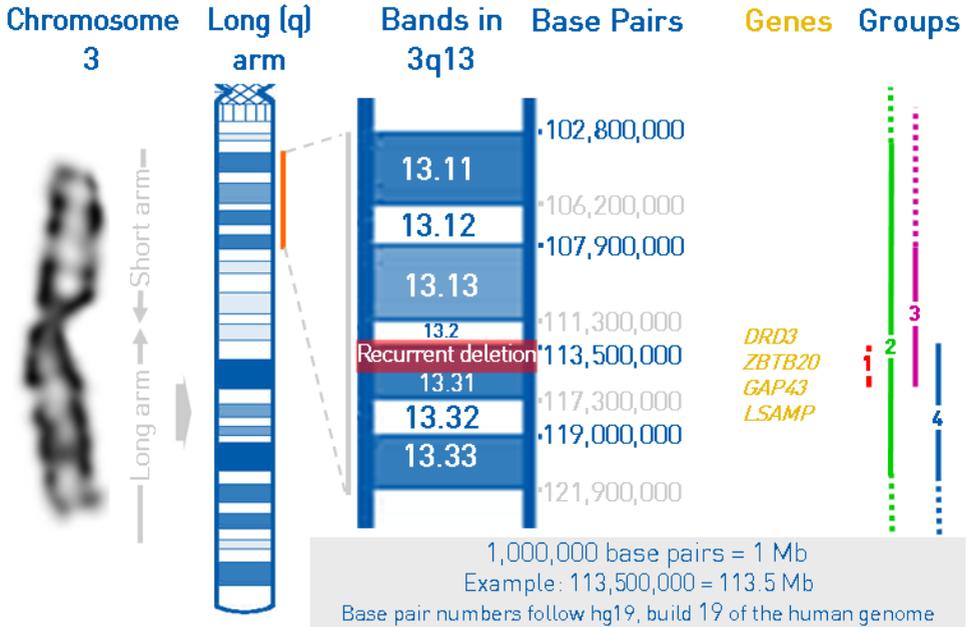
14 years

We wish we'd known ...

"I wish I had done less therapy. I would have done 1 hour a week at most of speech and occupational therapy. I would have spent more time around typical peers, more family time and time in public trying to incorporate more life skills." - 10½ years

"Everything! Her diagnosis has no matches, so being told that no one could prepare us for what she would be like was hard. Seeing her now, it's far better than we expected. Our motto is 'Expect nothing but shoot for everything' and 'Doctors can diagnose, but only God can prognose'. We learned that some medications were worse than the illness and we made many changes along the way. We learned we could refuse or insist on tests and treatments. I learned that while therapy is valuable and needed to be done, some days I needed to choose to just be mom and to love and play, and enjoy her where she was at. Taking those breaks, a week here and there throughout the year, always resulted in big progress leaps after we returned to programs!" - 14 years

Finding your way: chromosome 3q13



Looking at chromosome 3q13

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. Each band contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. Chromosome 3 has about 198 million base pairs, and band 3q13 alone has more than 29 million base pairs. This sounds a lot, but is actually a tiny fraction of the total; the whole of band 3q13 is less than 0.05 per cent of the total DNA in each cell.

In the diagram of chromosome 3 at the top of this page, the long arm meets the short arm about halfway down the chromosome. 3q13 is near the top of the long arm, marked with an orange bar. It is divided into 7 sub-bands with quite confusing numbering. Under [Base Pairs](#), you can see how the base pair numbers relate to the chromosome bands.

Has everyone with a 3q13 deletion got the same amount of missing DNA?

Not necessarily. People generally have different break points in chromosome 3; different amounts of missing DNA; and different numbers of missing genes – anything from a handful to more than 100. People with 3q13.1 deletion syndrome have all lost a specific 0.58 Mb segment of DNA in 3q13.1, including 5 genes, though most have lost more than this. This segment starts at 113.85 Mb

and ends at 114.4 Mb. Some people have very similar deletions with break points in 3q13.2 at 112.1 Mb and in 3q13.31 at 115.5 Mb. They have lost about 3.4 Mb of DNA, including the 0.58 Mb segment. This deletion is marked as 'Recurrent deletion' on the diagram (Molin 2012; Shuvarikov 2013; Decipher).

In the diagram, you can see 4 groups of people with a 3q13 deletion.

In **Group 1** are those with **3q13.31 deletion syndrome**. They have lost DNA between 3q13.2 and 3q13.31 with break points around 112-115.5 Mb, or the smaller segment of around 0.58 Mb between 113.9-114.4 Mb. This includes 9 people reported by Shuvarikov 2013; 5 reported by Molin 2012; and one in Shimojima 2009, as well as 6 in Decipher.

In **Group 2** are people with a larger deletion that overlaps the Group 1 deletion. This includes 14 people reported ; Ogilvie 1998; Lawson-Yuen 2006; Malan 2010; Molin 2012; Wisniowiecka-Kowalnik 2013) and 4 Unique members, as well as 3 in Decipher.

In **Group 3** are people with a deletion that overlaps the repeated deletion but extends towards the top of the long arm. This includes 4 people reported in the medical literature (Hou 2004; Kosaki 2005; Sato 2007; Simovich 2008; Molin 2012) and 3 Unique members, as well as 2 in Decipher.

In **Group 4** are people with a deletion that overlaps the repeated deletion but extends towards the tip of 3q. This includes two people reported in the medical literature (Molin 2012; Vuillaume 2013) and 4 Unique members, as well as 3 in Decipher.

Genetic testing

Looking at chromosomes under a microscope, it may be possible to see the missing genetic material if the piece is large enough. If the missing piece is very small, the chromosomes may look normal under a microscope. Changes smaller than 5 Mb are very hard to identify, and sometimes larger changes as big as 10 Mb can be hard to see. A very small deletion is often called a microdeletion.

Molecular DNA technology gives a more precise understanding of the size and position of the deletion. This is important as scientists identify genes and pinpoint their location on chromosomes.

A person's chromosome make up is called his/ her karyotype. Someone with 3q13.31 deletion syndrome might have a karyotype that looks like one of these two examples:

arr 3q13.12q13.33 x1dn

This result tells you that a microarray test (**arr**) found two break points in chromosome 3: the first at **3q13.12**, and the second in the band called **3q13.33**. There was only one [**x1**] copy of the DNA between the break points. The normal number of copies is two. **dn** de novo (Latin for 'from the beginning') means that the chromosome change has not been inherited from a parent but has arisen 'anew' in the child.

arr cgh[hg19] 3q13.2q13.31(112963753-116362963)x1

The test was by array comparative genomic hybridization (arr cgh). The results follow the Human Genome build 19 [hg19]. The human genome is updated as new information is found; each new version is called a 'build'. In each build the base pair numbers usually change slightly. The latest build is hg19.

3q13.2q13.31 shows that two break points were found, the first in band 3q13.2 and the second in band 3q13.31. (112138736-115515026)x1 shows that only one copy (x1) of the material between the break points was found. 112138736-115515026 are the start and end points of the missing copy, measured in base pairs. Take the first long number from the second and you find that there are 3,376,290 missing base pairs. This is about 3.4 Mb – a typical deletion for someone with 3q13.31 deletion syndrome.

Main features of 3q13.31 deletion syndrome

- Low muscle tone (hypotonia), so a baby feels floppy to hold
- Developmental delay, including mobility and speech
- Variable need for support with learning
- Above average growth rate in babies and children, including head size
- Small genitals in boys. Genitals in girls are normal
- Characteristic facial features
- High palate (roof of the mouth)

Less common features

- Brain and central nervous system involvement
- Seizures and/ or unusual patterns of electrical activity in the brain
- Eyesight problems including short or long sight (Molin 2012; Shuvarikov 2013)

Pregnancy

Usually uncomplicated

Pregnancy is usually uneventful, with babies delivered near term (Molin 2012). Individual pregnancy complications can occur, but not in any distinctive or characteristic pattern. In group 1, two pregnancies were marked by oligohydramnios, where there is very little amniotic fluid, but this was not associated with any kidney problem. In another pregnancy, ultrasound scans at 19 weeks suggested a possible chromosome abnormality, but no specific structural anomalies were seen (Molin 2012; Shuvarikov 2013). In group 2, one baby moved very little and was small for dates by 34 weeks of pregnancy (Unique); and another had a general swelling (lymphoedema) (Genuardi 1994). In group 3, one baby was small for dates and delivery was induced due to lack of fetal movement (Unique).

"She loves to help people, loves to snuggle, loves to participate with others. She greets people with high fives and will insist on a response, often cheering people up." - 14 years

New babies

Babies are usually born around their due date. Some have an unusually large head

Babies in group 1 are usually born around term, although one was born at 29 weeks. They are typically a good weight at birth, on average 3.36 kg (7lb 7oz) and some have an unusually large head. Four deliveries were by Caesarean section, including one for fetal distress. Babies faced a variety of difficulties immediately after birth: low Apgar scores; breathing difficulties, including the need for neonatal resuscitation; and feeding problems (latching on; weight loss). Two babies needed intensive care (Molin 2012; Shuvarikov 2013).



One year old

Babies in group 2 are smaller than those in group 1 and have more difficulties as newborns. Most are born near term, but one was born at 33 weeks. Average birth weight is 2.92 kg (6lb 7oz), range 2.4-3.68 kg (5lb 5oz-8lb 2oz). Among the neonatal difficulties seen in more than one baby are respiratory distress; jaundice – in babies born at term; low muscle tone; and lack of energy (Fujita 1992; Genuardi 1994; Lawson-Yuen 2006; Malan 2010; Wisniewiecka-Kowalnik 2013; Unique).

Among babies in group 3, a similar pattern was found: most born near term with a reasonable weight, but 1/7 born prematurely at 30 weeks and one baby having significant respiratory distress at birth (Sato 2007/ Hou 2004; Simovich 2008). Among babies in group 4 born at term, average birth weight is 3.1 kg (6lb 14oz), range 2.5-3.7kg (5lb 9oz-8lb 3oz), with great variation in the condition of babies, some entirely healthy, others with severe respiratory distress.

“No problems.” - 3q13.2q13.31 deletion

“She was born by emergency caesarean section, since the doctor didn’t think she would survive birth. The pulse was low and they thought the umbilical cord was around her neck. The placenta was partially damaged, so she did not get enough nourishment, but we didn’t know this before she was born. She was therefore a little limp so the nurse had to help her eat, and she slept a lot the first months.” - 3q13.31 deletion

Feeding

Newborn babies may have difficulty feeding. Establishing breastfeeding may be a struggle.

Some babies have difficulty establishing feeding, especially in the first days. Low muscle tone may affect the face, making it hard for babies to suck and swallow effectively. Establishing breastfeeding can be difficult and babies may need to take breast milk by tube or by bottle, if necessary with an adapted teat. Some babies thrive better on formula milk.

In the early days, babies may need to be woken for feeds. Gastro-oesophageal reflux (GORD, GERD) can occur, where the stomach contents return up the food pipe and can cause choking, vomiting and discomfort. Reflux raises a baby's risk of inhaling food contents and setting up an infection in the lungs known as aspiration pneumonia. Reflux can be eased by careful semi-upright positioning during and after feeds, sleeping in a prescribed sleep chair rather than a bed, raising the head end of the baby's cot and if necessary by prescribed medication that helps to keep the feed within the stomach and counteract any acidity.

Babies are usually late to handle lumps and to chew, and remain on puréed food for longer than typically developing babies. This is not always the case, and some babies eat the same range of foods as any typically developing baby. Difficulties using their hands mean that children are usually late to hold a bottle or cup and are better at feeding themselves, usually messily, with finger foods than at using cutlery, but this skill develops in time. After the early days, Unique's experience is that feeding problems ease and by the toddler years children are eating a varied, normal diet with a wide range of tastes and textures.

Constipation is common and can be troublesome, needing treatment with a high-fluid, high-fibre diet and usually with prescribed laxatives and stimulants. Some families also avoid milk (Unique).

"He eats well but doesn't hold a bottle or cup yet and only feeds himself to a limited extent." - 15 months

"He eats great but cannot drink milk due to severe constipation. He can feed himself items he can pick up but cannot use a spoon independently." - 6 years

"We put food on her spoon, and then she takes it and puts it in her mouth. Then she puts the spoon on the plate or table and waits for us to put more food on it. We have had help from a feeding team to help her to eat with a spoon by herself, and it has helped a little." - 8 years

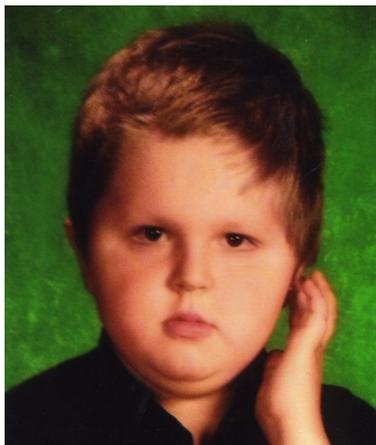
"Her favorite foods are sandwiches, yogurts, pizza and pastas, and she eats a bigger variety of foods than when she was younger. She's used a spoon since age 8 or 9. She tends to overstuff her mouth and has to be watched closely for choking. Delayed gastric emptying and constipation are still issues." - 14 years

Relatively rapid growth in babies and children, especially head size

Growth and height are typically above average

As a group, children and adults with chromosome conditions are often shorter than typically developing children. But children and adults with 3q13.31 deletion syndrome are often tall; they may be overweight; and very often their head is large in proportion to their body. The extra growth usually comes after birth, although the head may already be unusually or proportionately large when a baby is born. This pattern of increased growth can be seen in all four groups but is not consistent: some people are short; others are thin; and others have an average head size. The pattern of increased growth is most consistent in those in group 1.

In group 1, 9/20 people are unusually tall; 8/18 are overweight; and 12/19 have a large head (Molin 2012; Shuvarikov 2013; Decipher). In group 2, 6/16 people are unusually tall; 4 are of average height; and 4 are short. 4/11 are overweight; and 5 are thin. 8/15 have a large head; in 3 the head is of average size; in 2 it is small (Okada 1987; Fujita 1992; Genuardi 1994; Ogilvie 1998; Malan 2010; Molin 2012; Wisniowiecka-Kowalnik 2013; Decipher; Unique). For group 3 there is information on only 4 people: 2 are tall, one average height and one short; one is overweight; and one has an unusually large head (Sato 2007/ Hou 2004; Simovich 2008; Unique). For group 4, there is information on only 6 people of whom two are tall with a large head and three are overweight; another is of average height (Vuillaume 2013; Decipher; Unique).



“Sensitive, caring and loving”
8 years

As well as the typically large head, many children have an unusual head shape. A broad, prominent forehead is very typical. The head may also be unusually short from front to back (brachycephaly); or it may be long (dolichocephaly); or shaped like a parallelogram when viewed from on top (plagiocephaly) (Genuardi 1994; Molin 2012; Shuvarikov 2013; Decipher; Unique).

“Her face in general is small but her head is big.”
“Very tall, kinda big head, very skinny.”

Developmental problems affecting the genitals

Minor anomalies of the genitals and reproductive system appear to be somewhat more common among baby boys and children with a chromosome change than among others, and this is particularly true of those with 3q13.31 deletion syndrome. However, some baby boys and so far all girls have been born with normal genitals. Among the 24 males reported in the medical literature and at Unique, 15 were affected in some way. At Decipher, 4/9 males were affected. Eleven were born with undescended testes. Undescended testes are found quite commonly in baby boys with and without a chromosome condition. If the testes do not descend into the scrotum of their own accord, they can be brought down and fixed in a minor surgical procedure. In one boy, the testes had descended into the scrotum but retreated on examination (retractile). In three boys the testes were abnormally small, and in 6 boys the penis was very small. Two boys had what is known as shawl scrotum, where the scrotum surrounds the penis instead of lying behind it, and in one boy there was no penile structure present. One boy had a collection of fluid around the testis known as a hydrocele (McMorrow 1986; Fujita 1992; Genuardi 1994; Kosaki 2005; Simovich 2008; Malan 2010; Molin 2012; Shuvarikov 2013; Decipher).

Characteristic facial features

Some children and adults have similar facial features, so you might see a passing resemblance between people who are unrelated. These features are typically fairly subtle, with Unique families saying their children do not generally stand out as different. Among the more common features are a broad, prominent forehead; widely spaced and downwards-slanting eyes, sometimes with a tiny skinfold across the inner corners; a short but broad and sometimes upturned nose, perhaps with a slightly bulbous tip; a short space between the nose and the mouth; a full lower lip; ears set low on the sides of the head and sometimes with an unusual shape. Features seen less often include hooded eyelids; a pointed chin; sparse or non-existent eyebrows and midface hypoplasia (the upper jaw, cheekbones and eye sockets do not grow as much as the rest of the face, so the face below the eyes looks relatively flat). One baby was born without a developed nose (Okada 1987; Fujita 1992; Genuardi 1994; Sato 2007/ Hou 2004; Kosaki 2005; Lawson-Yuen 2006; Simovich 2008; Malan 2010; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Unique).

High palate

In at least 14 babies and children, the palate was unusually high. In itself, a high palate is a normal variant and if everything else is in order, it generally has no impact on speech or swallowing. If the palate is also narrow, and it often is, this can lead to later overcrowding of the teeth. Other possible problems associated with a high palate include disrupted sleep caused by nasal obstruction, and a feeding inconvenience where food gathers at the top of the palate, so a child needs frequent drinks while feeding (Kosaki 2005; Sato 2007/ Hou 2004; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Unique).

“Very narrow, unusually high arched palate.”

Brain

When the brain is imaged, the most common finding with 3q13.31 deletion syndrome is that the band of nervous tissue that connects the two sides of the brain has partly or completely failed to develop. This condition is known as agenesis/hypoplasia of the corpus callosum (HCC or ACC) and effects range from subtle to severe, depending partly on any other brain anomalies found. Overall, 12 children have been found to have ACC, including 3 in group 1, 6 in group 2, and 3 in group 4. Other structural brain anomalies found include enlarged ventricles (the fluid-filled spaces within the brain); abnormalities of the cerebellum at the back of the brain; delayed myelination (creation of a layer of insulation around nerve fibres); and thinning of the white matter with some scarring (McMorrow 1986; Ogilvie 1998; Genuardi 1994; Lawson-Yuen 2006; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Wisniowiecka-Kowalnik 2013; Decipher; Unique).

“A great sense of humor. She understands she is different and tries to fit in with other children. ” - 10½ years

Development

Expect some delay – but the range is very broad

Two children, both with group 3 deletions, showed no developmental delay and no low muscle tone (Simovich 2008; Molin 2012).

Sitting, standing, walking

Babies are late to sit, stand, and become mobile. Low muscle tone is often marked. Babies and children with 3q13.31 deletion syndrome typically face quite significant delay in reaching their mobility milestones. Underpinning the delay is a marked degree of low muscle tone, but with maturity and physiotherapy this generally improves. Some children have very flexible, loose joints, while others have some tight, contracted joints (McMorrow 1986; Okada 1987). Early intervention is important and to become mobile most children need lower limb support in the form of splints, ankle foot orthoses or supporting boots, as well as whole body support from standers or walkers.

Babies in groups 1 and 2 learned to roll over between the ages of 6 and 9 months and were able to sit up between 12 and 20 months. They became mobile from 8 months, and were walking between 16 months and 7 years, although this may not be possible for all. Children were much less steady on their feet than typically developing children.

“Uses a walker and is guided but still not walking independently.” - 6 years

“She started walking when she was 2 but was very uncoordinated and her movements now are different and slower than other children. It takes her longer to do things and if someone tries to push her even gently on the back to move her along, it makes her upset as she is anxious she might fall.” - 10½ years

“She was walking before 4 and started walking fully independently at 5. At first she fell over often, but made great progress and now moves around pretty well.

She can't run but uses a fast walk, and tries to jump. When climbing stairs, she leads with the right leg and both feet hit every step.” - 14 years

Babies in groups 3 and 4 were sitting between 6-22 months, becoming mobile from 9-21 months and walking from 12 months. Mobility was much improved in children without low muscle tone.

One child in group 3 sat and walked in line with typically developing children (Simovich 2008).

Other children showed delay, and had an unusual gait. (Molin 2012; Shuvarikov 2013; Wisniowiecka-Kowalnik 2013; Unique).

“She walked the day she was 18 months old. Her mobility is good: she walks, runs and loves to climb. But she can't go skiing or ride a bike.”

- 8 years



“His smile and giggles are addictive and keep us laughing!” - 12 months

Using their hands: fine motor skills and co-ordination

Hand use and control is quite delayed

Information from Unique shows that children's fine motor abilities are generally - but not always - quite delayed, and affected by their low musculature. Hand and eye co-ordination skills such as holding and playing with small toys and holding implements such as cutlery and writing implements is markedly delayed and children find gripping and grasping difficult and unrewarding. Children with weak hands or very flexible joints in their hands find holding objects especially difficult. Early intervention with play and occupational therapy to stimulate hand use is almost always very helpful, and parents recommend toys with lights and music and keyboards for early skills and touch screens for more advanced activities like writing (Unique).

"He opens his hands, can grab toys and transfer between hands." -12 months

"Always very good hand use: touch-screen, play, grabbing toys." - 19 months

"He prefers to use his thumbs versus his pointer finger on games and electronics. No handwriting skills yet." - 6 years

"She does not play with toys. She likes to look at books, and can turn over the pages. She can use touch screens but cannot write or draw: she'd rather bite the pencil!" - 8 years

"Little pretend play, no writing, but she can work an iPad like a champion. She is currently using touch chat to communicate as the keyboard is still too fine motor for her." - 10½ years

"Fine motor is poor. Still working on pincer grasp and finger strength."
-14 years

Personal care and toilet training

Daily tasks like getting dressed and undressed, washing and personal care are demanding, and children typically need a very high level of support. Toilet training is also significantly delayed, and may not be possible for all (Unique).

"She does not wash herself. She can help to take off and put on her jacket, and take off her cap, and she lifts her bottom when we change her diaper. If she is in the mood she can help a lot, but she is very stubborn, so if she doesn't want to she doesn't do anything. She helps her father more than she helps me, because he has taken on the 'teacher' rôle, and taught her many things, so she 'likes' to show him that she can." - 8 years

"Toilet training is in progress. I think it is hard for her to feel the urge to urinate, so we use a timing system. Dressing is minimal and washing is OK but I still have to go over the areas to make sure they are clean." - 10½ years

"Still in diapers. Prefers shower over bath but needs 100% assistance. If handed a shirt ready to pull over her head, she can get her arms in; pants are harder, but once her feet are in, she can pull them up most of the way. Cannot do buttons, snaps or zippers on pants. On coats or sweatshirts she can undo a zipper, and zip it up once it's started for her. She cannot put her own shoes on. She can take all her clothes off just fine." - 14 years

Learning

A range, usually from moderate to severe difficulties, but can be mild or normal. Children with 3q13.31 deletion syndrome are likely to need support with their learning. Evidence from the medical literature and from Unique families shows a scattered pattern. In group 1 there is great variation, from a child of 8 years with normal intellectual development to a child of almost 3 years with the developmental age of a 4-month-old baby. Generally, children in this group had a moderate level of difficulty (Molin 2012; Shuvarikov 2013).

In group 2, children generally needed more learning support than children in group 1, but one child of 4 was able to name some common animals in a drawing, recite the alphabet, and count to 10 while another child of 6 years could recognize objects, colours, and sort objects according to simple characteristics. Where a formal assessment of learning was performed, it was below 50 (Fujita 1992; Lawson-Yuen 2006; Molin 2012; Wisniowiecka-Kowalnik 2013). Reports from Unique members show that difficulties with fine motor skills undermine children's ability to write so they need alternative means of communication.



"Her sense of humor is amazing!" - 14 years

"He learns at his own pace and it's very slow, but once he masters something it looks like he has been doing it for years. He attends a public elementary school and is in a special needs class for his learning and therapies." - 6 years

"Still learning and mastering new skills all the time. Attends a public mainstream school. However, she is moving to private school for special needs children next year." - 10½ years

"Using a program called Handwriting Without Tears has helped a lot this year, she can build the letters of her name and with minimal help is starting to write them on a small chalkboard, also part of the program. She makes straight lines and circles with a pen but no letters yet, maneuvers the iPad and the Wii very well." - 14 years

Children in groups 3 and 4 generally seem to have somewhat less marked learning difficulties but there is considerable variation between individuals. One child of 13 was reported to be reading and writing, and to have a mild degree of learning difficulty (Vuillaume 2013). Among Unique families, children have generally needed a lot of learning support.

"Generally learning at a 2-year-old level. He is in 3rd grade in a special day class with support." - 8 years

"It is difficult to teach her anything because she does not mimic or copy us, and doesn't like to be hand-led or shown things." - 8 years

Speech and communication

Most children are late to talk. Some use other ways to communicate.

Some children in group 1 understand speech and learn to talk at the same age as typically developing children, but it is more common to show delay. Even among children who were late to talk, some showed catch-up, acquiring a varied vocabulary and learning to connect words and phrases. Babbling and sound-making occurred in the second year and first words generally emerged around 2-3 years. Some children spoke very unclearly and two children, including one with normal speech, stuttered (Molin 2012; Shuvarikov 2013).

Children in group 2 have markedly delayed speech and many rely on body language, single sounds and non-verbal means to express their needs and feelings. The use of words emerges in some children quite late, around the age of 6-8 or even later, but words may not be clear or easily understood by people other than family and teachers. In three children, few or no meaningful words were used and communication was largely by signing or gestures at the ages of 4½, 8 and 18 years (Molin 2012). This picture is not entirely consistent: there is one report of a child with significant language delay who nonetheless had a vocabulary of over 100 words and 2-3 word phrases by the age of 4. Signing and assistive communication are important. Understanding may also be limited, but enhanced by keeping speech short, clear, simple, and directed at the child in a familiar situation (Okada 1987; Fujita 1992; Lawson-Yuen 2006; Malan 2010; Molin 2012; Wisniowiecka-Kowalnik 2013; Unique).

“No signs or speech yet, but he hums and does a lot of stimming with his arms, and laughs a lot. He is learning switches but hasn't got it quite yet.” - 6 years

“She has no words, but signs *More* and *Yes*, and shakes her head for *No*. She will take you by the hand to show you what she wants. She uses the iPad to communicate.” - 10½ years

“She uses words for her basic needs, but is generally unable to communicate. She combines phrases as if they are one word, for example: *HeHeightHack* is ‘Be right back’; *Hatuzawesome* is ‘That was awesome’; and *IHoHahee* is ‘I go potty’.” - 14 years

Children in groups 3 and 4 show a wide range in speech abilities. Some children talk at the same age as typically developing children (Simovich 2008; Vuillaume 2013; Unique) while others struggle to use words (Unique).

“He smiles but no words yet.” - 12 months

“Says *mama*, *dada*, *hi*, and *nana* for grandma. She wears hearing aids for slight hearing problems to see if this will help with speech.” - 19 months

“He has about 150 words, and uses some signs.” - 8 years

“She makes sounds so you can understand if she is pleased or upset. She does not use signs, because she will not mimic or copy us, or look at us when we do sign. But she has begun to show us what she wants by eg getting a packet of biscuits if she can see it, though she does not go to the cupboard of her own initiative. She has no language, not a letter.” - 8 years

Behaviour

Many children have no behavioural problems but difficulty concentrating is common and a few children have an autism spectrum disorder

Parent reports of behaviour in children in groups 1 and 2 are generally more upbeat than reports in the medical literature, although one child of almost 5 years is reported to have no behaviour concerns (Shimojima 2009). Parents report that their children are affectionate, have a sense of humour, and behave appropriately at home and in social situations, although they can have difficulties when they feel overwhelmed (Unique). Reports in the medical literature reveal as problem areas anxiety; immaturity; a short attention span; risky behaviour; a low energy level and very little ability to co-operate and copy others; aggression and easy frustration; obsessive-compulsive behaviour like constant hand washing; and frequent examples of behaviour on the autistic spectrum, including repetitive behaviour, hand flapping, phrase-repeating (echolalia) and difficulties coping with sensory overload. On the positive side, individual children are reported to be outgoing and sociable; generally happy; and to overcome their behaviour problems with age (Molin 2012; Shuvarikov 2013; Wisniowiecka-Kowalnik 2013; Decipher).

“Good behavior, though he recently started getting more of an attitude and fussing when not wanting to do things.” - 8 years

“Every summer at camp she received behavior therapy and I have a helper starting for 1:1 life situations. She was having fits and would get mad appropriately but could not snap out of it, and would be upset for long periods of time, throwing tantrums. It was like her brain couldn’t move on to the next thing because she was so upset.” - 10½ years

“Pretty good: she has her triggers but is not too bad if prepared. Sensory issues aren’t too bad, but she will plug her ears when it’s loud or get whiney and want to go home. She is affectionate and blows kisses and gives hugs freely. An amazing sense of humour and laughs easily. A tender heart and will hug and console anyone who seems to be hurt. She is now a greeter at church and will stand and hand out bulletins, and gets very shy when any young man comes into church. She belongs to Fun Life, a social group for highschoolers with special needs and feels very secure and relaxed there. She can be a little unpredictable with people – some days she’s not shy, and other days she’s very shy and will hide her face in my arm.” - 14 years

“She brings an innocence that is moving and you cannot help but fall in love with her. Of course it’s stressful that she does not eat independently, or dress herself and such things, but there is so much positive that outweighs everything. She is so cuddly and we appreciate it when she looks us in the eye (she only does that when she wants to), and when she laughs her lovely laughter, it is very powerful!” - 8 years

Children in groups 3 and 4 show great variation between normal behaviour for any child, regardless of special needs, and significant difficulties including unresponsiveness and self-harm (Molin 2012; Unique).

“Very happy and easy-going; he likes to watch his sister and for us to interact with him.” - 12 months

“Happy, playful. Always seems to be in a good mood.” - 19 months

“When she wakes, she makes sounds so we can hear her. We open her bed (she uses a kind of big cot) and then she sits a while in bed and pokes the pillow or sheet, or looks at a book. This finger gesture she makes almost all the time, often in front of her eyes. She’s very tactile, so she likes to put on different fabrics. She still uses a comforter (dummy), and quickly starts complaining if she does not have it. Otherwise she is very easy-going, and seldom angry (the comforter helps a lot).” - 8 years

“A very sweet, loving little boy. Sensitive to people’s feelings. We have consulted a behaviourist to help with self harm.” - 8 years

Sleep

Unique members report few sleep difficulties. Two children (8 and 14 years) sleep in an enclosed bed, and another child of 8 wakes often at night, and needs frequent naps in the day. The 14 year old needs her pyjamas securing on to stop her stripping at night (Unique). A further child was reported with obstructive sleep apnoea, where breathing is interrupted during sleep, and disordered sleep (Shuvarikov 2013).

Feet

Some degree of foot anomaly has been found in almost one third of children and adults with 3q13.31 deletion syndrome, although foot problems are noted less often among Unique children. The most common problem is flat feet. Three babies were born with talipes equinovarus, where the foot points downwards and inwards. Among other positional anomalies reported is claw foot (pes cavus) in which the arch is very high and doesn’t flatten on weight bearing, and a marked inward-leaning (pronation) of the feet. The approach to positional foot anomalies depends on the severity and whether the foot can be manipulated. Some anomalies can be corrected with physiotherapy, splinting or the Ponseti method, where the foot is gently manipulated to gradually reduce the bend, and held in its new position after each correction in a plaster cast. Sometimes surgery is needed to correct the bend in the foot.

Other unusual features affecting the feet include a wide ‘sandal gap’ between the first and second toes; unusual creases on the sole of the foot; an unusual size or angle of some of the toes; joined toes (McMorrow 1986; Fujita 1992; Genuardi 1994; Simovich 2008; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Decipher; Unique).

Eyesight

The most common concerns are ptosis and long or short sight

A common feature of the eyes in a child with 3q13.31 deletion syndrome is ptosis. The upper eyelid of one eye or both droops; the droop may only be slight, so you hardly notice it; or it can obscure vision and require surgical correction. 12/46 children reported in the medical literature or at Unique are affected by ptosis (Fujita 1992; Shimojima 2009; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Unique). Babies with ptosis are regularly checked to ensure that vision is not affected. If there is any risk that eyesight is affected, surgical correction will be considered. This usually involves shortening the muscles that raise the eyelid or helping to raise the eyelid by inserting a sling of material between the forehead and the eyelid.

Short or long sight is also common, affecting 3/15 children in group 1, 6/18 in group 2 and 1/13 in groups 3 and 4. This is usually correctable with glasses, if a child will wear them (Lawson-Yuen 2006; Molin 2012; Shuvarikov 2013; Unique).

Strabismus, the medical term for squint or crossed eyes, can also occur on its own or with other vision problems. It affects 5/15 children in group 1, 2/18 in group 2 and 1/13 in groups 3 and 4 (Fujita 1992; Molin 2012; Shuvarikov 2013). The crossed eye can look inwards, outwards, up or down. The main effects of strabismus are that the person will usually have one eye which is stronger than the other. This is because the brain has to give priority to one eye over the other with the result that the weaker one does not 'learn' to see as well as the stronger one. Treatment of strabismus depends on the cause but can include patching the stronger eye, exercises, glasses to correct a refractive error such as long sight and surgery to realign the muscles that hold the eye in place.

Nystagmus (involuntary to and fro eye movements) has been observed in 3 people, in one case an adult who had nystagmus as a baby and at 42 years (Fujita 1992; Genuardi 1994; Shuvarikov 2013).

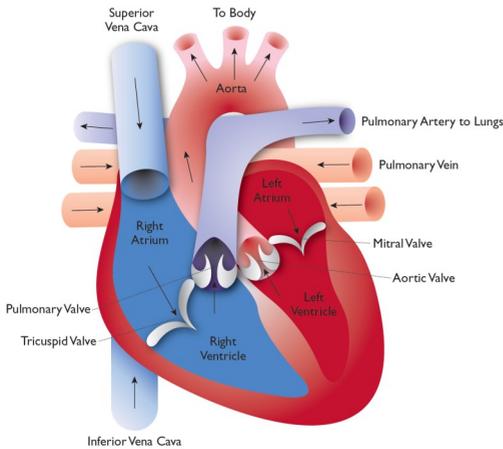
Other eye problems include a marked difficulty in moving the eyes (Shuvarikov 2013); cataract, that was removed (Fujita 1992); and cortical visual impairment (the visual systems in the brain do not understand or interpret what the eyes see), for which vision therapy is given (Unique).

"If walking from concrete to carpet in the same plane she takes a big step as if walking up a step. This has been explained as more of a brain problem than an eye problem." - 10½ years

"She prefers to use her peripheral vision so often turns her head to the side. She purposely crosses her eyes sometimes, but I don't know why." - 14 years

"It's the little things that other people for granted! It's amazing to see each step they take to master something. It is sometimes frustrating but once they get it, it's all worth it. The smile and laughter my son has brought me. And he loves to give hugs and snuggle. He has taught many people including myself and his family that some things take a lot of hard work but are worth it!" - 6 years

Heart



A normal heart

Four children were born with a heart condition. One child had small holes in the heart; another had persistent ductus arteriosus, where a channel between the aorta and the pulmonary artery that takes blood to the lungs remains open instead of closing shortly after birth; and another patent foramen ovale, where an opening between the two upper chambers of the heart does not close in the first year of life, as expected. In all three children the problem resolved spontaneously, or required no more than monitoring. A fourth child had tetralogy of Fallot, a complex

abnormality consisting of two main problems: the pulmonary valve that regulates blood leaving the heart for the lungs is narrow (pulmonary stenosis) and there is a large hole between the right and left ventricles, the lower pumping chambers. This means that less blood flows through to the lungs and the level of oxygen in the blood is low. Tetralogy of Fallot is corrected in a surgical operation (Simovich 2008; Molin 2012; Unique).

Epilepsy

Seizures are fairly common. In group 1, 5/15 children and adults have had one or more seizures. One child fell and hit the back of his head without losing consciousness; a few hours later he had multiple seizures, and at least one later seizure episode. A baby of 10 months had a febrile convulsion after a respiratory infection followed by a continuous fit lasting for more than an hour. One child and one adult had seizures (in one case possible silent ones) and an EEG (electroencephalogram) recording showing abnormal brain wave patterns. A further child had seizures but normal EEG patterns and did not take anti-epileptic medication (Shimajima 2009; Shuvarikov 2013). In group 2, 3/5 Unique children had seizures, but no-one reported in the medical literature. One child had a single seizure at 5 years; another child developed absence seizures (a brief loss of consciousness) at 4½ years and these are controlled with medication; a third child developed seizures after the age of 4 and while EEGs at first showed that seizure activity started in the right side of the brain, by 13 years it started from locations all over the brain. This child also has sub-clinical seizures, which can make her sleepy and vomit. An EEG then usually shows nearly constant seizure activity which is not obvious externally. Her seizures are 'quite well controlled' at 14 years but 'it has been a battle to achieve this' (Unique).

In group 3, 1/7 developed generalised seizures from the age of 1 year, well controlled with anti-epileptic medication (Sato 2007/ Hou 2004). In group 4, three children are affected. One child of 3 developed seizures with one-sided paralysis; another is treated with anti-epileptic medication but without a definite diagnosis of epilepsy (Vuillaume 2013; Decipher; Unique).

“She takes epilepsy medicine because she was measured with epileptic activity. We are not entirely sure that she has epilepsy, but the medicine works against the ‘twitching’ she had.” - 8 years

Genitourinary/ kidney

Kidney and urinary tract anomalies are occasionally seen. Five children were affected, all in groups 1 or 2, and none in Unique. One child had a single kidney, with compensatory enlargement (Shuvarikov 2013); another had incomplete duplication of the collecting system on the right side (Okada 1987); another had an enlarged kidney on one side (McMorrow 1986); another had an abnormally small right kidney (Molin 2012); and the fifth child had swelling of the tubes that connect the kidneys with the bladder and a blockage near the valves that lead out from the bladder (Genuardi 1994).

Spinal curvature

A spinal curvature is not unusual in children with significant low muscle tone, and is fairly common among those with 3q13.31 deletion syndrome. The curve may be sideways (scoliosis), forwards (lordosis) or backwards, with a humped appearance (kyphosis). Depending on the severity, it may only be necessary to monitor the curve. If it is impeding movement or, for example, breathing, it can be stabilised with a brace or if need be a surgical operation to straighten and fix the spine. In group 1, 3/15 children were affected; in group 2, 4/18 children were affected including one whose scoliosis was progressive and stopped the child from standing properly. In group 3, 4/8 and in group 4 1/6 were affected (Okada 1987; Sato 2007/ Hou 2004; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Wisniowiecka-Kowalnik 2013; Decipher; Unique).

General wellbeing

Unique records show that as a group, children with chromosome conditions tend to be unwell more often than typically developing children, and when they are unwell take longer to get better. Children with 3q13.31 deletion syndrome fit this pattern. While some are perfectly healthy, others are particularly prone to repeated upper respiratory tract infections in early childhood and may need hospital treatment. By later childhood they outgrow this tendency and are generally healthy (Unique).

“Fine, just gets sick very easily and takes a lot longer to feel better.” - 6 years
“Her lungs and general health are much better. She is on a mostly gluten free diet, we use essential oils and homeopathy as needed. Peppermint oil on the bottom of the feet drops her fever and has prevented many complications from high fevers.” - 14 years

Teeth

Dental disorders appear to be more common among children with a chromosome condition than among typically developing children. Among the problems noted among children with a 3q13.31 deletion are crowded teeth; weak enamel and many cavities; very small and crooked teeth; overbite; black spots attributed to excessive drooling; and grinding (Molin 2012; Unique).

“Brushing is a challenge, but her last exam showed no cavities.”

Hands

The hands of a child with 3q13.31 deletion syndrome may be slightly unusual: the hands may be small and one or more fingers surprisingly long or short. The fingers may taper towards a point and the fifth fingers, and occasionally other fingers, may curve inwards. Thumbs may be set unusually close to the wrist. These features do not generally affect function, but very flexible joints and low muscle tone typically do, making it harder for children to grasp, grip and control their hand movements (Fujita 1992; Genuardi 1994; Simovich 2008; Molin 2012; Shuvarikov 2013; Vuillaume 2013; Unique).

Other

Other problems reported in individual children include in group 1 constipation (Shuvarikov 2013); in group 2 chronic lung disease (Unique); hypothyroidism (Molin 2012; Wisniowiecka-Kowalnik 2013); tracheomalacia and laryngomalacia, where the cartilage rings that keep the windpipe and voice box open are too soft, so the airway can close off more than it should, together with laryngeal cleft, a gap between the food pipe (oesophagus) and the trachea (airway), allowing fluid or food to pass through (Unique). In group 3, two babies were born with major anomalies: in one case, the baby was born without nasal structures in the face (Sato 2007/ Hou 2004); in the other, the baby had OEIS complex, where among other problems the liver, bowel, bladder and other organs are on the outside of the abdomen (Kosaki 2005).

Why did the 3q13.31 deletion occur? Did my baby get it from me? Was it my fault?

3q13 deletions usually occur out of the blue for no obvious reason. Tiny microdeletions can sometimes be inherited direct either from the mother or the father, but this has not yet been seen with 3q13.31 deletions (Molin 2012; Shuvarikov 2013; Decipher).

The genetic term for a new event is de novo (dn). A new 3q13 deletion has been caused by a mistake either when the parents' sperm or egg cells were formed or in the very earliest days after fertilisation. As a parent there is nothing you could have done to change or control this. Nothing in the environment, diet, workplace or lifestyle is known to cause these chromosome changes.

In people who have the repeated 3q13 microdeletion between 112 Mb - 115.5 Mb marked as 'Recurrent deletion' on red in the diagram on page 4, one cause of the microdeletion is believed to be short stretches of DNA at both ends of the deletion that are very similar to each other. These look-alike stretches of DNA occupy about 8 per cent of the human genome and are the remnants of viral infections in the cells of our distant ancestors. It is believed that they can cause mistakes in the natural process of DNA-exchange that occurs when sperm or eggs are formed (Shuvarikov 2013).

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 3q13 deletion or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 3q13 deletion. This is called **germline mosaicism** and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the deletion.

In families where the 3q13 deletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 3q13 deletion rises to 50% in each pregnancy. However, the effect of the microdeletion on the child's development, health and behaviour cannot be reliably predicted.

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

Can my child have children of their own?

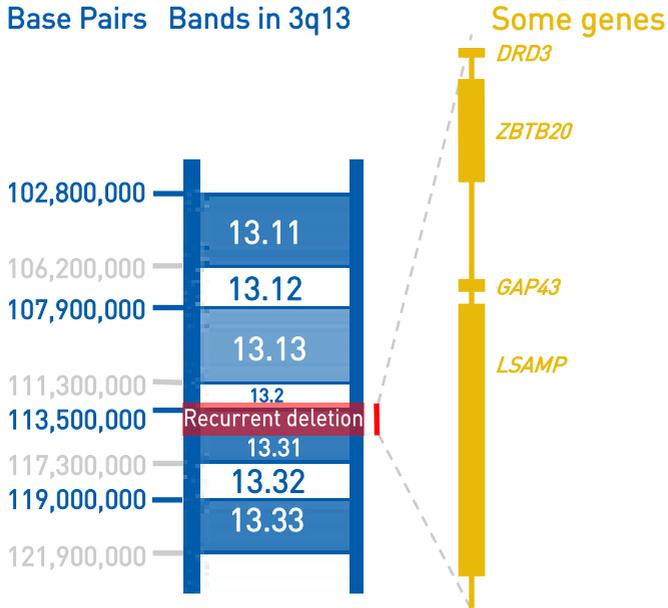
Theoretically, anyone with a 3q13 deletion has around a 1:2 (50 per cent) chance in each pregnancy of passing it on. In practice, the genital involvement in some males suggests that their fertility could be affected.



"We were told she wouldn't live to see her first birthday"
14 years

Genes

The 3q13 region is rich in genes, and it is generally believed that the 3q13.31 deletion syndrome is caused by losing one or more of them. One difficulty for researchers investigating which genes underlie the difficulties faced by people with a 3q13 deletion is that the key genes are specifically active in the brain, and it is not possible to test brain tissue for gene activity.



DRD3 (113,847,499-113,918,254) is found within the 0.58 Mb segment of DNA that everyone with 3q13.31 deletion syndrome has lost. It provides instructions for making a protein that is important in the brain, taking part in communication between dopamine cells and the outside world. It is important in movement, learning and emotion and very probably contributes to developmental delay. Mice without the gene are hyperactive and have problems with spatial working memory. It has been suggested that *DRD3* might also be related to obesity, and it has been linked with impulsive personality traits and addictive behaviour. This gene could also contribute to structural brain disorders, and unusual skull formations (Molin 2012; Shuvarikov 2013; Vuillaume 2013).

ZBTB20 (114,056,941-114,866,118) is found within the 0.58 Mb segment of DNA that everyone with 3q13.31 deletion syndrome has lost, and is believed to contribute to developmental delay. It gives instructions for making a protein important in the nerve cells of a part of the brain known as the hippocampus. In mice where production of this protein was disturbed, one effect was abnormal development of the corpus callosum, a part of the brain sometimes disrupted in

people with a 3q13 deletion. The ZBTB20 protein regulates other genes responsible for similar genetic syndromes. It also regulates genes involved in growth and metabolism and in glucose metabolism, so could be relevant to the rapid growth seen in some people (Molin 2012; Shuvarikov 2013; Vuillaume 2013).

GAP43 (115,342,171-115,440,337) is involved in conduction between nerve cells and has been recently identified as one of the genes possibly underlying the development of features of autism including anxiety, stress-related withdrawal and resistance to change. It is also suspected to be involved in the formation of the corpus callosum. It is a strong candidate gene for developmental delay (Genuardi 1994; Molin 2012; Vuillaume 2013).

LSAMP (115,528,641-117,716,095) is involved in learning and behaviour (Molin 2012).

While identifying the gene(s) responsible for certain features of a 3q13.31 deletion is valuable and may help to guide future studies, it does not lead directly to immediate improved treatment. Also, 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 play a role in determining the presence or absence of a particular feature.

What do children enjoy?

Music, reading books, playing with toys that make a noise & light up
- 12 months

Swinging, any TV show, toys that light up or make a noise, and books: he will flip through the pages all day long - 6 years

Splashing her hands in water - 8 years

Video games; computers; the park, especially the swings - 8 years

Music and swimming. Water provides her body with constant feedback which is reduced with her hypotonia: she seems more coordinated and alert after a swim. Also YouTube on the iPad: she can then watch cartoons and videos as she pleases - 10½ years

She loves to go bowling or any outdoor activity with the family like baseball, the park, walks, and riding quads. She likes to play games on her iPad, the Wii - Hot Wheels and My Little Pony mostly - 14 years

Support and Information



Understanding Chromosome & Gene Disorders

Rare Chromosome Disorder Support Group,

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

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